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

***Labstat International ULC
Test Report***



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

Project Code: M100

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

1	USE OF LABSTAT'S ANALYTICAL REPORTS.....	4
2	ADMINISTRATIVE INFORMATION.....	5
2.1	Quotation Reference	5
2.2	Client Identification	5
2.3	Date of Sample Receipt	5
2.4	Sample Characteristics	5
2.5	Test Article Identification	5
2.6	Special Instructions	5
2.7	Date of Test Report	5
2.8	Revision History	6
2.8.1	Revision 1.....	6
2.8.2	Revision 2.....	6
2.8.3	Revision 3.....	6
2.8.4	Revision 5.....	6
3	ACCREDITATION.....	6
3.1	Scope (refer to appendix A).....	6
3.2	International Recognition of Tests	6
4	METHODS.....	7
4.1	General References	7
4.2	Preparation of Solutions and Media	7
4.3	Preparation of CHO-WBL Cell Culture Suspension.....	7
4.4	Collection of Total Particulate Matter (TPM).....	7
4.4.1	Processing of TPM	8
4.4.2	Test Method Deviations.....	8
4.5	Smokeless Tobacco Sample Preparation	8
4.6	Clastogenicity/Genotoxicity Testing.....	8
4.6.1	Preparation of CHO-WBL Cells and Exposure to Test Articles	8
4.6.2	Harvesting and Counting of Cells	9
4.6.3	Micronucleus Staining and Scoring	9
4.7	Method Deviations.....	9
5	RESULTS.....	9
5.1	Data Files	9
5.1.1	Moisture-Corrected, Nicotine and 'Unit of Use' Doses	9
5.2	Quality Control.....	10
5.2.1	Chemicals and Media	10
5.2.2	Cell Culture Maintenance	10

5.2.3	Evaluation of Negative Controls	10
5.2.4	Evaluation of Cell Proliferation	11
5.2.5	Evaluation of Positive Controls	11
5.2.6	Evaluation of Laboratory Controls (Kentucky Reference 3R4F)	13
5.2.7	Cytotoxicity	13
6	GENOTOXICITY COMPARISONS	14
6.1	Data Files	14
6.2	Methodology	14
6.3	Specific Activity Determinations	15
6.4	Comparisons among Smokeless Tobacco Products	15
6.4.1	Individual Replicate Slopes and Slope Statistics	15
6.4.2	Data Plots	17
6.4.3	One-Way ANOVA Results	20
6.4.4	Contrasts of Interest	22
6.5	Comparisons between Smoked and Smokeless Tobacco Products	36
6.5.1	Individual Replicate Slopes and Slope Statistics	36
6.5.2	Data Plots	38
6.5.3	One-Way ANOVA Results	39
6.5.4	Contrasts of Interest	40
7	SUMMARY	45
8	ATTRIBUTION	46
8.1	Original	46
8.1.1	Technical Director (Toxicology)	46
8.1.2	Senior Statistician	46
8.2	Revision 1	46
8.3	Revision 2	47
8.3.1	Technical Director (Toxicology)	47
8.3.2	Senior Statistician	47
8.4	Revision 3	47
8.4.1	Technical Director (Toxicology)	47
8.5	Revision 5	48
8.5.1	Technical Director (Toxicology)	48
8.5.2	Senior Statistician	48

1 Use of Labstat's¹ Analytical Reports²

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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

Original: January 12, 2009

Revision 1: November 3, 2009

Revision 2: December 17, 2009

Revision 3: April 23, 2010

Revision 5: December 22, 2010

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

2.8 Revision History

2.8.1 Revision 1

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

2.8.2 Revision 2

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

2.8.3 Revision 3

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

2.8.4 Revision 5⁵

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

3 Accreditation

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

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



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

3.2 International Recognition of Tests

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

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

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 SMOKE⁶

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)

(b) (4)

4.4 Collection of Total Particulate Matter (TPM)⁷

(b) (4)

⁶ 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.

⁷ 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)

⁸ 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.

4.4.1 Processing of TPM(b) (4)
A large grey rectangular box redacting the content of section 4.4.1.**4.4.2 Test Method Deviations**(b) (4)
A grey rectangular box redacting the content of section 4.4.2.**4.5 Smokeless Tobacco Sample Preparation**(b) (4)
A large grey rectangular box redacting the content of section 4.5.**4.6 Clastogenicity/Genotoxicity Testing****4.6.1 Preparation of CHO-WBL Cells and Exposure to Test Articles**(b) (4)
A large grey rectangular box redacting the content of section 4.6.1.

⁹ 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.

4.6.2 Harvesting and Counting of Cells

(b) (4)

4.6.3 Micronucleus Staining and Scoring

(b) (4)

4.7 Method Deviations

(b) (4)

5 Results

5.1 Data Files

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

5.1.1 Moisture-Corrected, Nicotine and 'Unit of Use' Doses

(b) (4)

5.2 Quality Control

5.2.1 Chemicals and Media

5.2.1.1 Requirement

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

5.2.1.2 Conclusion

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

5.2.2 Cell Culture Maintenance

5.2.2.1 Requirement

(b) (4)

5.2.2.2 Conclusion

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

5.2.3 Evaluation of Negative Controls

5.2.3.1 Acceptance Criteria for Negative Controls

(b) (4)

5.2.3.2 Conclusion

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

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

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

5.2.4 Evaluation of Cell Proliferation

5.2.4.1 Acceptance Criteria for Cell Proliferation

(b) (4)

5.2.4.2 Conclusion

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

5.2.5 Evaluation of Positive Controls

5.2.5.1 Acceptance Criteria for Positive Controls¹⁰

(b) (4)

¹⁰ Acceptance criteria have not been defined in the Official Health Canada Test Method T-503

(b) (4)

5.2.5.2 Conclusion

Treatment Schedule	Assay Date	Positive Control	[Conc] [µg/mL]	Expected		Flask 1 Observed		Flask 2 Observed	
				(% MN)	SD	(% MN)	p-value	(% MN)	p-value
Schedule (i)	28-Nov-08	Mitomycin C	2	17.6	0.6	17.5	0.868	18.3	0.243
Schedule (i)	28-Nov-08	Mitomycin C	2	17.6	0.6	18.7	0.067	17.9	0.617
Schedule (i)	28-Nov-08	Mitomycin C	2	17.6	0.6	17.5	0.868	17.3	0.617
Schedule (i)	28-Nov-08	Mitomycin C	2	17.6	0.6	18.5	0.134	17.7	0.868
Schedule (i)	04-Dec-08	Mitomycin C	2	17.6	0.6	18.7	0.067	17.8	0.739
Schedule (i)	04-Dec-08	Mitomycin C	2	17.6	0.6	18.4	0.182	18.2	0.317
Schedule (i)	04-Dec-08	Mitomycin C	2	17.6	0.6	17.3	0.617	17.8	0.739
Schedule (i)	04-Dec-08	Mitomycin C	2	17.6	0.6	17.3	0.617	17.8	0.739
Schedule (i)	05-Dec-08	Mitomycin C	2	17.6	0.6	18.4	0.182	18.1	0.405
Schedule (i)	05-Dec-08	Mitomycin C	2	17.6	0.6	18.2	0.317	17.7	0.868
Schedule (i)	05-Dec-08	Mitomycin C	2	17.6	0.6	18.1	0.405	17.8	0.739
Schedule (i)	05-Dec-08	Mitomycin C	2	17.6	0.6	18.4	0.182	18.1	0.405
Schedule (i)	28-Nov-08	Colchicine	2	10.3	0.4	9.5	0.046	10.3	1.000
Schedule (i)	28-Nov-08	Colchicine	2	10.3	0.4	10.8	0.211	10.4	0.803
Schedule (i)	28-Nov-08	Colchicine	2	10.3	0.4	10.1	0.617	10.0	0.453
Schedule (i)	28-Nov-08	Colchicine	2	10.3	0.4	10.4	0.803	10.3	1.000
Schedule (i)	04-Dec-08	Colchicine	2	10.3	0.4	10.3	1.000	10.7	0.317
Schedule (i)	04-Dec-08	Colchicine	2	10.3	0.4	10.2	0.803	10.2	0.803
Schedule (i)	04-Dec-08	Colchicine	2	10.3	0.4	9.4	0.024	9.8	0.211
Schedule (i)	04-Dec-08	Colchicine	2	10.3	0.4	10.0	0.453	10.3	1.000
Schedule (i)	05-Dec-08	Colchicine	2	10.3	0.4	9.6	0.080	10.2	0.803
Schedule (i)	05-Dec-08	Colchicine	2	10.3	0.4	10.1	0.617	9.8	0.211
Schedule (i)	05-Dec-08	Colchicine	2	10.3	0.4	9.9	0.317	10.0	0.453
Schedule (i)	05-Dec-08	Colchicine	2	10.3	0.4	10.0	0.453	10.2	0.803
Schedule (ii)	11-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.5	0.617	3.5	0.617
Schedule (ii)	11-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.6	0.317
Schedule (ii)	11-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.4	1.000	3.6	0.317
Schedule (ii)	11-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.1	0.134
Schedule (ii)	12-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.4	1.000	3.3	0.617
Schedule (ii)	12-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.4	1.000
Schedule (ii)	12-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.5	0.617
Schedule (ii)	12-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.4	1.000
Schedule (ii)	17-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.2	0.317	3.2	0.317
Schedule (ii)	17-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.3	0.617	3.5	0.617
Schedule (ii)	17-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.5	0.617	3.3	0.617
Schedule (ii)	17-Dec-08	Cyclophosphamide	7.5	3.40	0.20	3.4	1.000	3.2	0.317

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

5.2.6 Evaluation of Laboratory Controls (Kentucky Reference 3R4F)

5.2.6.1 Acceptance Criteria for Clastogenicity/Genotoxicity

(b) (4)

5.2.6.2 Conclusion

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

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

5.2.7 Cytotoxicity

5.2.7.1 Requirement

(b) (4)

¹¹ A minimum of 30 results is normally required for the purpose of this comparison.

¹² www.oecd.org/env/testguidelines

5.2.7.2 Conclusions

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

6 Genotoxicity Comparisons

6.1 Data Files

Data files containing calculated specific activities (slope of the linear portion of the dose-response curve) may be found on the compact disk (CD) that accompanies this report. The data files have been labeled *M100_mn_tpm_stats.xls* (dose-response curve analysis results for TPM of tobacco brand 084396), *M100_mn_wt_stats_ST.xls* (dose-response curve analysis results for smokeless tobacco products on a 'mg extracted smokeless tobacco in DMSO/mL' dose basis), *M100_mn_wt_stats_ST-H2O.xls* (dose-response curve analysis results for smokeless tobacco products on a 'mg extracted moisture-corrected smokeless tobacco in DMSO/mL' dose basis), *M100_mn_wt_stats_Nicotine.xls* (dose-response curve analysis results for smokeless tobacco products on a 'mg extracted Nicotine in DMSO/mL' dose basis) and *M100_mn_tpm+wt_stats_Nicotine.xls* (dose-response curve analysis results for smoked and smokeless tobacco products on a Nicotine dose basis).

6.2 Methodology

1. (b) (4)

2.

3.

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5.

6.

6.3 Specific Activity Determinations

(b) (4)

6.4 Comparisons among Smokeless Tobacco Products

6.4.1 Individual Replicate Slopes and Slope Statistics

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

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

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

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

		Replicate Slope Analysis [%MNC/(mg 'ST-H ₂ O'/mL)]								
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3		Slope Statistics		
Schedule	ID	'ST-H ₂ O' Dose (mg/mL)	slope	'ST-H ₂ O' Dose (mg/mL)	slope	'ST-H ₂ O' Dose (mg/mL)	slope	mean	S.E.	95% C.I.
Schedule (i)	084394	0 - 1.52	0.387	0 - 1.52	0.393	0 - 1.52	0.372	0.384	0.006	0.358 - 0.410
Schedule (i)	084395	0 - 1.02	0.602	0 - 1.02	0.502	0 - 1.02	0.553	0.552	0.029	0.428 - 0.676
Schedule (i)	084454	0 - 1.98	0.400	0 - 1.98	0.440	0 - 1.98	0.366	0.402	0.021	0.311 - 0.494
Schedule (i)	084455	0 - 2.09	0.418	0 - 2.09	0.363	0 - 2.09	0.332	0.371	0.025	0.263 - 0.480
Schedule (i)	084456	0 - 0.992	0.730	0 - 0.992	0.769	0 - 0.992	0.495	0.665	0.086	0.297 - 1.03
Schedule (i)	084457	0 - 2.14	0.533	0 - 2.14	0.374	0 - 2.14	0.296	0.401	0.070	0.100 - 0.702
Schedule (i)	084458	0 - 2.11	0.527	0 - 2.11	0.371	0 - 2.11	0.380	0.426	0.051	0.209 - 0.643
Schedule (ii)	084394	0 - 1.52	0.235	0 - 1.52	0.348	0 - 1.52	0.326	0.303	0.035	0.154 - 0.453
Schedule (ii)	084395	0 - 1.02	0.408	0 - 1.02	0.338	0 - 1.02	0.461	0.403	0.036	0.249 - 0.556

Replicate Slope Analysis [%MNC/(mg 'ST-H ₂ O'/mL)]										
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3		Slope Statistics		
Schedule	ID	'ST-H ₂ O' Dose (mg/mL)	slope	'ST-H ₂ O' Dose (mg/mL)	slope	'ST-H ₂ O' Dose (mg/mL)	slope	mean	S.E.	95% C.I.
Schedule (ii)	084454	0 - 1.98	0.283	0 - 1.98	0.277	0 - 1.98	0.274	0.278	0.003	0.267 - 0.289
Schedule (ii)	084455	0 - 2.09	0.193	0 - 2.09	0.246	0 - 2.09	0.284	0.241	0.027	0.126 - 0.355
Schedule (ii)	084456	0 - 0.992	0.436	0 - 0.992	0.412	0 - 0.992	0.399	0.416	0.011	0.369 - 0.462
Schedule (ii)	084457	0 - 2.14	0.185	0 - 2.14	0.283	0 - 2.14	0.301	0.256	0.036	0.101 - 0.411
Schedule (ii)	084458	0 - 2.11	0.400	0 - 2.11	0.317	0 - 2.11	0.336	0.351	0.025	0.243 - 0.459

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

Replicate Slope Analysis [%MNC/(mg 'Nic.'/mL)]										
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3		Slope Statistics		
Schedule	ID	'Nic' Dose (mg/mL)	slope	'Nic' Dose (mg/mL)	slope	'Nic' Dose (mg/mL)	slope	mean	S.E.	95% C.I.
Schedule (i)	084394	0 - 0.028	21.1	0 - 0.029	20.8	0 - 0.029	19.2	20.3	0.594	17.8 - 22.9
Schedule (i)	084395	0 - 0.030	20.5	0 - 0.029	17.5	0 - 0.031	18.0	18.6	0.940	14.6 - 22.7
Schedule (i)	084454	0 - 0.008	96.3	0 - 0.008	109	0 - 0.008	94.5	99.8	4.45	80.6 - 119
Schedule (i)	084455	0 - 0.009	99.0	0 - 0.011	70.7	0 - 0.008	86.0	85.2	8.17	50.1 - 120
Schedule (i)	084456	0 - 0.028	25.6	0 - 0.027	27.8	0 - 0.027	18.1	23.8	2.95	11.1 - 36.5
Schedule (i)	084457	0 - 0.013	91.3	0 - 0.012	64.2	0 - 0.012	50.6	68.7	11.9	17.3 - 120
Schedule (i)	084458	0 - 0.005	240	0 - 0.005	150	0 - 0.005	162	184	28.2	62.4 - 305
Schedule (ii)	084394	0 - 0.028	12.8	0 - 0.029	18.4	0 - 0.029	16.8	16.0	1.66	8.86 - 23.2
Schedule (ii)	084395	0 - 0.030	13.9	0 - 0.029	11.8	0 - 0.031	15.0	13.6	0.952	9.46 - 17.7
Schedule (ii)	084454	0 - 0.008	68.0	0 - 0.008	68.5	0 - 0.008	70.6	69.0	0.817	65.5 - 72.5
Schedule (ii)	084455	0 - 0.009	45.5	0 - 0.011	47.8	0 - 0.008	73.6	55.6	8.98	17.0 - 94.3
Schedule (ii)	084456	0 - 0.028	15.3	0 - 0.027	14.9	0 - 0.027	14.5	14.9	0.211	14.0 - 15.8
Schedule (ii)	084457	0 - 0.013	31.6	0 - 0.012	48.6	0 - 0.012	51.5	43.9	6.20	17.3 - 70.6
Schedule (ii)	084458	0 - 0.005	182	0 - 0.005	128	0 - 0.005	143	151	16.1	81.8 - 221

6.4.1.1 % micronucleated cells (% MNC)/['Unit of Use'/mL]

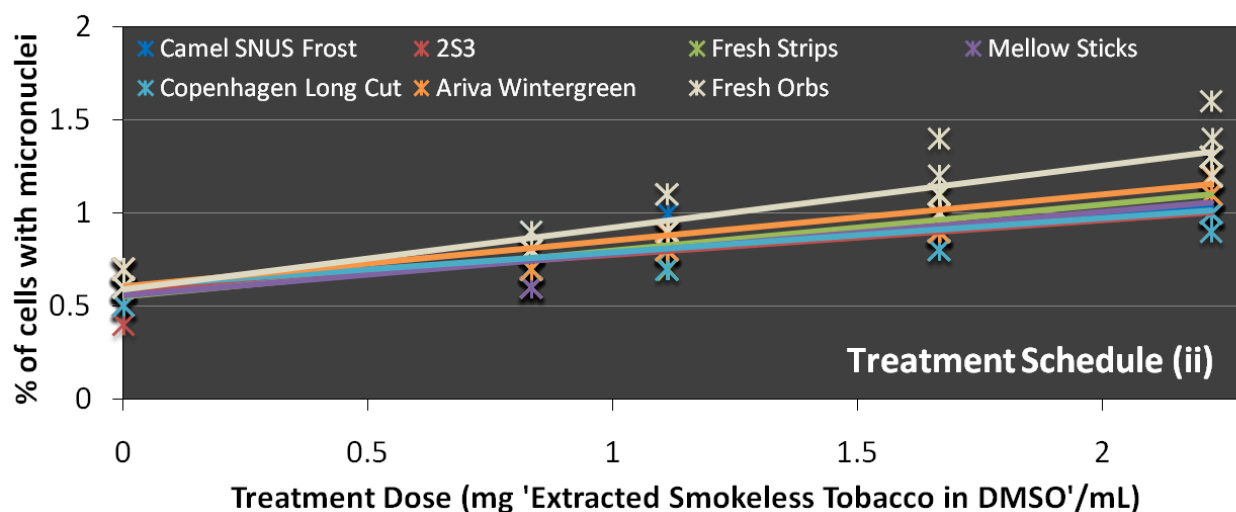
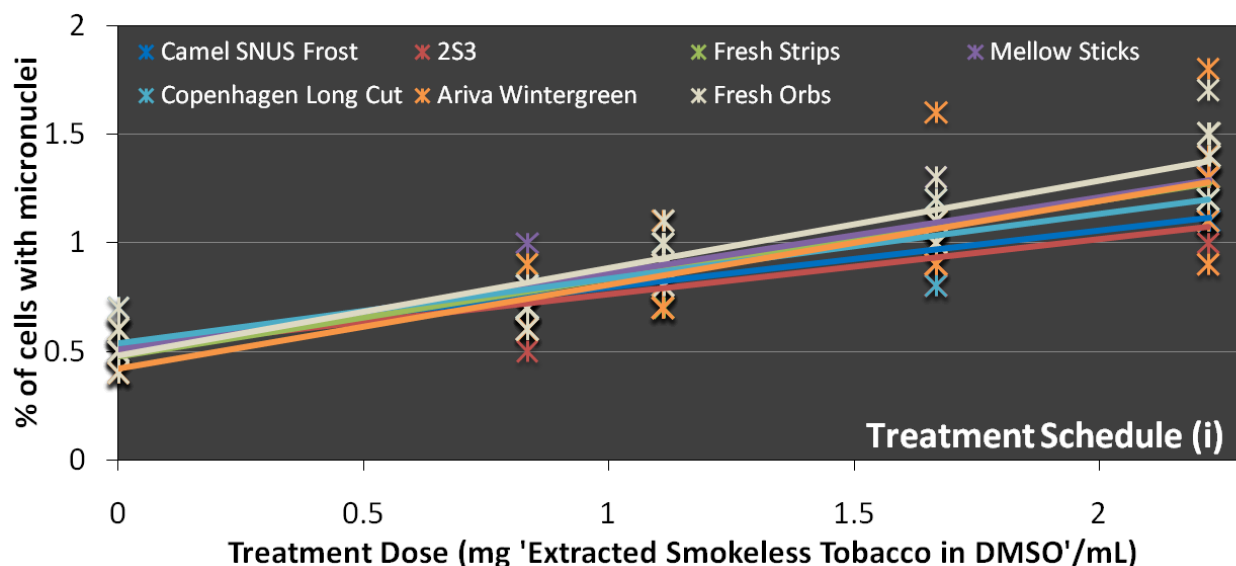
Replicate Slope Analysis [%MNC/('Unit'/mL)]										
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3		Slope Statistics		
Schedule	ID	'Unit' Dose (units/mL)	slope	'Unit' Dose (units/mL)	slope	'Unit' Dose (units/mL)	slope	mean	S.E.	95% C.I.
Schedule (i)	084394	0 - 0.0037	158	0 - 0.0037	161	0 - 0.0037	152	157	2	147 - 168
Schedule (i)	084395	0 - 0.0009	692	0 - 0.0009	577	0 - 0.0009	636	635	33	492 - 777
Schedule (i)	084454	0 - 0.0178	44.5	0 - 0.0178	48.9	0 - 0.0178	40.7	44.7	2.4	34.5 - 54.8
Schedule (i)	084455	0 - 0.0043	203	0 - 0.0043	176	0 - 0.0043	161	180	12	127 - 233
Schedule (i)	084456	0 - 0.0009	814	0 - 0.0009	858	0 - 0.0009	552	742	95	331 - 1152
Schedule (i)	084457	0 - 0.0079	144	0 - 0.0079	101	0 - 0.0079	79.7	108	19	27 - 189
Schedule (i)	084458	0 - 0.0099	112	0 - 0.0099	79.2	0 - 0.0099	81.2	90.9	10.8	44.6 - 137
Schedule (ii)	084394	0 - 0.0037	96.2	0 - 0.0037	143	0 - 0.0037	134	124	14	63 - 185
Schedule (ii)	084395	0 - 0.0009	469	0 - 0.0009	389	0 - 0.0009	530	463	41	286 - 639
Schedule (ii)	084454	0 - 0.0178	31.4	0 - 0.0178	30.8	0 - 0.0178	30.4	30.9	0.3	29.7 - 32.1
Schedule (ii)	084455	0 - 0.0043	93.3	0 - 0.0043	119	0 - 0.0043	138	117	13	61.3 - 172
Schedule (ii)	084456	0 - 0.0009	486	0 - 0.0009	460	0 - 0.0009	445	464	12	411 - 516

		Replicate Slope Analysis [%MNC/('Unit'/mL)]								
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3		Slope Statistics		
Schedule	ID	'Unit' Dose (units/mL)	slope	'Unit' Dose (units/mL)	slope	'Unit' Dose (units/mL)	slope	mean	S.E.	95% C.I.
Schedule (ii)	084457	0 - 0.0079	49.8	0 - 0.0079	76.4	0 - 0.0079	81.1	69.1	9.7	27.3 - 111
Schedule (ii)	084458	0 - 0.0099	85.4	0 - 0.0099	67.7	0 - 0.0099	71.7	75.0	5.3	51.9 - 98

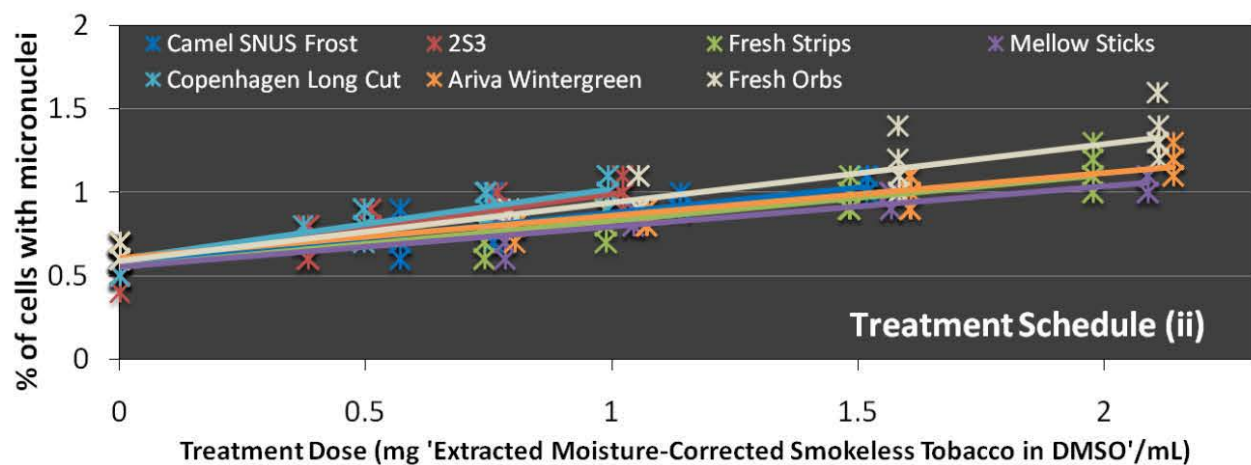
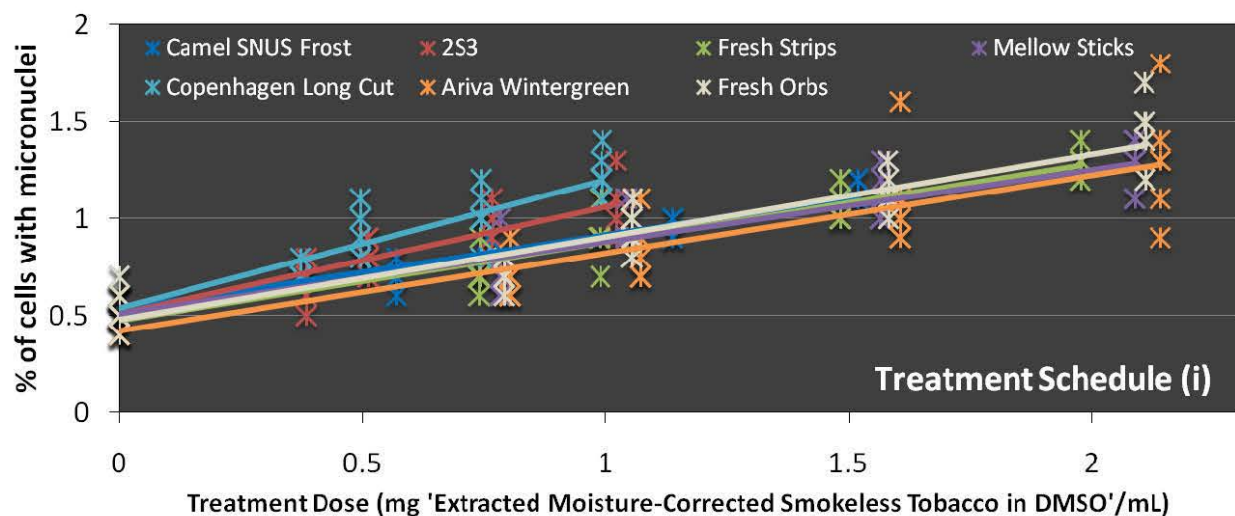
6.4.2 Data Plots

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

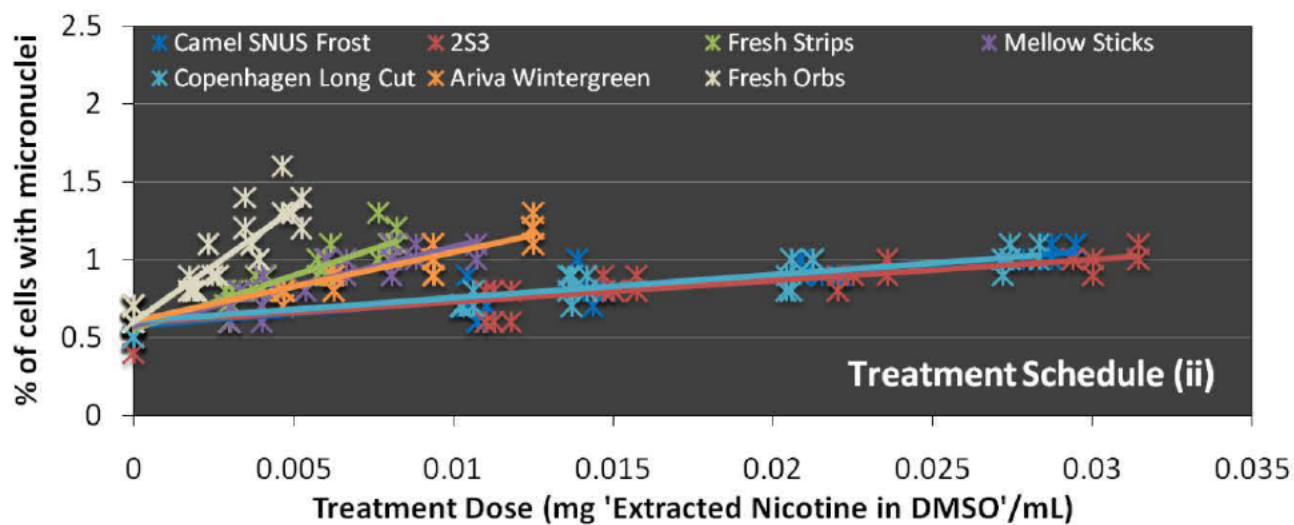
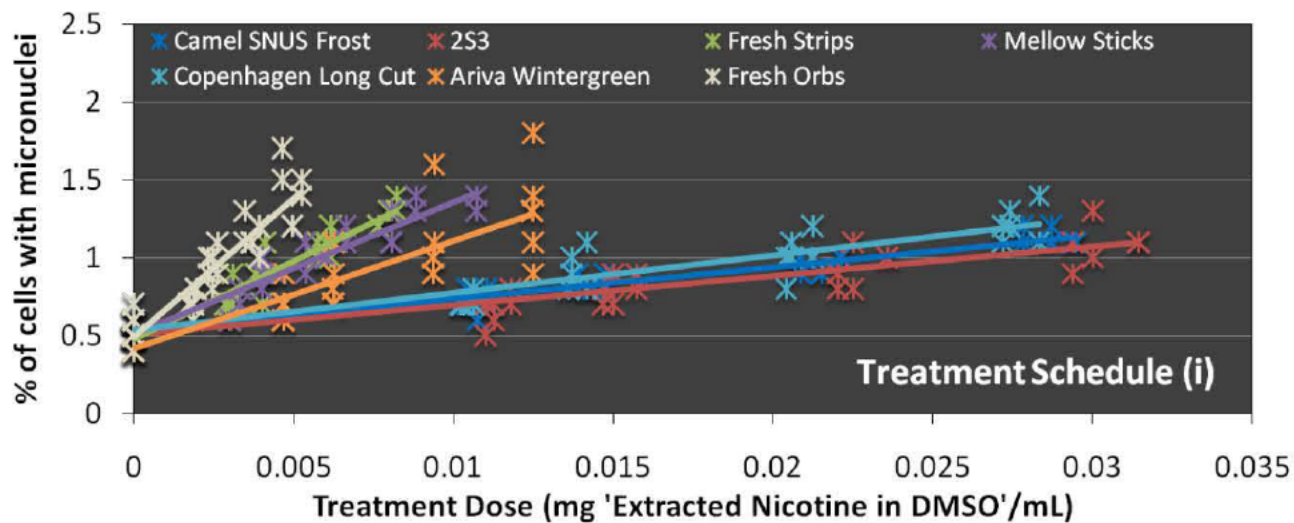
6.4.2.1 % micronucleated cells vs. [mg 'Extracted Smokeless Tobacco in DMSO'/mL]



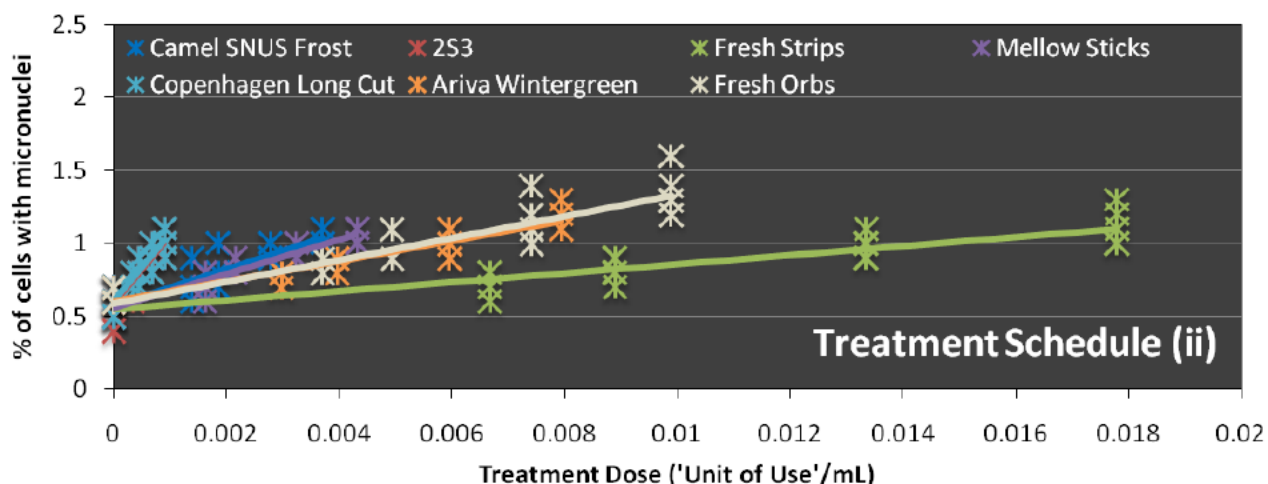
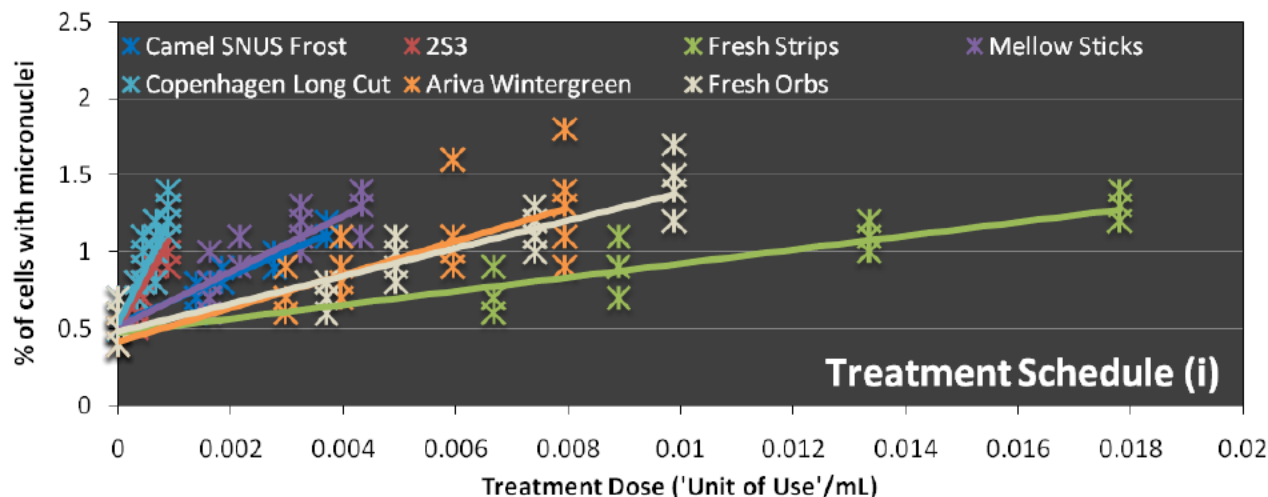
6.4.2.2 % micronucleated cells vs. [mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL]



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



6.4.2.4 % micronucleated cells vs. ['Unit of Use'/mL]



6.4.3 One-Way ANOVA Results

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

6.4.3.1 'Extracted Smokeless Tobacco in DMSO'

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

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

6.4.3.2 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'

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

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

6.4.3.3 'Extracted Nicotine in DMSO'

Treatment Schedule	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Treatment Schedule (i)	Among Samples	63980.62	6	10663.44	24.00	< 0.001
	Within Samples	6220.57	14	444.33		
	Total	70201.19	20			
Treatment Schedule (ii)	Among Samples	43067.44	6	7177.91	43.66	< 0.001
	Within Samples	2301.79	14	164.41		
	Total	45369.22	20			

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

6.4.3.4 'Unit of Use'

Treatment Schedule	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Treatment Schedule (i)	Among Samples	1454272	6	242379	52.15	< 0.001
	Within Samples	65064	14	4647		
	Total	1519336	20			
Treatment Schedule (ii)	Among Samples	636679	6	106113	106.64	< 0.001
	Within Samples	13931	14	995		
	Total	650610	20			

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

6.4.4 Contrasts of Interest

(b) (4)

The tables below show both ANOVA-based and pairwise t-test comparison results for both treatment schedules along with identified homogenous brand groupings.

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

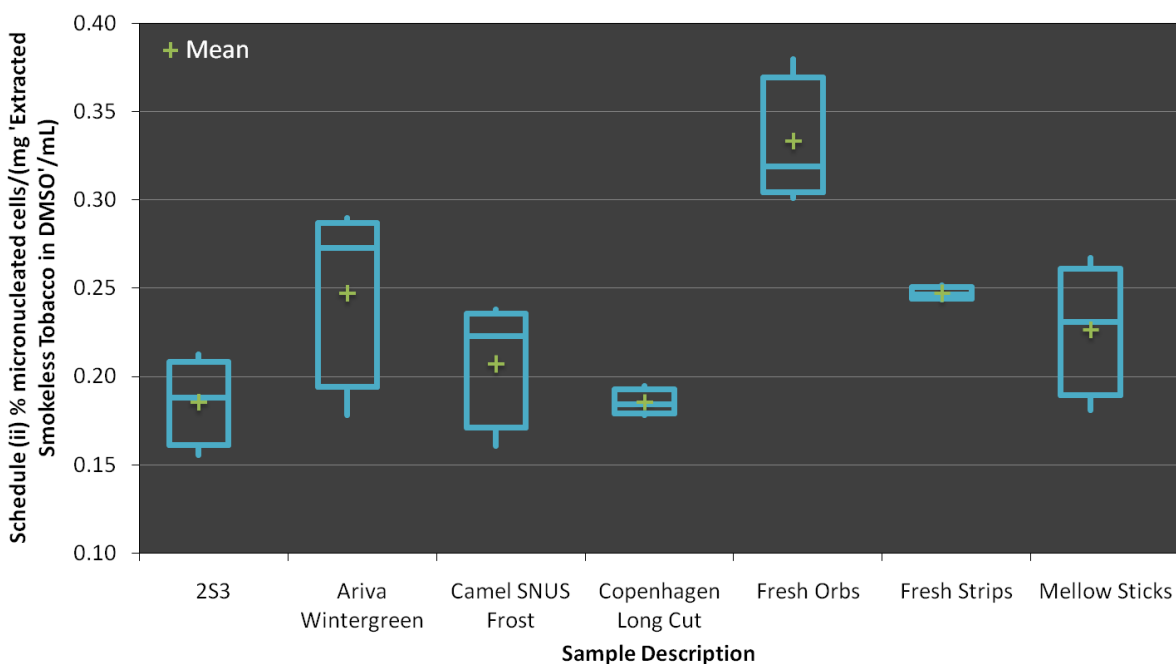
	Treatment Schedule (i)			Treatment Schedule (ii)		
ANOVA-Based Comparison	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	0.0246	0.8776	not significant	0.5124	0.4859	not significant
084394 vs. 084454	3.3936	0.0867	not significant	1.7258	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

	Treatment Schedule (i)			Treatment Schedule (ii)		
Pairwise T-Test Comparison	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

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

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

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



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

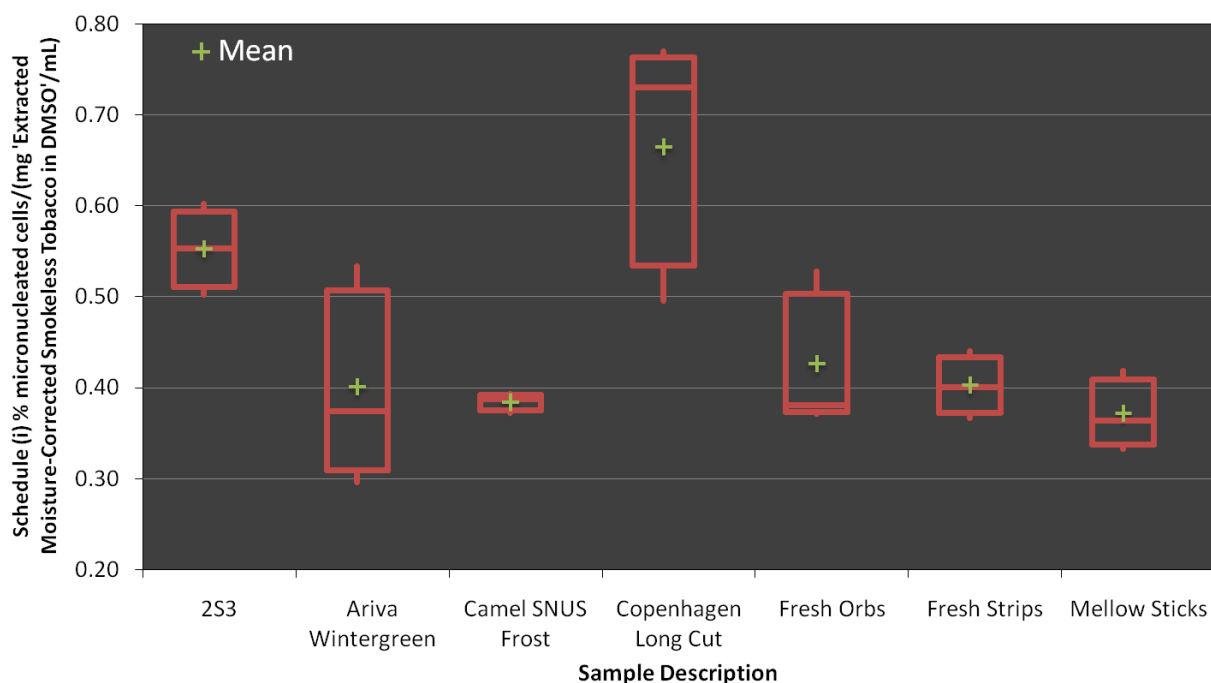
	Treatment Schedule (i)			Treatment Schedule (ii)		
ANOVA-Based Comparison	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	5.9387	0.0288	not significant	6.6128	0.0222	not significant
084394 vs. 084454	0.0705	0.7945	not significant	0.4261	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

	Treatment Schedule (i)			Treatment Schedule (ii)		
Pairwise T-Test Comparison	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	5.7156	0.0046	not significant	1.9986	0.1163	not significant
084394 vs. 084454	0.8307	0.4529	not significant	0.7256	0.5083	not significant
084394 vs. 084455	0.4838	0.6538	not significant	1.4250	0.2273	not significant
084394 vs. 084456	3.2745	0.0307	not significant	3.0898	0.0366	not significant
084394 vs. 084457	0.2413	0.8212	not significant	0.9373	0.4017	not significant
084394 vs. 084458	0.8308	0.4528	not significant	1.1216	0.3248	not significant
084395 vs. 084454	4.1887	0.0138	not significant	3.4876	0.0252	not significant
084395 vs. 084455	4.7239	0.0091	not significant	3.6362	0.0220	not significant
084395 vs. 084456	1.2453	0.2810	not significant	0.3467	0.7463	not significant
084395 vs. 084457	2.0028	0.1157	not significant	2.8862	0.0447	not significant
084395 vs. 084458	2.1684	0.0960	not significant	1.1804	0.3032	not significant
084454 vs. 084455	0.9368	0.4019	not significant	1.3874	0.2376	not significant
084454 vs. 084456	2.9777	0.0408	not significant	12.3047	0.0003	significant
084454 vs. 084457	0.0194	0.9855	not significant	0.5993	0.5813	not significant
084454 vs. 084458	0.4364	0.6851	not significant	2.9092	0.0437	not significant
084455 vs. 084456	3.2894	0.0302	not significant	6.0798	0.0037	not significant
084455 vs. 084457	0.3966	0.7119	not significant	0.3437	0.7484	not significant
084455 vs. 084458	0.9707	0.3867	not significant	3.0196	0.0392	not significant
084456 vs. 084457	2.3886	0.0753	not significant	4.2299	0.0134	not significant
084456 vs. 084458	2.4012	0.0743	not significant	2.3566	0.0780	not significant
084457 vs. 084458	0.2937	0.7836	not significant	2.1620	0.0967	not significant

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

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

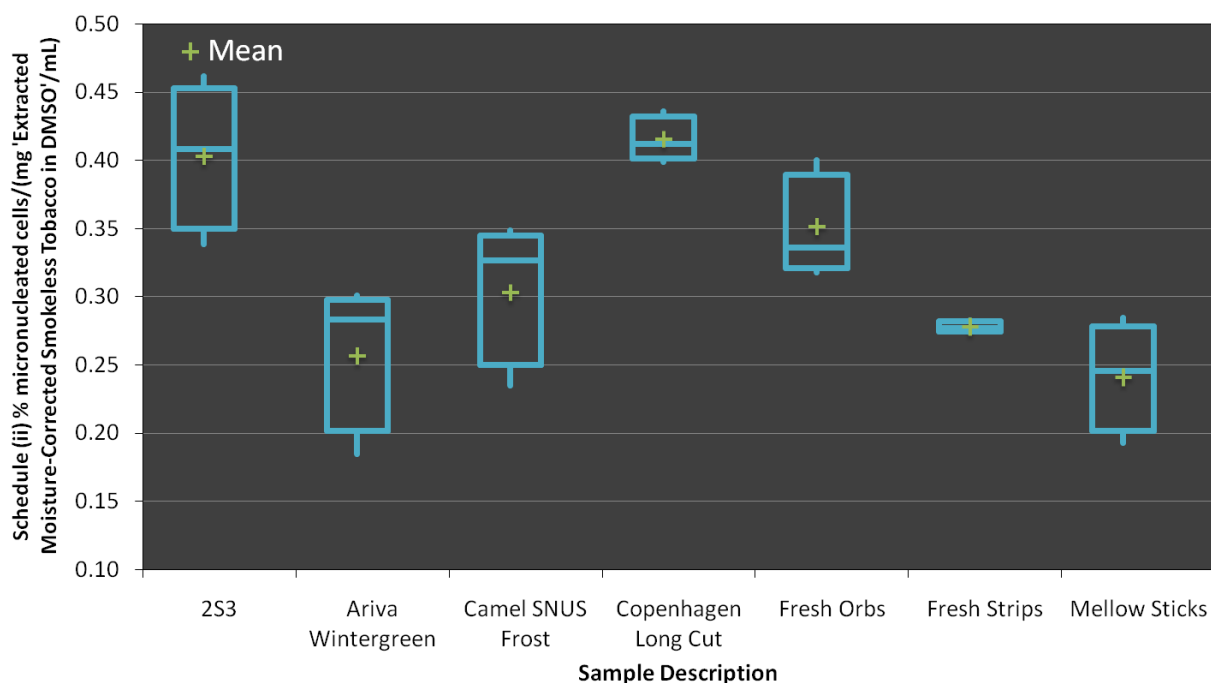
No pairwise t-test comparison p-values were less than the Bonferroni- adjusted $\alpha = 0.05$, indicating no significant differences in mean 'extracted moisture-corrected smokeless tobacco' slope were detected between any brand pairs under treatment schedule (i).



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

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

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



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

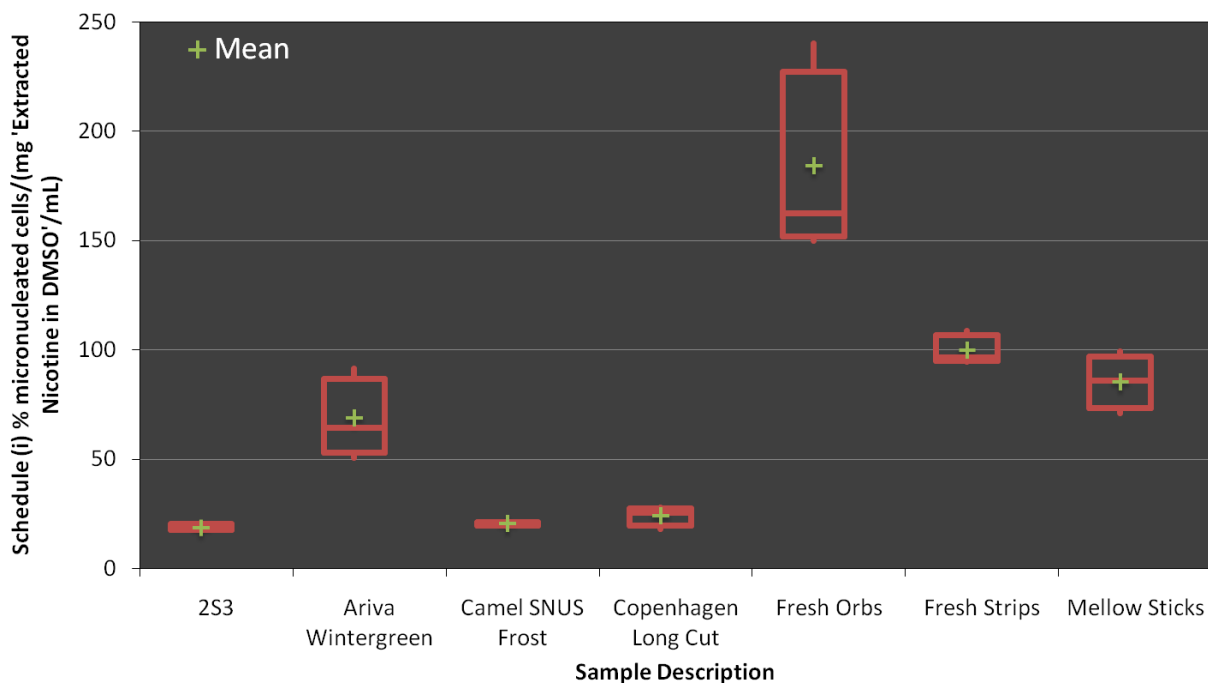
	Treatment Schedule (i)			Treatment Schedule (ii)		
ANOVA-Based Comparison	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	0.0097	0.9229	not significant	0.0549	0.8182	not significant
084394 vs. 084454	21.3194	0.0004	significant	25.6450	0.0002	significant
084394 vs. 084455	14.2040	0.0021	significant	14.3259	0.0020	significant
084394 vs. 084456	0.0407	0.8431	not significant	0.0112	0.9174	not significant
084394 vs. 084457	7.8904	0.0139	not significant	7.1109	0.0184	not significant
084394 vs. 084458	90.3636	0.0000	significant	166.7119	0.0000	significant
084395 vs. 084454	22.2393	0.0003	significant	28.0728	0.0001	significant
084395 vs. 084455	14.9566	0.0017	significant	16.1543	0.0013	significant
084395 vs. 084456	0.0901	0.7684	not significant	0.0166	0.8994	not significant
084395 vs. 084457	8.4539	0.0115	not significant	8.4154	0.0116	not significant
084395 vs. 084458	92.2471	0.0000	significant	172.8169	0.0000	significant
084454 vs. 084455	0.7199	0.4104	not significant	1.6362	0.2216	not significant
084454 vs. 084456	19.4979	0.0006	significant	26.7256	0.0001	significant
084454 vs. 084457	3.2700	0.0921	not significant	5.7478	0.0310	not significant
084454 vs. 084458	23.8992	0.0002	significant	61.5849	0.0000	significant
084455 vs. 084456	12.7246	0.0031	not significant	15.1364	0.0016	significant
084455 vs. 084457	0.9213	0.3534	not significant	1.2506	0.2823	not significant
084455 vs. 084458	32.9150	0.0001	significant	83.2974	0.0000	significant
084456 vs. 084457	6.7982	0.0207	not significant	7.6853	0.0150	not significant
084456 vs. 084458	86.5704	0.0000	significant	169.4498	0.0000	significant
084457 vs. 084458	44.8496	0.0000	significant	104.9613	0.0000	significant

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

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

Sample ID	Sample Description	Mean Slope	ANOVA-based Homogenous Groups
084395	2S3	18.6	X
084394	Camel SNUS Frost	20.3	X
084456	Copenhagen Long Cut	23.8	X X
084457	Ariva Wintergreen	68.7	X X X
084455	Mellow Sticks	85.2	X X
084454	Fresh Strips	99.8	X
084458	Fresh Orbs	184	X

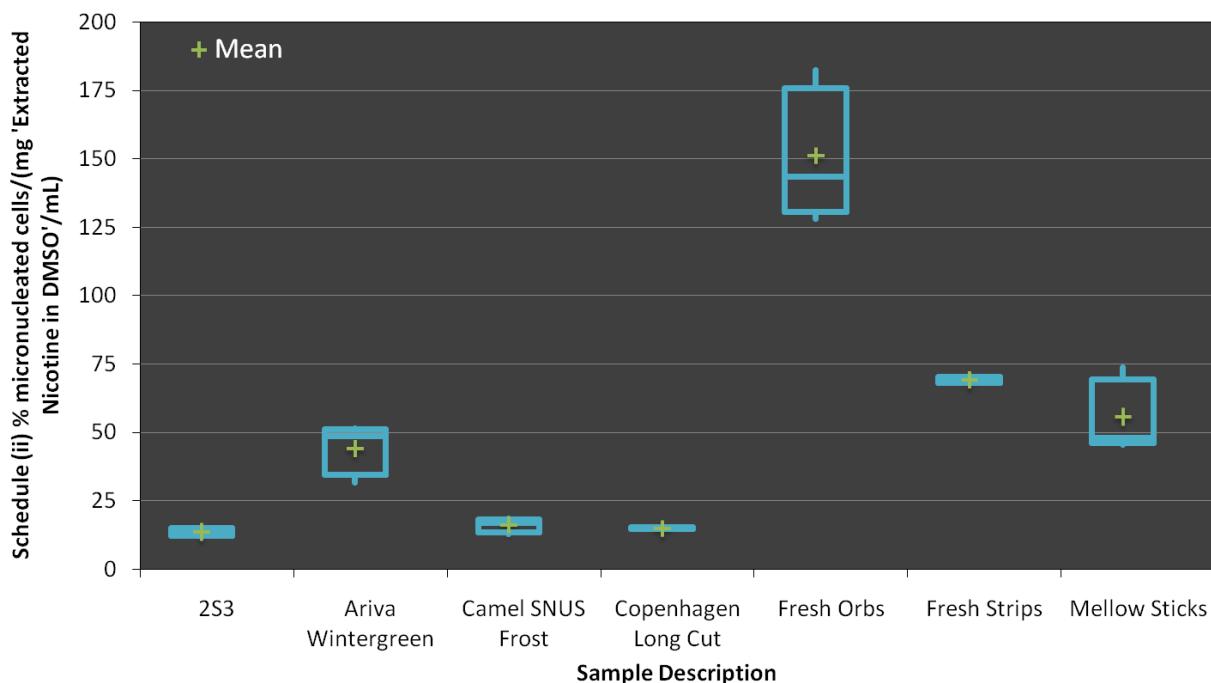
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted nicotine' slope were detected between **Fresh Strips (084454)** as well as **Mellow Sticks (084455)** and each of {**Camel SNUS Frost (084394)**, **2S3 Research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



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

Sample ID	Sample Description	Mean Slope	ANOVA-based Homogenous Groups
084395	2S3	13.6	X
084456	Copenhagen Long Cut	14.9	X
084394	Camel SNUS Frost	16.0	X
084457	Ariva Wintergreen	43.9	X X
084455	Mellow Sticks	55.6	X
084454	Fresh Strips	69.0	X
084458	Fresh Orbs	151	X

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



6.4.4.4 % micronucleated cells/('Unit of Use'/mL)

	Treatment Schedule (i)			Treatment Schedule (ii)		
ANOVA-Based Comparison	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	73.62	0.0000	significant	172.91	0.0000	significant
084394 vs. 084454	4.09	0.0627	not significant	13.12	0.0028	not significant
084394 vs. 084455	0.17	0.6894	not significant	0.08	0.7762	not significant
084394 vs. 084456	110.23	0.0000	significant	173.78	0.0000	significant
084394 vs. 084457	0.78	0.3922	not significant	4.57	0.0506	not significant
084394 vs. 084458	1.42	0.2535	not significant	3.65	0.0766	not significant
084395 vs. 084454	112.40	0.0000	significant	281.31	0.0000	significant
084395 vs. 084455	66.78	0.0000	significant	180.61	0.0000	significant
084395 vs. 084456	3.68	0.0756	not significant	0.00	0.9742	not significant
084395 vs. 084457	89.55	0.0000	significant	233.72	0.0000	significant
084395 vs. 084458	95.47	0.0000	significant	226.83	0.0000	significant
084454 vs. 084455	5.91	0.0291	not significant	11.11	0.0049	not significant
084454 vs. 084456	156.78	0.0000	significant	282.41	0.0000	significant
084454 vs. 084457	1.30	0.2738	not significant	2.20	0.1599	not significant
084454 vs. 084458	0.69	0.4199	not significant	2.93	0.1091	not significant
084455 vs. 084456	101.83	0.0000	significant	181.50	0.0000	significant
084455 vs. 084457	1.67	0.2176	not significant	3.42	0.0857	not significant
084455 vs. 084458	2.56	0.1321	not significant	2.63	0.1272	not significant
084456 vs. 084457	129.55	0.0000	significant	234.73	0.0000	significant
084456 vs. 084458	136.66	0.0000	significant	227.83	0.0000	significant
084457 vs. 084458	0.09	0.7626	not significant	0.05	0.8238	not significant

	Treatment Schedule (i)			Treatment Schedule (ii)		
Pairwise T-Test Comparison	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	14.3657	0.0001	significant	7.8018	0.0015	significant
084394 vs. 084454	32.9417	0.0000	significant	6.5598	0.0028	not significant
084394 vs. 084455	1.8226	0.1424	not significant	0.3889	0.7172	not significant
084394 vs. 084456	6.1201	0.0036	not significant	18.1445	0.0001	significant
084394 vs. 084457	2.5845	0.0610	not significant	3.1968	0.0330	not significant
084394 vs. 084458	5.9935	0.0039	not significant	3.2403	0.0317	not significant
084395 vs. 084454	17.7552	0.0001	significant	10.5321	0.0005	significant
084395 vs. 084455	12.8742	0.0002	significant	8.0512	0.0013	significant
084395 vs. 084456	1.0571	0.3501	not significant	0.0198	0.9851	not significant
084395 vs. 084457	13.8106	0.0002	significant	9.3413	0.0007	significant
084395 vs. 084458	15.6008	0.0001	significant	9.3784	0.0007	significant
084454 vs. 084455	10.8712	0.0004	significant	6.6582	0.0026	not significant
084454 vs. 084456	7.2989	0.0019	significant	35.5799	0.0000	significant
084454 vs. 084457	3.3363	0.0289	not significant	3.9290	0.0171	not significant
084454 vs. 084458	4.1906	0.0138	not significant	8.2282	0.0012	significant
084455 vs. 084456	5.8366	0.0043	not significant	19.5802	0.0000	significant
084455 vs. 084457	3.1986	0.0329	not significant	2.9487	0.0420	not significant
084455 vs. 084458	5.4628	0.0055	not significant	2.9930	0.0402	not significant
084456 vs. 084457	6.5112	0.0029	not significant	25.3401	0.0000	significant

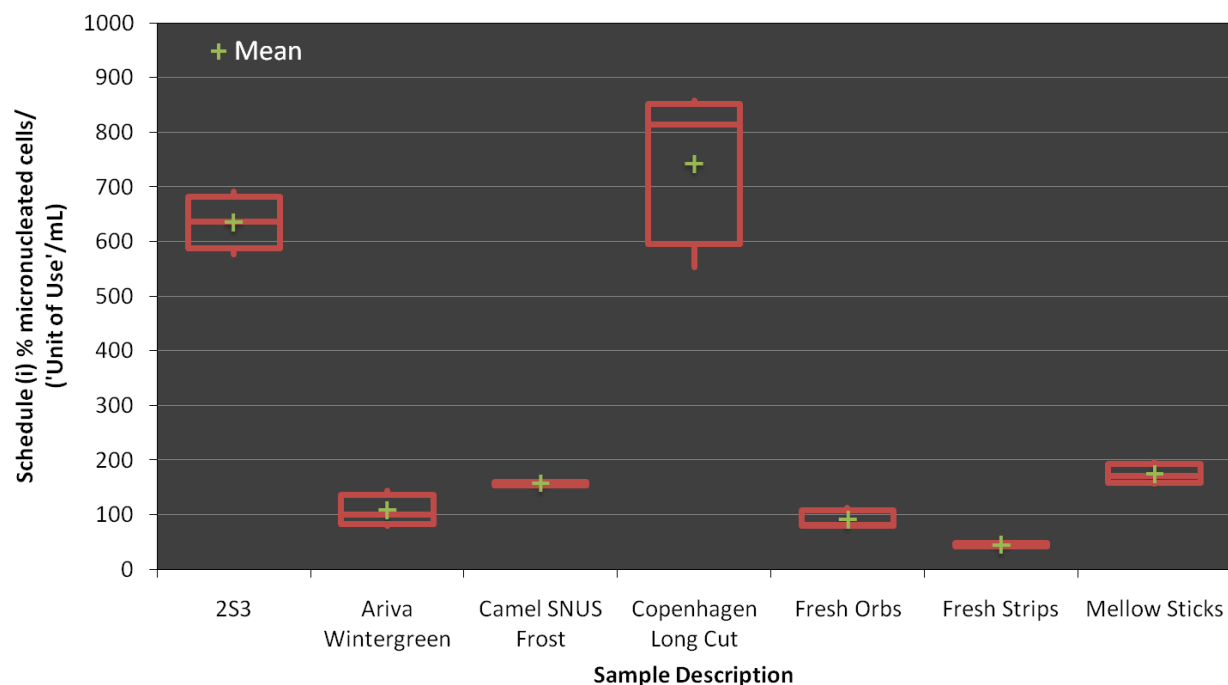
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	Treatment Schedule (i)			Treatment Schedule (ii)		
Pairwise T-Test Comparison	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084456 vs. 084458	6.7735	0.0025	not significant	29.2606	0.0000	significant
084457 vs. 084458	0.7894	0.4740	not significant	0.5266	0.6263	not significant

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

Sample ID	Sample Description	Mean Slope	ANOVA-based Homogenous Groups
084454	Fresh Strips	44.7	X
084458	Fresh Orbs	90.9	X
084457	Ariva Wintergreen	108	X
084394	Camel SNUS Frost	157	X
084455	Mellow Sticks	180	X
084395	2S3	635	X
084456	Copenhagen Long Cut	742	X

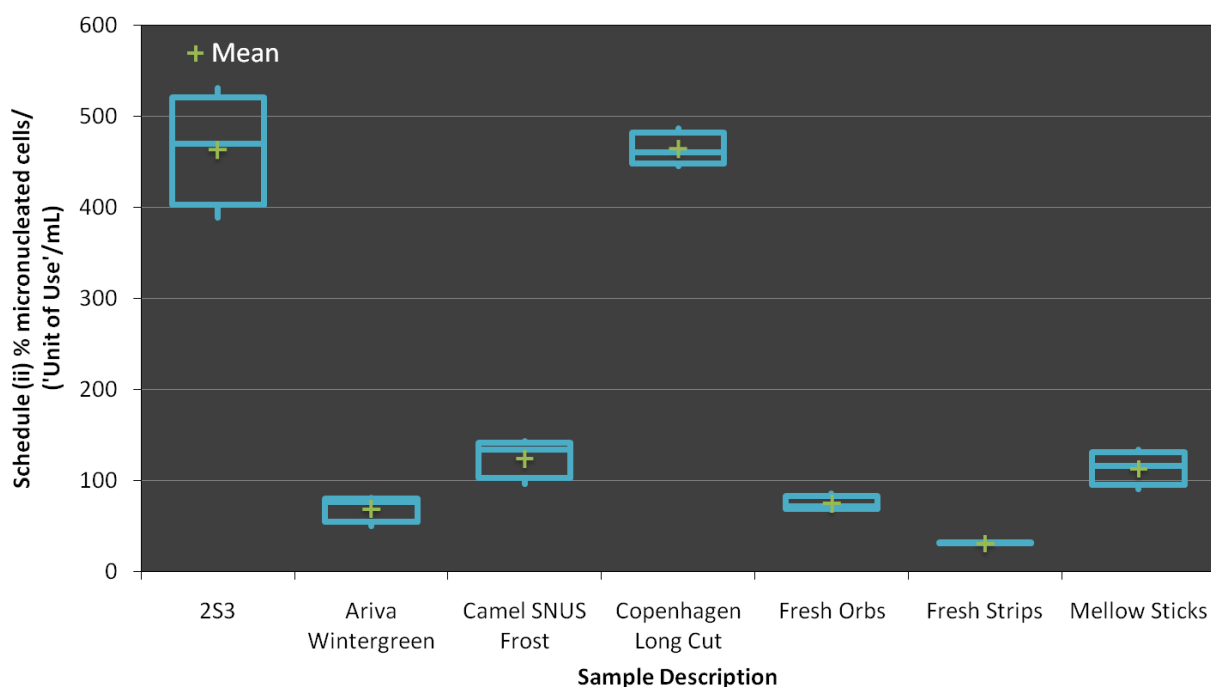
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'unit of use' slope were detected between **Fresh Strips (084454)** and each of **{Camel SNUS Frost (084394), Mellow Sticks (084455), 2S3 (084395), Copenhagen Long Cut (084456)}** as well as **2S3 (084395)** and each of **{Fresh Orbs (084458), Ariva Wintergreen (084457), Camel SNUS Frost (084394), Mellow Sticks (084455)}** under treatment schedule (i).



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

Sample ID	Sample Description	Mean Slope	ANOVA-based Homogenous Groups
084454	Fresh Strips	30.9	X
084457	Ariva Wintergreen	69.1	X
084458	Fresh Orbs	75.0	X
084455	Mellow Sticks	117	X
084394	Camel SNUS Frost	124	X
084395	2S3	463	X
084456	Copenhagen Long Cut	464	X

Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'unit of use' slope were detected between **2S3 (084395)** as well as **Copenhagen Long Cut (084456)** and each of {**Camel SNUS Frost (084394)**, **Mellow Sticks (084455)**, **Fresh Orbs (084458)**, **Ariva Wintergreen (084457)**, **Fresh Strips (084454)**} plus **Fresh Strips (084454)** and **Fresh Orbs (084458)** under treatment schedule (ii).



6.5 Comparisons between Smoked and Smokeless Tobacco Products

6.5.1 Individual Replicate Slopes and Slope Statistics

Tables of results were obtained for the individual replicate slope estimates, and the summary statistics, on both a 'Nicotine' and 'Unit of Use' dose basis over the three replicate slopes for each smoked and smokeless tobacco test sample under both treatment schedules. The file *M100_mn_tpm+wt_stats_Nicotine.xls* gives tables of results for all the smokeless tobacco samples plus the tobacco smoke CSC of the KR 2R4F (084396) samples on an 'extracted nicotine in DMSO' and 'Nicotine in CSC' dose basis, respectively. The file *M100_mn_tpm+wt_stats_Unit.xls* gives tables of results for all the smokeless tobacco samples plus the tobacco smoke CSC of the KR 2R4F (084396) samples on a 'unit of use' dose basis (see table in section 5.1.1 for defined units).

6.5.1.1 % micronucleated cells/(mg 'Nicotine'/mL)

		Replicate Slope Analysis [%MNC/(mg 'Nic.'/mL)]						Slope Statistics		
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3				
Schedule	ID	'Nic' Dose (mg/mL)	slope	'Nic' Dose (mg/mL)	slope	'Nic' Dose (mg/mL)	slope	mean	S.E.	95% C.I.
Schedule (i)	084394	0 - 0.028	21.1	0 - 0.029	20.8	0 - 0.029	19.2	20.3	0.594	17.8 - 22.9
Schedule (i)	084395	0 - 0.030	20.5	0 - 0.029	17.5	0 - 0.031	18.0	18.6	0.940	14.6 - 22.7
Schedule (i)	084396	0 - 0.013	120	0 - 0.014	108	0 - 0.014	104	111	4.9	90 - 132
Schedule (i)	084454	0 - 0.008	96.3	0 - 0.008	109	0 - 0.008	94.5	99.8	4.45	80.6 - 119
Schedule (i)	084455	0 - 0.009	99.0	0 - 0.011	70.7	0 - 0.008	86.0	85.2	8.17	50.1 - 120
Schedule (i)	084456	0 - 0.028	25.6	0 - 0.027	27.8	0 - 0.027	18.1	23.8	2.95	11.1 - 36.5
Schedule (i)	084457	0 - 0.013	91.3	0 - 0.012	64.2	0 - 0.012	50.6	68.7	11.9	17.3 - 120
Schedule (i)	084458	0 - 0.005	240	0 - 0.005	150	0 - 0.005	162	184	28.2	62.4 - 305
Schedule (ii)	084394	0 - 0.028	12.8	0 - 0.029	18.4	0 - 0.029	16.8	16.0	1.66	8.86 - 23.2
Schedule (ii)	084395	0 - 0.030	13.9	0 - 0.029	11.8	0 - 0.031	15.0	13.6	0.952	9.46 - 17.7
Schedule (ii)	084396	0 - 0.013	81.1	0 - 0.014	75.4	0 - 0.014	73.1	76.5	2.4	66.4 - 86.7
Schedule (ii)	084454	0 - 0.008	68.0	0 - 0.008	68.5	0 - 0.008	70.6	69.0	0.817	65.5 - 72.5
Schedule (ii)	084455	0 - 0.009	45.5	0 - 0.011	47.8	0 - 0.008	73.6	55.6	8.98	17.0 - 94.3
Schedule (ii)	084456	0 - 0.028	15.3	0 - 0.027	14.9	0 - 0.027	14.5	14.9	0.211	14.0 - 15.8
Schedule (ii)	084457	0 - 0.013	31.6	0 - 0.012	48.6	0 - 0.012	51.5	43.9	6.20	17.3 - 70.6
Schedule (ii)	084458	0 - 0.005	182	0 - 0.005	128	0 - 0.005	143	151	16.1	81.8 - 221

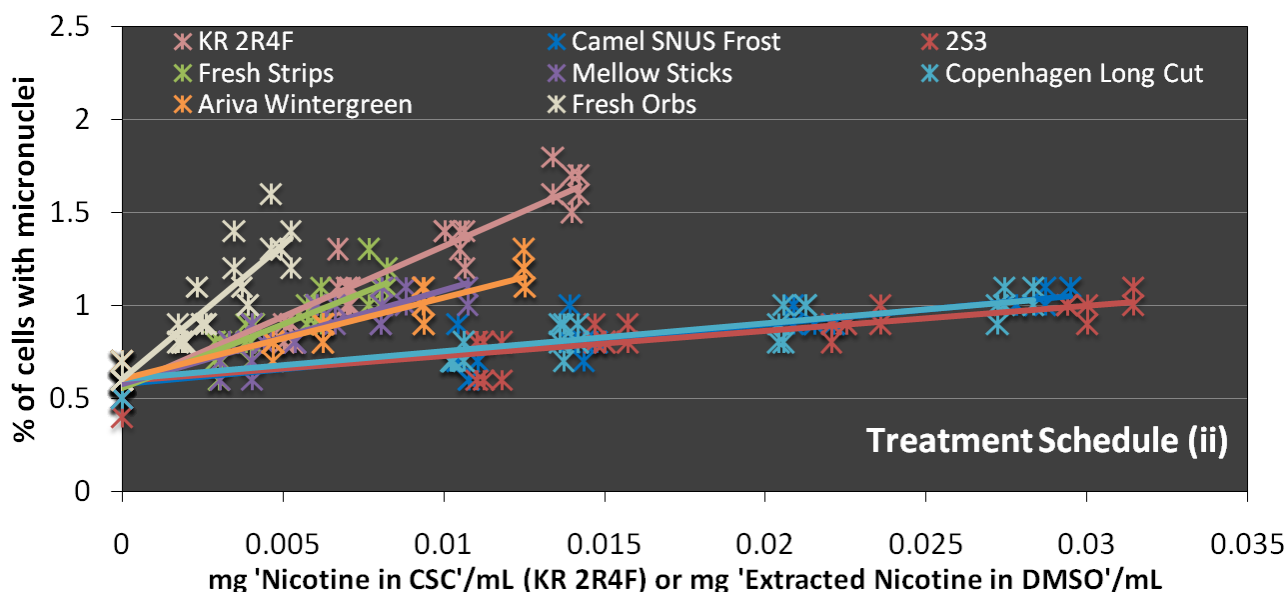
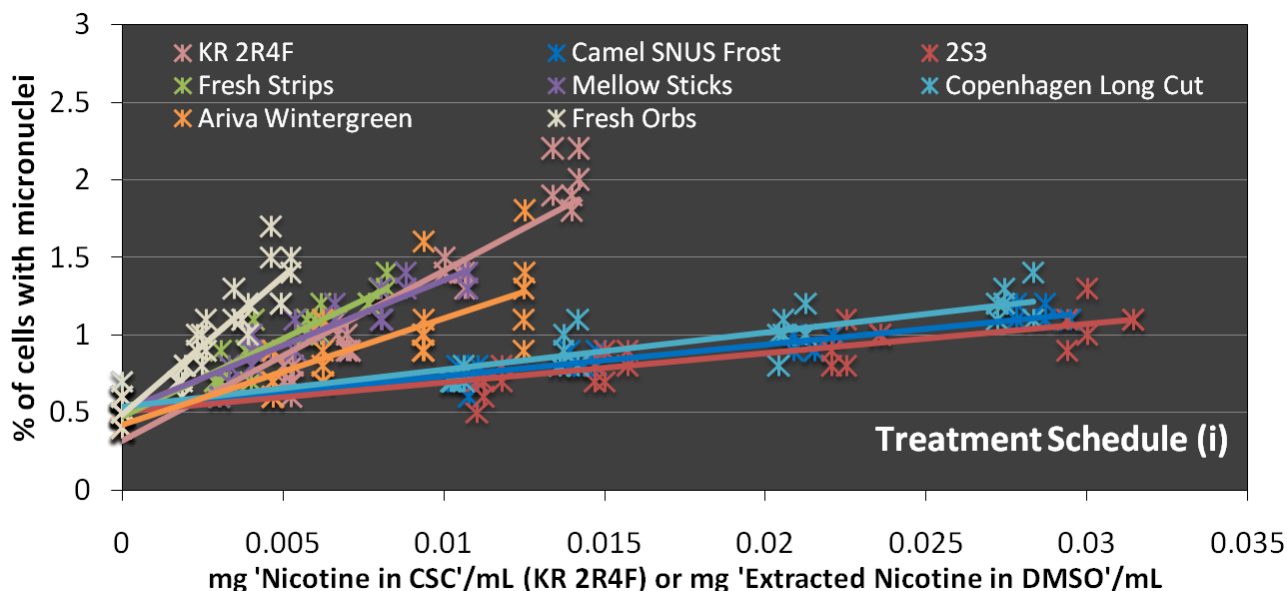
6.5.1.2 % micronucleated cells/('Unit of Use'/mL)

		Replicate Slope Analysis [%MNC/('Unit'/mL)]								
Treatment	Sample	Replicate 1		Replicate 2		Replicate 3		Slope Statistics		
Schedule	ID	Unit Dose (unit/mL)	slope	Unit Dose (unit/mL)	slope	Unit Dose (unit/mL)	slope	mean	S.E.	95% C.I.
Schedule (i)	084394	0 - 0.0037	158	0 - 0.0037	161	0 - 0.0037	152	157	2	147 - 168
Schedule (i)	084395	0 - 0.0009	692	0 - 0.0009	577	0 - 0.0009	636	635	33	492 - 777
Schedule (i)	084396	0 - 0.0182	88.3	0 - 0.0185	82.5	0 - 0.0191	76.0	82.3	3.5	67 - 97.5
Schedule (i)	084454	0 - 0.0178	44.5	0 - 0.0178	48.9	0 - 0.0178	40.7	44.7	2.4	34.5 - 54.8
Schedule (i)	084455	0 - 0.0043	203	0 - 0.0043	176	0 - 0.0043	161	180	12	127 - 233
Schedule (i)	084456	0 - 0.0009	814	0 - 0.0009	858	0 - 0.0009	552	742	95	331 - 1152
Schedule (i)	084457	0 - 0.0079	144	0 - 0.0079	101	0 - 0.0079	79.7	108	19	27 - 189
Schedule (i)	084458	0 - 0.0099	112	0 - 0.0099	79.2	0 - 0.0099	81.2	90.9	10.8	44.6 - 137
Schedule (ii)	084394	0 - 0.0037	96.2	0 - 0.0037	143	0 - 0.0037	134	124	14	63 - 185
Schedule (ii)	084395	0 - 0.0009	469	0 - 0.0009	389	0 - 0.0009	530	463	41	286 - 639
Schedule (ii)	084396	0 - 0.0182	59.5	0 - 0.0185	57.8	0 - 0.0191	53.4	56.9	1.8	49.1 - 64.8
Schedule (ii)	084454	0 - 0.0178	31.4	0 - 0.0178	30.8	0 - 0.0178	30.4	30.9	0.3	29.7 - 32.1
Schedule (ii)	084455	0 - 0.0043	93.3	0 - 0.0043	119	0 - 0.0043	138	117	13	61.3 - 172
Schedule (ii)	084456	0 - 0.0009	486	0 - 0.0009	460	0 - 0.0009	445	464	12	411 - 516
Schedule (ii)	084457	0 - 0.0079	49.8	0 - 0.0079	76.4	0 - 0.0079	81.1	69.1	9.7	27.3 - 111
Schedule (ii)	084458	0 - 0.0099	85.4	0 - 0.0099	67.7	0 - 0.0099	71.7	75.0	5.3	51.9 - 98

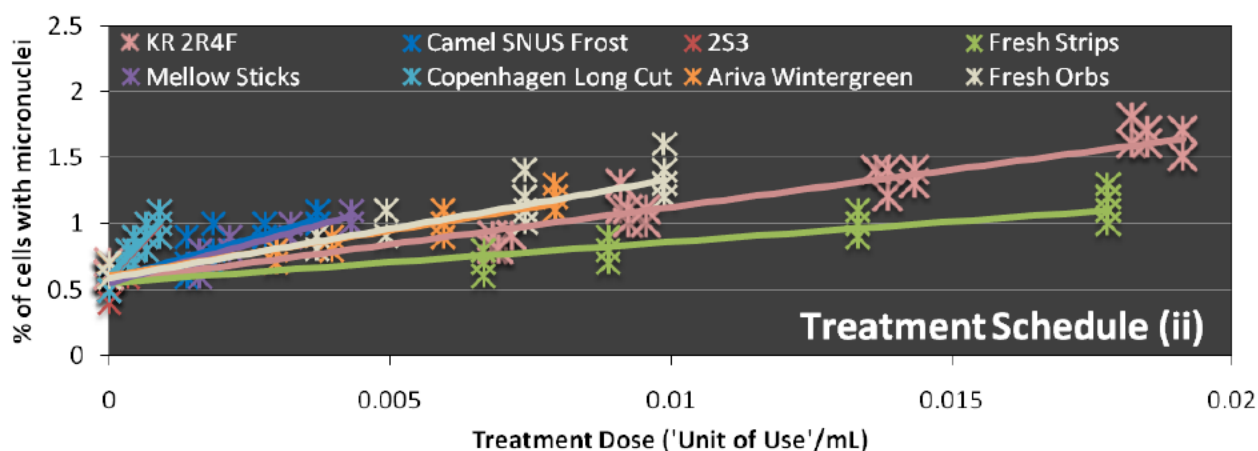
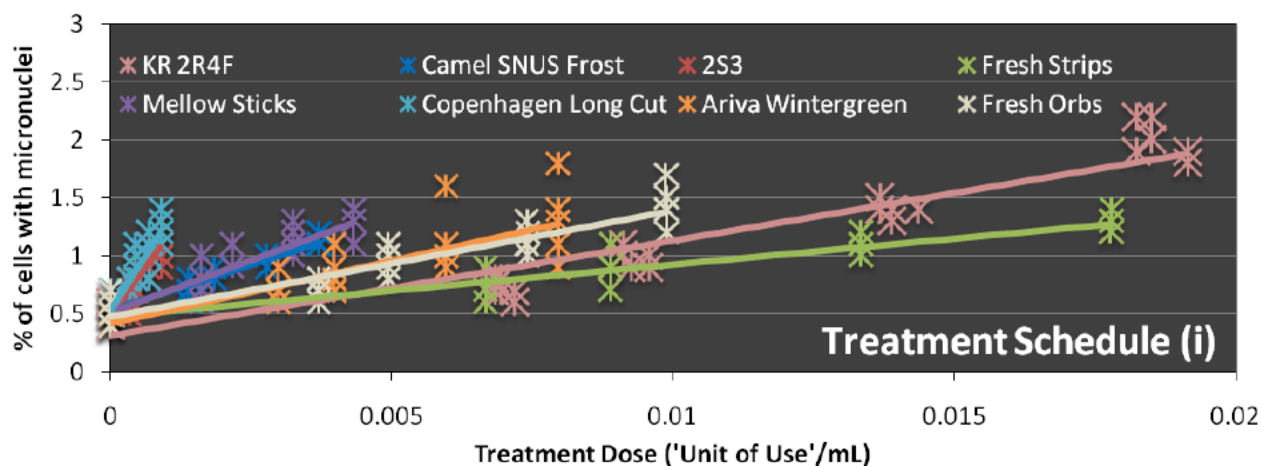
6.5.2 Data Plots

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

6.5.2.1 % micronucleated cells vs. [mg 'Nicotine'/mL]



6.5.2.2 % micronucleated cells vs. ['Unit of Use'/mL]



6.5.3 One-Way ANOVA Results

6.5.3.1 % micronucleated cells/(mg 'Nicotine'/mL)

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

Treatment Schedule	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Treatment Schedule (i)	Among Samples	67999.07	7	9714.15	24.42	< 0.001
	Within Samples	6364.65	16	397.79		
	Total	74363.72	23			
Treatment Schedule (ii)	Among Samples	44641.31	7	6377.33	43.69	< 0.001
	Within Samples	2335.27	16	145.95		
	Total	46976.59	23			

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

6.5.3.2 % micronucleated cells/('Unit of Use'/mL)

One-way ANOVA comparisons of mean 'unit of use' and 'cigarette' slope estimates among all 7 smokeless and one smoked tobacco test sample yielded the following:

Treatment Schedule	Variation Source	Sum of Squares	d.f.	Mean Square	F Ratio	P value
Treatment Schedule (i)	Among Samples	1556508	7	222358	54.62	< 0.001
	Within Samples	65139	16	4071		
	Total	1621646	23			
Treatment Schedule (ii)	Among Samples	684414	7	97773	112.13	< 0.001
	Within Samples	13951	16	872		
	Total	698365	23			

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

6.5.4 Contrasts of Interest

(b) (4)

6.5.4.1 % micronucleated cells/(mg 'Nicotine'/mL)

Since the variation in slope estimates differs by a factor of 11.2 for samples 084396 and 084456 under treatment schedule (ii), both ANOVA-based and pairwise t-test comparisons were applied for this treatment schedule.

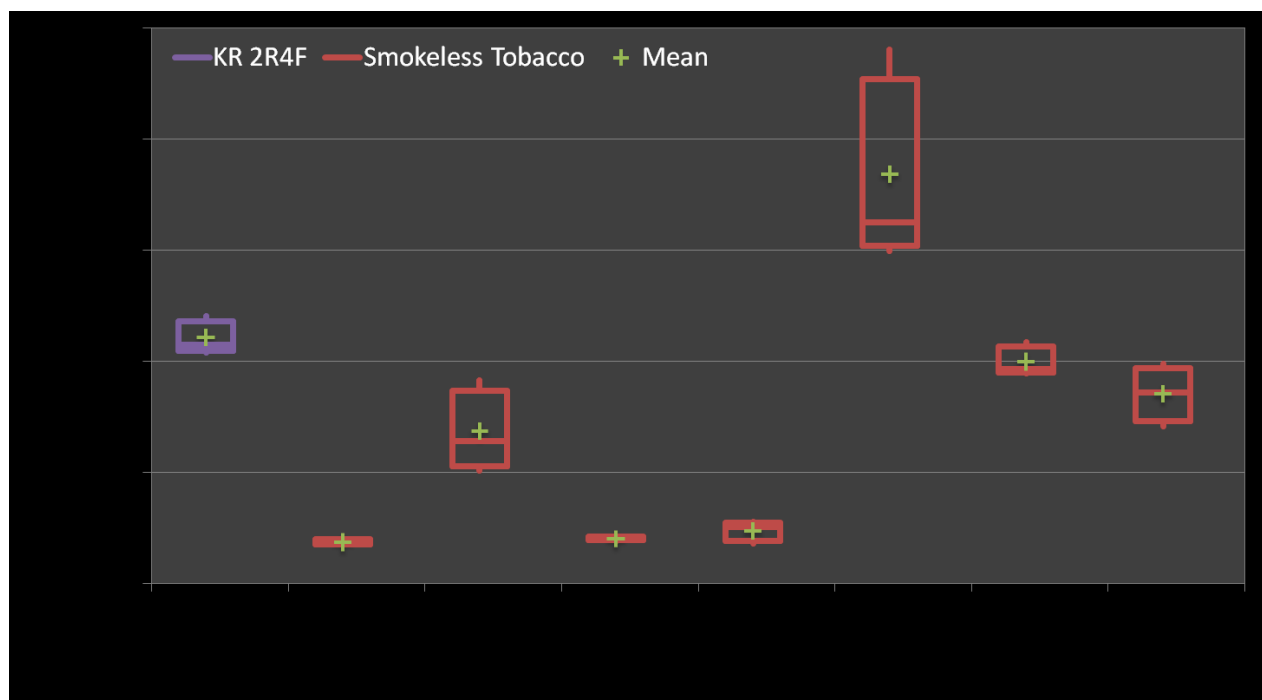
The tables below show both ANOVA-based comparison results for both treatment schedules and pairwise t-test results for treatment schedule (ii) along with identified significant differences.

	Treatment Schedule (i)			Treatment Schedule (ii)		
ANOVA-Based Comparison	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

Pairwise T-Test Comparison	Treatment Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084396	20.9526	3.1E-05	significant
084395 vs. 084396	24.7207	1.6E-05	significant
084454 vs. 084396	2.9980	0.0400	not significant
084455 vs. 084396	2.2482	0.0878	not significant
084456 vs. 084396	25.9795	1.3E-05	significant
084457 vs. 084396	4.9121	0.0080	not significant
084458 vs. 084396	4.5810	0.0102	not significant

ANOVA-Based Comparison Results: Treatment Schedule (i)

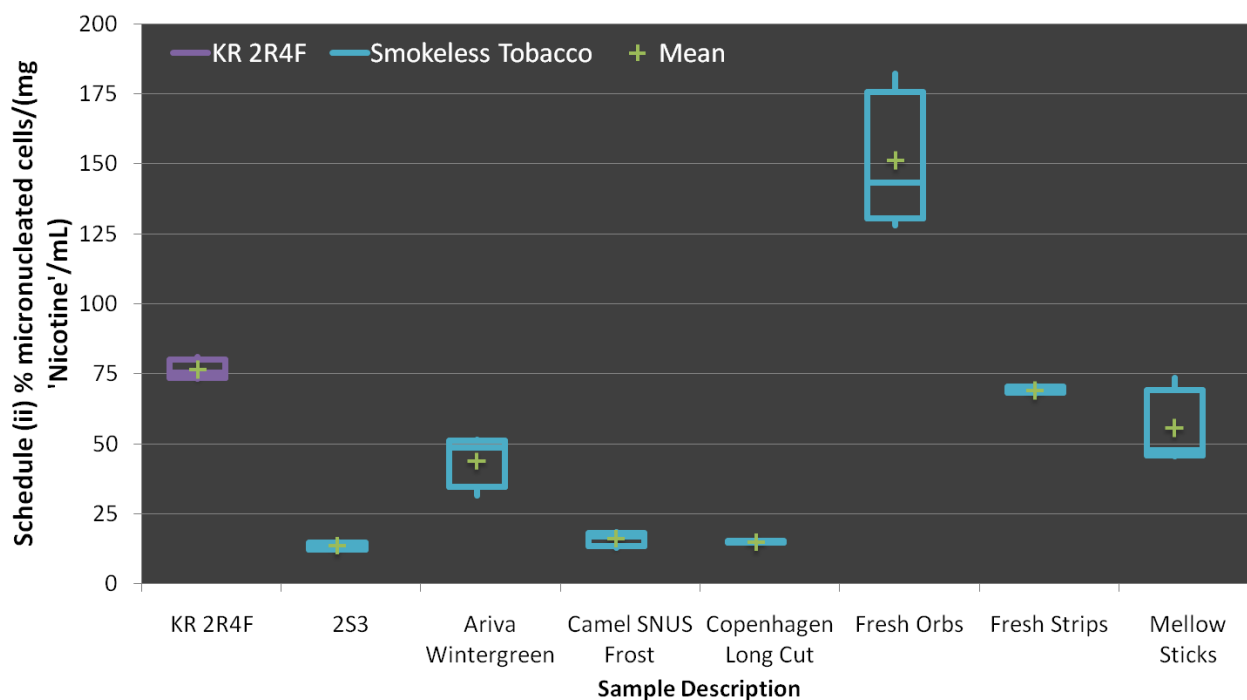
ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that under treatment schedule (i), significant differences in mean specific activity slope were detected between the cigarette smoke condensate of KR 2R4F (084396) and the following smokeless tobacco extracts on a 'Nicotine' dose basis: **{Camel SNUS Frost (084394), 2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456), Fresh Orbs (084458)}**.



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

ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that under treatment schedule (ii), significant differences in mean specific activity slope were detected between the cigarette smoke condensate of KR 2R4F (084396) and the following smokeless tobacco extracts on a 'Nicotine' dose basis: {**Camel SNUS Frost (084394)**, **2S3 Research Moist Snuff (084395)**, **Copenhagen Long Cut (084456)**, **Ariva Wintergreen (084457)**, **Fresh Orbs (084458)**}.

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



6.5.4.2 % micronucleated cells/('Unit of Use'/mL)

Since the variation in slope estimates does not satisfy the defined limit of sample standard deviations differing by a factor of 10 or less for the 'unit of use' dose basis under either treatment schedule, both ANOVA-based and pairwise t-test comparisons were applied in each case.

The tables below show both ANOVA-based comparison results for both treatment schedules and pairwise t-test results for treatment schedule (ii) along with identified significant differences.

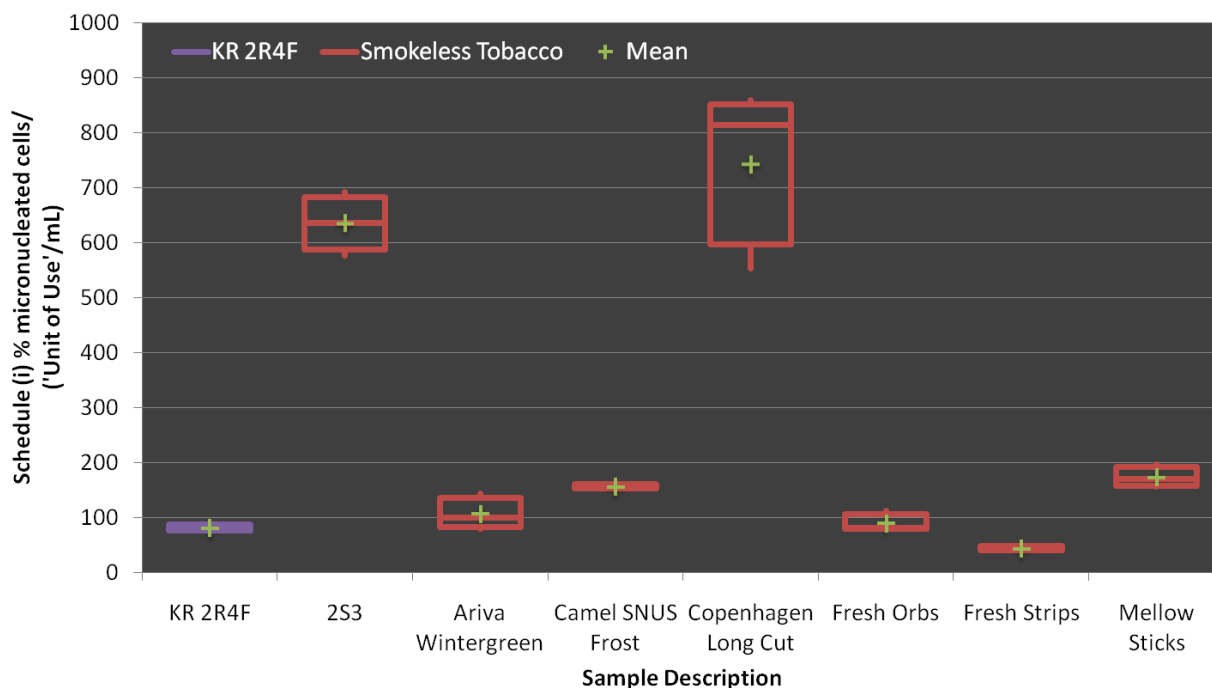
	Treatment Schedule (i)			Treatment Schedule (ii)		
ANOVA-Based Comparison	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084396	2.070	0.1695	not significant	7.783	0.0131	not significant
084395 vs. 084396	112	1.2E-08	significant	283	1.3E-11	significant
084454 vs. 084396	0.520	0.4810	not significant	1.167	0.2960	not significant
084455 vs. 084396	3.515	0.0792	not significant	6.151	0.0246	not significant
084456 vs. 084396	160	9.5E-10	significant	285	1.3E-11	significant
084457 vs. 084396	0.246	0.6270	not significant	0.255	0.6202	not significant
084458 vs. 084396	0.028	0.8699	not significant	0.559	0.4655	not significant

	Treatment Schedule (i)			Treatment Schedule (ii)		
Pariwise T-test Comparison	f-ratio	p-value	significance at $\alpha = 0.05$	f-ratio	p-value	significance at $\alpha = 0.05$
084394 vs. 084396	17.37	0.0001	significant	4.691	0.0094	not significant
084395 vs. 084396	16.57	0.0001	significant	9.888	0.0006	significant
084454 vs. 084396	8.835	0.0009	significant	14.12	1.5E-04	significant
084455 vs. 084396	7.680	0.0015	significant	4.593	0.0101	not significant
084456 vs. 084396	6.903	0.0023	significant	33.08	5.0E-06	significant
084457 vs. 084396	1.346	0.2497	not significant	1.231	0.2857	not significant
084458 vs. 084396	0.7638	0.4875	not significant	3.190	0.0332	not significant

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

ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that under treatment schedule (i), significant differences in mean 'unit of use' specific activity slope were detected between KR 2R4F (084396) and the following smokeless tobacco extracts on a 'unit of use' dose basis: **{2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456)}**.

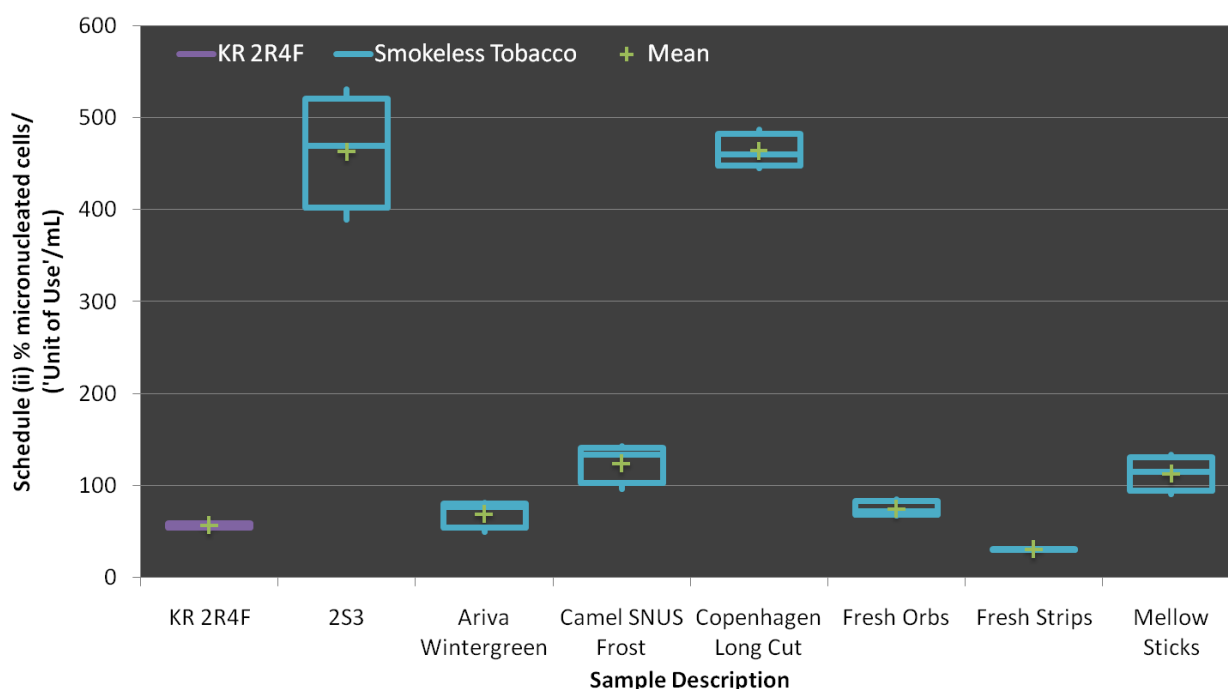
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that under treatment schedule (i), significant differences in mean 'unit of use' specific activity slope were detected between KR 2R4F (084396) and the following smokeless tobacco extracts on a 'unit of use' dose basis: **{Camel SNUS Frost (084394), 2S3 (084395), Fresh Strips (084454), Mellow Sticks (084455), Copenhagen Long Cut (084456)}**.



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

ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that under treatment schedule (ii), significant differences in mean 'unit of use' specific activity slope were detected between KR 2R4F (084396) and the following smokeless tobacco extracts on a 'unit of use' dose basis: **{2S3 (084395), Copenhagen Long Cut (084456)}**.

Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that under treatment schedule (ii), significant differences in mean 'unit of use' specific activity slope were detected between KR 2R4F (084396) and the following smokeless tobacco extracts on a 'unit of use' dose basis: **{2S3 (084395), Fresh Strips (084454), Copenhagen Long Cut (084456)}**.



7 Summary

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

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

8 Attribution

8.1 Original

8.1.1 Technical Director (Toxicology)

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

Dated: January 12, 2009




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

8.1.2 Senior Statistician

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

Dated: January 12, 2009



Wendy Wagstaff
Senior Statistician
Labstat International ULC

8.2 Revision 1

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

Dated: November 3, 2009



Wendy Wagstaff
Senior Statistician
Labstat International ULC

8.3 Revision 2

8.3.1 Technical Director (Toxicology)

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

Dated: December 17, 2009

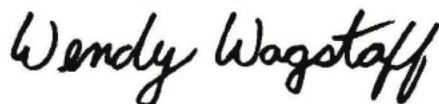


Amit Trivedi, Ph.D.,
Technical Director (Toxicology)
Labstat International ULC

8.3.2 Senior Statistician

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

Dated: December 17, 2009



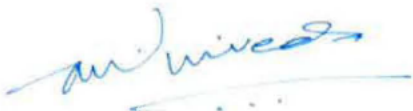
Wendy Wagstaff
Senior Statistician
Labstat International ULC

8.4 Revision 3

8.4.1 Technical Director (Toxicology)

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

Dated: April 23, 2010

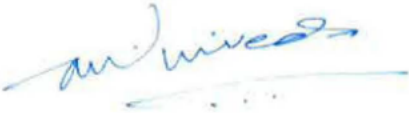


Amit Trivedi, Ph.D.,
Technical Director (Toxicology)
Labstat International ULC

8.5 Revision 5**8.5.1 Technical Director (Toxicology)**

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

Dated: December 22, 2010

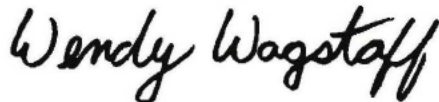


Amit Trivedi, Ph.D.,
Technical Director (Toxicology)
Labstat International ULC

8.5.2 Senior Statistician

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

Dated: December 22, 2010



Wendy Wagstaff
Senior Statistician
Labstat International ULC

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>

Page 1 of 6

Standards Council of Canada Accredited Laboratory No. 368

	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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Page 2 of 6

Standards Council of Canada Accredited Laboratory No. 368

	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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Page 3 of 6

Standards Council of Canada Accredited Laboratory No. 368

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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Page 4 of 6

Standards Council of Canada Accredited Laboratory No. 368

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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Page 5 of 6

Standards Council of Canada Accredited Laboratory No. 368

Partner File #0

Partner: None

Appendix B

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

Use of Labstat's¹ Analytical Reports²

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

It should be noted³, in this regard, that

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

The following also applies to reported data.

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

¹. Labstat International ULC,
262 Manitou Drive, Kitchener, ON Canada N2C 1L3
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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

LABSTAT INTERNATIONAL ULC

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Project: M100

Period: November 28 - December 17, 2008

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

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

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

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

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

Control Substance	Assay Date	Treatment Schedule	Treatment Time (h)	Metabolic Activation	Concentration ($\mu\text{g/mL}$)	Flask Number 1				Flask Number 2			
						Normal Cells	MN Cells	No. of MN	cells ($\times 10^5/\text{mL}$)	Normal Cells	MN Cells	No. of MN	cells ($\times 10^5/\text{mL}$)
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
Negative Control (-)	28-Nov-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.500	< 2.5% MN
	28-Nov-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.500	< 2.5% MN
	28-Nov-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.700	< 2.5% MN
	28-Nov-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.600	< 2.5% MN
	04-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.700	< 2.5% MN
	04-Dec-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.500	< 2.5% MN
	04-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.600	< 2.5% MN
	04-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.400	< 2.5% MN
	05-Dec-08	Schedule (i)	3	-S9					0.400	< 2.5% MN	0.400	< 2.5% MN
	05-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.700	< 2.5% MN
	05-Dec-08	Schedule (i)	3	-S9					0.500	< 2.5% MN	0.600	< 2.5% MN
	05-Dec-08	Schedule (i)	3	-S9					0.600	< 2.5% MN	0.500	< 2.5% MN
	11-Dec-08	Schedule (ii)	3	+S9					0.700	< 2.5% MN	0.600	< 2.5% MN
	11-Dec-08	Schedule (ii)	3	+S9					0.700	< 2.5% MN	0.600	< 2.5% MN
	11-Dec-08	Schedule (ii)	3	+S9					0.500	< 2.5% MN	0.700	< 2.5% MN
	11-Dec-08	Schedule (ii)	3	+S9					0.400	< 2.5% MN	0.700	< 2.5% MN
	12-Dec-08	Schedule (ii)	3	+S9					0.600	< 2.5% MN	0.600	< 2.5% MN
	12-Dec-08	Schedule (ii)	3	+S9					0.600	< 2.5% MN	0.700	< 2.5% MN
	12-Dec-08	Schedule (ii)	3	+S9					0.500	< 2.5% MN	0.600	< 2.5% MN
	12-Dec-08	Schedule (ii)	3	+S9					0.600	< 2.5% MN	0.700	< 2.5% MN
	17-Dec-08	Schedule (ii)	3	+S9					0.600	< 2.5% MN	0.600	< 2.5% MN
	17-Dec-08	Schedule (ii)	3	+S9					0.500	< 2.5% MN	0.600	< 2.5% MN
	17-Dec-08	Schedule (ii)	3	+S9					0.700	< 2.5% MN	0.500	< 2.5% MN
	17-Dec-08	Schedule (ii)	3	+S9					0.500	< 2.5% MN	0.700	< 2.5% MN

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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
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
	28-Nov-08	Schedule (i)	3	-S9	2	43.0	47.7	45.3	18.7	0.067	17.9	0.617
	28-Nov-08	Schedule (i)	3	-S9	2	41.8	40.3	41.0	17.5	0.868	17.3	0.617
	28-Nov-08	Schedule (i)	3	-S9	2	45.6	43.4	44.5	18.5	0.134	17.7	0.868
	04-Dec-08	Schedule (i)	3	-S9	2	38.1	43.4	40.7	18.7	0.067	17.8	0.739
	04-Dec-08	Schedule (i)	3	-S9	2	40.7	39.9	40.3	18.4	0.182	18.2	0.317
	04-Dec-08	Schedule (i)	3	-S9	2	44.6	42.8	43.7	17.3	0.617	17.8	0.739
	04-Dec-08	Schedule (i)	3	-S9	2	49.3	46.6	48.0	17.3	0.617	17.8	0.739
	05-Dec-08	Schedule (i)	3	-S9	2	43.2	42.2	42.7	18.4	0.182	18.1	0.405
	05-Dec-08	Schedule (i)	3	-S9	2	43.1	45.8	44.4	18.2	0.317	17.7	0.868
	05-Dec-08	Schedule (i)	3	-S9	2	48.6	50.8	49.7	18.1	0.405	17.8	0.739
	05-Dec-08	Schedule (i)	3	-S9	2	51.5	50.9	51.2	18.4	0.182	18.1	0.405
Colchicine	28-Nov-08	Schedule (i)	3	-S9	2	66.8	64.9	65.9	9.5	0.046	10.3	1.000
	28-Nov-08	Schedule (i)	3	-S9	2	64.2	66.7	65.5	10.8	0.211	10.4	0.803
	28-Nov-08	Schedule (i)	3	-S9	2	70.6	67.9	69.2	10.1	0.617	10.0	0.453
	28-Nov-08	Schedule (i)	3	-S9	2	72.5	69.3	70.9	10.4	0.803	10.3	1.000
	04-Dec-08	Schedule (i)	3	-S9	2	68.4	70.4	69.4	10.3	1.000	10.7	0.317
	04-Dec-08	Schedule (i)	3	-S9	2	72.7	75.6	74.1	10.2	0.803	10.2	0.803
	04-Dec-08	Schedule (i)	3	-S9	2	71.0	70.0	70.5	9.4	0.024	9.8	0.211
	04-Dec-08	Schedule (i)	3	-S9	2	71.2	68.8	70.0	10.0	0.453	10.3	1.000
	05-Dec-08	Schedule (i)	3	-S9	2	72.3	74.3	73.3	9.6	0.080	10.2	0.803
	05-Dec-08	Schedule (i)	3	-S9	2	71.8	68.9	70.3	10.1	0.617	9.8	0.211
	05-Dec-08	Schedule (i)	3	-S9	2	75.3	74.0	74.6	9.9	0.317	10.0	0.453
	05-Dec-08	Schedule (i)	3	-S9	2	74.9	74.3	74.6	10.0	0.453	10.2	0.803

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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
Cyclophosphamide	11-Dec-08	Schedule (ii)	3	+S9	7.5	41.5	43.3	42.4	3.5	0.617	3.5	0.617
	11-Dec-08	Schedule (ii)	3	+S9	7.5	47.3	44.3	45.8	3.2	0.317	3.6	0.317
	11-Dec-08	Schedule (ii)	3	+S9	7.5	41.7	38.6	40.2	3.4	1.000	3.6	0.317
	11-Dec-08	Schedule (ii)	3	+S9	7.5	42.6	43.6	43.1	3.2	0.317	3.1	0.134
	12-Dec-08	Schedule (ii)	3	+S9	7.5	45.1	46.8	46.0	3.4	1.000	3.3	0.617
	12-Dec-08	Schedule (ii)	3	+S9	7.5	48.0	44.9	46.5	3.2	0.317	3.4	1.000
	12-Dec-08	Schedule (ii)	3	+S9	7.5	41.1	40.8	41.0	3.2	0.317	3.5	0.617
	12-Dec-08	Schedule (ii)	3	+S9	7.5	45.5	46.5	46.0	3.2	0.317	3.4	1.000
	17-Dec-08	Schedule (ii)	3	+S9	7.5	34.5	40.3	37.4	3.2	0.317	3.2	0.317
	17-Dec-08	Schedule (ii)	3	+S9	7.5	33.1	32.7	32.9	3.3	0.617	3.5	0.617
	17-Dec-08	Schedule (ii)	3	+S9	7.5	34.1	36.4	35.3	3.5	0.617	3.3	0.617
	17-Dec-08	Schedule (ii)	3	+S9	7.5	39.4	39.7	39.5	3.4	1.000	3.2	0.317

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

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0.500	
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<div><div></div><div>Average</div></div>	
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	18.3
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	10.6
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	10.5
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	9.9
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Average

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3.4

3.3

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

Sample ID	Replicate Number	Treatment Schedule	TPM (mg/mL)	Treatment Time (h)	Metabolic Activation	Cell Counts (Flask 1)			
						Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)
control	1	Schedule (i)	0	3	-S9	995	5	6	7.76
control	1	Schedule (i)	0.075	3	-S9	992	8	8	6.56
control	1	Schedule (i)	0.100	3	-S9	990	10	11	5.96
control	1	Schedule (i)	0.150	3	-S9	987	13	13	5.40
control	1	Schedule (i)	0.200	3	-S9	985	15	16	4.52
control	2	Schedule (i)	0	3	-S9	995	5	5	7.88
control	2	Schedule (i)	0.075	3	-S9	992	8	9	6.88
control	2	Schedule (i)	0.100	3	-S9	990	10	11	5.80
control	2	Schedule (i)	0.150	3	-S9	988	12	13	5.52
control	2	Schedule (i)	0.200	3	-S9	984	16	17	4.80
control	3	Schedule (i)	0	3	-S9	994	6	7	6.40
control	3	Schedule (i)	0.075	3	-S9	992	8	8	5.68
control	3	Schedule (i)	0.100	3	-S9	989	11	12	4.80
control	3	Schedule (i)	0.150	3	-S9	987	13	14	4.12
control	3	Schedule (i)	0.200	3	-S9	985	15	16	2.88
control	4	Schedule (i)	0	3	-S9	996	4	5	7.28
control	4	Schedule (i)	0.075	3	-S9	992	8	8	6.76
control	4	Schedule (i)	0.100	3	-S9	990	10	11	5.88
control	4	Schedule (i)	0.150	3	-S9	987	13	14	4.92
control	4	Schedule (i)	0.200	3	-S9	985	15	17	3.72
control	5	Schedule (i)	0	3	-S9	995	5	5	7.72
control	5	Schedule (i)	0.075	3	-S9	993	7	7	7.08
control	5	Schedule (i)	0.100	3	-S9	991	9	9	6.32
control	5	Schedule (i)	0.150	3	-S9	987	13	13	5.56
control	5	Schedule (i)	0.200	3	-S9	986	14	15	4.32
control	6	Schedule (i)	0	3	-S9	995	5	5	9.60
control	6	Schedule (i)	0.075	3	-S9	993	7	7	8.96
control	6	Schedule (i)	0.100	3	-S9	990	10	10	8.36
control	6	Schedule (i)	0.150	3	-S9	987	13	13	6.80
control	6	Schedule (i)	0.200	3	-S9	985	15	15	5.44

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

Sample ID	Replicate Number	Treatment Schedule	TPM (mg/mL)	Treatment Time (h)	Metabolic Activation	Cell Counts (Flask 1)			
						Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)
control	1	Schedule (ii)	0	3	+S9	995	5	5	7.56
control	1	Schedule (ii)	0.075	3	+S9	993	7	7	6.96
control	1	Schedule (ii)	0.100	3	+S9	992	8	9	6.72
control	1	Schedule (ii)	0.150	3	+S9	990	10	10	6.24
control	1	Schedule (ii)	0.200	3	+S9	988	12	13	5.44
control	2	Schedule (ii)	0	3	+S9	994	6	7	7.24
control	2	Schedule (ii)	0.075	3	+S9	993	7	7	6.72
control	2	Schedule (ii)	0.100	3	+S9	991	9	9	6.08
control	2	Schedule (ii)	0.150	3	+S9	990	10	10	5.72
control	2	Schedule (ii)	0.200	3	+S9	988	12	14	5.00
control	3	Schedule (ii)	0	3	+S9	994	6	7	8.36
control	3	Schedule (ii)	0.075	3	+S9	993	7	8	7.88
control	3	Schedule (ii)	0.100	3	+S9	992	8	8	7.20
control	3	Schedule (ii)	0.150	3	+S9	990	10	12	6.48
control	3	Schedule (ii)	0.200	3	+S9	988	12	13	6.00
control	4	Schedule (ii)	0	3	+S9	993	7	7	8.04
control	4	Schedule (ii)	0.075	3	+S9	993	7	8	7.44
control	4	Schedule (ii)	0.100	3	+S9	992	8	9	6.88
control	4	Schedule (ii)	0.150	3	+S9	990	10	11	6.04
control	4	Schedule (ii)	0.200	3	+S9	988	12	13	5.56
control	5	Schedule (ii)	0	3	+S9	994	6	6	7.52
control	5	Schedule (ii)	0.075	3	+S9	993	7	7	6.84
control	5	Schedule (ii)	0.100	3	+S9	991	9	9	6.20
control	5	Schedule (ii)	0.150	3	+S9	990	10	11	5.52
control	5	Schedule (ii)	0.200	3	+S9	989	11	13	4.88
control	6	Schedule (ii)	0	3	+S9	994	6	6	7.36
control	6	Schedule (ii)	0.075	3	+S9	993	7	7	6.80
control	6	Schedule (ii)	0.100	3	+S9	991	9	9	6.28
control	6	Schedule (ii)	0.150	3	+S9	989	11	11	5.84
control	6	Schedule (ii)	0.200	3	+S9	987	13	15	5.16

***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

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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
control	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92		7.76		≥ 90%	
control	2	28-Nov-08	Schedule (i)	-S9	3	27	1.96		7.88		≥ 90%	
control	3	04-Dec-08	Schedule (i)	-S9	3	27	1.96		6.40		≥ 90%	
control	4	04-Dec-08	Schedule (i)	-S9	3	27	1.96		7.28		≥ 90%	
control	5	05-Dec-08	Schedule (i)	-S9	3	27	2.08		7.72		≥ 90%	
control	6	05-Dec-08	Schedule (i)	-S9	3	27	2.08		9.60		≥ 90%	
control	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.04		7.56		≥ 90%	
control	2	11-Dec-08	Schedule (ii)	+S9	3	27	2.00		7.24		≥ 90%	
control	3	12-Dec-08	Schedule (ii)	+S9	3	27	2.12		8.36		≥ 90%	
control	4	12-Dec-08	Schedule (ii)	+S9	3	27	1.92		8.04		≥ 90%	
control	5	17-Dec-08	Schedule (ii)	+S9	3	27	1.96		7.52		≥ 90%	
control	6	17-Dec-08	Schedule (ii)	+S9	3	27	2.04		7.36		≥ 90%	

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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.

**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.

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Project: M100
Period: November 6, 2008

Smoking Data† for <i>In Vitro</i> Micronucleus Assay analysis										TPM, Nicotine and 'Unit of Use' Dose Data for <i>In Vitro</i> 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 (mg/mL media)					'Unit of Use' Dose (cigs/mL media)				
										1	2	3	4	5	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	0.005	0.007	0.010	0.013	0	0.007	0.009	0.014	0.018
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	0.005	0.007	0.011	0.014	0	0.007	0.009	0.014	0.018
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	0.005	0.007	0.010	0.014	0	0.007	0.010	0.014	0.019

† 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
(Observations per flask)**

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	TPM (mg/mL)	Nicotine (mg/mL)	Unit of Use (cigs/mL)	Treatment Time (h)	Metabolic Activation	Cell Counts (Flask 1)				Cell Counts (Flask 2)			
										Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)
1	2	084396	1	Schedule (i)	0	0	0	3	-S9	996	4	5	7.44	995	5	5	7.36
1	2	084396	1	Schedule (i)	0.075	0.005	0.007	3	-S9	993	7	8	6.40	992	8	8	6.68
1	2	084396	1	Schedule (i)	0.100	0.007	0.009	3	-S9	989	11	12	5.92	990	10	11	5.96
1	2	084396	1	Schedule (i)	0.150	0.010	0.014	3	-S9	986	14	15	4.76	985	15	15	4.60
1	2	084396	1	Schedule (i)	0.200	0.013	0.018	3	-S9	981	19	22	2.96	978	22	24	3.20
1	3	084396	2	Schedule (i)	0	0	0	3	-S9	994	6	7	6.40	995	5	5	6.64
1	3	084396	2	Schedule (i)	0.075	0.005	0.007	3	-S9	992	8	8	5.52	993	7	7	5.68
1	3	084396	2	Schedule (i)	0.100	0.007	0.009	3	-S9	991	9	10	5.00	991	9	9	4.68
1	3	084396	2	Schedule (i)	0.150	0.011	0.014	3	-S9	987	13	14	3.64	986	14	15	3.96
1	3	084396	2	Schedule (i)	0.200	0.014	0.018	3	-S9	980	20	21	2.68	978	22	23	2.48
1	4	084396	3	Schedule (i)	0	0	0	3	-S9	996	4	4	8.20	995	5	5	8.08
1	4	084396	3	Schedule (i)	0.075	0.005	0.007	3	-S9	994	6	6	7.56	993	7	8	7.36
1	4	084396	3	Schedule (i)	0.100	0.007	0.010	3	-S9	991	9	10	6.28	990	10	11	6.24
1	4	084396	3	Schedule (i)	0.150	0.010	0.014	3	-S9	986	14	14	5.08	986	14	15	4.88
1	4	084396	3	Schedule (i)	0.200	0.014	0.019	3	-S9	982	18	18	3.16	981	19	20	2.92
1	2	084396	1	Schedule (ii)	0	0	0	3	+S9	993	7	7	7.36	994	6	7	7.24
1	2	084396	1	Schedule (ii)	0.075	0.005	0.007	3	+S9	991	9	9	7.08	992	8	9	6.96
1	2	084396	1	Schedule (ii)	0.100	0.007	0.009	3	+S9	987	13	13	6.68	989	11	12	6.72
1	2	084396	1	Schedule (ii)	0.150	0.010	0.014	3	+S9	986	14	16	6.04	986	14	14	6.00
1	2	084396	1	Schedule (ii)	0.200	0.013	0.018	3	+S9	982	18	19	5.48	984	16	17	5.24
1	3	084396	2	Schedule (ii)	0	0	0	3	+S9	994	6	6	7.92	994	6	6	7.64
1	3	084396	2	Schedule (ii)	0.075	0.005	0.007	3	+S9	992	8	9	7.00	992	8	8	7.08
1	3	084396	2	Schedule (ii)	0.100	0.007	0.009	3	+S9	990	10	11	6.60	989	11	11	6.68
1	3	084396	2	Schedule (ii)	0.150	0.011	0.014	3	+S9	988	12	13	6.00	986	14	14	5.84
1	3	084396	2	Schedule (ii)	0.200	0.014	0.018	3	+S9	984	16	16	5.48	983	17	17	5.36
1	4	084396	3	Schedule (ii)	0	0	0	3	+S9	994	6	6	7.16	994	6	6	7.08
1	4	084396	3	Schedule (ii)	0.075	0.005	0.007	3	+S9	991	9	10	6.28	991	9	9	6.20
1	4	084396	3	Schedule (ii)	0.100	0.007	0.010	3	+S9	990	10	11	5.64	989	11	11	5.80
1	4	084396	3	Schedule (ii)	0.150	0.010	0.014	3	+S9	986	14	15	5.28	987	13	13	5.24
1	4	084396	3	Schedule (ii)	0.200	0.014	0.019	3	+S9	983	17	17	4.88	985	15	15	4.96

***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 (mg/mL)	Unit of Use (cigs/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	0	3	-S9	0	0	0	0.50	0.50	0.50
1	2	084396	1	Schedule (i)	0.075	0.005	0.007	3	-S9	19.0	12.7	15.8	0.80	0.80	0.80
1	2	084396	1	Schedule (i)	0.100	0.007	0.009	3	-S9	27.7	26.1	26.9	1.20	1.10	1.15
1	2	084396	1	Schedule (i)	0.150	0.010	0.014	3	-S9	48.9	51.5	50.2	1.50	1.50	1.50
1	2	084396	1	Schedule (i)	0.200	0.013	0.018	3	-S9	81.8	77.6	79.7	2.20	2.40	2.30
1	3	084396	2	Schedule (i)	0	0	0	3	-S9	0	0	0	0.70	0.50	0.60
1	3	084396	2	Schedule (i)	0.075	0.005	0.007	3	-S9	19.8	20.7	20.3	0.80	0.70	0.75
1	3	084396	2	Schedule (i)	0.100	0.007	0.009	3	-S9	31.5	42.2	36.9	1.00	0.90	0.95
1	3	084396	2	Schedule (i)	0.150	0.011	0.014	3	-S9	62.2	57.8	60.0	1.40	1.50	1.45
1	3	084396	2	Schedule (i)	0.200	0.014	0.018	3	-S9	83.8	89.7	86.7	2.10	2.30	2.20
1	4	084396	3	Schedule (i)	0	0	0	3	-S9	0	0	0	0.40	0.50	0.45
1	4	084396	3	Schedule (i)	0.075	0.005	0.007	3	-S9	10.4	12.0	11.2	0.60	0.80	0.70
1	4	084396	3	Schedule (i)	0.100	0.007	0.010	3	-S9	31.2	30.7	30.9	1.00	1.10	1.05
1	4	084396	3	Schedule (i)	0.150	0.010	0.014	3	-S9	50.6	53.3	52.0	1.40	1.50	1.45
1	4	084396	3	Schedule (i)	0.200	0.014	0.019	3	-S9	81.8	86.0	83.9	1.80	2.00	1.90
1	2	084396	1	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.70	0.70	0.70
1	2	084396	1	Schedule (ii)	0.075	0.005	0.007	3	+S9	5.3	5.4	5.4	0.90	0.90	0.90
1	2	084396	1	Schedule (ii)	0.100	0.007	0.009	3	+S9	12.9	10.1	11.5	1.30	1.20	1.25
1	2	084396	1	Schedule (ii)	0.150	0.010	0.014	3	+S9	25.0	24.0	24.5	1.60	1.40	1.50
1	2	084396	1	Schedule (ii)	0.200	0.013	0.018	3	+S9	35.6	38.8	37.2	1.90	1.70	1.80
1	3	084396	2	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.60	0.60
1	3	084396	2	Schedule (ii)	0.075	0.005	0.007	3	+S9	15.8	10.1	12.9	0.90	0.80	0.85
1	3	084396	2	Schedule (ii)	0.100	0.007	0.009	3	+S9	22.6	17.3	19.9	1.10	1.10	1.10
1	3	084396	2	Schedule (ii)	0.150	0.011	0.014	3	+S9	32.9	32.4	32.6	1.30	1.40	1.35
1	3	084396	2	Schedule (ii)	0.200	0.014	0.018	3	+S9	41.8	41.0	41.4	1.60	1.70	1.65
1	4	084396	3	Schedule (ii)	0	0	0	3	+S9	0	0	0	0.60	0.60	0.60
1	4	084396	3	Schedule (ii)	0.075	0.005	0.007	3	+S9	16.9	17.2	17.1	1.00	0.90	0.95
1	4	084396	3	Schedule (ii)	0.100	0.007	0.010	3	+S9	29.2	25.0	27.1	1.10	1.10	1.10
1	4	084396	3	Schedule (ii)	0.150	0.010	0.014	3	+S9	36.2	35.9	36.0	1.50	1.30	1.40
1	4	084396	3	Schedule (ii)	0.200	0.014	0.019	3	+S9	43.8	41.4	42.6	1.70	1.50	1.60

LABSTAT INTERNATIONAL ULC

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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)		Incr > 9
							Flask 1	Flask 2	Flask 1	Flask 2	Flask 1
084396	1	28-Nov-08	Schedule (i)	-S9	3	27	1.96	2.00	7.44	7.36	≥ 90%
084396	2	04-Dec-08	Schedule (i)	-S9	3	27	1.96	2.00	6.40	6.64	≥ 90%
084396	3	05-Dec-08	Schedule (i)	-S9	3	27	2.04	2.08	8.20	8.08	≥ 90%
084396	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.08	7.36	7.24	≥ 90%
084396	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.08	7.92	7.64	≥ 90%
084396	3	17-Dec-08	Schedule (ii)	+S9	3	27	1.96	1.96	7.16	7.08	≥ 90%

ease
10%
Flask 2
≥ 90%
≥ 90%
≥ 90%
≥ 90%
≥ 90%
≥ 90%

LABSTAT INTERNATIONAL ULC

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

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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	mg Nicotine in Smokeless Tobacco/mL media				
			1	2	3	4	5
3-4	084394	1	0	0.010	0.014	0.021	0.028
3-6	084394	2	0	0.011	0.014	0.022	0.029
3-13	084394	3	0	0.011	0.015	0.022	0.029
3-9	084395	1	0	0.011	0.015	0.023	0.030
3-11	084395	2	0	0.011	0.015	0.022	0.029
3-15	084395	3	0	0.012	0.016	0.024	0.031
3-2	084454	1	0	0.003	0.004	0.006	0.008
3-10	084454	2	0	0.003	0.004	0.006	0.008
3-12	084454	3	0	0.003	0.004	0.006	0.008
3-1	084455	1	0	0.003	0.004	0.007	0.009
3-3	084455	2	0	0.004	0.005	0.008	0.011
3-7	084455	3	0	0.003	0.004	0.006	0.008
2-7	084456	1	0	0.011	0.014	0.021	0.028
2-9	084456	2	0	0.010	0.014	0.021	0.027
2-10	084456	3	0	0.010	0.014	0.020	0.027
2-3	084457	1	0	0.005	0.006	0.009	0.013
2-5	084457	2	0	0.005	0.006	0.009	0.012
2-6	084457	3	0	0.005	0.006	0.009	0.012
2-2	084458	1	0	0.002	0.002	0.003	0.005
2-4	084458	2	0	0.002	0.003	0.004	0.005
2-8	084458	3	0	0.002	0.002	0.004	0.005

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	Cell Counts (Flask 1)				Cell Counts (Flask 2)			
										Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)
3	4	084394	1	Schedule (i)	0	0	0.000	3	-S9	994	6	6	7.44	995	5	5	7.68
3	4	084394	1	Schedule (i)	0.834	0.569	0.010	3	-S9	992	8	8	6.72	993	7	7	6.92
3	4	084394	1	Schedule (i)	1.11	0.759	0.014	3	-S9	991	9	9	6.08	992	8	8	6.20
3	4	084394	1	Schedule (i)	1.67	1.14	0.021	3	-S9	990	10	10	5.24	991	9	10	5.08
3	4	084394	1	Schedule (i)	2.22	1.52	0.028	3	-S9	989	11	11	4.24	988	12	13	4.60
3	6	084394	2	Schedule (i)	0	0	0.000	3	-S9	994	6	6	7.44	995	5	6	7.20
3	6	084394	2	Schedule (i)	0.833	0.569	0.011	3	-S9	993	7	7	6.68	994	6	6	6.64
3	6	084394	2	Schedule (i)	1.11	0.759	0.014	3	-S9	992	8	9	5.88	992	8	8	5.80
3	6	084394	2	Schedule (i)	1.67	1.14	0.022	3	-S9	991	9	11	4.92	991	9	9	5.16
3	6	084394	2	Schedule (i)	2.22	1.52	0.029	3	-S9	988	12	12	4.08	989	11	12	4.36
3	13	084394	3	Schedule (i)	0	0	0.000	3	-S9	994	6	6	9.84	995	5	5	10.28
3	13	084394	3	Schedule (i)	0.834	0.569	0.011	3	-S9	992	8	8	9.44	993	7	7	9.56
3	13	084394	3	Schedule (i)	1.11	0.759	0.015	3	-S9	991	9	9	9.12	992	8	8	8.96
3	13	084394	3	Schedule (i)	1.67	1.14	0.022	3	-S9	990	10	10	7.52	990	10	10	8.00
3	13	084394	3	Schedule (i)	2.22	1.52	0.029	3	-S9	989	11	13	6.52	989	11	11	7.12
3	9	084395	1	Schedule (i)	0	0	0.000	3	-S9	995	5	5	7.72	994	6	6	7.56
3	9	084395	1	Schedule (i)	0.834	0.383	0.011	3	-S9	994	6	6	6.36	993	7	8	6.44
3	9	084395	1	Schedule (i)	1.11	0.511	0.015	3	-S9	993	7	8	5.80	991	9	9	5.48
3	9	084395	1	Schedule (i)	1.67	0.767	0.023	3	-S9	992	8	10	5.04	989	11	11	4.92
3	9	084395	1	Schedule (i)	2.22	1.02	0.030	3	-S9	990	10	11	4.36	987	13	14	4.48
3	11	084395	2	Schedule (i)	0	0	0.000	3	-S9	994	6	6	8.20	996	4	4	8.32
3	11	084395	2	Schedule (i)	0.834	0.383	0.011	3	-S9	993	7	8	7.60	995	5	5	7.68
3	11	084395	2	Schedule (i)	1.11	0.511	0.015	3	-S9	992	8	8	7.28	993	7	8	7.08
3	11	084395	2	Schedule (i)	1.67	0.767	0.022	3	-S9	991	9	10	6.52	992	8	9	6.76
3	11	084395	2	Schedule (i)	2.22	1.02	0.029	3	-S9	989	11	11	5.96	991	9	10	6.08
3	15	084395	3	Schedule (i)	0	0	0.000	3	-S9	994	6	6	9.40	995	5	5	9.04
3	15	084395	3	Schedule (i)	0.834	0.383	0.012	3	-S9	993	7	7	8.80	992	8	8	8.64
3	15	084395	3	Schedule (i)	1.11	0.511	0.016	3	-S9	992	8	8	8.56	991	9	9	8.56
3	15	084395	3	Schedule (i)	1.67	0.767	0.024	3	-S9	990	10	11	8.12	990	10	10	7.84
3	15	084395	3	Schedule (i)	2.22	1.02	0.031	3	-S9	989	11	11	7.44	989	11	11	6.80
3	2	084454	1	Schedule (i)	0	0	0.000	3	-S9	995	5	5	7.76	994	6	7	7.84
3	2	084454	1	Schedule (i)	0.834	0.741	0.003	3	-S9	993	7	7	6.44	991	9	10	6.52
3	2	084454	1	Schedule (i)	1.11	0.988	0.004	3	-S9	991	9	9	5.64	989	11	12	5.80
3	2	084454	1	Schedule (i)	1.67	1.48	0.006	3	-S9	990	10	11	5.04	988	12	12	4.88
3	2	084454	1	Schedule (i)	2.22	1.98	0.008	3	-S9	986	14	14	4.04	987	13	15	3.72

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	Cell Counts (Flask 1)				Cell Counts (Flask 2)			
										Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)
3	10	084454	2	Schedule (i)	0	0	0.000	3	-S9	995	5	5	7.84	996	4	5	8.00
3	10	084454	2	Schedule (i)	0.834	0.741	0.003	3	-S9	994	6	7	7.44	993	7	7	7.36
3	10	084454	2	Schedule (i)	1.11	0.988	0.004	3	-S9	991	9	9	6.92	993	7	10	6.76
3	10	084454	2	Schedule (i)	1.67	1.48	0.006	3	-S9	990	10	11	6.32	989	11	12	6.40
3	10	084454	2	Schedule (i)	2.22	1.98	0.008	3	-S9	987	13	13	5.84	987	13	15	5.64
3	12	084454	3	Schedule (i)	0	0	0.000	3	-S9	996	4	5	9.88	994	6	6	9.84
3	12	084454	3	Schedule (i)	0.834	0.741	0.003	3	-S9	993	7	7	9.40	993	7	8	9.28
3	12	084454	3	Schedule (i)	1.11	0.988	0.004	3	-S9	991	9	9	8.80	991	9	9	9.00
3	12	084454	3	Schedule (i)	1.67	1.48	0.006	3	-S9	990	10	12	8.12	989	11	12	8.28
3	12	084454	3	Schedule (i)	2.22	1.98	0.008	3	-S9	988	12	14	7.60	988	12	13	7.76
3	1	084455	1	Schedule (i)	0	0	0.000	3	-S9	995	5	6	7.52	995	5	5	7.64
3	1	084455	1	Schedule (i)	0.834	0.783	0.003	3	-S9	992	8	8	6.56	993	7	8	6.28
3	1	084455	1	Schedule (i)	1.11	1.04	0.004	3	-S9	991	9	10	5.52	991	9	9	5.68
3	1	084455	1	Schedule (i)	1.67	1.57	0.007	3	-S9	989	11	12	4.48	988	12	13	4.76
3	1	084455	1	Schedule (i)	2.22	2.09	0.009	3	-S9	986	14	15	3.96	987	13	14	3.68
3	3	084455	2	Schedule (i)	0	0	0.000	3	-S9	995	5	6	7.64	993	7	7	7.40
3	3	084455	2	Schedule (i)	0.834	0.783	0.004	3	-S9	992	8	8	6.76	990	10	10	6.64
3	3	084455	2	Schedule (i)	1.11	1.04	0.005	3	-S9	991	9	10	5.60	989	11	11	5.60
3	3	084455	2	Schedule (i)	1.67	1.57	0.008	3	-S9	989	11	11	5.16	987	13	13	4.92
3	3	084455	2	Schedule (i)	2.22	2.09	0.011	3	-S9	987	13	14	4.04	986	14	14	3.88
3	7	084455	3	Schedule (i)	0	0	0.000	3	-S9	996	4	4	10.48	995	5	5	10.60
3	7	084455	3	Schedule (i)	0.833	0.783	0.003	3	-S9	994	6	6	9.92	994	6	7	9.80
3	7	084455	3	Schedule (i)	1.11	1.04	0.004	3	-S9	991	9	10	9.04	991	9	9	8.96
3	7	084455	3	Schedule (i)	1.67	1.57	0.006	3	-S9	990	10	10	8.12	990	10	10	8.16
3	7	084455	3	Schedule (i)	2.22	2.09	0.008	3	-S9	989	11	11	7.36	989	11	12	7.68
2	7	084456	1	Schedule (i)	0	0	0.000	3	-S9	994	6	6	7.72	995	5	5	7.80
2	7	084456	1	Schedule (i)	0.834	0.372	0.011	3	-S9	992	8	9	6.40	993	7	8	6.28
2	7	084456	1	Schedule (i)	1.11	0.496	0.014	3	-S9	989	11	11	5.88	992	8	9	5.76
2	7	084456	1	Schedule (i)	1.67	0.744	0.021	3	-S9	988	12	12	5.12	990	10	10	5.36
2	7	084456	1	Schedule (i)	2.22	0.992	0.028	3	-S9	986	14	14	4.24	989	11	13	4.40
2	9	084456	2	Schedule (i)	0	0	0.000	3	-S9	995	5	5	6.88	995	5	5	6.72
2	9	084456	2	Schedule (i)	0.833	0.372	0.010	3	-S9	993	7	7	6.00	993	7	8	5.96
2	9	084456	2	Schedule (i)	1.11	0.496	0.014	3	-S9	990	10	11	5.48	991	9	10	5.68
2	9	084456	2	Schedule (i)	1.67	0.744	0.021	3	-S9	989	11	12	5.28	990	10	11	5.24
2	9	084456	2	Schedule (i)	2.22	0.992	0.027	3	-S9	987	13	13	4.56	988	12	12	4.76

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	Cell Counts (Flask 1)				Cell Counts (Flask 2)			
										Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)
2	10	084456	3	Schedule (i)	0	0	0.000	3	-S9	994	6	6	8.64	993	7	7	8.48
2	10	084456	3	Schedule (i)	0.834	0.372	0.010	3	-S9	993	7	7	7.84	993	7	8	7.76
2	10	084456	3	Schedule (i)	1.11	0.496	0.014	3	-S9	992	8	8	7.36	992	8	9	7.48
2	10	084456	3	Schedule (i)	1.67	0.744	0.020	3	-S9	992	8	10	6.88	990	10	11	6.92
2	10	084456	3	Schedule (i)	2.22	0.992	0.027	3	-S9	989	11	12	6.60	988	12	12	6.40
2	3	084457	1	Schedule (i)	0	0	0.000	3	-S9	994	6	6	7.56	996	4	5	7.32
2	3	084457	1	Schedule (i)	0.833	0.803	0.005	3	-S9	991	9	9	6.60	993	7	8	6.48
2	3	084457	1	Schedule (i)	1.11	1.07	0.006	3	-S9	989	11	11	6.04	991	9	10	5.80
2	3	084457	1	Schedule (i)	1.67	1.61	0.009	3	-S9	984	16	16	5.04	989	11	12	5.12
2	3	084457	1	Schedule (i)	2.22	2.14	0.013	3	-S9	982	18	19	4.52	986	14	14	4.64
2	5	084457	2	Schedule (i)	0	0	0.000	3	-S9	995	5	5	6.56	995	5	5	6.80
2	5	084457	2	Schedule (i)	0.833	0.803	0.005	3	-S9	994	6	7	6.12	994	6	6	5.84
2	5	084457	2	Schedule (i)	1.11	1.07	0.006	3	-S9	993	7	8	5.24	992	8	8	5.40
2	5	084457	2	Schedule (i)	1.67	1.61	0.009	3	-S9	991	9	10	4.80	990	10	10	4.92
2	5	084457	2	Schedule (i)	2.22	2.14	0.012	3	-S9	987	13	14	4.44	987	13	14	4.28
2	6	084457	3	Schedule (i)	0	0	0.000	3	-S9	996	4	4	8.24	996	4	4	8.24
2	6	084457	3	Schedule (i)	0.833	0.803	0.005	3	-S9	993	7	7	7.48	994	6	6	7.60
2	6	084457	3	Schedule (i)	1.11	1.07	0.006	3	-S9	993	7	8	6.88	993	7	8	6.92
2	6	084457	3	Schedule (i)	1.67	1.61	0.009	3	-S9	991	9	9	6.12	990	10	10	6.24
2	6	084457	3	Schedule (i)	2.22	2.14	0.012	3	-S9	991	9	11	5.44	989	11	11	5.72
2	2	084458	1	Schedule (i)	0	0	0.000	3	-S9	995	5	5	7.72	995	5	5	7.52
2	2	084458	1	Schedule (i)	0.833	0.790	0.002	3	-S9	993	7	9	7.16	993	7	7	7.00
2	2	084458	1	Schedule (i)	1.11	1.05	0.002	3	-S9	990	10	11	6.12	991	9	9	6.04
2	2	084458	1	Schedule (i)	1.67	1.58	0.003	3	-S9	987	13	14	4.76	989	11	12	5.00
2	2	084458	1	Schedule (i)	2.22	2.11	0.005	3	-S9	983	17	18	4.32	985	15	16	4.08
2	4	084458	2	Schedule (i)	0	0	0.000	3	-S9	994	6	6	6.20	993	7	7	6.36
2	4	084458	2	Schedule (i)	0.834	0.791	0.002	3	-S9	992	8	8	5.48	992	8	8	5.40
2	4	084458	2	Schedule (i)	1.11	1.05	0.003	3	-S9	991	9	10	4.64	989	11	11	4.84
2	4	084458	2	Schedule (i)	1.67	1.58	0.004	3	-S9	990	10	11	4.12	988	12	13	4.16
2	4	084458	2	Schedule (i)	2.22	2.11	0.005	3	-S9	986	14	15	3.56	985	15	15	3.36
2	8	084458	3	Schedule (i)	0	0	0.000	3	-S9	995	5	5	8.52	996	4	4	8.36
2	8	084458	3	Schedule (i)	0.834	0.791	0.002	3	-S9	993	7	7	7.72	994	6	7	7.88
2	8	084458	3	Schedule (i)	1.11	1.05	0.002	3	-S9	990	10	10	7.52	992	8	9	7.52
2	8	084458	3	Schedule (i)	1.67	1.58	0.004	3	-S9	989	11	12	6.96	989	11	11	6.88
2	8	084458	3	Schedule (i)	2.22	2.11	0.005	3	-S9	988	12	14	6.36	988	12	13	6.24

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	Cell Counts (Flask 1)				Cell Counts (Flask 2)			
										Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)
3	4	084394	1	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	7.36	993	7	7	7.16
3	4	084394	1	Schedule (ii)	0.834	0.569	0.010	3	+S9	993	7	7	7.00	991	9	9	6.88
3	4	084394	1	Schedule (ii)	1.11	0.759	0.014	3	+S9	992	8	9	6.80	990	10	10	6.76
3	4	084394	1	Schedule (ii)	1.67	1.14	0.021	3	+S9	991	9	10	6.16	990	10	10	6.04
3	4	084394	1	Schedule (ii)	2.22	1.52	0.028	3	+S9	990	10	11	5.40	990	10	10	5.56
3	6	084394	2	Schedule (ii)	0	0	0.000	3	+S9	995	5	5	7.00	994	6	6	7.16
3	6	084394	2	Schedule (ii)	0.833	0.569	0.011	3	+S9	994	6	6	6.60	994	6	7	6.56
3	6	084394	2	Schedule (ii)	1.11	0.759	0.014	3	+S9	992	8	8	6.08	993	7	8	6.12
3	6	084394	2	Schedule (ii)	1.67	1.14	0.022	3	+S9	991	9	9	5.56	991	9	9	5.68
3	6	084394	2	Schedule (ii)	2.22	1.52	0.029	3	+S9	989	11	11	5.00	990	10	10	4.92
3	13	084394	3	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	7.12	994	6	6	6.92
3	13	084394	3	Schedule (ii)	0.834	0.569	0.011	3	+S9	993	7	7	6.32	993	7	7	6.48
3	13	084394	3	Schedule (ii)	1.11	0.759	0.015	3	+S9	992	8	9	5.60	992	8	9	5.80
3	13	084394	3	Schedule (ii)	1.67	1.14	0.022	3	+S9	991	9	10	5.32	991	9	9	5.28
3	13	084394	3	Schedule (ii)	2.22	1.52	0.029	3	+S9	989	11	11	4.72	989	11	12	4.64
3	9	084395	1	Schedule (ii)	0	0	0.000	3	+S9	996	4	4	7.04	993	7	7	7.24
3	9	084395	1	Schedule (ii)	0.834	0.383	0.011	3	+S9	994	6	6	6.48	992	8	8	6.56
3	9	084395	1	Schedule (ii)	1.11	0.511	0.015	3	+S9	992	8	8	6.24	992	8	8	6.12
3	9	084395	1	Schedule (ii)	1.67	0.767	0.023	3	+S9	991	9	9	5.56	991	9	10	5.64
3	9	084395	1	Schedule (ii)	2.22	1.02	0.030	3	+S9	991	9	10	5.20	990	10	10	5.32
3	11	084395	2	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	7.48	993	7	7	7.40
3	11	084395	2	Schedule (ii)	0.834	0.383	0.011	3	+S9	994	6	7	7.04	992	8	8	7.20
3	11	084395	2	Schedule (ii)	1.11	0.511	0.015	3	+S9	992	8	9	6.80	991	9	9	6.76
3	11	084395	2	Schedule (ii)	1.67	0.767	0.022	3	+S9	992	8	9	6.04	991	9	10	6.20
3	11	084395	2	Schedule (ii)	2.22	1.02	0.029	3	+S9	990	10	10	5.88	990	10	10	5.72
3	15	084395	3	Schedule (ii)	0	0	0.000	3	+S9	995	5	5	7.20	993	7	7	6.96
3	15	084395	3	Schedule (ii)	0.834	0.383	0.012	3	+S9	994	6	6	6.40	992	8	8	6.76
3	15	084395	3	Schedule (ii)	1.11	0.511	0.016	3	+S9	992	8	8	6.16	991	9	9	5.88
3	15	084395	3	Schedule (ii)	1.67	0.767	0.024	3	+S9	991	9	9	5.36	990	10	10	5.56
3	15	084395	3	Schedule (ii)	2.22	1.02	0.031	3	+S9	990	10	10	4.96	989	11	11	4.84
3	2	084454	1	Schedule (ii)	0	0	0.000	3	+S9	995	5	5	7.20	993	7	7	7.04
3	2	084454	1	Schedule (ii)	0.834	0.741	0.003	3	+S9	993	7	7	6.72	992	8	8	6.52
3	2	084454	1	Schedule (ii)	1.11	0.988	0.004	3	+S9	991	9	9	5.84	991	9	9	5.64
3	2	084454	1	Schedule (ii)	1.67	1.48	0.006	3	+S9	991	9	10	5.16	989	11	11	5.24
3	2	084454	1	Schedule (ii)	2.22	1.98	0.008	3	+S9	988	12	12	4.76	989	11	12	4.52

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	Cell Counts (Flask 1)				Cell Counts (Flask 2)			
										Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)
3	10	084454	2	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	7.56	995	5	5	7.52
3	10	084454	2	Schedule (ii)	0.834	0.741	0.003	3	+S9	994	6	6	7.40	994	6	6	7.32
3	10	084454	2	Schedule (ii)	1.11	0.988	0.004	3	+S9	993	7	7	7.00	992	8	8	7.12
3	10	084454	2	Schedule (ii)	1.67	1.48	0.006	3	+S9	991	9	9	6.28	990	10	10	6.36
3	10	084454	2	Schedule (ii)	2.22	1.98	0.008	3	+S9	989	11	11	6.08	990	10	12	6.00
3	12	084454	3	Schedule (ii)	0	0	0.000	3	+S9	993	7	7	6.80	995	5	5	6.92
3	12	084454	3	Schedule (ii)	0.834	0.741	0.003	3	+S9	992	8	8	6.48	993	7	7	6.64
3	12	084454	3	Schedule (ii)	1.11	0.988	0.004	3	+S9	992	8	10	6.32	991	9	9	6.36
3	12	084454	3	Schedule (ii)	1.67	1.48	0.006	3	+S9	991	9	11	5.40	990	10	10	5.48
3	12	084454	3	Schedule (ii)	2.22	1.98	0.008	3	+S9	990	10	12	5.00	987	13	13	4.88
3	1	084455	1	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	7.08	993	7	7	6.92
3	1	084455	1	Schedule (ii)	0.834	0.783	0.003	3	+S9	992	8	8	6.20	992	8	8	6.12
3	1	084455	1	Schedule (ii)	1.11	1.04	0.004	3	+S9	992	8	9	5.40	992	8	9	5.56
3	1	084455	1	Schedule (ii)	1.67	1.57	0.007	3	+S9	991	9	10	4.96	990	10	10	5.12
3	1	084455	1	Schedule (ii)	2.22	2.09	0.009	3	+S9	990	10	11	4.36	989	11	11	4.44
3	3	084455	2	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	7.08	995	5	5	7.32
3	3	084455	2	Schedule (ii)	0.834	0.783	0.004	3	+S9	993	7	8	6.60	994	6	7	6.44
3	3	084455	2	Schedule (ii)	1.11	1.04	0.005	3	+S9	992	8	8	5.88	992	8	8	5.84
3	3	084455	2	Schedule (ii)	1.67	1.57	0.008	3	+S9	991	9	9	5.44	991	9	9	5.56
3	3	084455	2	Schedule (ii)	2.22	2.09	0.011	3	+S9	989	11	12	5.00	990	10	11	5.04
3	7	084455	3	Schedule (ii)	0	0	0.000	3	+S9	995	5	5	6.72	995	5	5	6.92
3	7	084455	3	Schedule (ii)	0.833	0.783	0.003	3	+S9	994	6	7	5.92	993	7	7	6.04
3	7	084455	3	Schedule (ii)	1.11	1.04	0.004	3	+S9	991	9	9	5.56	991	9	9	5.44
3	7	084455	3	Schedule (ii)	1.67	1.57	0.006	3	+S9	990	10	10	5.00	990	10	10	4.84
3	7	084455	3	Schedule (ii)	2.22	2.09	0.008	3	+S9	990	10	11	4.44	989	11	11	4.56
2	7	084456	1	Schedule (ii)	0	0	0.000	3	+S9	993	7	7	7.52	994	6	6	7.32
2	7	084456	1	Schedule (ii)	0.834	0.372	0.011	3	+S9	992	8	8	6.72	993	7	7	6.64
2	7	084456	1	Schedule (ii)	1.11	0.496	0.014	3	+S9	991	9	9	6.12	992	8	8	6.08
2	7	084456	1	Schedule (ii)	1.67	0.744	0.021	3	+S9	990	10	10	6.04	990	10	10	5.84
2	7	084456	1	Schedule (ii)	2.22	0.992	0.028	3	+S9	989	11	11	5.64	990	10	11	5.72
2	9	084456	2	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	8.08	993	7	7	7.92
2	9	084456	2	Schedule (ii)	0.833	0.372	0.010	3	+S9	993	7	7	7.48	993	7	7	7.60
2	9	084456	2	Schedule (ii)	1.11	0.496	0.014	3	+S9	991	9	9	7.20	993	7	8	7.00
2	9	084456	2	Schedule (ii)	1.67	0.744	0.021	3	+S9	990	10	10	6.44	992	8	8	6.60
2	9	084456	2	Schedule (ii)	2.22	0.992	0.027	3	+S9	989	11	11	6.04	990	10	10	6.12

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	Cell Counts (Flask 1)				Cell Counts (Flask 2)			
										Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)	Normal Cells	MN Cells	No. of MN	Cells (x10 ⁵ /mL)
2	10	084456	3	Schedule (ii)	0	0	0.000	3	+S9	995	5	5	6.52	994	6	6	6.72
2	10	084456	3	Schedule (ii)	0.834	0.372	0.010	3	+S9	993	7	7	5.92	993	7	7	5.80
2	10	084456	3	Schedule (ii)	1.11	0.496	0.014	3	+S9	992	8	8	5.52	991	9	9	5.32
2	10	084456	3	Schedule (ii)	1.67	0.744	0.020	3	+S9	992	8	9	4.96	991	9	10	5.16
2	10	084456	3	Schedule (ii)	2.22	0.992	0.027	3	+S9	991	9	10	4.44	990	10	11	4.32
2	3	084457	1	Schedule (ii)	0	0	0.000	3	+S9	993	7	7	7.20	993	7	7	7.12
2	3	084457	1	Schedule (ii)	0.833	0.803	0.005	3	+S9	992	8	8	6.88	992	8	8	6.84
2	3	084457	1	Schedule (ii)	1.11	1.07	0.006	3	+S9	991	9	9	6.36	992	8	9	6.28
2	3	084457	1	Schedule (ii)	1.67	1.61	0.009	3	+S9	990	10	11	6.16	991	9	10	6.04
2	3	084457	1	Schedule (ii)	2.22	2.14	0.013	3	+S9	989	11	12	5.76	989	11	12	5.84
2	5	084457	2	Schedule (ii)	0	0	0.000	3	+S9	994	6	7	7.64	994	6	6	7.84
2	5	084457	2	Schedule (ii)	0.833	0.803	0.005	3	+S9	992	8	8	7.52	992	8	8	7.36
2	5	084457	2	Schedule (ii)	1.11	1.07	0.006	3	+S9	991	9	10	6.84	991	9	9	6.68
2	5	084457	2	Schedule (ii)	1.67	1.61	0.009	3	+S9	990	10	11	6.48	989	11	11	6.44
2	5	084457	2	Schedule (ii)	2.22	2.14	0.012	3	+S9	988	12	12	6.28	988	12	13	6.12
2	6	084457	3	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	6.96	994	6	6	7.24
2	6	084457	3	Schedule (ii)	0.833	0.803	0.005	3	+S9	992	8	8	6.68	993	7	7	6.40
2	6	084457	3	Schedule (ii)	1.11	1.07	0.006	3	+S9	991	9	9	5.80	992	8	9	6.12
2	6	084457	3	Schedule (ii)	1.67	1.61	0.009	3	+S9	989	11	11	5.32	991	9	10	5.44
2	6	084457	3	Schedule (ii)	2.22	2.14	0.012	3	+S9	987	13	13	4.88	988	12	12	4.68
2	2	084458	1	Schedule (ii)	0	0	0.000	3	+S9	993	7	7	7.32	994	6	6	7.20
2	2	084458	1	Schedule (ii)	0.833	0.790	0.002	3	+S9	991	9	9	7.00	992	8	8	6.92
2	2	084458	1	Schedule (ii)	1.11	1.05	0.002	3	+S9	989	11	12	6.76	989	11	11	6.76
2	2	084458	1	Schedule (ii)	1.67	1.58	0.003	3	+S9	986	14	14	6.56	988	12	13	6.40
2	2	084458	1	Schedule (ii)	2.22	2.11	0.005	3	+S9	984	16	16	6.08	987	13	15	6.20
2	4	084458	2	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	7.36	994	6	6	7.52
2	4	084458	2	Schedule (ii)	0.834	0.791	0.002	3	+S9	992	8	8	7.00	992	8	8	7.08
2	4	084458	2	Schedule (ii)	1.11	1.05	0.003	3	+S9	991	9	10	6.72	991	9	9	6.84
2	4	084458	2	Schedule (ii)	1.67	1.58	0.004	3	+S9	990	10	11	6.68	990	10	11	6.60
2	4	084458	2	Schedule (ii)	2.22	2.11	0.005	3	+S9	988	12	13	5.80	986	14	14	5.68
2	8	084458	3	Schedule (ii)	0	0	0.000	3	+S9	994	6	6	6.44	994	6	6	6.44
2	8	084458	3	Schedule (ii)	0.834	0.791	0.002	3	+S9	992	8	8	5.84	992	8	8	5.76
2	8	084458	3	Schedule (ii)	1.11	1.05	0.002	3	+S9	991	9	9	5.24	991	9	9	5.00
2	8	084458	3	Schedule (ii)	1.67	1.58	0.004	3	+S9	989	11	11	4.40	989	11	11	4.64
2	8	084458	3	Schedule (ii)	2.22	2.11	0.005	3	+S9	987	13	13	4.12	987	13	14	4.36

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
3	4	084394	1	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.50	0.55
3	4	084394	1	Schedule (i)	0.834	0.569	0.010	3	-S9	9.7	9.9	9.8	0.80	0.70	0.75
3	4	084394	1	Schedule (i)	1.11	0.759	0.014	3	-S9	18.3	19.3	18.8	0.90	0.80	0.85
3	4	084394	1	Schedule (i)	1.67	1.14	0.021	3	-S9	29.6	33.9	31.7	1.00	1.00	1.00
3	4	084394	1	Schedule (i)	2.22	1.52	0.028	3	-S9	43.0	40.1	41.6	1.10	1.30	1.20
3	6	084394	2	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.60	0.60
3	6	084394	2	Schedule (i)	0.833	0.569	0.011	3	-S9	10.2	7.8	9.0	0.70	0.60	0.65
3	6	084394	2	Schedule (i)	1.11	0.759	0.014	3	-S9	21.0	19.4	20.2	0.90	0.80	0.85
3	6	084394	2	Schedule (i)	1.67	1.14	0.022	3	-S9	33.9	28.3	31.1	1.10	0.90	1.00
3	6	084394	2	Schedule (i)	2.22	1.52	0.029	3	-S9	45.2	39.4	42.3	1.20	1.20	1.20
3	13	084394	3	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.50	0.55
3	13	084394	3	Schedule (i)	0.834	0.569	0.011	3	-S9	4.1	7.0	5.5	0.80	0.70	0.75
3	13	084394	3	Schedule (i)	1.11	0.759	0.015	3	-S9	7.3	12.8	10.1	0.90	0.80	0.85
3	13	084394	3	Schedule (i)	1.67	1.14	0.022	3	-S9	23.6	22.2	22.9	1.00	1.00	1.00
3	13	084394	3	Schedule (i)	2.22	1.52	0.029	3	-S9	33.7	30.7	32.2	1.30	1.10	1.20
3	9	084395	1	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.50	0.60	0.55
3	9	084395	1	Schedule (i)	0.834	0.383	0.011	3	-S9	17.6	14.8	16.2	0.60	0.80	0.70
3	9	084395	1	Schedule (i)	1.11	0.511	0.015	3	-S9	24.9	27.5	26.2	0.80	0.90	0.85
3	9	084395	1	Schedule (i)	1.67	0.767	0.023	3	-S9	34.7	34.9	34.8	1.00	1.10	1.05
3	9	084395	1	Schedule (i)	2.22	1.02	0.030	3	-S9	43.5	40.7	42.1	1.10	1.40	1.25
3	11	084395	2	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.40	0.50
3	11	084395	2	Schedule (i)	0.834	0.383	0.011	3	-S9	7.3	7.7	7.5	0.80	0.50	0.65
3	11	084395	2	Schedule (i)	1.11	0.511	0.015	3	-S9	11.2	14.9	13.1	0.80	0.80	0.80
3	11	084395	2	Schedule (i)	1.67	0.767	0.022	3	-S9	20.5	18.8	19.6	1.00	0.90	0.95
3	11	084395	2	Schedule (i)	2.22	1.02	0.029	3	-S9	27.3	26.9	27.1	1.10	1.00	1.05
3	15	084395	3	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.50	0.55
3	15	084395	3	Schedule (i)	0.834	0.383	0.012	3	-S9	6.4	4.4	5.4	0.70	0.80	0.75
3	15	084395	3	Schedule (i)	1.11	0.511	0.016	3	-S9	8.9	5.3	7.1	0.80	0.90	0.85
3	15	084395	3	Schedule (i)	1.67	0.767	0.024	3	-S9	13.6	13.3	13.4	1.10	1.00	1.05
3	15	084395	3	Schedule (i)	2.22	1.02	0.031	3	-S9	20.9	24.8	22.8	1.10	1.10	1.10
3	2	084454	1	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.50	0.70	0.60
3	2	084454	1	Schedule (i)	0.834	0.741	0.003	3	-S9	17.0	16.8	16.9	0.70	1.00	0.85
3	2	084454	1	Schedule (i)	1.11	0.988	0.004	3	-S9	27.3	26.0	26.7	0.90	1.20	1.05
3	2	084454	1	Schedule (i)	1.67	1.48	0.006	3	-S9	35.1	37.8	36.4	1.10	1.20	1.15
3	2	084454	1	Schedule (i)	2.22	1.98	0.008	3	-S9	47.9	52.6	50.2	1.40	1.50	1.45

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
3	10	084454	2	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.50	0.50	0.50
3	10	084454	2	Schedule (i)	0.834	0.741	0.003	3	-S9	5.1	8.0	6.6	0.70	0.70	0.70
3	10	084454	2	Schedule (i)	1.11	0.988	0.004	3	-S9	11.7	15.5	13.6	0.90	1.00	0.95
3	10	084454	2	Schedule (i)	1.67	1.48	0.006	3	-S9	19.4	20.0	19.7	1.10	1.20	1.15
3	10	084454	2	Schedule (i)	2.22	1.98	0.008	3	-S9	25.5	29.5	27.5	1.30	1.50	1.40
3	12	084454	3	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.50	0.60	0.55
3	12	084454	3	Schedule (i)	0.834	0.741	0.003	3	-S9	4.9	5.7	5.3	0.70	0.80	0.75
3	12	084454	3	Schedule (i)	1.11	0.988	0.004	3	-S9	10.9	8.5	9.7	0.90	0.90	0.90
3	12	084454	3	Schedule (i)	1.67	1.48	0.006	3	-S9	17.8	15.9	16.8	1.20	1.20	1.20
3	12	084454	3	Schedule (i)	2.22	1.98	0.008	3	-S9	23.1	21.1	22.1	1.40	1.30	1.35
3	1	084455	1	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.50	0.55
3	1	084455	1	Schedule (i)	0.834	0.783	0.003	3	-S9	12.8	17.8	15.3	0.80	0.80	0.80
3	1	084455	1	Schedule (i)	1.11	1.04	0.004	3	-S9	26.6	25.7	26.1	1.00	0.90	0.95
3	1	084455	1	Schedule (i)	1.67	1.57	0.007	3	-S9	40.4	37.7	39.1	1.20	1.30	1.25
3	1	084455	1	Schedule (i)	2.22	2.09	0.009	3	-S9	47.3	51.8	49.6	1.50	1.40	1.45
3	3	084455	2	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.70	0.65
3	3	084455	2	Schedule (i)	0.834	0.783	0.004	3	-S9	11.5	10.3	10.9	0.80	1.00	0.90
3	3	084455	2	Schedule (i)	1.11	1.04	0.005	3	-S9	26.7	24.3	25.5	1.00	1.10	1.05
3	3	084455	2	Schedule (i)	1.67	1.57	0.008	3	-S9	32.5	33.5	33.0	1.10	1.30	1.20
3	3	084455	2	Schedule (i)	2.22	2.09	0.011	3	-S9	47.1	47.6	47.3	1.40	1.40	1.40
3	7	084455	3	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.40	0.50	0.45
3	7	084455	3	Schedule (i)	0.833	0.783	0.003	3	-S9	5.3	7.5	6.4	0.60	0.70	0.65
3	7	084455	3	Schedule (i)	1.11	1.04	0.004	3	-S9	13.7	15.5	14.6	1.00	0.90	0.95
3	7	084455	3	Schedule (i)	1.67	1.57	0.006	3	-S9	22.5	23.0	22.8	1.00	1.00	1.00
3	7	084455	3	Schedule (i)	2.22	2.09	0.008	3	-S9	29.8	27.5	28.7	1.10	1.20	1.15
2	7	084456	1	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.50	0.55
2	7	084456	1	Schedule (i)	0.834	0.372	0.011	3	-S9	17.1	19.5	18.3	0.90	0.80	0.85
2	7	084456	1	Schedule (i)	1.11	0.496	0.014	3	-S9	23.8	26.2	25.0	1.10	0.90	1.00
2	7	084456	1	Schedule (i)	1.67	0.744	0.021	3	-S9	33.7	31.3	32.5	1.20	1.00	1.10
2	7	084456	1	Schedule (i)	2.22	0.992	0.028	3	-S9	45.1	43.6	44.3	1.40	1.30	1.35
2	9	084456	2	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.50	0.50	0.50
2	9	084456	2	Schedule (i)	0.833	0.372	0.010	3	-S9	12.8	11.3	12.1	0.70	0.80	0.75
2	9	084456	2	Schedule (i)	1.11	0.496	0.014	3	-S9	20.3	15.5	17.9	1.10	1.00	1.05
2	9	084456	2	Schedule (i)	1.67	0.744	0.021	3	-S9	23.3	22.0	22.6	1.20	1.10	1.15
2	9	084456	2	Schedule (i)	2.22	0.992	0.027	3	-S9	33.7	29.2	31.4	1.30	1.20	1.25

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
2	10	084456	3	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.70	0.65
2	10	084456	3	Schedule (i)	0.834	0.372	0.010	3	-S9	9.3	8.5	8.9	0.70	0.80	0.75
2	10	084456	3	Schedule (i)	1.11	0.496	0.014	3	-S9	14.8	11.8	13.3	0.80	0.90	0.85
2	10	084456	3	Schedule (i)	1.67	0.744	0.020	3	-S9	20.4	18.4	19.4	1.00	1.10	1.05
2	10	084456	3	Schedule (i)	2.22	0.992	0.027	3	-S9	23.6	24.5	24.1	1.20	1.20	1.20
2	3	084457	1	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.50	0.55
2	3	084457	1	Schedule (i)	0.833	0.803	0.005	3	-S9	12.7	11.5	12.1	0.90	0.80	0.85
2	3	084457	1	Schedule (i)	1.11	1.07	0.006	3	-S9	20.1	20.8	20.4	1.10	1.00	1.05
2	3	084457	1	Schedule (i)	1.67	1.61	0.009	3	-S9	33.3	30.1	31.7	1.60	1.20	1.40
2	3	084457	1	Schedule (i)	2.22	2.14	0.013	3	-S9	40.2	36.6	38.4	1.90	1.40	1.65
2	5	084457	2	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.50	0.50	0.50
2	5	084457	2	Schedule (i)	0.833	0.803	0.005	3	-S9	6.7	14.1	10.4	0.70	0.60	0.65
2	5	084457	2	Schedule (i)	1.11	1.07	0.006	3	-S9	20.1	20.6	20.4	0.80	0.80	0.80
2	5	084457	2	Schedule (i)	1.67	1.61	0.009	3	-S9	26.8	27.6	27.2	1.00	1.00	1.00
2	5	084457	2	Schedule (i)	2.22	2.14	0.012	3	-S9	32.3	37.1	34.7	1.40	1.40	1.40
2	6	084457	3	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.40	0.40	0.40
2	6	084457	3	Schedule (i)	0.833	0.803	0.005	3	-S9	9.2	7.8	8.5	0.70	0.60	0.65
2	6	084457	3	Schedule (i)	1.11	1.07	0.006	3	-S9	16.5	16.0	16.3	0.80	0.80	0.80
2	6	084457	3	Schedule (i)	1.67	1.61	0.009	3	-S9	25.7	24.3	25.0	0.90	1.00	0.95
2	6	084457	3	Schedule (i)	2.22	2.14	0.012	3	-S9	34.0	30.6	32.3	1.10	1.10	1.10
2	2	084458	1	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.50	0.50	0.50
2	2	084458	1	Schedule (i)	0.833	0.790	0.002	3	-S9	7.3	6.9	7.1	0.90	0.70	0.80
2	2	084458	1	Schedule (i)	1.11	1.05	0.002	3	-S9	20.7	19.7	20.2	1.10	0.90	1.00
2	2	084458	1	Schedule (i)	1.67	1.58	0.003	3	-S9	38.3	33.5	35.9	1.40	1.20	1.30
2	2	084458	1	Schedule (i)	2.22	2.11	0.005	3	-S9	44.0	45.7	44.9	1.80	1.60	1.70
2	4	084458	2	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.60	0.70	0.65
2	4	084458	2	Schedule (i)	0.834	0.791	0.002	3	-S9	11.6	15.1	13.4	0.80	0.80	0.80
2	4	084458	2	Schedule (i)	1.11	1.05	0.003	3	-S9	25.2	23.9	24.5	1.00	1.10	1.05
2	4	084458	2	Schedule (i)	1.67	1.58	0.004	3	-S9	33.5	34.6	34.1	1.10	1.30	1.20
2	4	084458	2	Schedule (i)	2.22	2.11	0.005	3	-S9	42.6	47.2	44.9	1.50	1.50	1.50
2	8	084458	3	Schedule (i)	0	0	0.000	3	-S9	0	0	0	0.50	0.40	0.45
2	8	084458	3	Schedule (i)	0.834	0.791	0.002	3	-S9	9.4	5.7	7.6	0.70	0.70	0.70
2	8	084458	3	Schedule (i)	1.11	1.05	0.002	3	-S9	11.7	10.0	10.9	1.00	0.90	0.95
2	8	084458	3	Schedule (i)	1.67	1.58	0.004	3	-S9	18.3	17.7	18.0	1.20	1.10	1.15
2	8	084458	3	Schedule (i)	2.22	2.11	0.005	3	-S9	25.4	25.4	25.4	1.40	1.30	1.35

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
3	4	084394	1	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.70	0.65
3	4	084394	1	Schedule (ii)	0.834	0.569	0.010	3	+S9	4.9	3.9	4.4	0.70	0.90	0.80
3	4	084394	1	Schedule (ii)	1.11	0.759	0.014	3	+S9	7.6	5.6	6.6	0.90	1.00	0.95
3	4	084394	1	Schedule (ii)	1.67	1.14	0.021	3	+S9	16.3	15.6	16.0	1.00	1.00	1.00
3	4	084394	1	Schedule (ii)	2.22	1.52	0.028	3	+S9	26.6	22.3	24.5	1.10	1.00	1.05
3	6	084394	2	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.50	0.60	0.55
3	6	084394	2	Schedule (ii)	0.833	0.569	0.011	3	+S9	5.7	8.4	7.0	0.60	0.70	0.65
3	6	084394	2	Schedule (ii)	1.11	0.759	0.014	3	+S9	13.1	14.5	13.8	0.80	0.80	0.80
3	6	084394	2	Schedule (ii)	1.67	1.14	0.022	3	+S9	20.6	20.7	20.6	0.90	0.90	0.90
3	6	084394	2	Schedule (ii)	2.22	1.52	0.029	3	+S9	28.6	31.3	29.9	1.10	1.00	1.05
3	13	084394	3	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.60	0.60
3	13	084394	3	Schedule (ii)	0.834	0.569	0.011	3	+S9	11.2	6.4	8.8	0.70	0.70	0.70
3	13	084394	3	Schedule (ii)	1.11	0.759	0.015	3	+S9	21.3	16.2	18.8	0.90	0.90	0.90
3	13	084394	3	Schedule (ii)	1.67	1.14	0.022	3	+S9	25.3	23.7	24.5	1.00	0.90	0.95
3	13	084394	3	Schedule (ii)	2.22	1.52	0.029	3	+S9	33.7	32.9	33.3	1.10	1.20	1.15
3	9	084395	1	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.40	0.70	0.55
3	9	084395	1	Schedule (ii)	0.834	0.383	0.011	3	+S9	8.0	9.4	8.7	0.60	0.80	0.70
3	9	084395	1	Schedule (ii)	1.11	0.511	0.015	3	+S9	11.4	15.5	13.4	0.80	0.80	0.80
3	9	084395	1	Schedule (ii)	1.67	0.767	0.023	3	+S9	21.0	22.1	21.6	0.90	1.00	0.95
3	9	084395	1	Schedule (ii)	2.22	1.02	0.030	3	+S9	26.1	26.5	26.3	1.00	1.00	1.00
3	11	084395	2	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.70	0.65
3	11	084395	2	Schedule (ii)	0.834	0.383	0.011	3	+S9	5.9	2.7	4.3	0.70	0.80	0.75
3	11	084395	2	Schedule (ii)	1.11	0.511	0.015	3	+S9	9.1	8.6	8.9	0.90	0.90	0.90
3	11	084395	2	Schedule (ii)	1.67	0.767	0.022	3	+S9	19.3	16.2	17.7	0.90	1.00	0.95
3	11	084395	2	Schedule (ii)	2.22	1.02	0.029	3	+S9	21.4	22.7	22.0	1.00	1.00	1.00
3	15	084395	3	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.50	0.70	0.60
3	15	084395	3	Schedule (ii)	0.834	0.383	0.012	3	+S9	11.1	2.9	7.0	0.60	0.80	0.70
3	15	084395	3	Schedule (ii)	1.11	0.511	0.016	3	+S9	14.4	15.5	15.0	0.80	0.90	0.85
3	15	084395	3	Schedule (ii)	1.67	0.767	0.024	3	+S9	25.6	20.1	22.8	0.90	1.00	0.95
3	15	084395	3	Schedule (ii)	2.22	1.02	0.031	3	+S9	31.1	30.5	30.8	1.00	1.10	1.05
3	2	084454	1	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.50	0.70	0.60
3	2	084454	1	Schedule (ii)	0.834	0.741	0.003	3	+S9	6.7	7.4	7.0	0.70	0.80	0.75
3	2	084454	1	Schedule (ii)	1.11	0.988	0.004	3	+S9	18.9	19.9	19.4	0.90	0.90	0.90
3	2	084454	1	Schedule (ii)	1.67	1.48	0.006	3	+S9	28.3	25.6	27.0	1.00	1.10	1.05
3	2	084454	1	Schedule (ii)	2.22	1.98	0.008	3	+S9	33.9	35.8	34.8	1.20	1.20	1.20

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
3	10	084454	2	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.50	0.55
3	10	084454	2	Schedule (ii)	0.834	0.741	0.003	3	+S9	2.1	2.7	2.4	0.60	0.60	0.60
3	10	084454	2	Schedule (ii)	1.11	0.988	0.004	3	+S9	7.4	5.3	6.4	0.70	0.80	0.75
3	10	084454	2	Schedule (ii)	1.67	1.48	0.006	3	+S9	16.9	15.4	16.2	0.90	1.00	0.95
3	10	084454	2	Schedule (ii)	2.22	1.98	0.008	3	+S9	19.6	20.2	19.9	1.10	1.20	1.15
3	12	084454	3	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.70	0.50	0.60
3	12	084454	3	Schedule (ii)	0.834	0.741	0.003	3	+S9	4.7	4.0	4.4	0.80	0.70	0.75
3	12	084454	3	Schedule (ii)	1.11	0.988	0.004	3	+S9	7.1	8.1	7.6	1.00	0.90	0.95
3	12	084454	3	Schedule (ii)	1.67	1.48	0.006	3	+S9	20.6	20.8	20.7	1.10	1.00	1.05
3	12	084454	3	Schedule (ii)	2.22	1.98	0.008	3	+S9	26.5	29.5	28.0	1.20	1.30	1.25
3	1	084455	1	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.70	0.65
3	1	084455	1	Schedule (ii)	0.834	0.783	0.003	3	+S9	12.4	11.6	12.0	0.80	0.80	0.80
3	1	084455	1	Schedule (ii)	1.11	1.04	0.004	3	+S9	23.7	19.7	21.7	0.90	0.90	0.90
3	1	084455	1	Schedule (ii)	1.67	1.57	0.007	3	+S9	29.9	26.0	28.0	1.00	1.00	1.00
3	1	084455	1	Schedule (ii)	2.22	2.09	0.009	3	+S9	38.4	35.8	37.1	1.10	1.10	1.10
3	3	084455	2	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.50	0.55
3	3	084455	2	Schedule (ii)	0.834	0.783	0.004	3	+S9	6.8	12.0	9.4	0.80	0.70	0.75
3	3	084455	2	Schedule (ii)	1.11	1.04	0.005	3	+S9	16.9	20.2	18.6	0.80	0.80	0.80
3	3	084455	2	Schedule (ii)	1.67	1.57	0.008	3	+S9	23.2	24.0	23.6	0.90	0.90	0.90
3	3	084455	2	Schedule (ii)	2.22	2.09	0.011	3	+S9	29.4	31.1	30.3	1.20	1.10	1.15
3	7	084455	3	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.50	0.50	0.50
3	7	084455	3	Schedule (ii)	0.833	0.783	0.003	3	+S9	11.9	12.7	12.3	0.70	0.70	0.70
3	7	084455	3	Schedule (ii)	1.11	1.04	0.004	3	+S9	17.3	21.4	19.3	0.90	0.90	0.90
3	7	084455	3	Schedule (ii)	1.67	1.57	0.006	3	+S9	25.6	30.1	27.8	1.00	1.00	1.00
3	7	084455	3	Schedule (ii)	2.22	2.09	0.008	3	+S9	33.9	34.1	34.0	1.10	1.10	1.10
2	7	084456	1	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.70	0.60	0.65
2	7	084456	1	Schedule (ii)	0.834	0.372	0.011	3	+S9	10.6	9.3	10.0	0.80	0.70	0.75
2	7	084456	1	Schedule (ii)	1.11	0.496	0.014	3	+S9	18.6	16.9	17.8	0.90	0.80	0.85
2	7	084456	1	Schedule (ii)	1.67	0.744	0.021	3	+S9	19.7	20.2	19.9	1.00	1.00	1.00
2	7	084456	1	Schedule (ii)	2.22	0.992	0.028	3	+S9	25.0	21.9	23.4	1.10	1.10	1.10
2	9	084456	2	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.70	0.65
2	9	084456	2	Schedule (ii)	0.833	0.372	0.010	3	+S9	7.4	4.0	5.7	0.70	0.70	0.70
2	9	084456	2	Schedule (ii)	1.11	0.496	0.014	3	+S9	10.9	11.6	11.3	0.90	0.80	0.85
2	9	084456	2	Schedule (ii)	1.67	0.744	0.021	3	+S9	20.3	16.7	18.5	1.00	0.80	0.90
2	9	084456	2	Schedule (ii)	2.22	0.992	0.027	3	+S9	25.2	22.7	24.0	1.10	1.00	1.05

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

Set Number	Run Number	Sample ID	Replicate Number	Treatment Schedule	ST Dose (mg/mL)	ST-H ₂ O Dose (mg/mL)	Nicotine Dose (mg/mL)	Treatment Time (h)	Metabolic Activation	% Cytotoxicity			% Micronuclei		
										Flask 1	Flask 2	Average	Flask 1	Flask 2	Average
2	10	084456	3	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.50	0.60	0.55
2	10	084456	3	Schedule (ii)	0.834	0.372	0.010	3	+S9	9.2	13.7	11.4	0.70	0.70	0.70
2	10	084456	3	Schedule (ii)	1.11	0.496	0.014	3	+S9	15.3	20.8	18.1	0.80	0.90	0.85
2	10	084456	3	Schedule (ii)	1.67	0.744	0.020	3	+S9	23.9	23.2	23.6	0.90	1.00	0.95
2	10	084456	3	Schedule (ii)	2.22	0.992	0.027	3	+S9	31.9	35.7	33.8	1.00	1.10	1.05
2	3	084457	1	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.70	0.70	0.70
2	3	084457	1	Schedule (ii)	0.833	0.803	0.005	3	+S9	4.4	3.9	4.2	0.80	0.80	0.80
2	3	084457	1	Schedule (ii)	1.11	1.07	0.006	3	+S9	11.7	11.8	11.7	0.90	0.90	0.90
2	3	084457	1	Schedule (ii)	1.67	1.61	0.009	3	+S9	14.4	15.2	14.8	1.10	1.00	1.05
2	3	084457	1	Schedule (ii)	2.22	2.14	0.013	3	+S9	20.0	18.0	19.0	1.20	1.20	1.20
2	5	084457	2	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.70	0.60	0.65
2	5	084457	2	Schedule (ii)	0.833	0.803	0.005	3	+S9	1.6	6.1	3.8	0.80	0.80	0.80
2	5	084457	2	Schedule (ii)	1.11	1.07	0.006	3	+S9	10.5	14.8	12.6	1.00	0.90	0.95
2	5	084457	2	Schedule (ii)	1.67	1.61	0.009	3	+S9	15.2	17.9	16.5	1.10	1.10	1.10
2	5	084457	2	Schedule (ii)	2.22	2.14	0.012	3	+S9	17.8	21.9	19.9	1.20	1.30	1.25
2	6	084457	3	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.60	0.60
2	6	084457	3	Schedule (ii)	0.833	0.803	0.005	3	+S9	4.0	11.6	7.8	0.80	0.70	0.75
2	6	084457	3	Schedule (ii)	1.11	1.07	0.006	3	+S9	16.7	15.5	16.1	0.90	0.90	0.90
2	6	084457	3	Schedule (ii)	1.67	1.61	0.009	3	+S9	23.6	24.9	24.2	1.10	1.00	1.05
2	6	084457	3	Schedule (ii)	2.22	2.14	0.012	3	+S9	29.9	35.4	32.6	1.30	1.20	1.25
2	2	084458	1	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.70	0.60	0.65
2	2	084458	1	Schedule (ii)	0.833	0.790	0.002	3	+S9	4.4	3.9	4.1	0.90	0.80	0.85
2	2	084458	1	Schedule (ii)	1.11	1.05	0.002	3	+S9	7.7	6.1	6.9	1.20	1.10	1.15
2	2	084458	1	Schedule (ii)	1.67	1.58	0.003	3	+S9	10.4	11.1	10.7	1.40	1.30	1.35
2	2	084458	1	Schedule (ii)	2.22	2.11	0.005	3	+S9	16.9	13.9	15.4	1.60	1.50	1.55
2	4	084458	2	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.60	0.60
2	4	084458	2	Schedule (ii)	0.834	0.791	0.002	3	+S9	4.9	5.9	5.4	0.80	0.80	0.80
2	4	084458	2	Schedule (ii)	1.11	1.05	0.003	3	+S9	8.7	9.0	8.9	1.00	0.90	0.95
2	4	084458	2	Schedule (ii)	1.67	1.58	0.004	3	+S9	9.2	12.2	10.7	1.10	1.10	1.10
2	4	084458	2	Schedule (ii)	2.22	2.11	0.005	3	+S9	21.2	24.5	22.8	1.30	1.40	1.35
2	8	084458	3	Schedule (ii)	0	0	0.000	3	+S9	0	0	0	0.60	0.60	0.60
2	8	084458	3	Schedule (ii)	0.834	0.791	0.002	3	+S9	9.3	10.6	9.9	0.80	0.80	0.80
2	8	084458	3	Schedule (ii)	1.11	1.05	0.002	3	+S9	18.6	22.4	20.5	0.90	0.90	0.90
2	8	084458	3	Schedule (ii)	1.67	1.58	0.004	3	+S9	31.7	28.0	29.8	1.10	1.10	1.10
2	8	084458	3	Schedule (ii)	2.22	2.11	0.005	3	+S9	36.0	32.3	34.2	1.30	1.40	1.35

LABSTAT INTERNATIONAL ULC

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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)		Incr > 9
							Flask 1	Flask 2	Flask 1	Flask 2	Flask 1
084394	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	2.00	7.44	7.68	≥ 90%
084394	2	04-Nov-08	Schedule (i)	-S9	3	27	1.92	2.08	7.44	7.20	≥ 90%
084394	3	05-Nov-08	Schedule (i)	-S9	3	27	2.12	2.04	9.84	10.28	≥ 90%
084395	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	1.96	7.72	7.56	≥ 90%
084395	2	04-Nov-08	Schedule (i)	-S9	3	27	1.96	1.96	8.20	8.32	≥ 90%
084395	3	05-Nov-08	Schedule (i)	-S9	3	27	2.04	2.04	9.40	9.04	≥ 90%
084454	1	28-Nov-08	Schedule (i)	-S9	3	27	1.96	1.96	7.76	7.84	≥ 90%
084454	2	04-Nov-08	Schedule (i)	-S9	3	27	2.08	2.04	7.84	8.00	≥ 90%
084454	3	05-Nov-08	Schedule (i)	-S9	3	27	2.08	2.04	9.88	9.84	≥ 90%
084455	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	1.96	7.52	7.64	≥ 90%
084455	2	04-Nov-08	Schedule (i)	-S9	3	27	2.04	1.96	7.64	7.40	≥ 90%
084455	3	05-Nov-08	Schedule (i)	-S9	3	27	2.08	2.12	10.48	10.60	≥ 90%
084456	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	1.96	7.72	7.80	≥ 90%
084456	2	04-Nov-08	Schedule (i)	-S9	3	27	1.96	2.08	6.88	6.72	≥ 90%
084456	3	05-Nov-08	Schedule (i)	-S9	3	27	2.12	2.04	8.64	8.48	≥ 90%
084457	1	28-Nov-08	Schedule (i)	-S9	3	27	1.96	2.00	7.56	7.32	≥ 90%
084457	2	04-Nov-08	Schedule (i)	-S9	3	27	2.04	1.96	6.56	6.80	≥ 90%
084457	3	05-Nov-08	Schedule (i)	-S9	3	27	2.00	2.12	8.24	8.24	≥ 90%
084458	1	28-Nov-08	Schedule (i)	-S9	3	27	1.92	1.96	7.72	7.52	≥ 90%
084458	2	04-Nov-08	Schedule (i)	-S9	3	27	1.96	2.08	6.20	6.36	≥ 90%
084458	3	05-Nov-08	Schedule (i)	-S9	3	27	2.08	2.00	8.52	8.36	≥ 90%

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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)		Incr > 9
							Flask 1	Flask 2	Flask 1	Flask 2	Flask 1
084394	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.04	7.36	7.16	≥ 90%
084394	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.00	7.00	7.16	≥ 90%
084394	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.00	7.12	6.92	≥ 90%
084395	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.12	2.12	7.04	7.24	≥ 90%
084395	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.04	1.92	7.48	7.40	≥ 90%
084395	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.00	1.96	7.20	6.96	≥ 90%
084454	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.00	7.20	7.04	≥ 90%
084454	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.00	2.04	7.56	7.52	≥ 90%
084454	3	17-Dec-08	Schedule (ii)	+S9	3	27	1.96	1.96	6.80	6.92	≥ 90%
084455	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.04	7.08	6.92	≥ 90%
084455	2	12-Dec-08	Schedule (ii)	+S9	3	27	1.96	2.00	7.08	7.32	≥ 90%
084455	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.04	1.96	6.72	6.92	≥ 90%
084456	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.12	7.52	7.32	≥ 90%
084456	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.12	8.08	7.92	≥ 90%
084456	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.00	2.04	6.52	6.72	≥ 90%
084457	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.08	7.20	7.12	≥ 90%
084457	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.04	2.08	7.64	7.84	≥ 90%
084457	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.00	1.96	6.96	7.24	≥ 90%
084458	1	11-Dec-08	Schedule (ii)	+S9	3	27	2.08	2.00	7.32	7.20	≥ 90%
084458	2	12-Dec-08	Schedule (ii)	+S9	3	27	2.12	2.16	7.36	7.52	≥ 90%
084458	3	17-Dec-08	Schedule (ii)	+S9	3	27	2.00	2.00	6.44	6.44	≥ 90%

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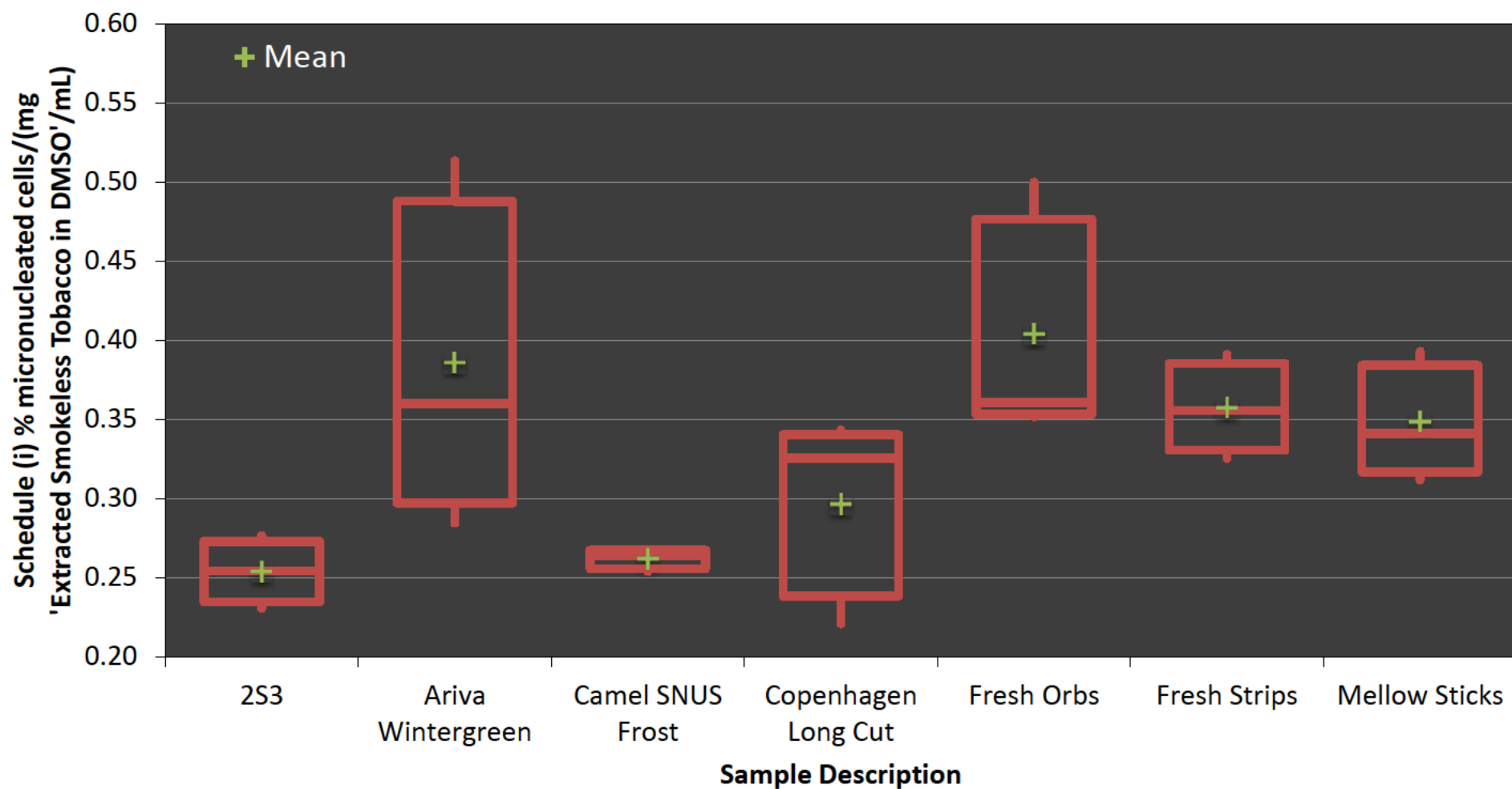
Test Describe - Comparative

Performed by

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

Date

2 November 2009



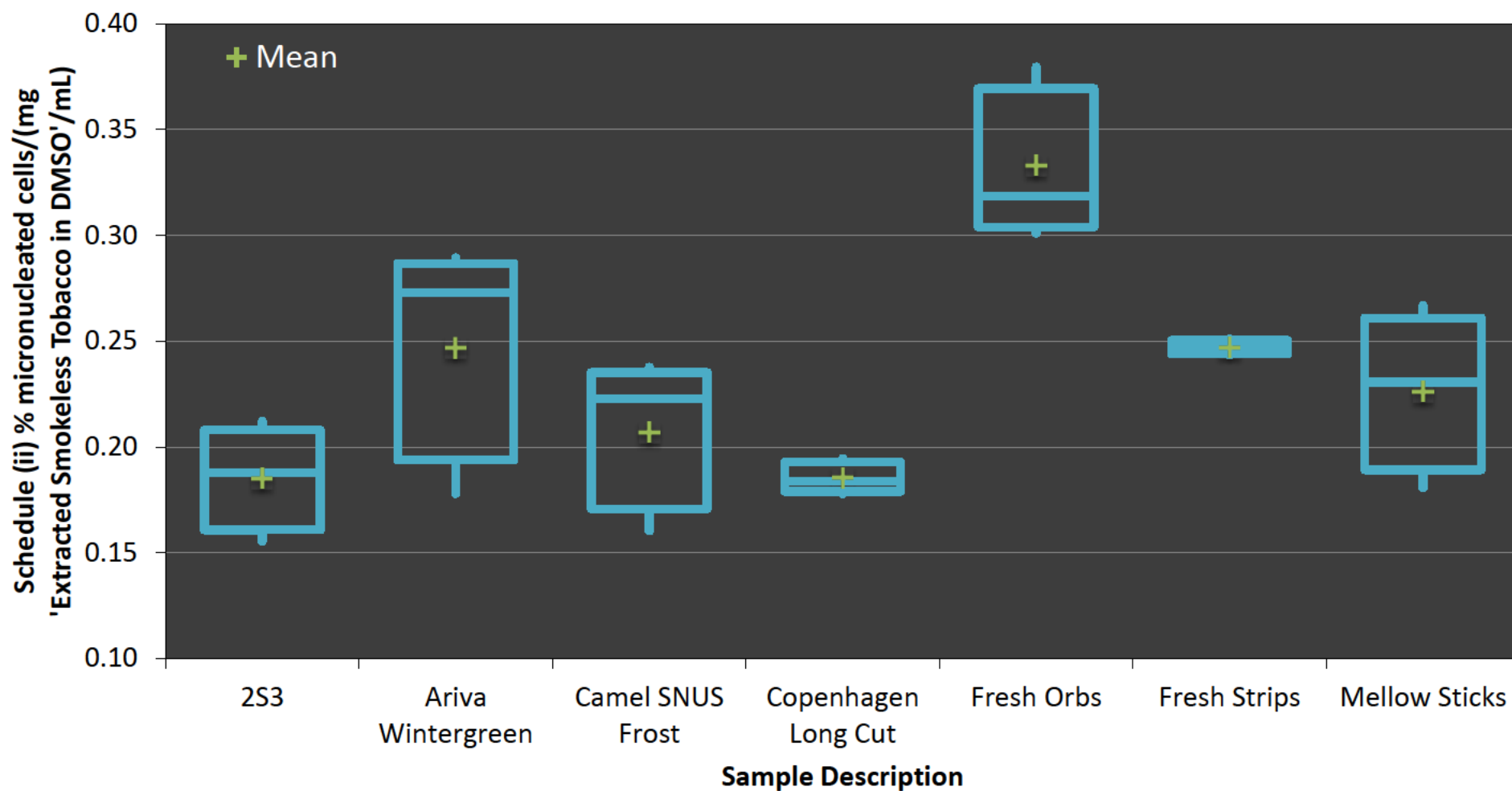
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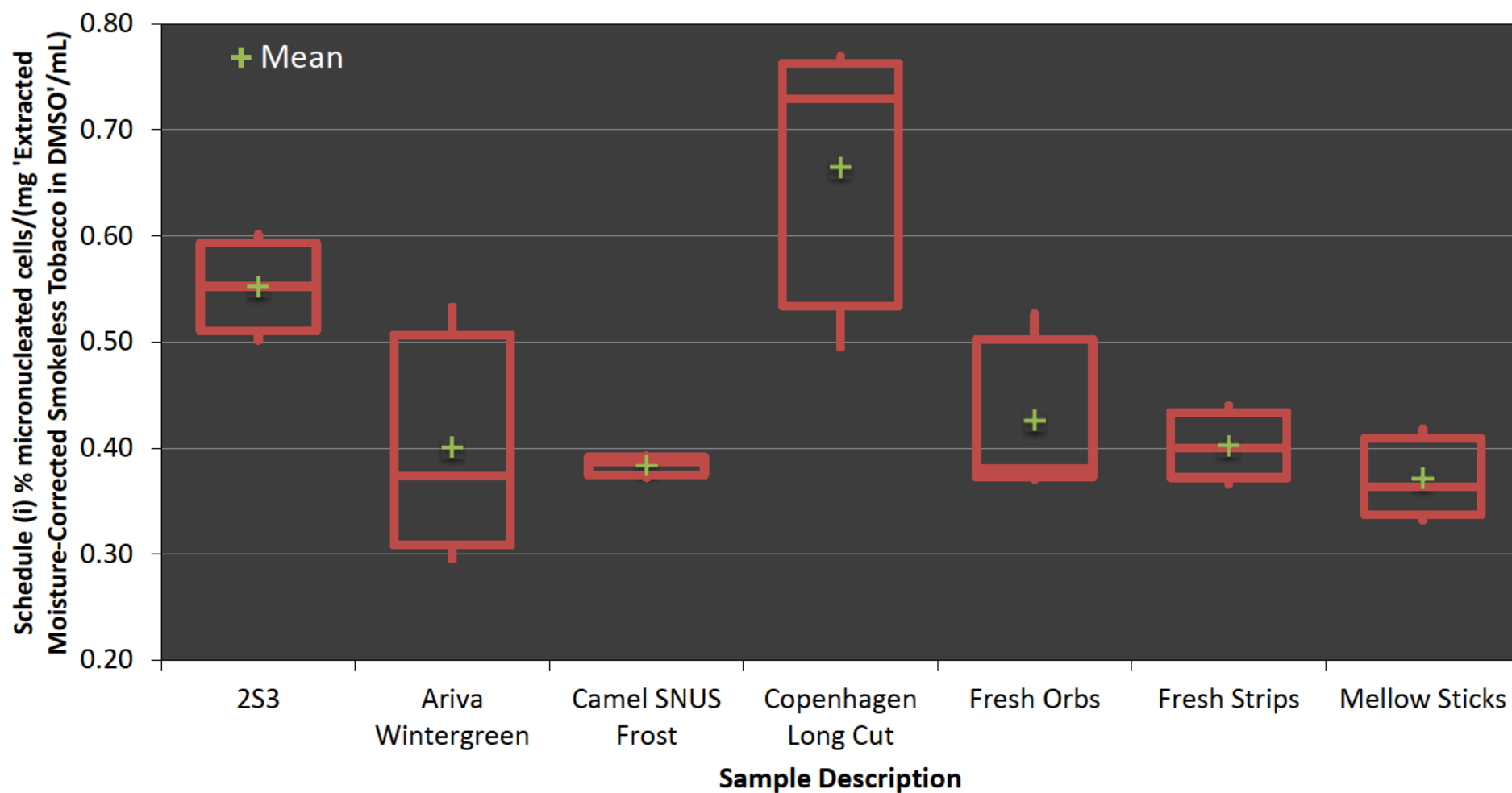
Performed by

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

Date

2 November 2009



Test **Describe - Comparative**Performed by **Schedule (i) % micronucleated cells/(mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL) by Sample Description**
Wendy WagstaffDate **2 November 2009**

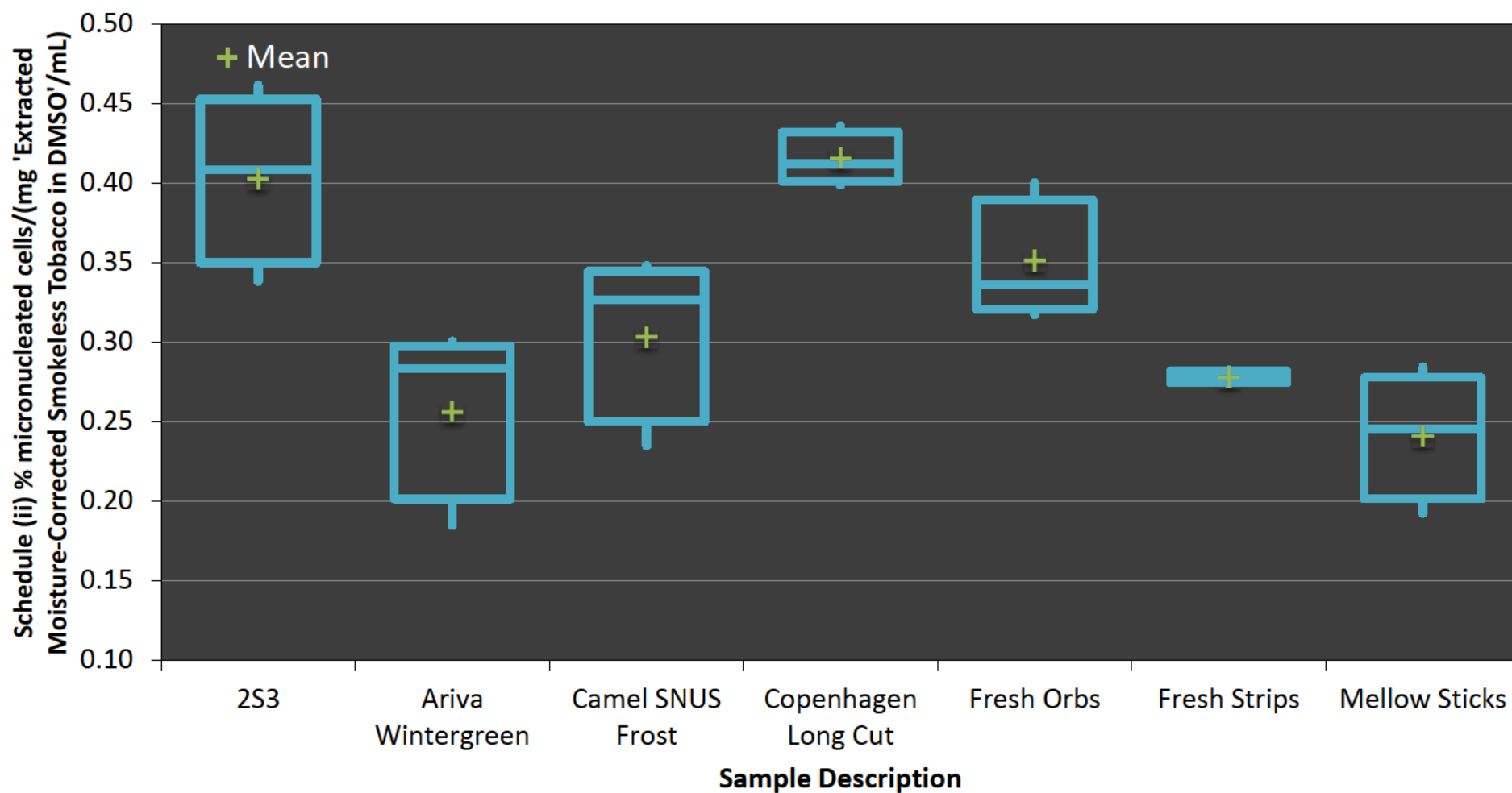
Test Describe - Comparative

Performed by

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

Date

2 November 2009



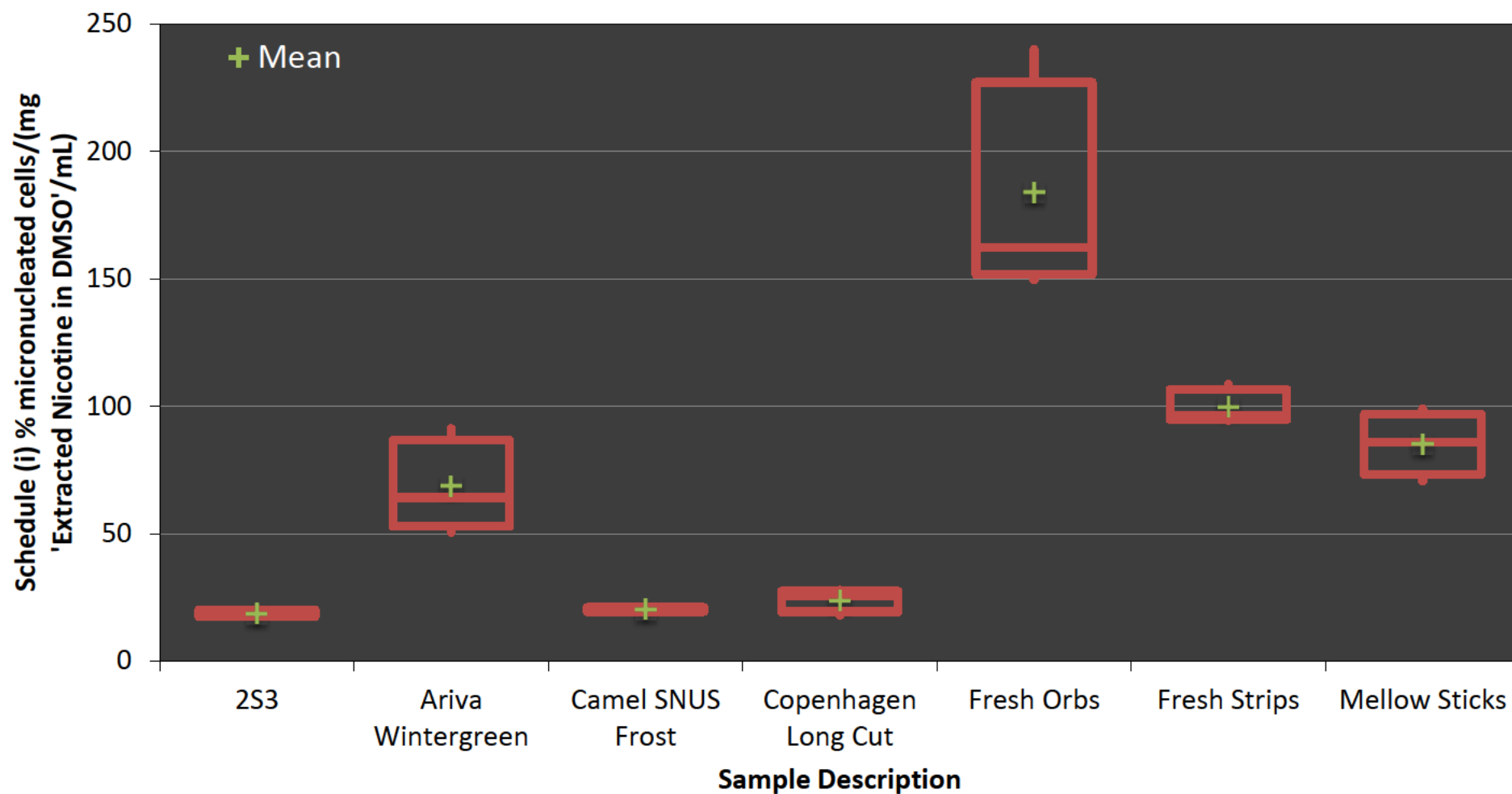
Test Describe - Comparative

Performed by

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

Date

2 November 2009



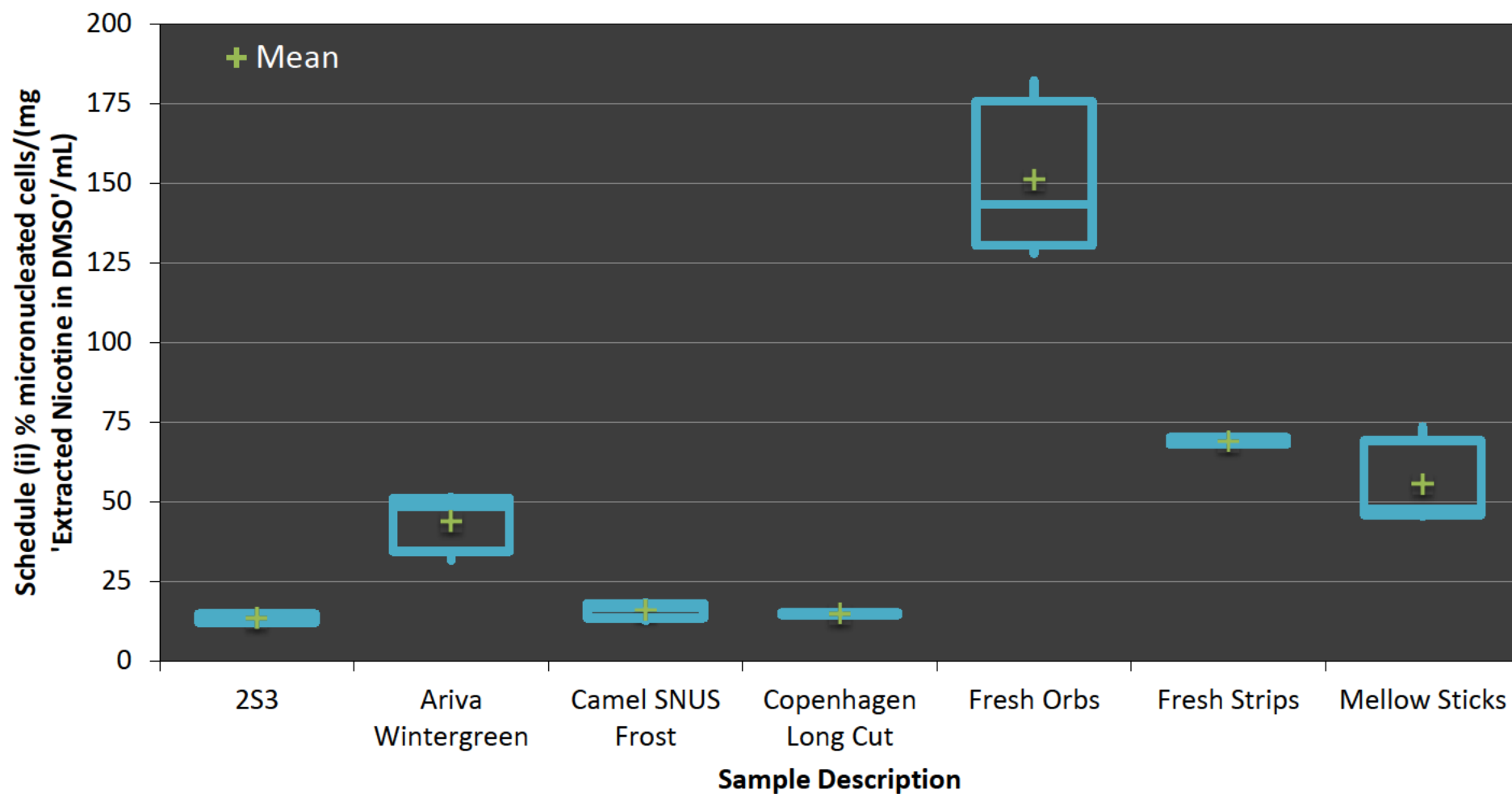
Test Describe - Comparative

Performed by

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

Date

2 November 2009



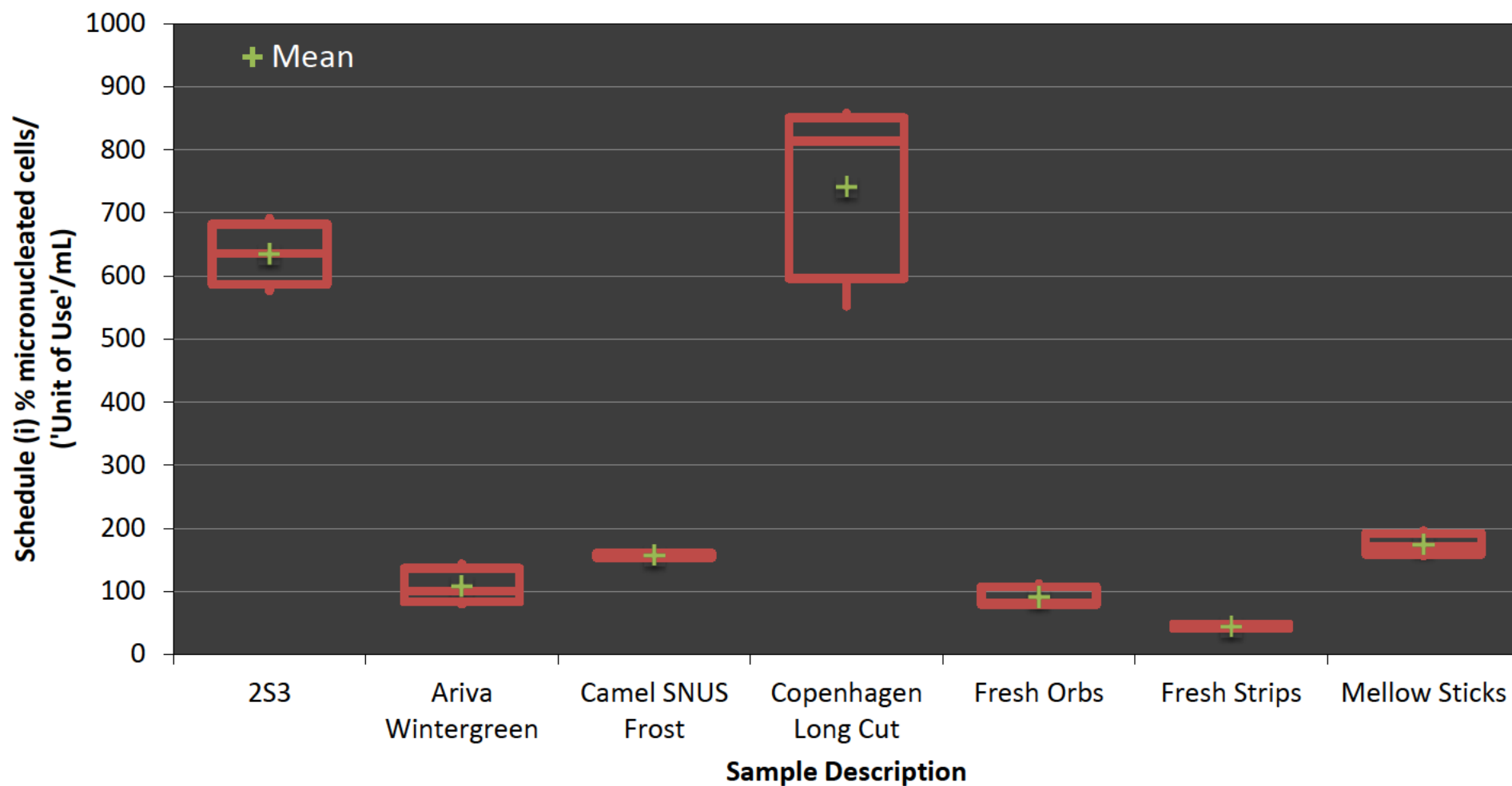
Test **Describe - Comparative**

Performed by

Schedule (i) % micronucleated cells/('Unit of Use'/mL) by Sample Description
Wendy Wagstaff

Date

8 December 2010



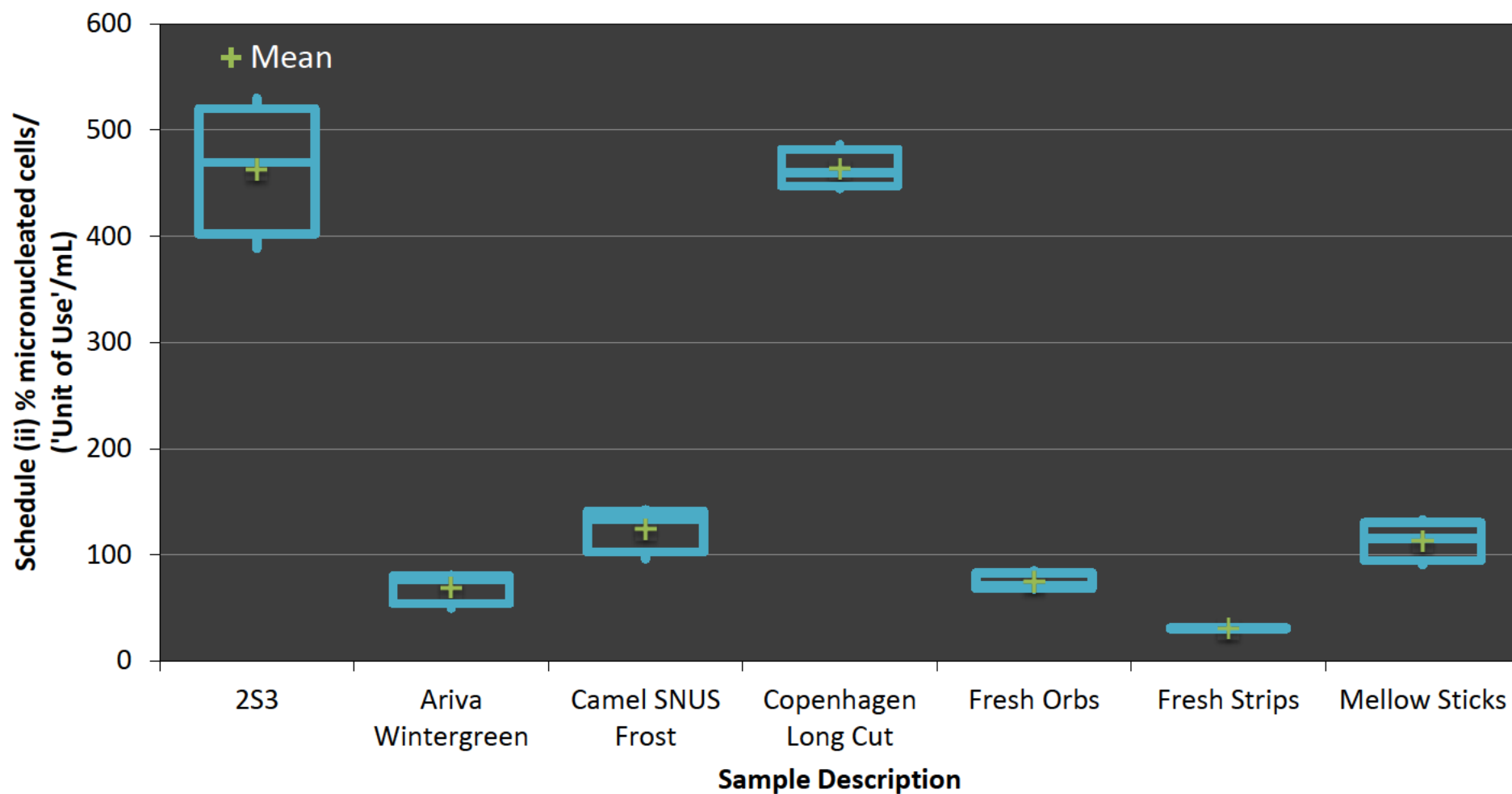
Test **Describe - Comparative**

Performed by

Schedule (ii) % micronucleated cells/('Unit of Use'/mL) by Sample Description
Wendy Wagstaff

Date

8 December 2010



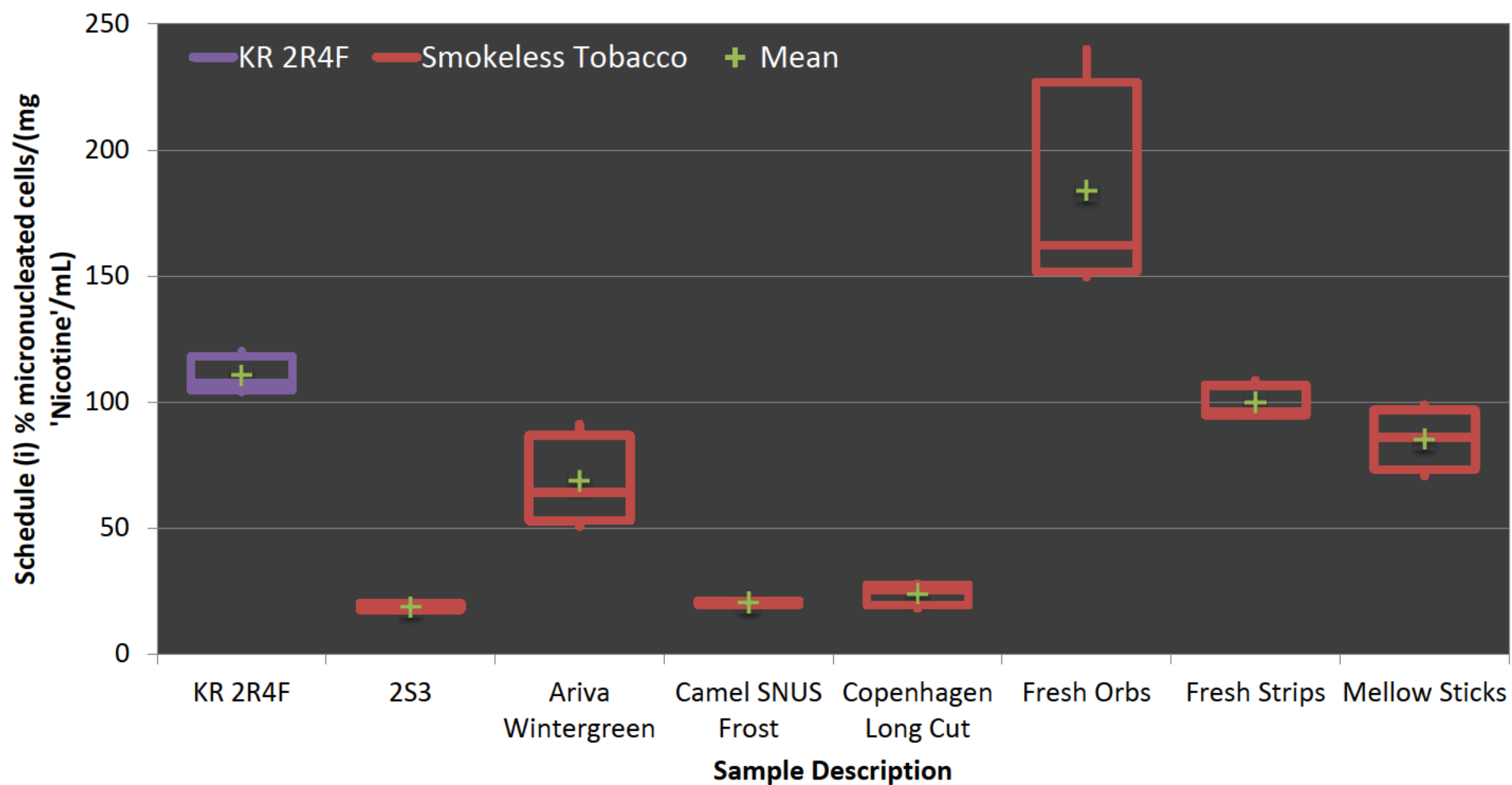
Test Describe - Comparative

Performed by

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

Date

16 December 2009



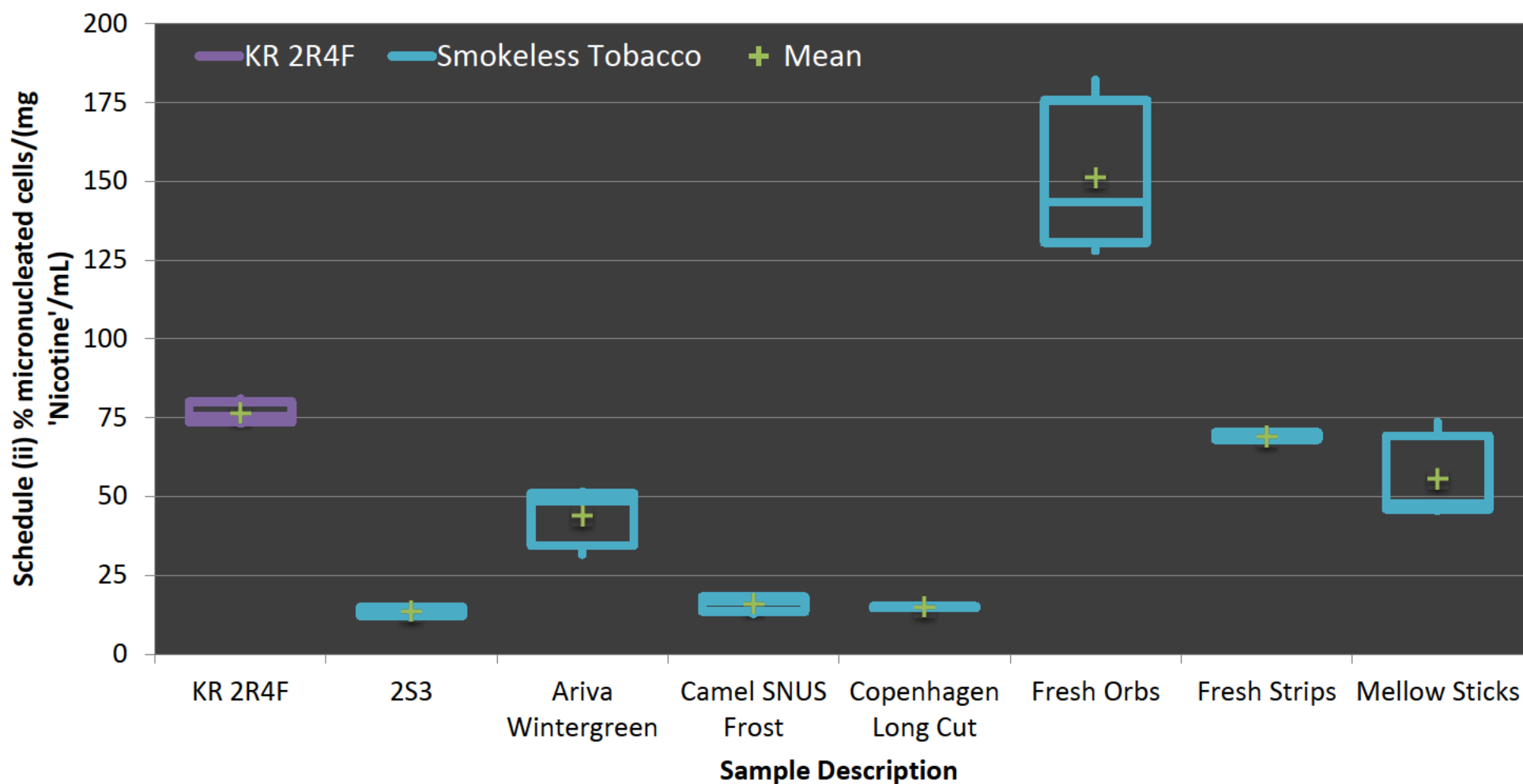
Test Describe - Comparative

Performed by

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

Date

16 December 2009



Schedule (ii) Nicotine (tpm+wt)

Revision: 0

M100_mn_Box and Whisker.xls

Labstat International ULC

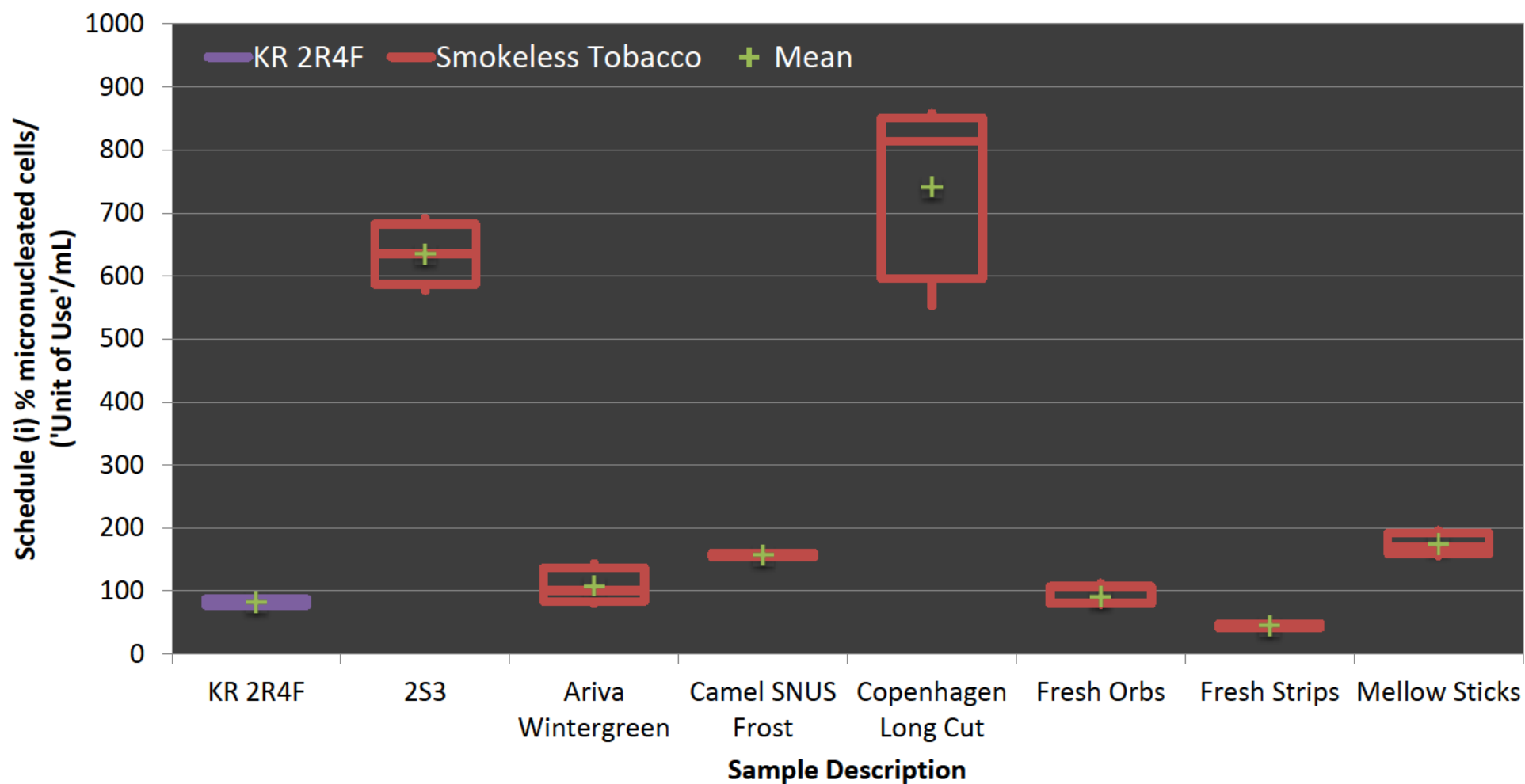
Test Describe - Comparative

Performed by

Schedule (i) % micronucleated cells/(cigarette/mL) (KR 2R4F) and % micronucleated cells/('Unit of Use'/mL) by Sample Description

Date

8 December 2010



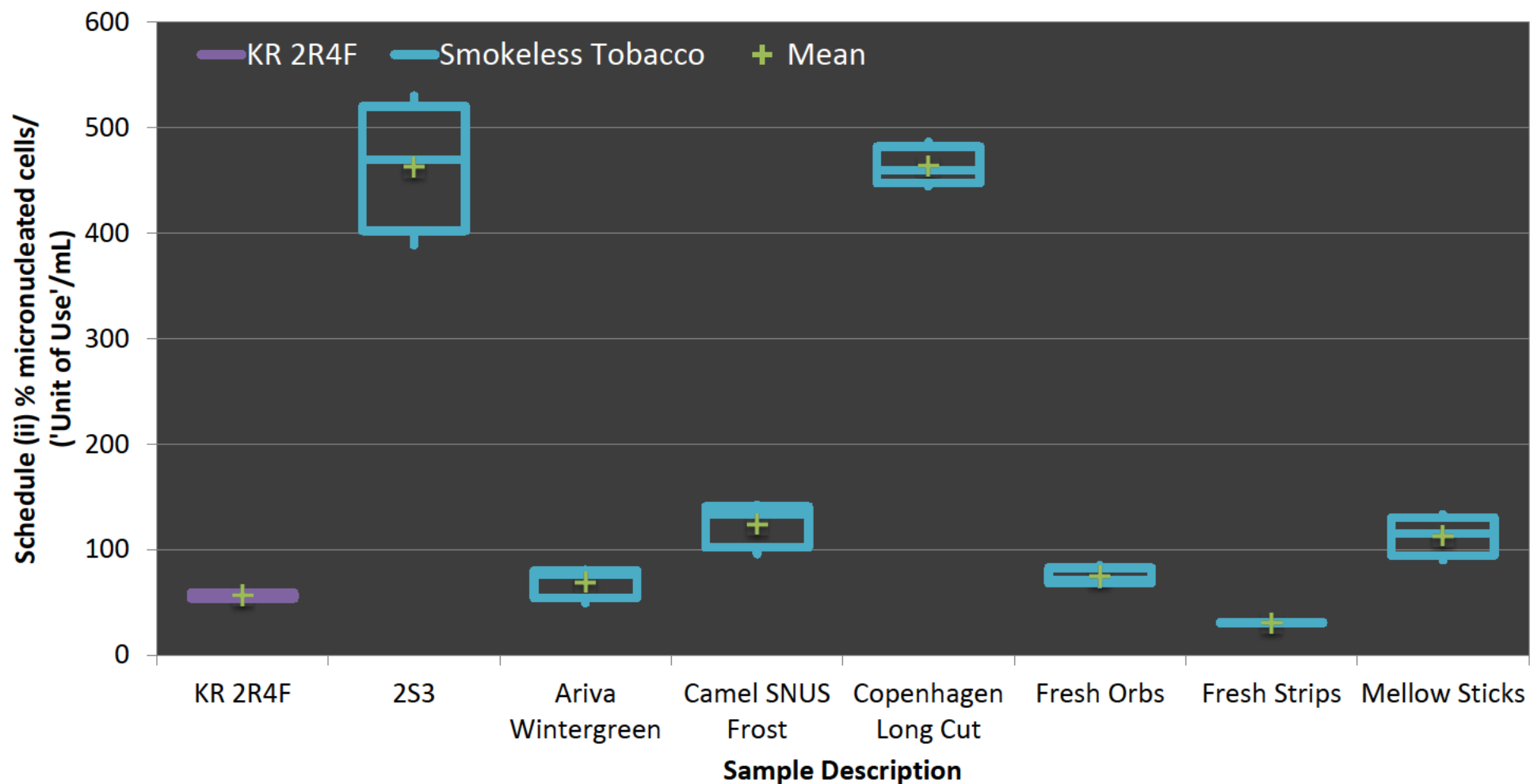
Test Describe - Comparative

Performed by

Schedule (ii) % micronucleated cells/(cigarette/mL) (KR 2R4F) and % micronucleated cells/('Unit of Use'/mL) by Sample Description

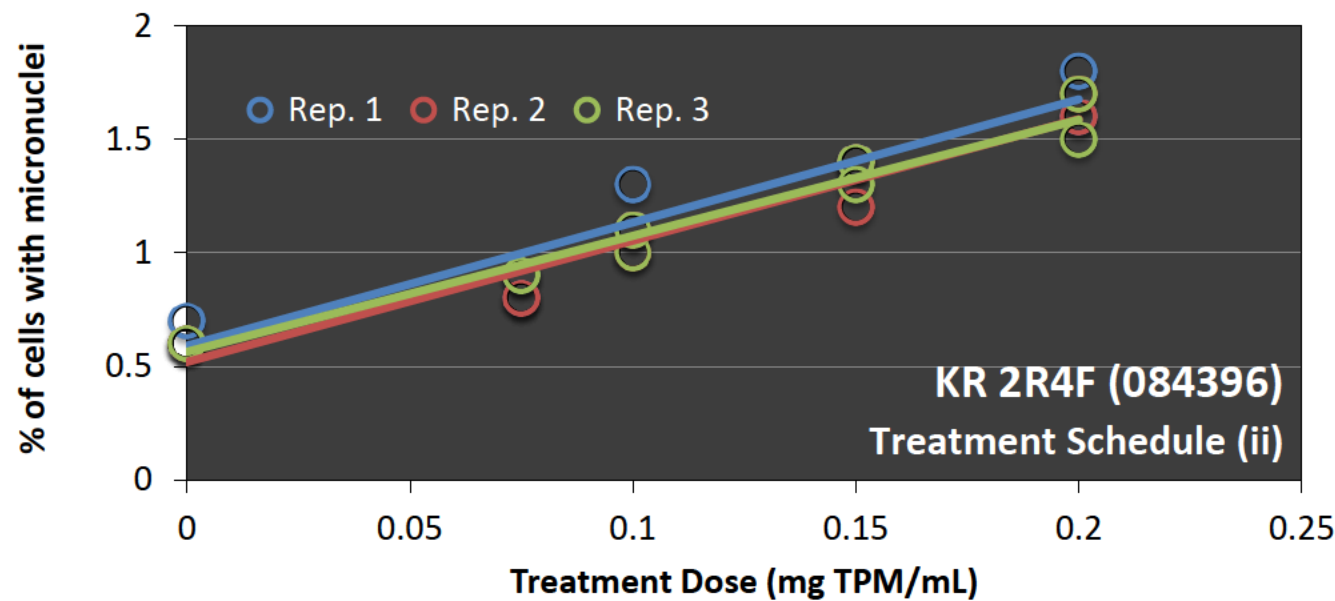
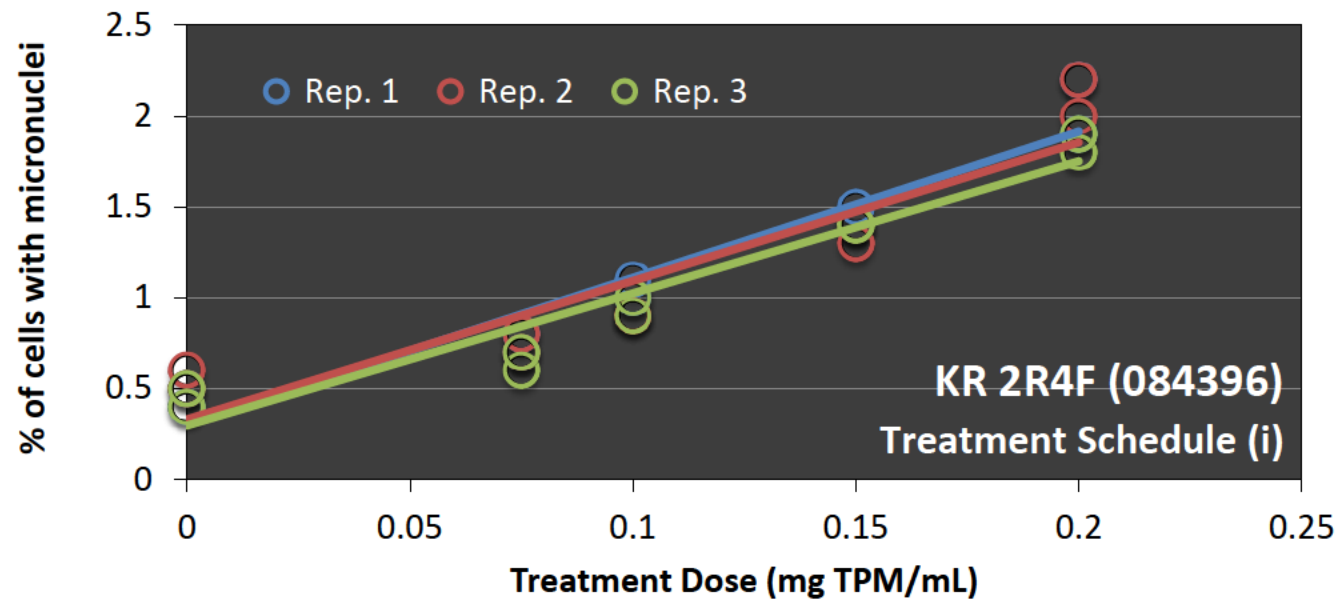
Date

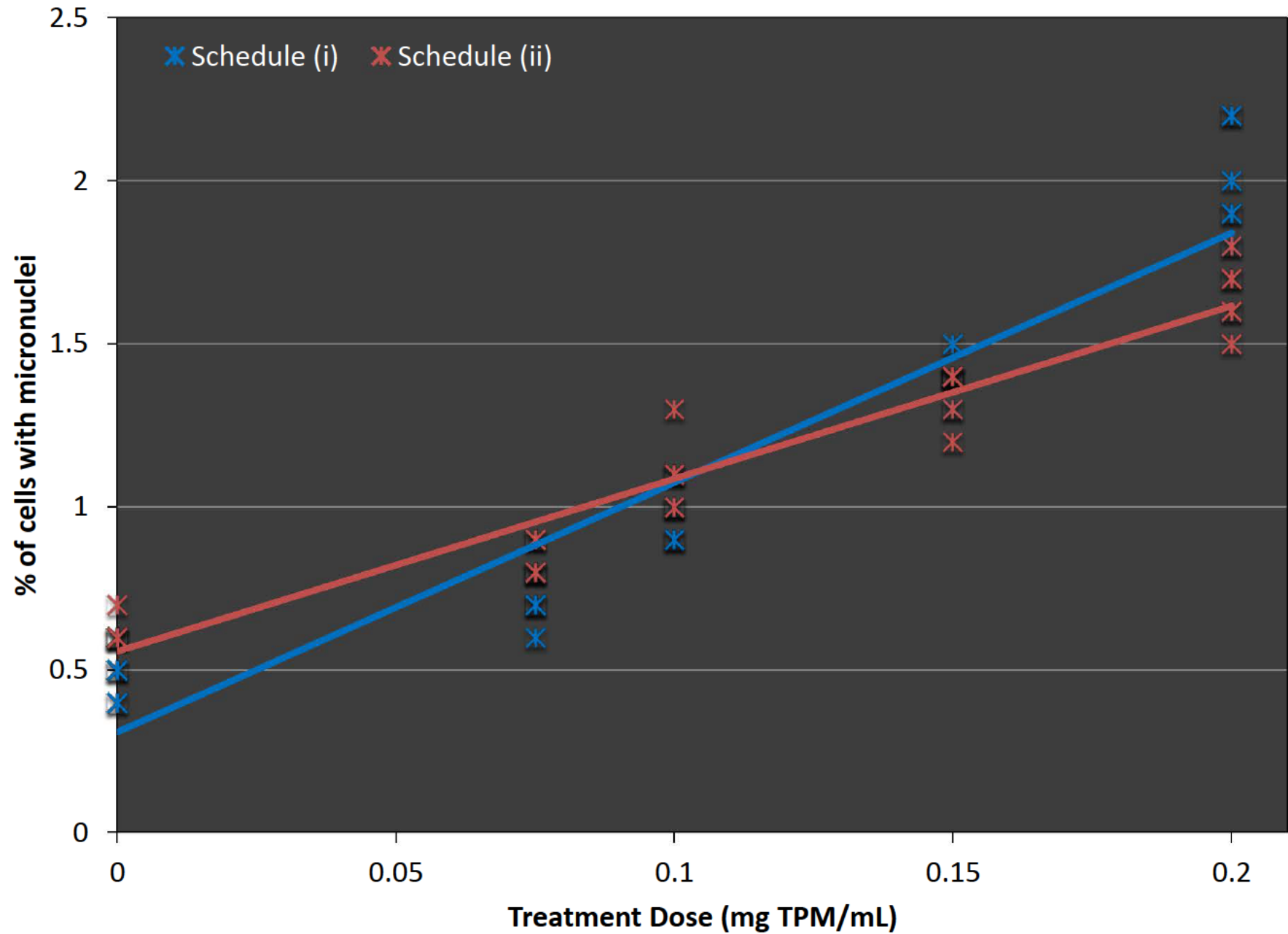
8 December 2010



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

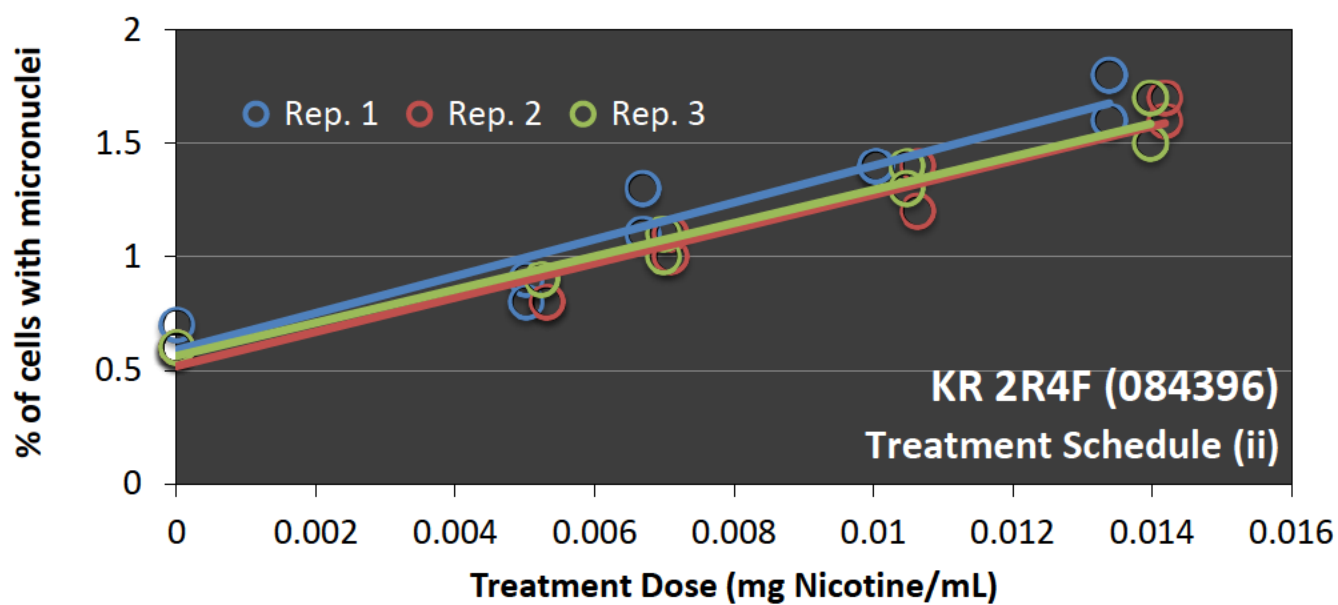
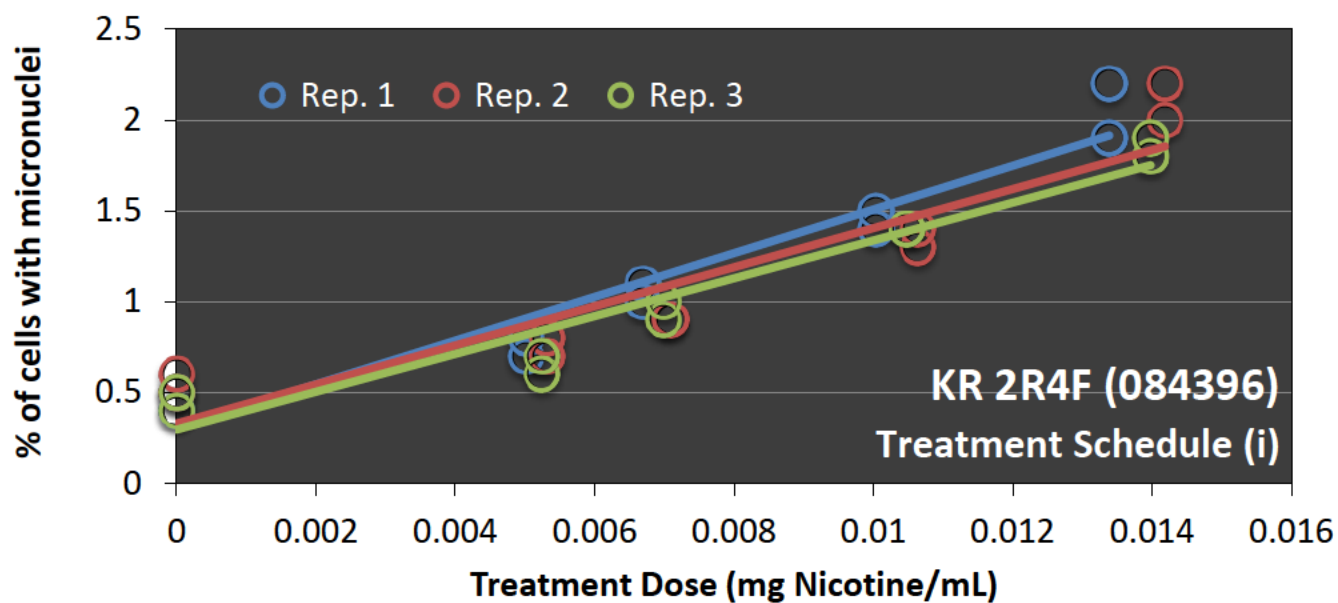
			% micronucleated cells/(mg TPM/mL)										
Treatment Schedule	Sample ID	Sample Description	Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate TPM Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard			t-test p-value (H ₀ : mean = 0)	
			(mg TPM/mL)	slope	(mg TPM/mL)	slope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

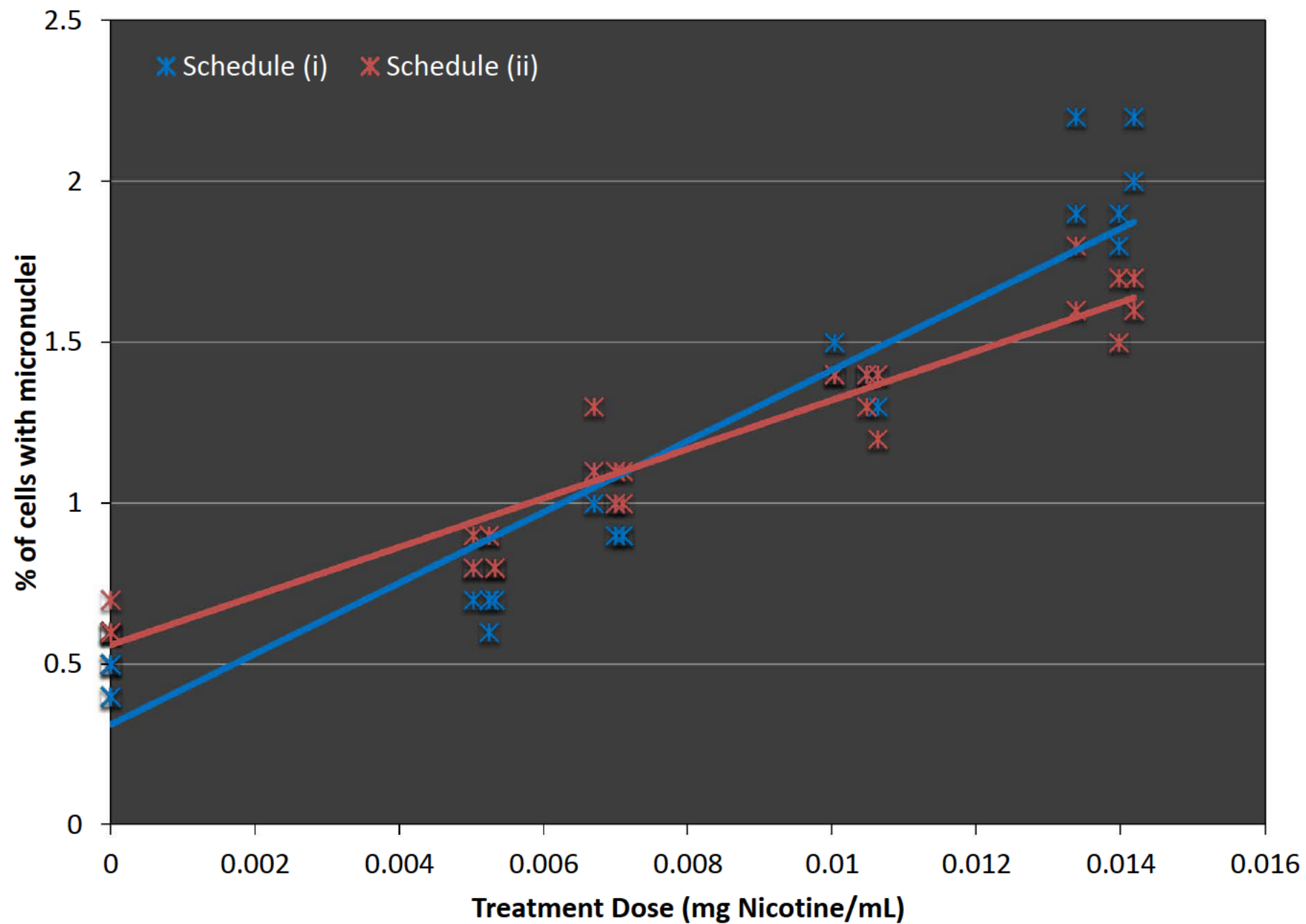




Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of mononucleated cells with micronuclei/(mg Nicotine/mL)]

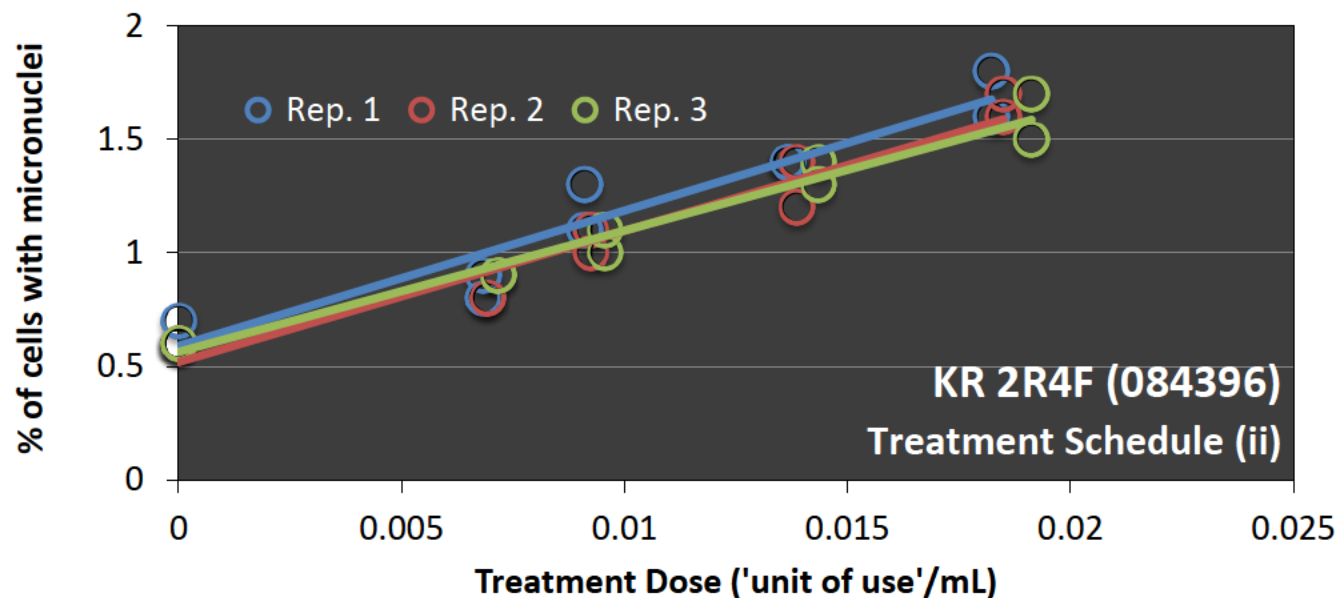
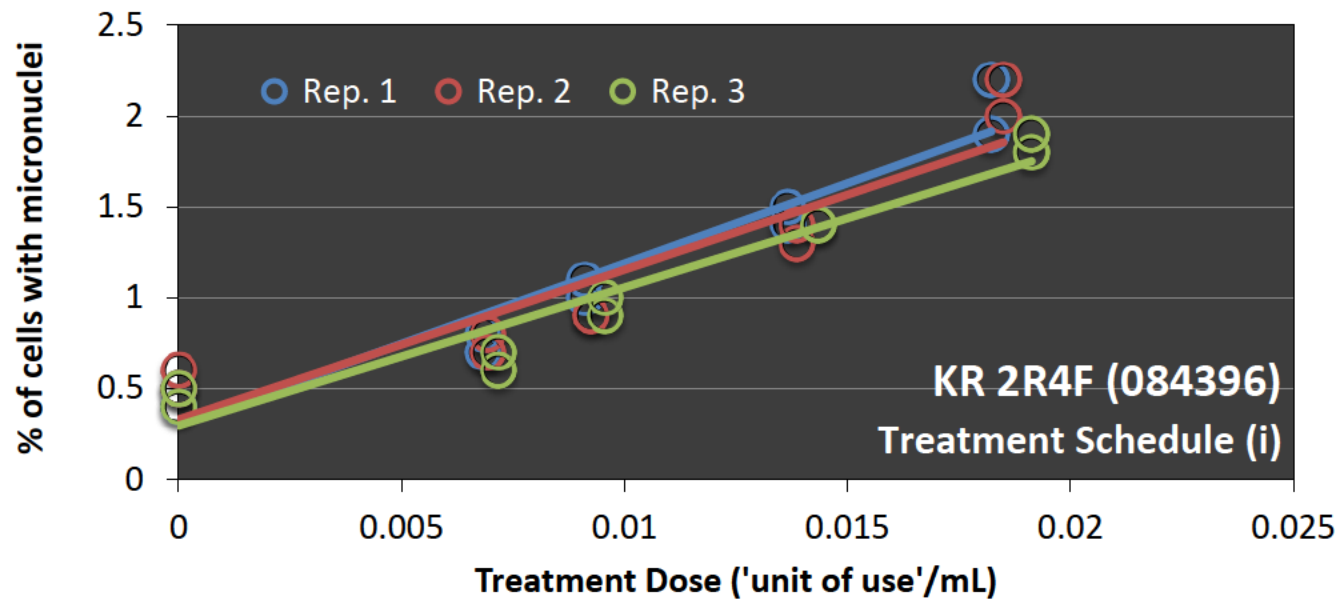
			% micronucleated cells/(mg Nicotine/mL)										
Treatment Schedule	Sample ID	Sample Description	Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate Nicotine Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard			t-test p-value (H ₀ : mean = 0)	
			(mg Nic./mL)	slope	(mg Nic./mL)	slope	(mg Nic./mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084396	Kentucky Reference 2R4F	0 - 0.013	120	0 - 0.014	108	0 - 0.014	104	111	5	89.5 - 132	0.002	significant
Schedule (ii)	084396	Kentucky Reference 2R4F	0 - 0.013	81.1	0 - 0.014	75.4	0 - 0.014	73.1	76.5	2.4	66.4 - 86.7	0.001	significant

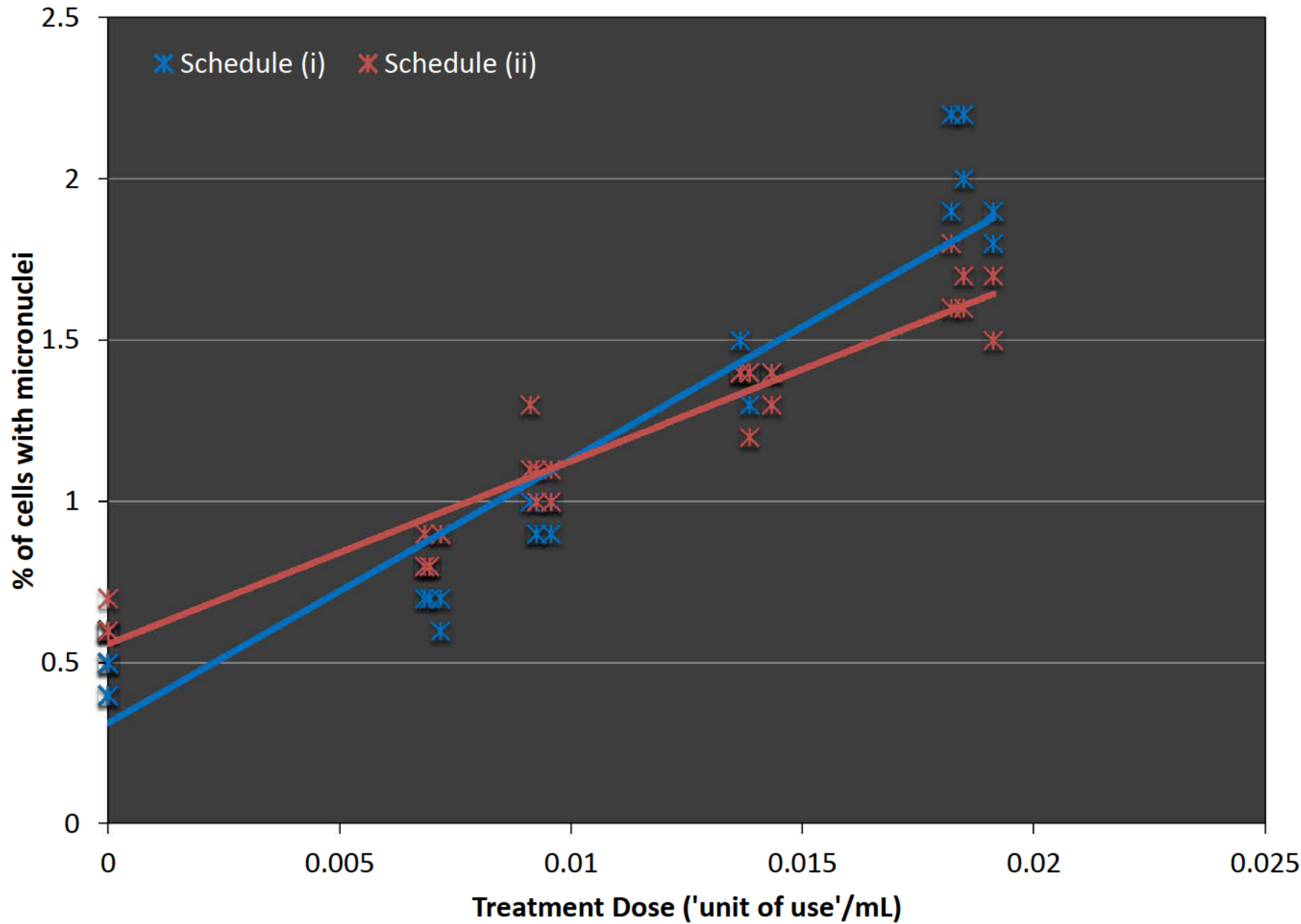




Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of mononucleated cells with micronuclei/('unit of use'/mL)]

			% micronucleated cells/('unit of use'/mL)										
Treatment Schedule	Sample ID	Sample Description	Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate 'Unit' Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard			t-test p-value (H ₀ : mean = 0)	
			('unit'/mL)	slope	('unit'/mL)	slope	('unit'/mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084396	Kentucky Reference 2R4F	0 - 0.018	88.3	0 - 0.018	82.5	0 - 0.019	76.0	82.3	3.5	67 - 97.5	0.002	significant
Schedule (ii)	084396	Kentucky Reference 2R4F	0 - 0.018	59.5	0 - 0.018	57.8	0 - 0.019	53.4	56.9	1.8	49.1 - 64.8	0.001	significant





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			

Schedule (ii)

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

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

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

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

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

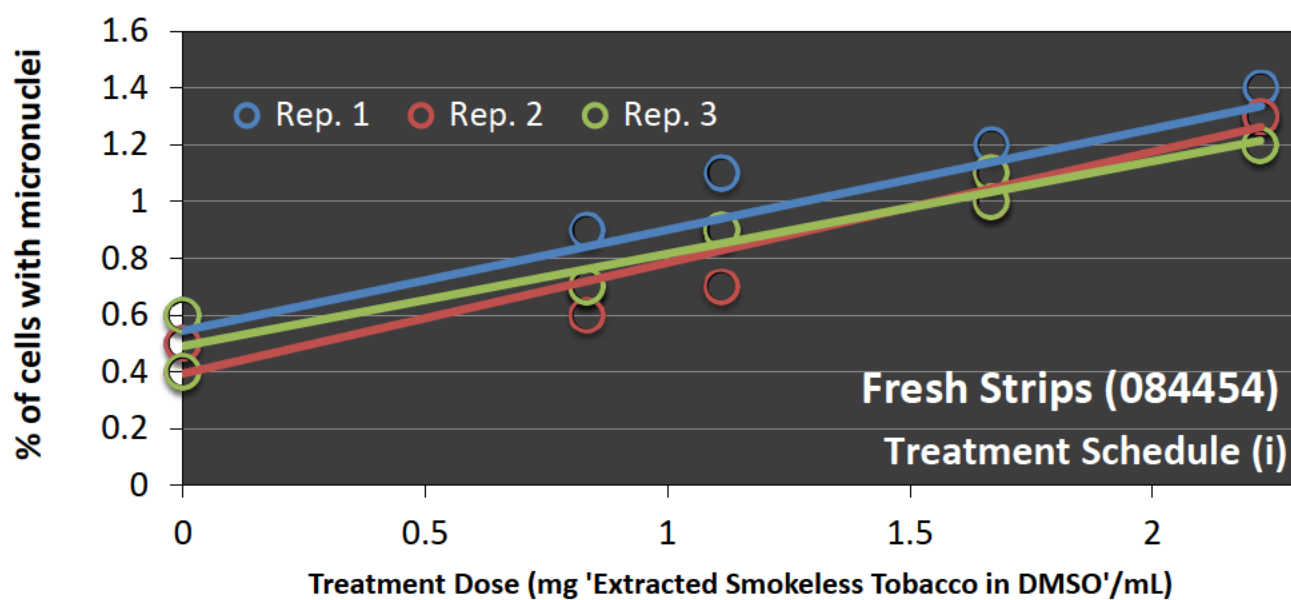
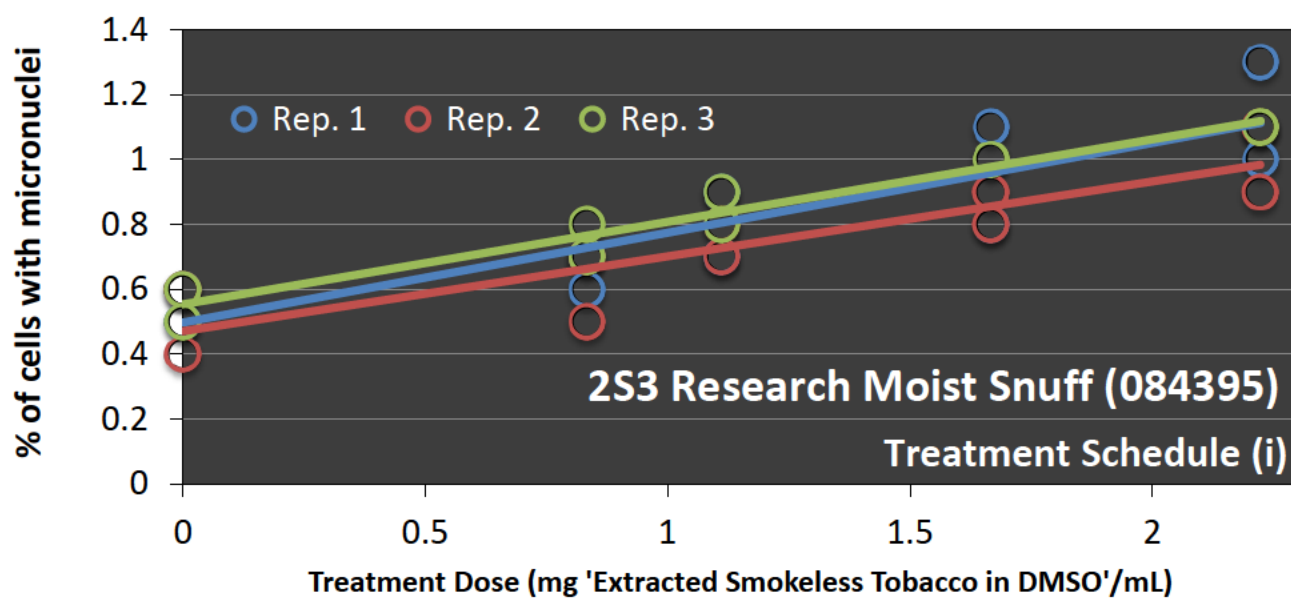
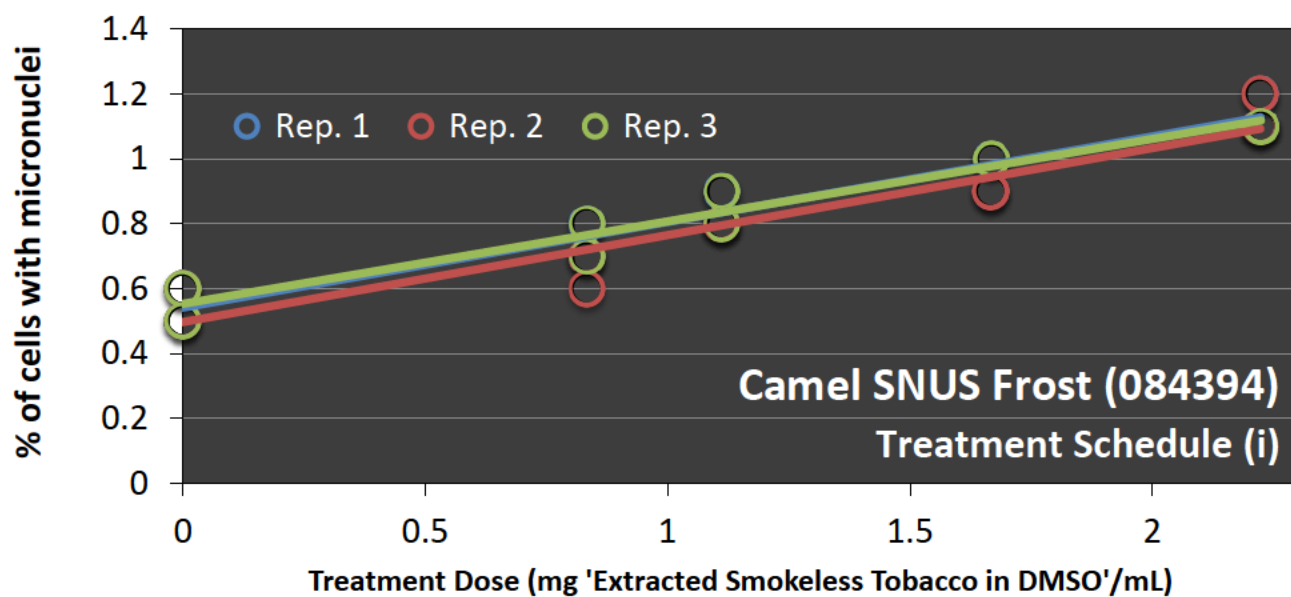
Schedule (ii)

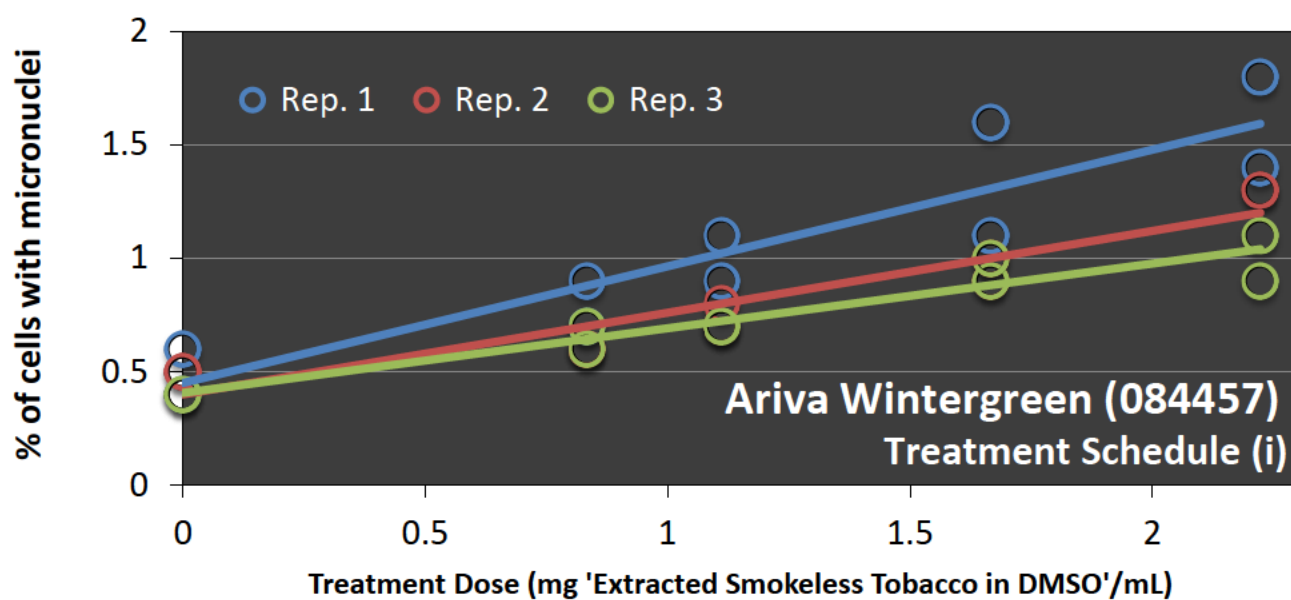
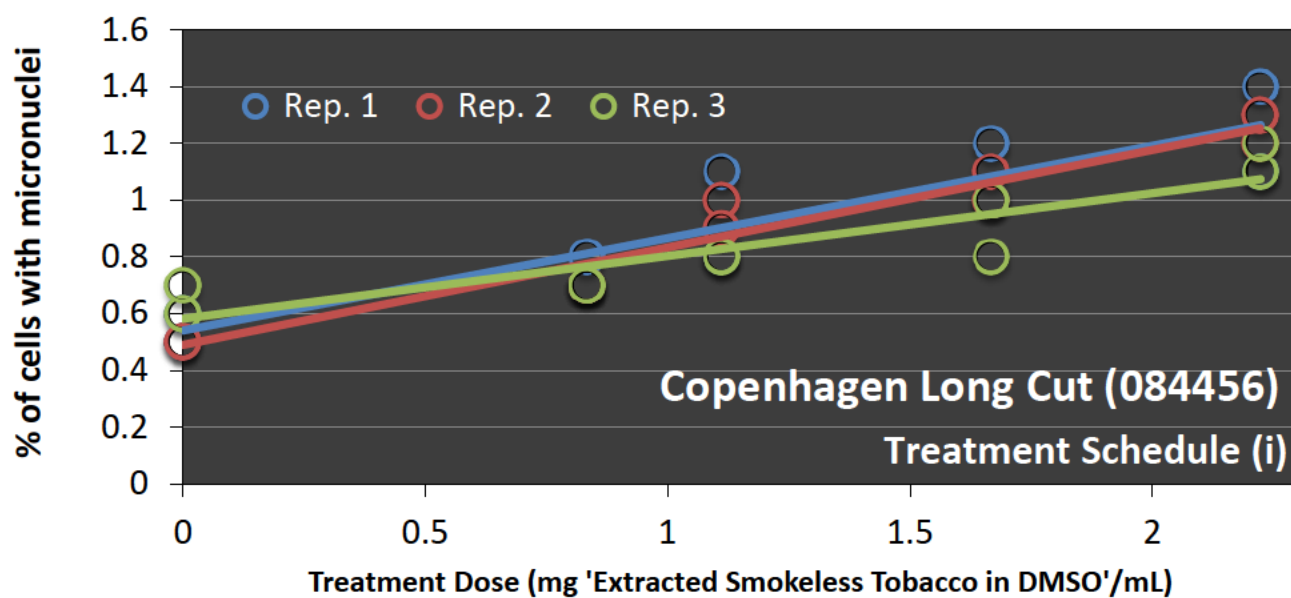
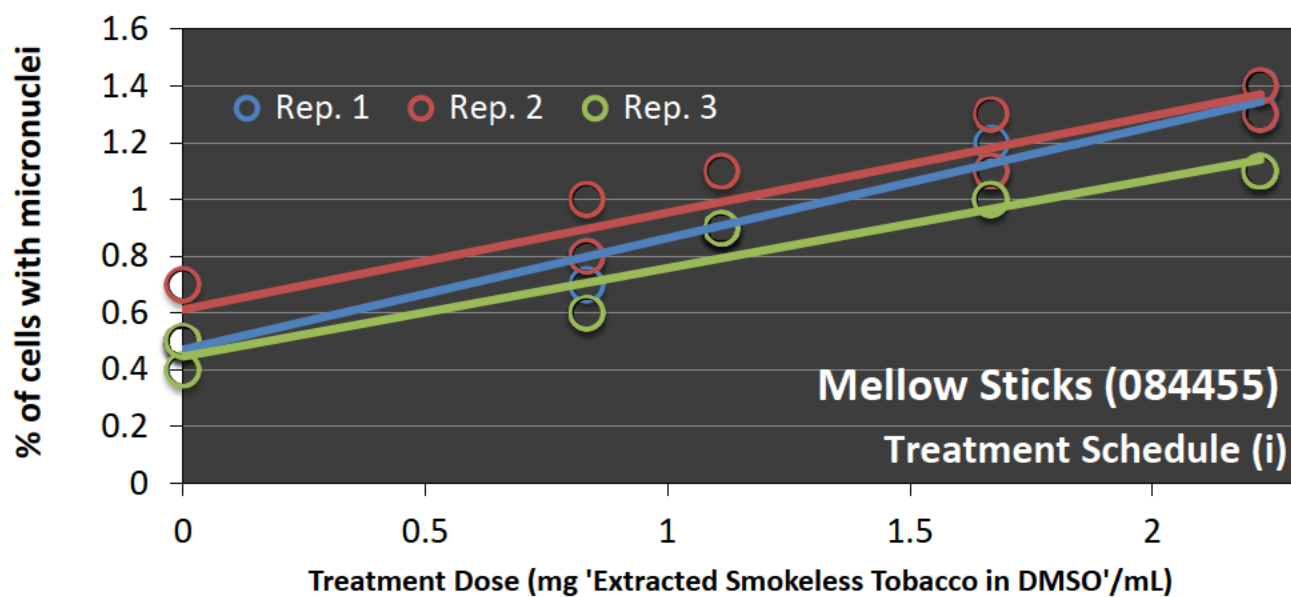
Sample Description	Sample ID	Mean Slope	Homogenous Groupings
2S3	084395	0.185	X
Copenhagen Long Cut	084456	0.185	X
Camel SNUS Frost	084394	0.207	X
Mellow Sticks	084455	0.226	XX
Ariva Wintergreen	084457	0.247	XX
Fresh Strips	084454	0.247	XX
Fresh Orbs	084458	0.333	X

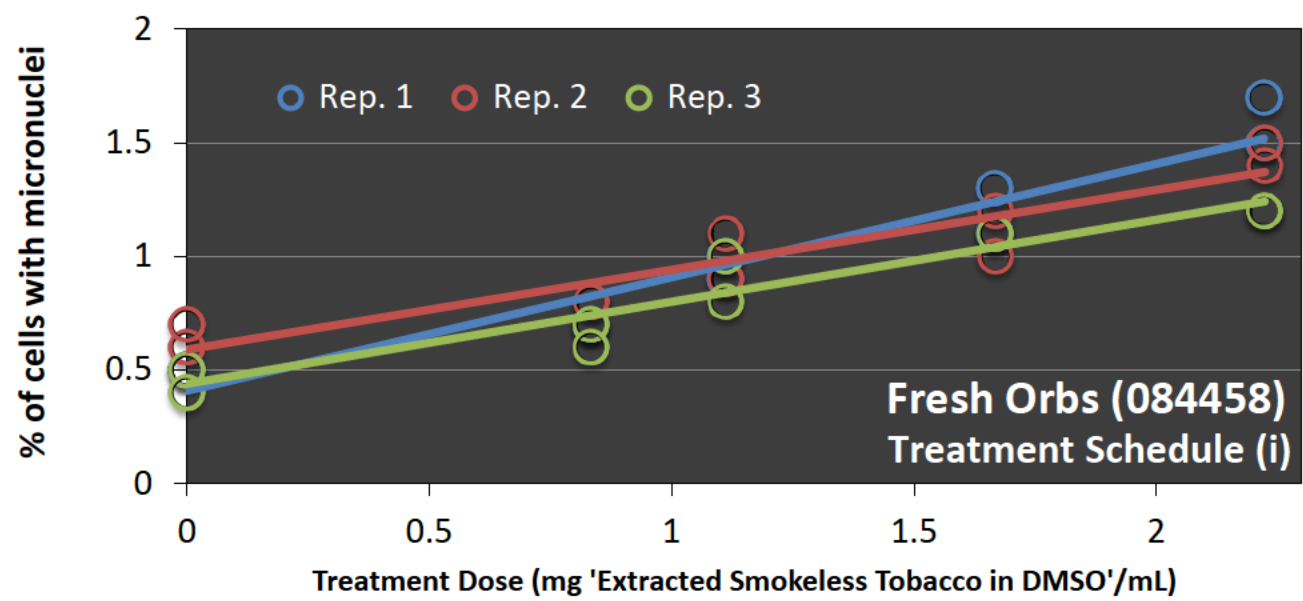
**Pairwise T-Test Comparisons of Mean 'Extracted Smokeless Tobacco'
Slope for Contrasts of Interest using Bonferroni-adjusted p-values**

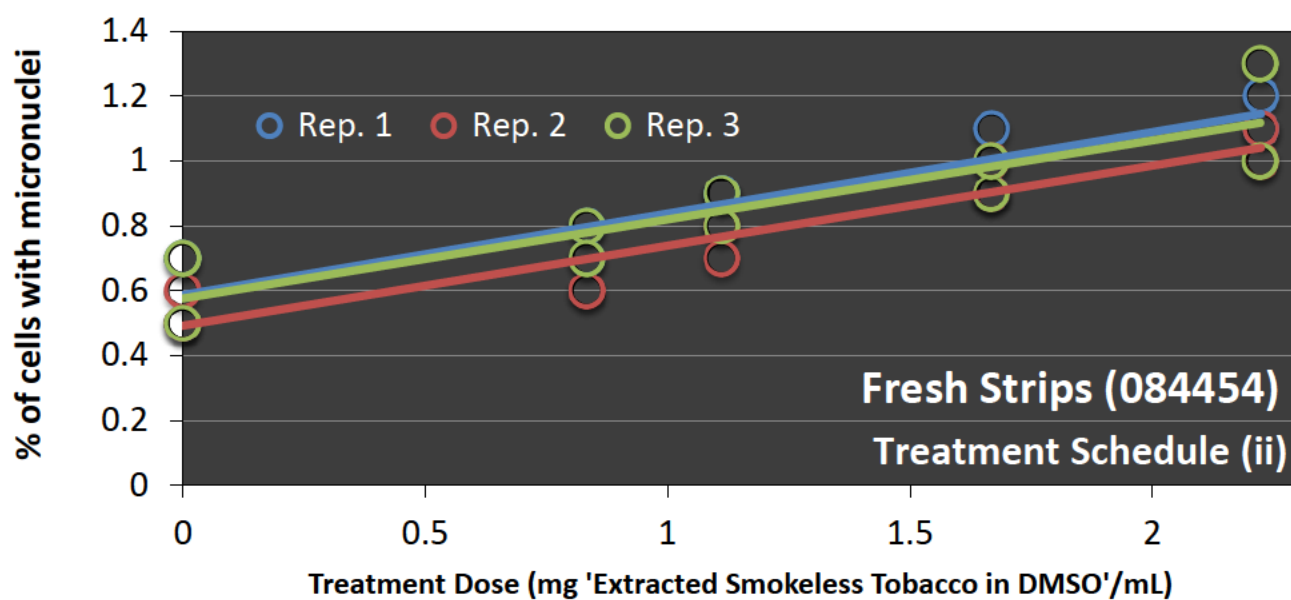
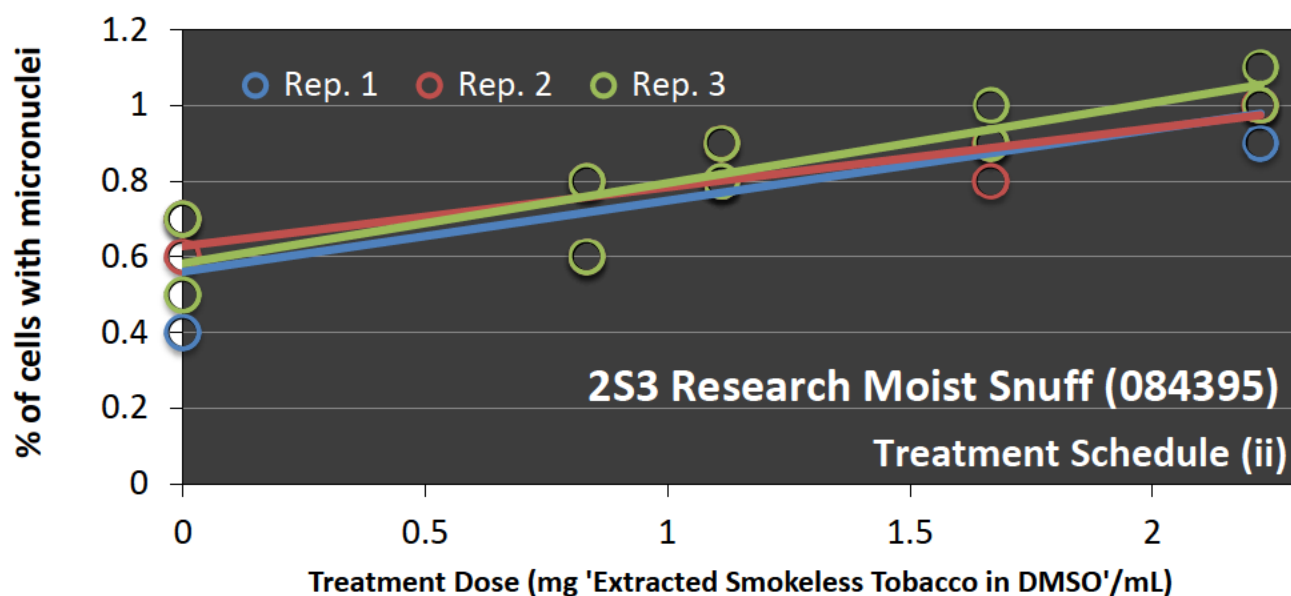
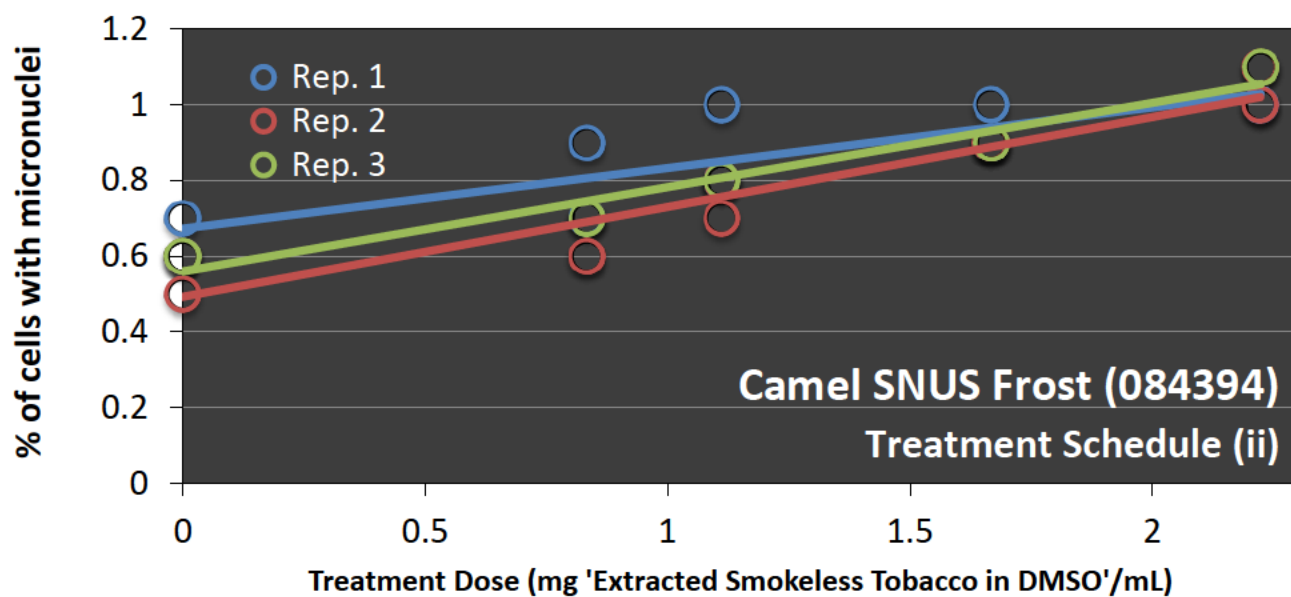
Pairwise T-Test Comparison	Schedule (i)			Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	0.5856	0.5896	not significant	0.7573	0.4910	not significant
084394 vs. 084454	4.9378	0.0078	not significant	1.6827	0.1677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

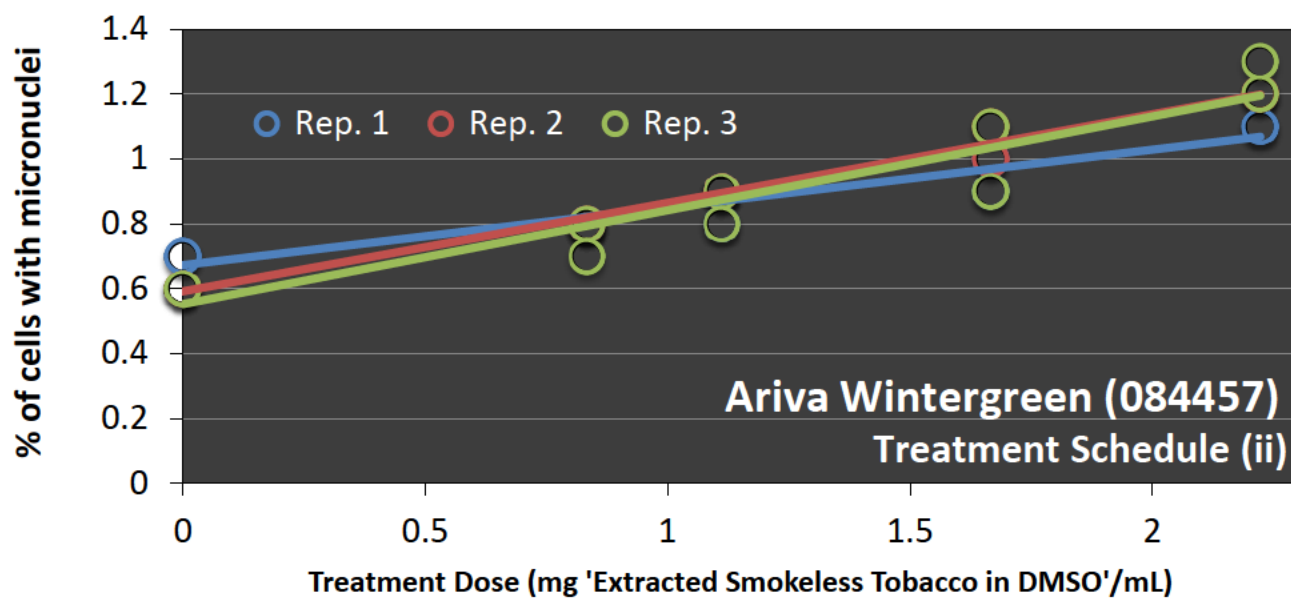
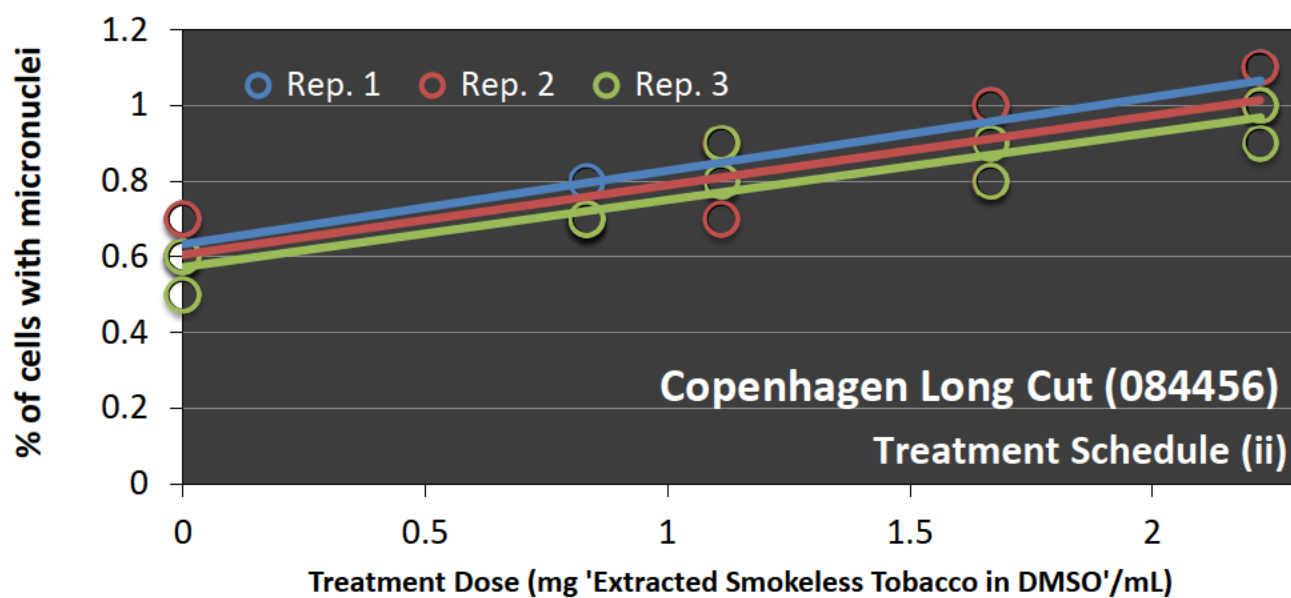
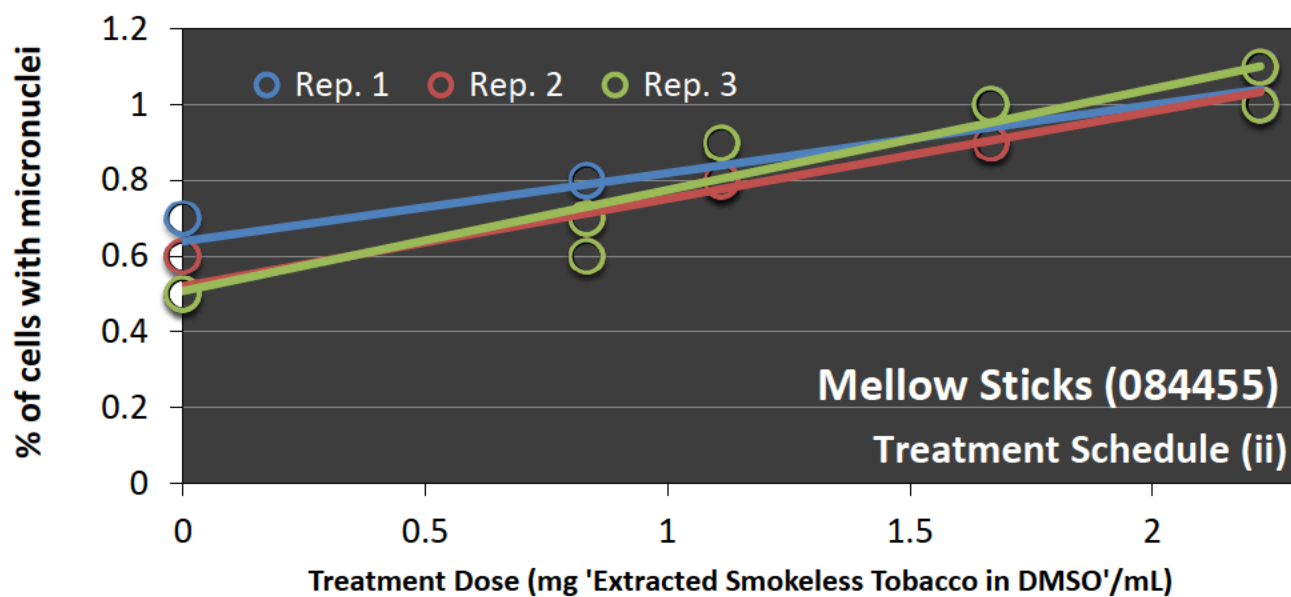
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted smokeless tobacco' slope were detected between Fresh Strips (084454) and Copenhagen Long Cut (084456) under treatment schedule (ii).

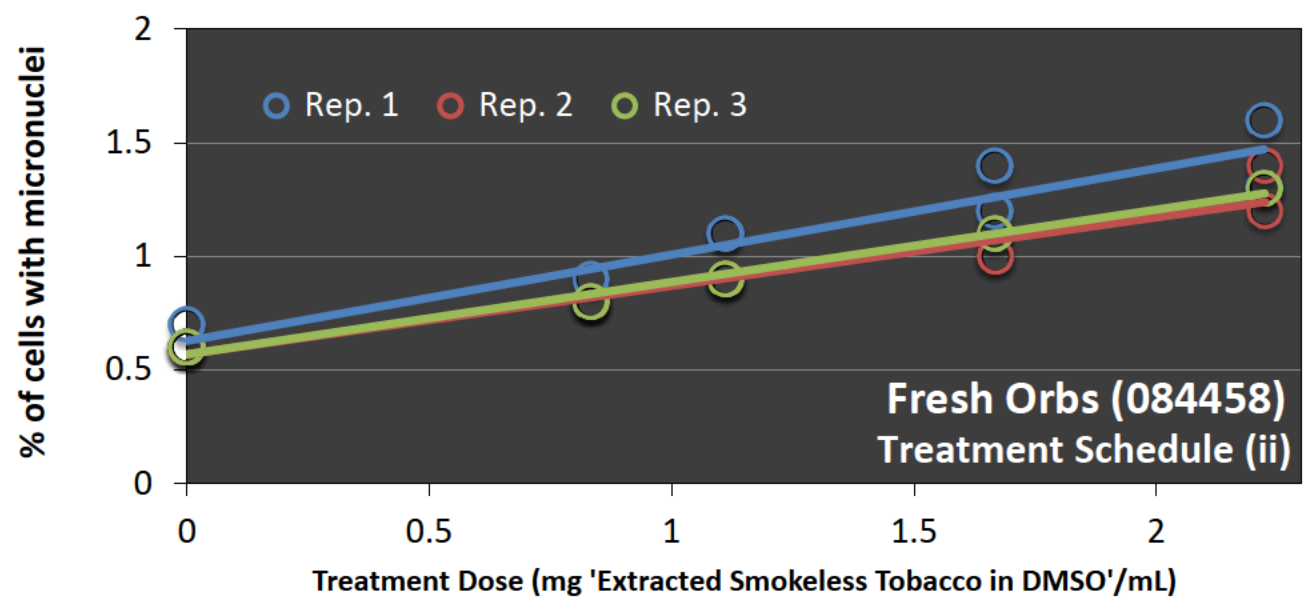


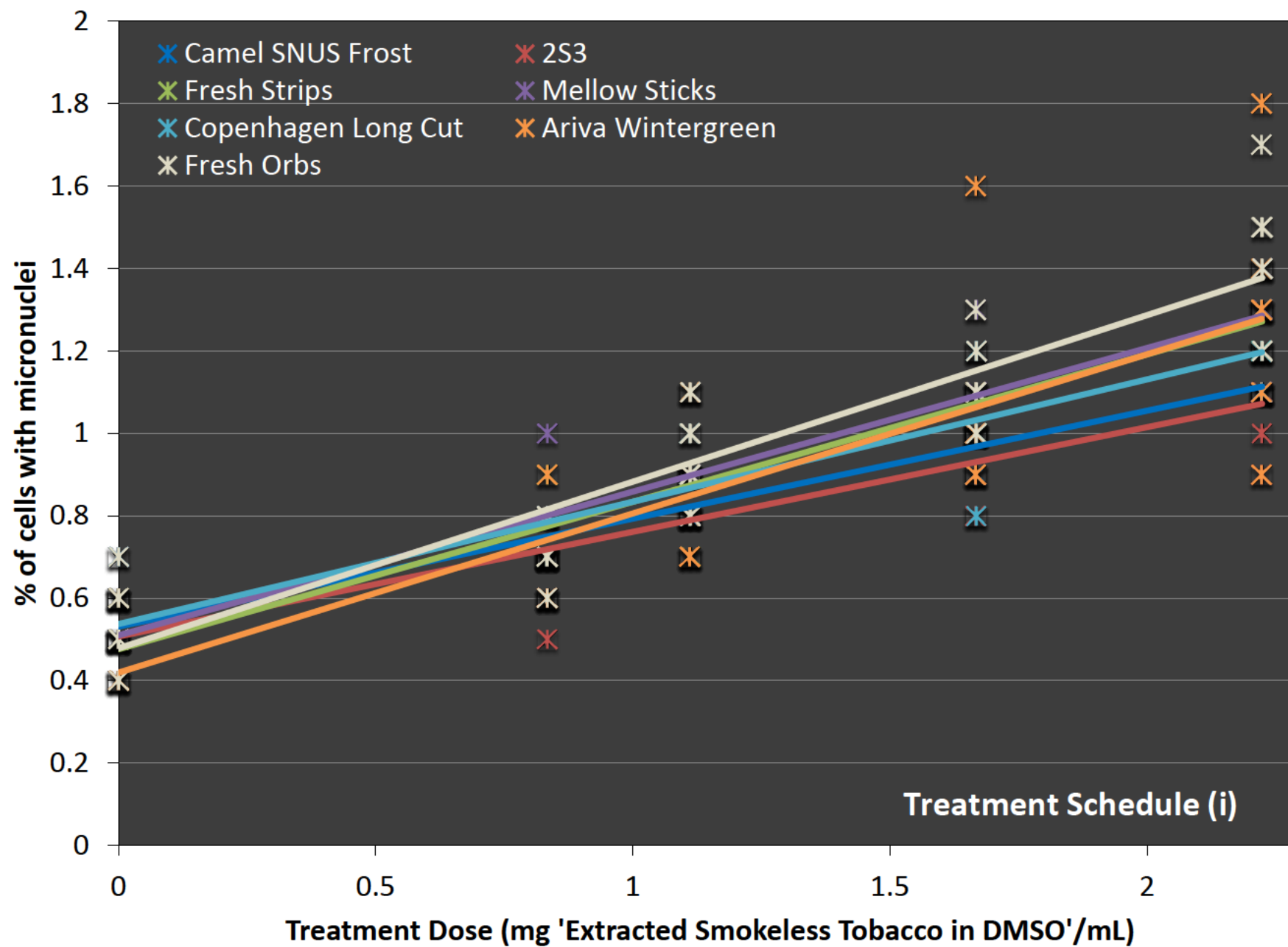


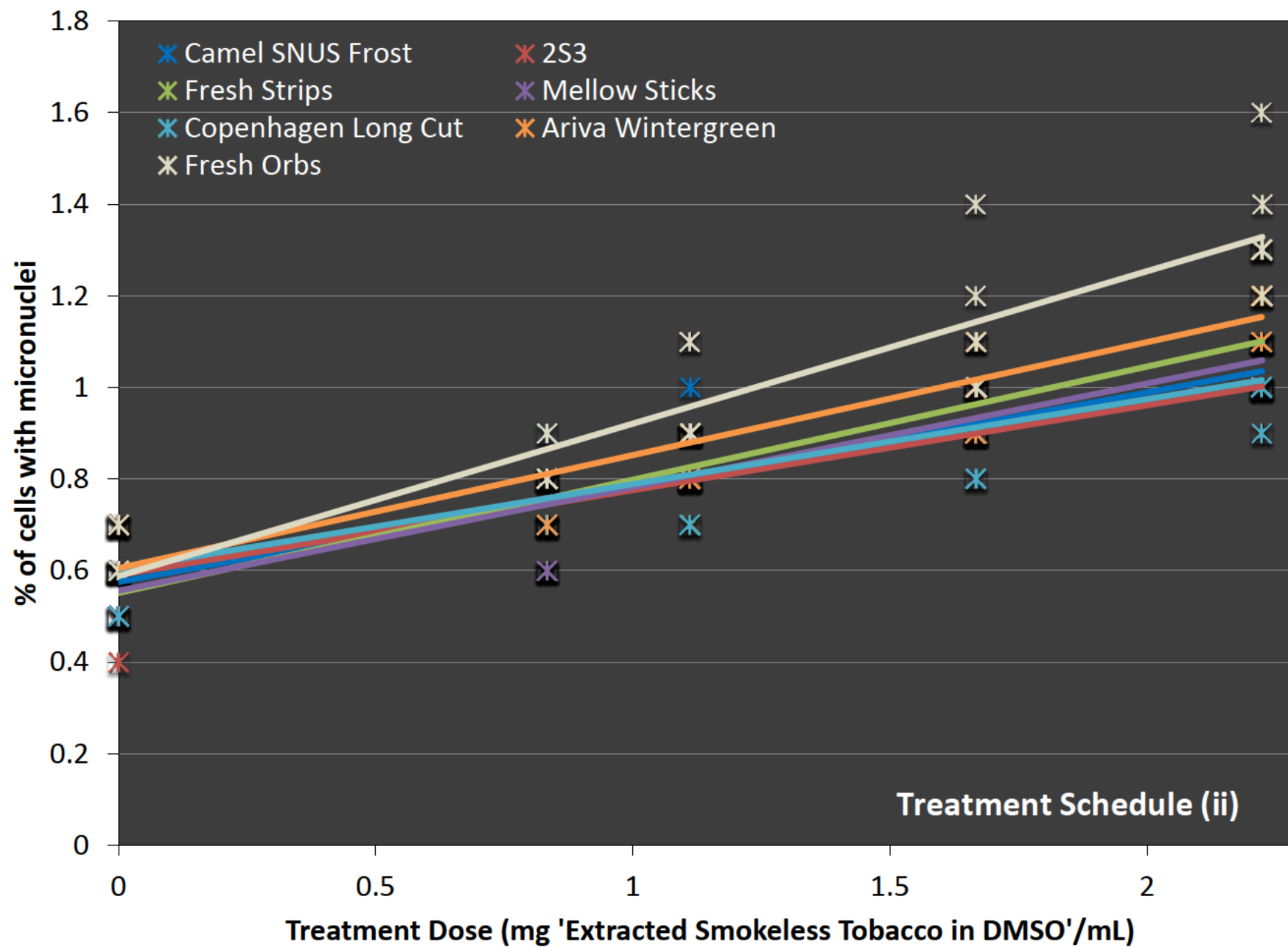












Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of cells with micronuclei/(mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL)] (ST-H₂O)

			% micronucleated cells /(mg 'Extracted Moisture-Corrected Smokeless Tobacco in DMSO'/mL)										
Treatment Schedule	Sample ID	Sample Description	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).

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

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

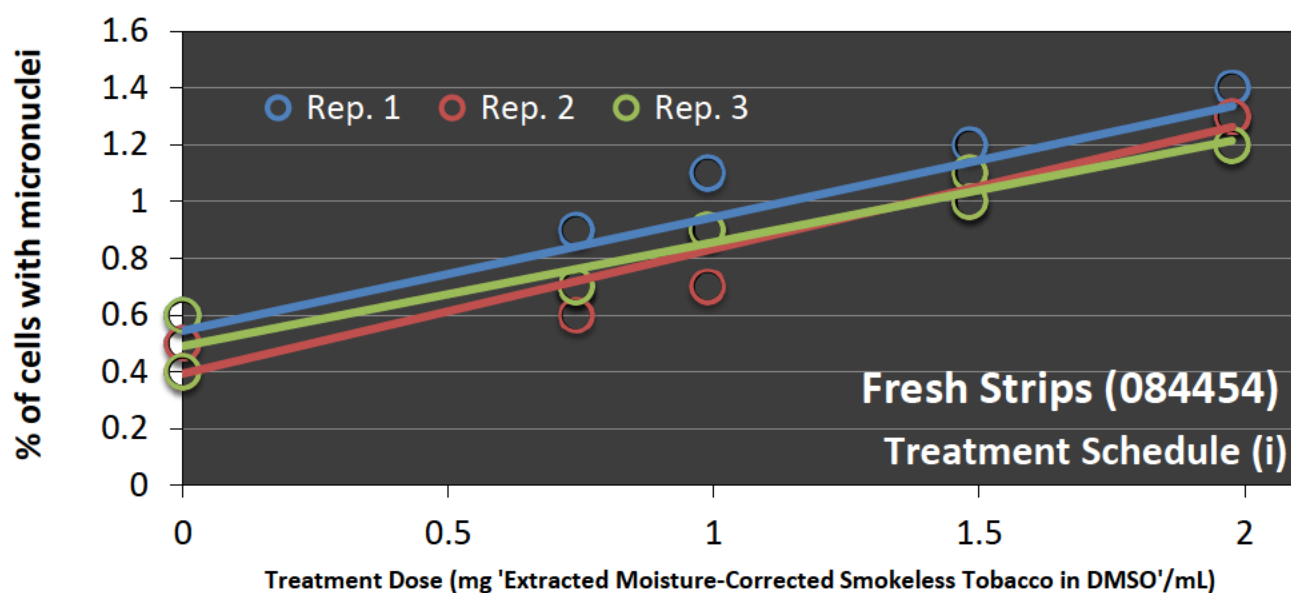
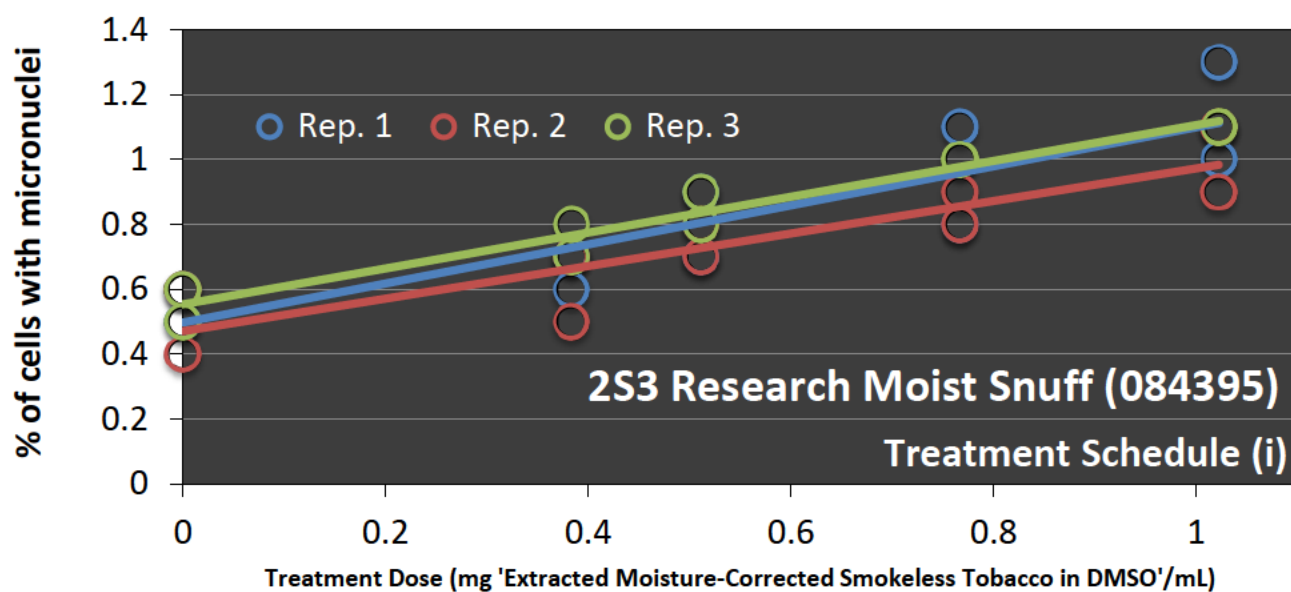
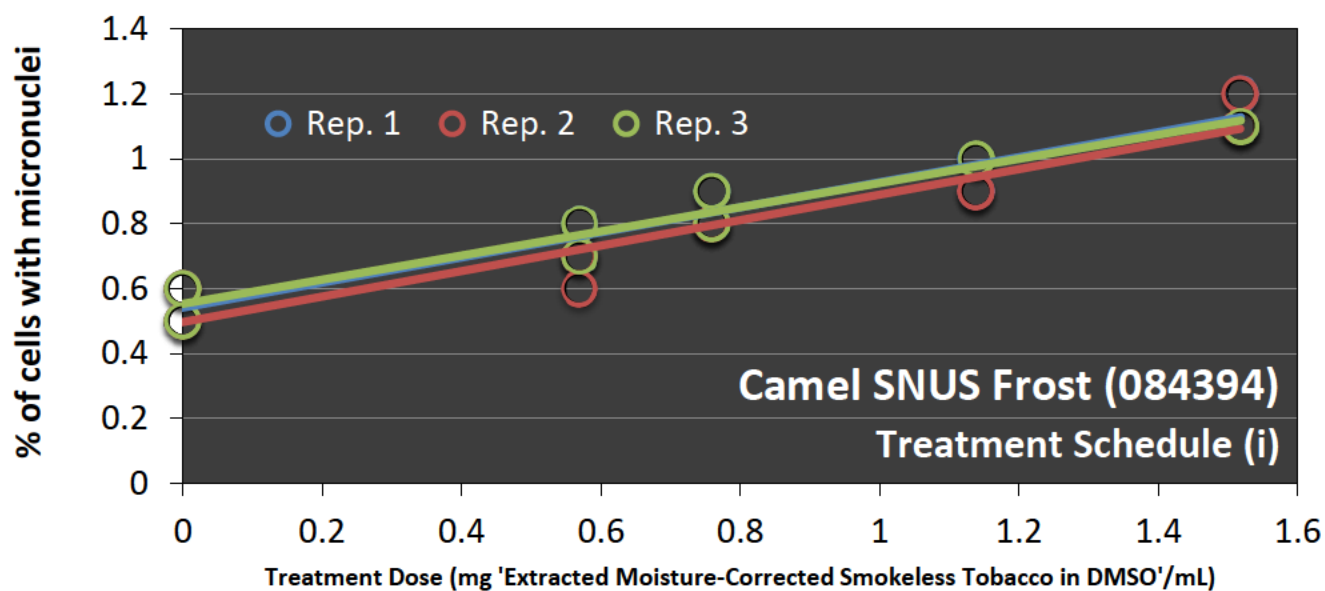
ANOVA-based comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted moisture-corrected smokeless tobacco' slope were as follows:

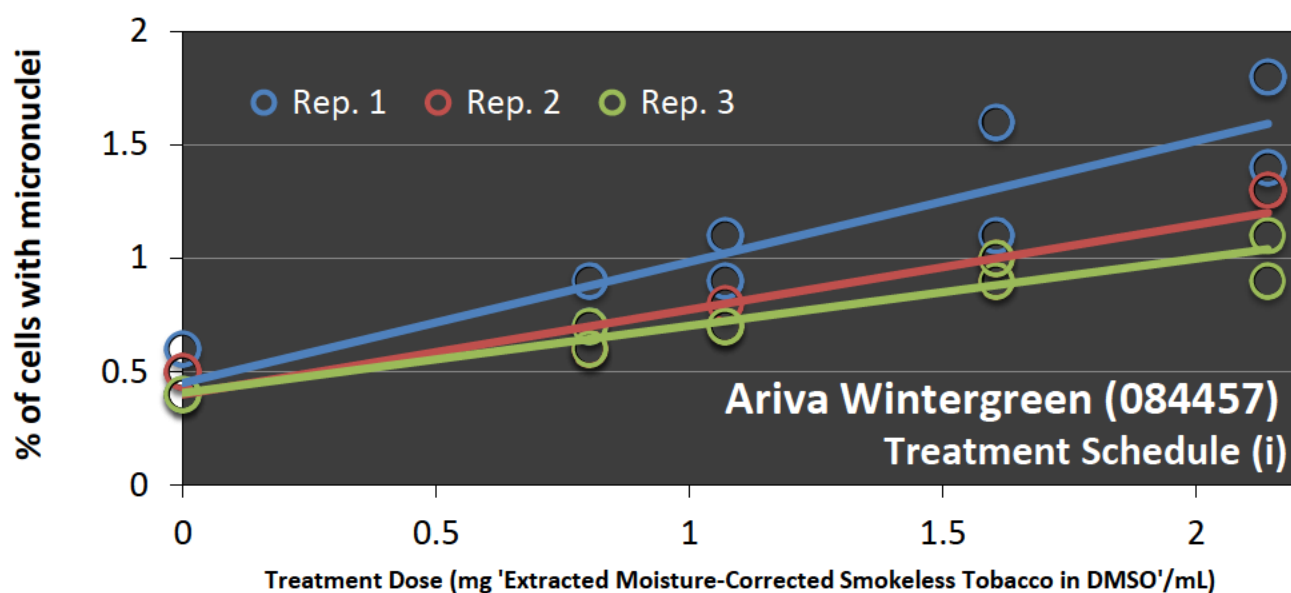
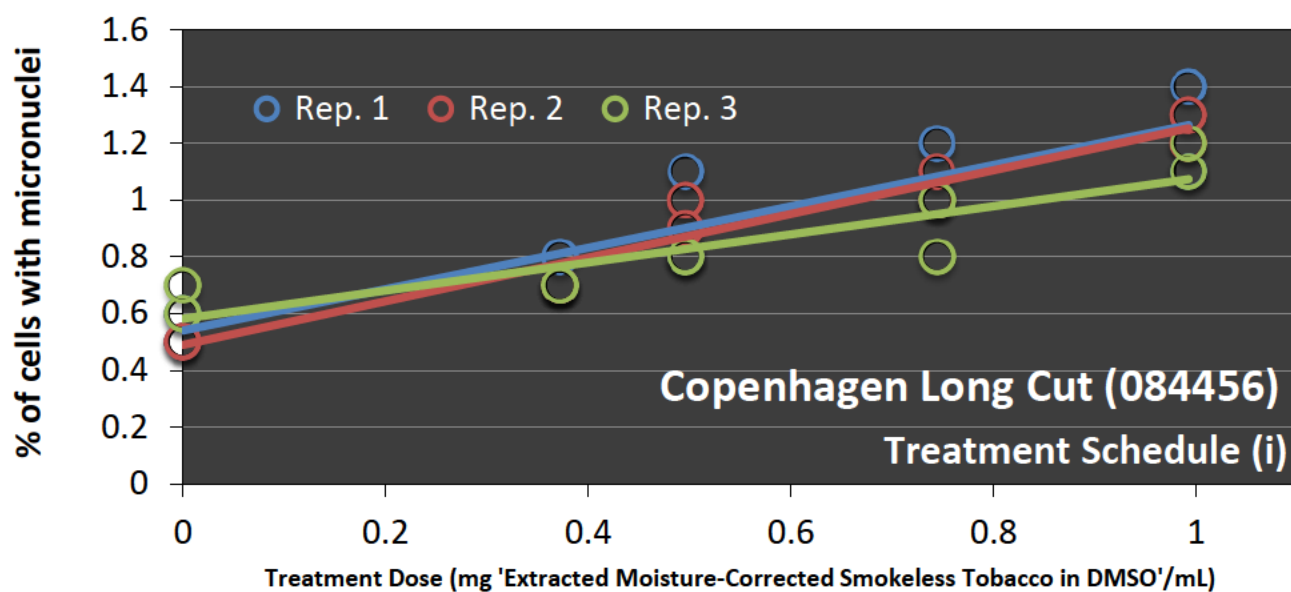
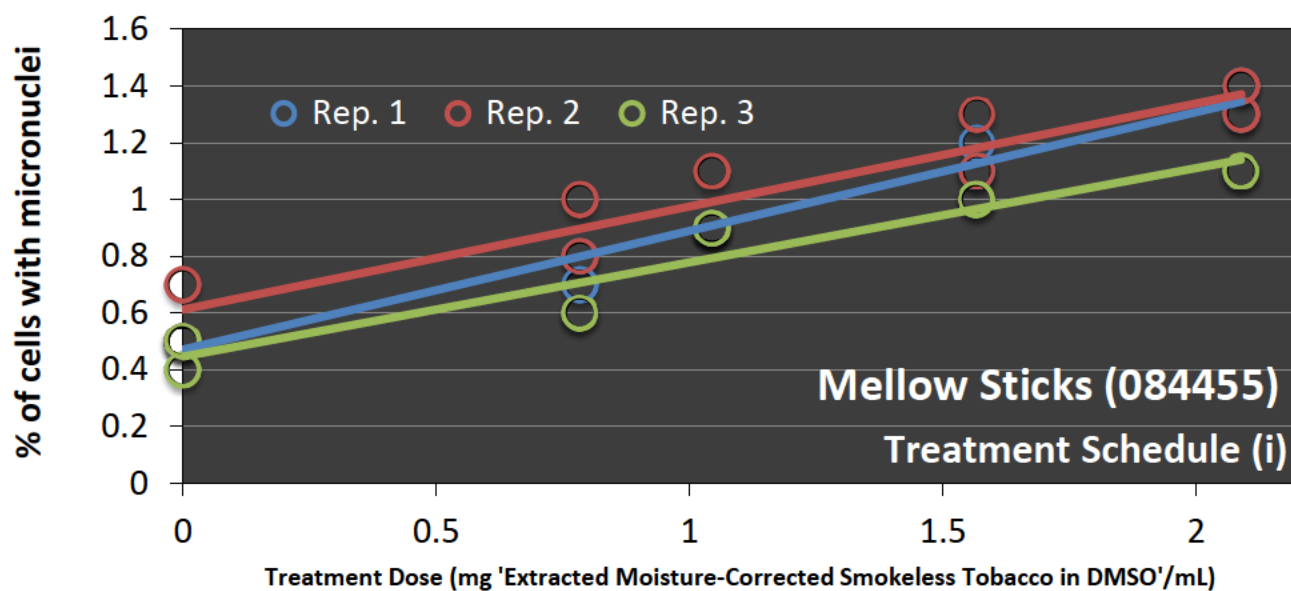
Schedule (i)				Schedule (ii)			
Sample Description	Sample ID	Mean Slope	Homogenous Groupings	Sample Description	Sample ID	Mean Slope	Homogenous Groupings
Mellow Sticks	084455	0.371	X	Mellow Sticks	084455	0.241	X
Camel SNUS Frost	084394	0.384	X	Ariva Wintergreen	084457	0.256	X
Ariva Wintergreen	084457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

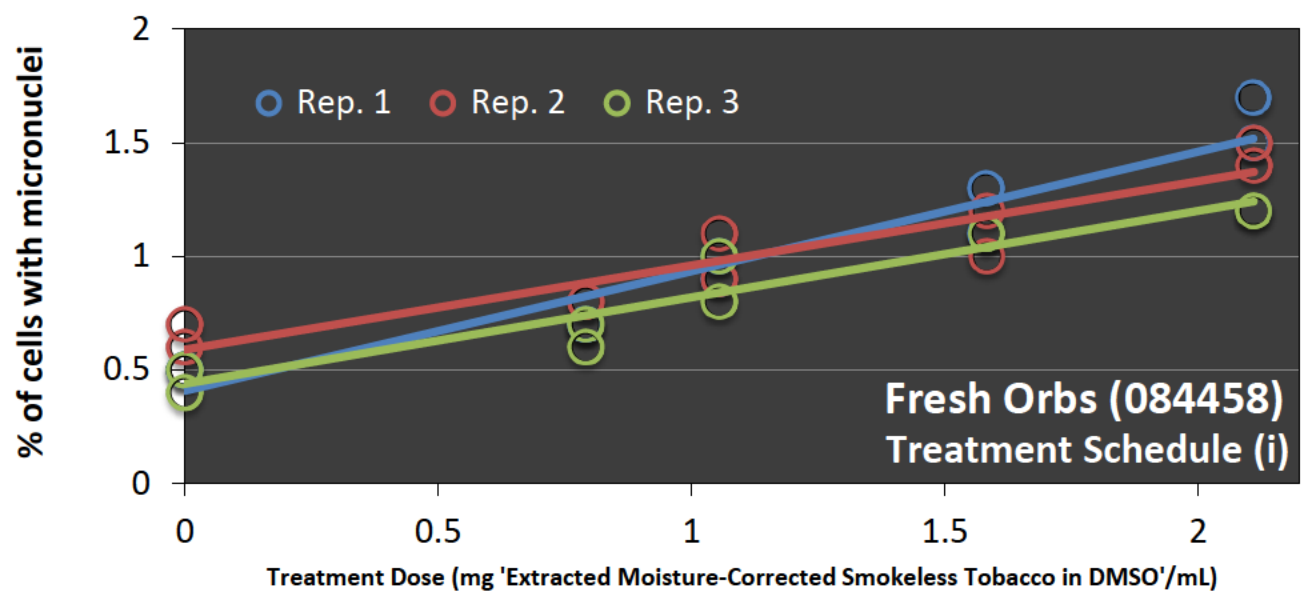
Pairwise T-Test Comparisons of Mean 'Extracted Moisture-Corrected Smokeless Tobacco' Slope for Contrasts of Interest

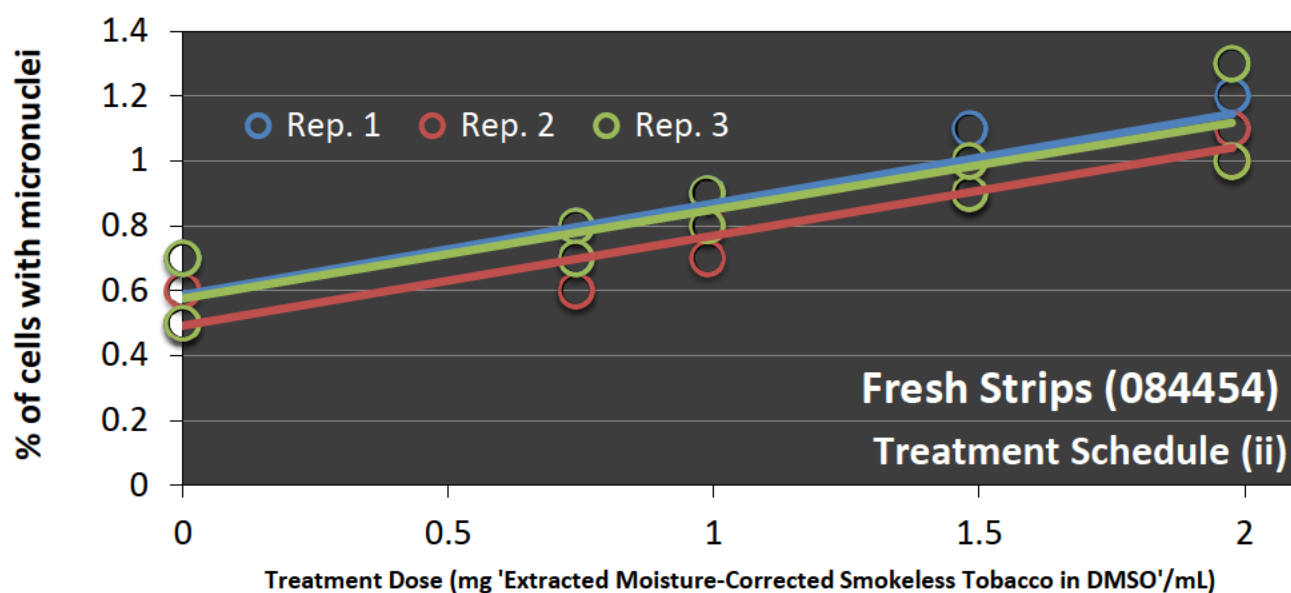
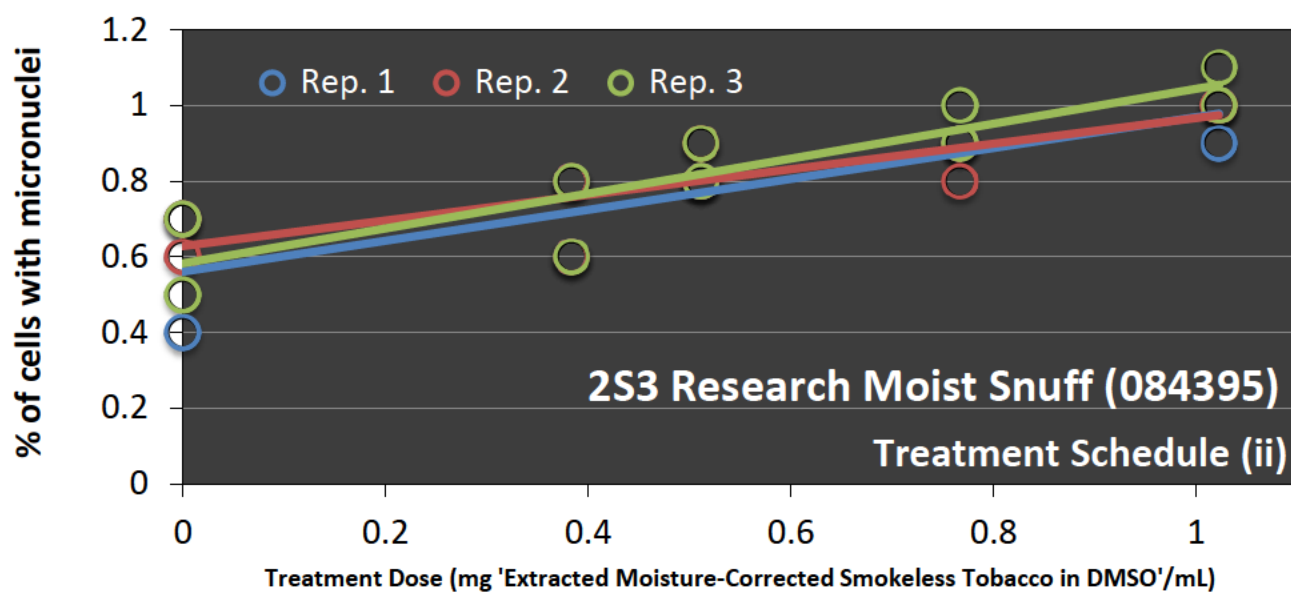
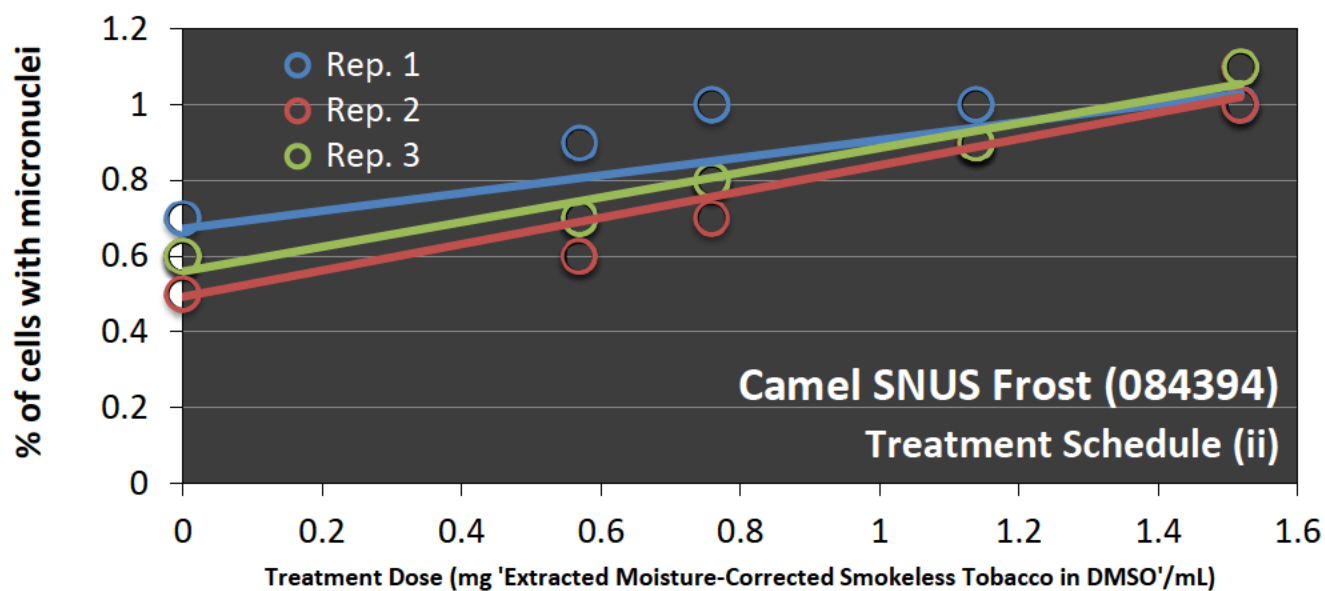
Pairwise T-Test Comparison	Schedule (i)			Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	5.7156	0.0046	not significant	1.9986	0.1163	not significant
084394 vs. 084454	0.8307	0.4529	not significant	0.7256	0.5083	not significant
084394 vs. 084455	0.4838	0.6538	not significant	1.4250	0.2273	not significant
084394 vs. 084456	3.2745	0.0307	not significant	3.0898	0.0366	not significant
084394 vs. 084457	0.2413	0.8212	not significant	0.9373	0.4017	not significant
084394 vs. 084458	0.8308	0.4528	not significant	1.1216	0.3248	not significant
084395 vs. 084454	4.1887	0.0138	not significant	3.4876	0.0252	not significant
084395 vs. 084455	4.7239	0.0091	not significant	3.6362	0.0220	not significant
084395 vs. 084456	1.2453	0.2810	not significant	0.3467	0.7463	not significant
084395 vs. 084457	2.0028	0.1157	not significant	2.8862	0.0447	not significant
084395 vs. 084458	2.1684	0.0960	not significant	1.1804	0.3032	not significant
084454 vs. 084455	0.9368	0.4019	not significant	1.3874	0.2376	not significant
084454 vs. 084456	2.9777	0.0408	not significant	12.3047	0.0003	significant
084454 vs. 084457	0.0194	0.9855	not significant	0.5993	0.5813	not significant
084454 vs. 084458	0.4364	0.6851	not significant	2.9092	0.0437	not significant
084455 vs. 084456	3.2894	0.0302	not significant	6.0798	0.0037	not significant
084455 vs. 084457	0.3966	0.7119	not significant	0.3437	0.7484	not significant
084455 vs. 084458	0.9707	0.3867	not significant	3.0196	0.0392	not significant
084456 vs. 084457	2.3886	0.0753	not significant	4.2299	0.0134	not significant
084456 vs. 084458	2.4012	0.0743	not significant	2.3566	0.0780	not significant
084457 vs. 084458	0.2937	0.7836	not significant	2.1620	0.0967	not significant

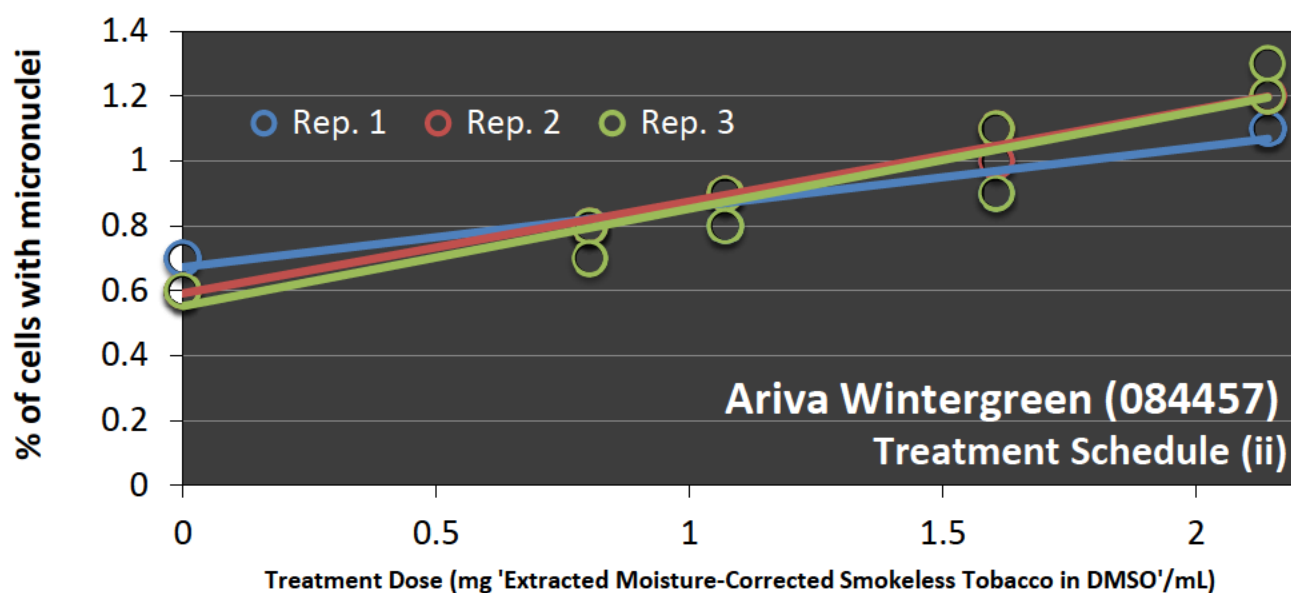
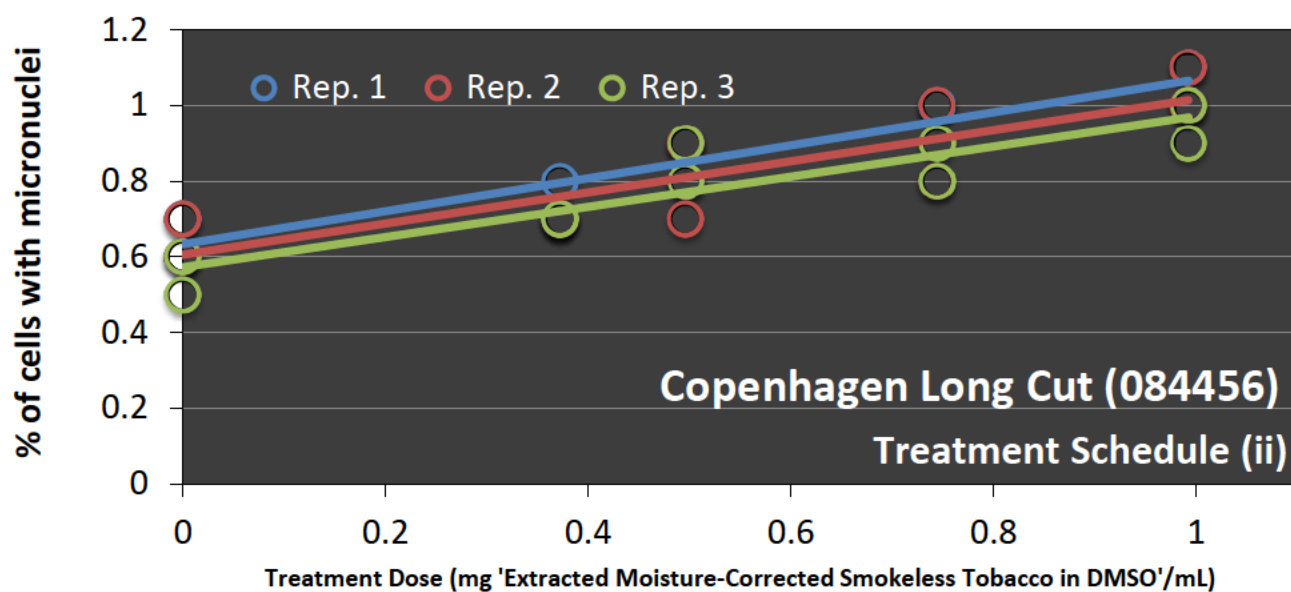
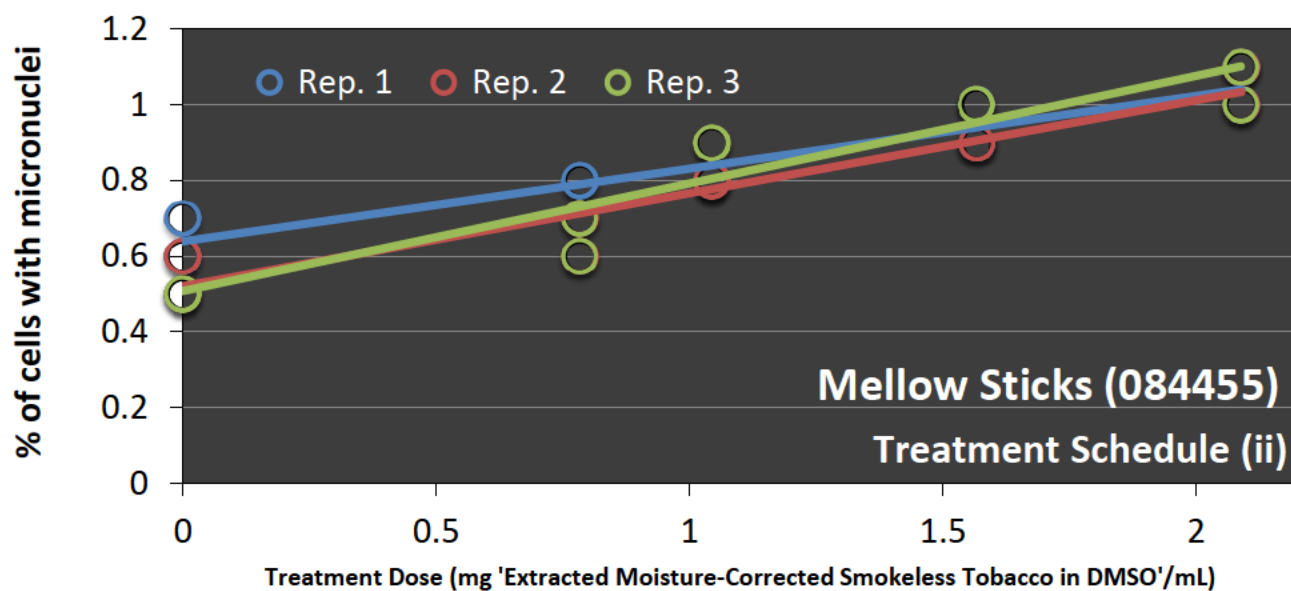
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted moisture-corrected smokeless tobacco' slope were detected between Fresh Strips (084454) and Copenhagen Long Cut (084456) under treatment schedule (ii).

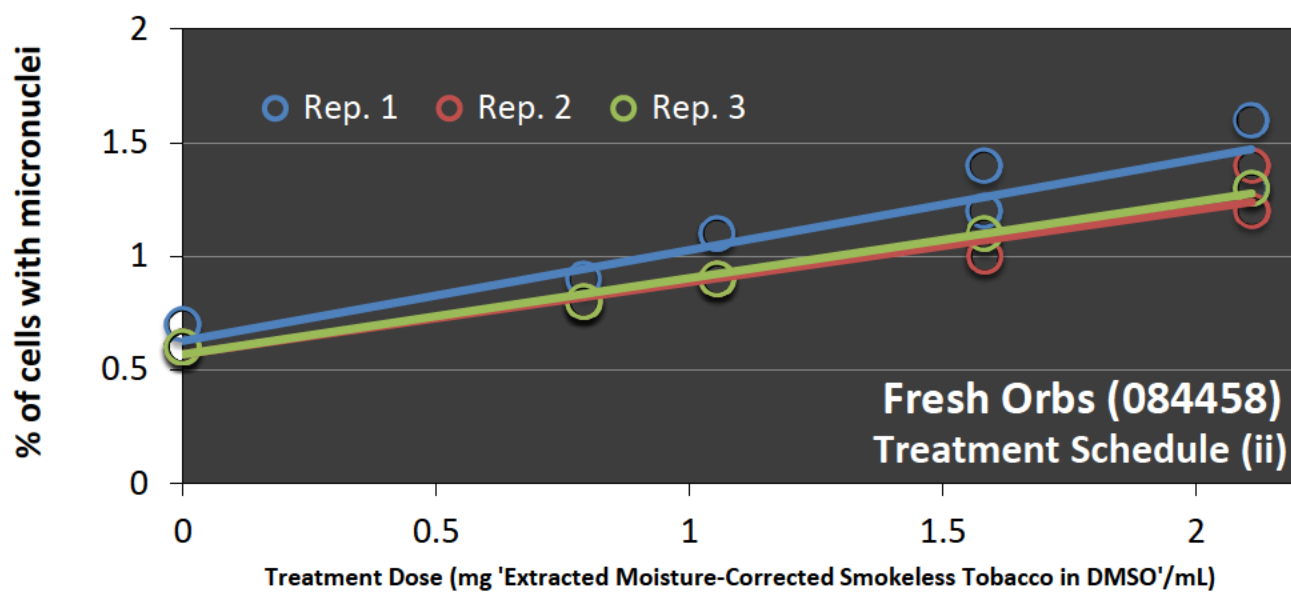


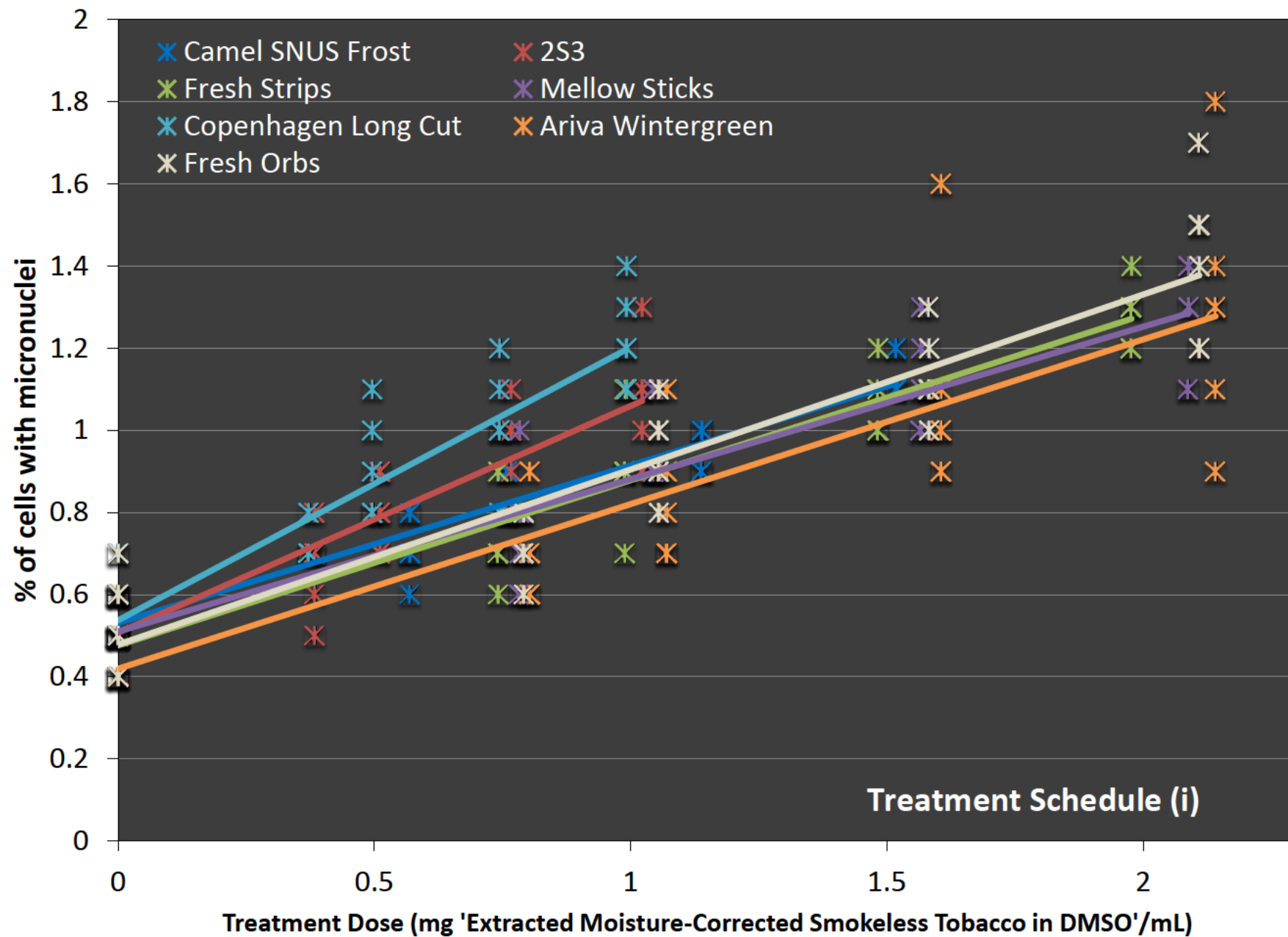


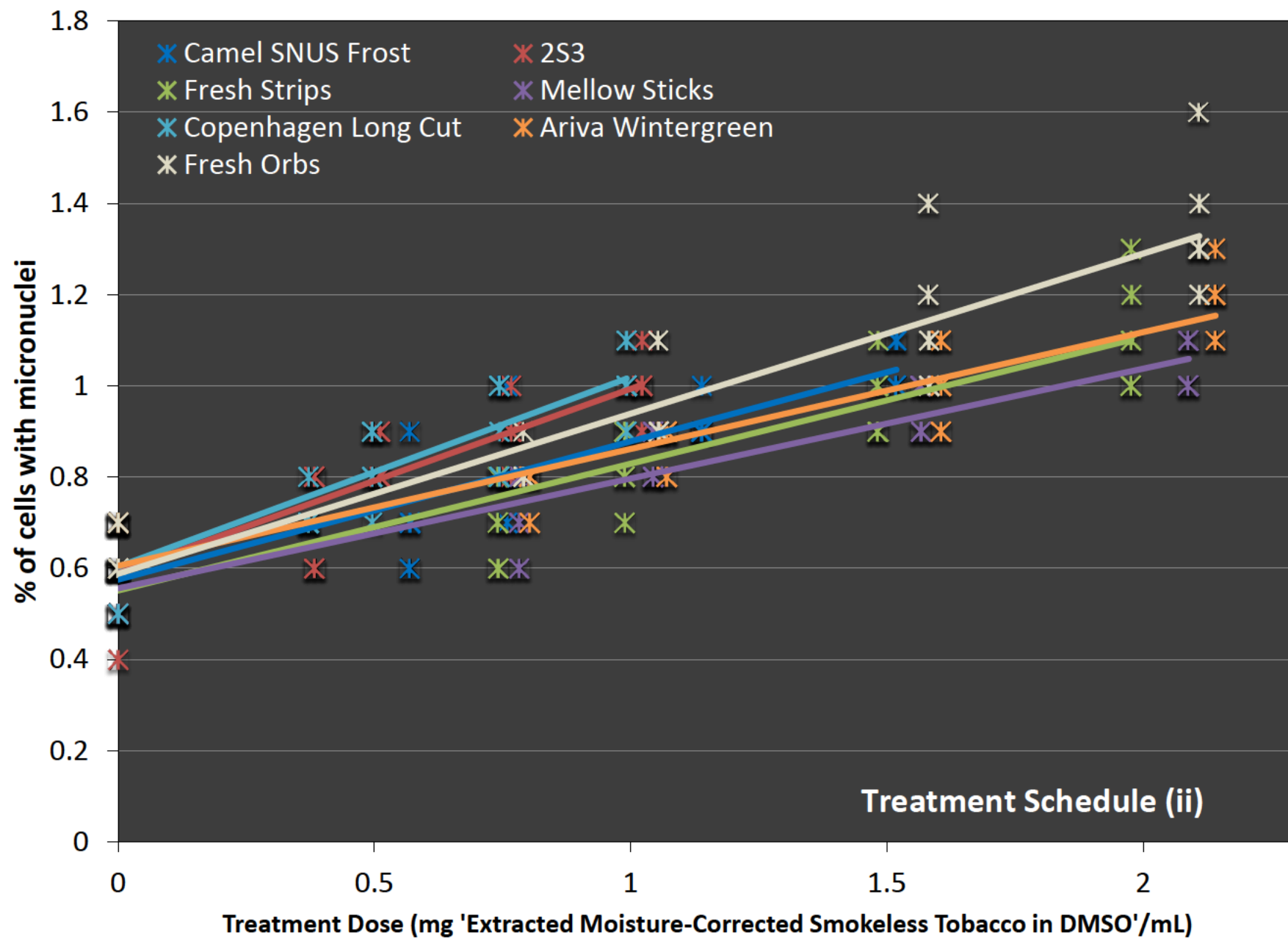












Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of cells with micronuclei/(mg 'Extracted Nicotine in DMSO'/mL)] ('Nic.')

			% micronucleated cells /(mg '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)	
			(mg 'Nic.'/mL)	slope	(mg 'Nic.'/mL)	slope	(mg 'Nic.'/mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084394	Camel SNUS Frost	0 - 0.028	21.1	0 - 0.029	20.8	0 - 0.029	19.2	20.3	0.594	17.8 - 22.9	0.001	significant
Schedule (i)	084395	2S3	0 - 0.03	20.5	0 - 0.029	17.5	0 - 0.031	18.0	18.6	0.940	14.6 - 22.7	0.003	significant
Schedule (i)	084454	Fresh Strips	0 - 0.008	96.3	0 - 0.008	109	0 - 0.008	94.5	99.8	4.45	80.6 - 119	0.002	significant
Schedule (i)	084455	Mellow Sticks	0 - 0.009	99.0	0 - 0.011	70.7	0 - 0.008	86.0	85.2	8.17	50.1 - 120	0.009	significant
Schedule (i)	084456	Copenhagen Long Cut	0 - 0.028	25.6	0 - 0.027	27.8	0 - 0.027	18.1	23.8	2.95	11.1 - 36.5	0.015	significant
Schedule (i)	084457	Ariva Wintergreen	0 - 0.013	91.3	0 - 0.012	64.2	0 - 0.012	50.6	68.7	11.9	17.3 - 120	0.029	significant
Schedule (i)	084458	Fresh Orbs	0 - 0.005	240	0 - 0.005	150	0 - 0.005	162	184	28.2	62.4 - 305	0.023	significant
Schedule (ii)	084394	Camel SNUS Frost	0 - 0.028	12.8	0 - 0.029	18.4	0 - 0.029	16.8	16.0	1.66	8.86 - 23.2	0.011	significant
Schedule (ii)	084395	2S3	0 - 0.03	13.9	0 - 0.029	11.8	0 - 0.031	15.0	13.6	0.952	9.46 - 17.7	0.005	significant
Schedule (ii)	084454	Fresh Strips	0 - 0.008	68.0	0 - 0.008	68.5	0 - 0.008	70.6	69.0	0.817	65.5 - 72.5	0.000	significant
Schedule (ii)	084455	Mellow Sticks	0 - 0.009	45.5	0 - 0.011	47.8	0 - 0.008	73.6	55.6	8.98	17 - 94.3	0.025	significant
Schedule (ii)	084456	Copenhagen Long Cut	0 - 0.028	15.3	0 - 0.027	14.9	0 - 0.027	14.5	14.9	0.211	14 - 15.8	0.000	significant
Schedule (ii)	084457	Ariva Wintergreen	0 - 0.013	31.6	0 - 0.012	48.6	0 - 0.012	51.5	43.9	6.20	17.3 - 70.6	0.019	significant
Schedule (ii)	084458	Fresh Orbs	0 - 0.005	182	0 - 0.005	128	0 - 0.005	143	151	16.1	81.8 - 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	63980.62	6	10663.44	24.00	0.000
Within Samples	6220.57	14	444.33		
Total (Corr.)	70201.19	20			

Schedule (ii)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	43067.44	6	7177.91	43.66	0.000
Within Samples	2301.79	14	164.41		
Total (Corr.)	45369.22	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).

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	0.0097	0.9229	not significant	0.0549	0.8182	not significant
084394 vs. 084454	21.3194	0.0004	significant	25.6450	0.0002	significant
084394 vs. 084455	14.2040	0.0021	significant	14.3259	0.0020	significant
084394 vs. 084456	0.0407	0.8431	not significant	0.0112	0.9174	not significant
084394 vs. 084457	7.8904	0.0139	not significant	7.1109	0.0184	not significant
084394 vs. 084458	90.3636	0.0000	significant	166.7119	0.0000	significant
084395 vs. 084454	22.2393	0.0003	significant	28.0728	0.0001	significant
084395 vs. 084455	14.9566	0.0017	significant	16.1543	0.0013	significant
084395 vs. 084456	0.0901	0.7684	not significant	0.0166	0.8994	not significant
084395 vs. 084457	8.4539	0.0115	not significant	8.4154	0.0116	not significant
084395 vs. 084458	92.2471	0.0000	significant	172.8169	0.0000	significant
084454 vs. 084455	0.7199	0.4104	not significant	1.6362	0.2216	not significant
084454 vs. 084456	19.4979	0.0006	significant	26.7256	0.0001	significant
084454 vs. 084457	3.2700	0.0921	not significant	5.7478	0.0310	not significant
084454 vs. 084458	23.8992	0.0002	significant	61.5849	0.0000	significant
084455 vs. 084456	12.7246	0.0031	not significant	15.1364	0.0016	significant
084455 vs. 084457	0.9213	0.3534	not significant	1.2506	0.2823	not significant
084455 vs. 084458	32.9150	0.0001	significant	83.2974	0.0000	significant
084456 vs. 084457	6.7982	0.0207	not significant	7.6853	0.0150	not significant
084456 vs. 084458	86.5704	0.0000	significant	169.4498	0.0000	significant
084457 vs. 084458	44.8496	0.0000	significant	104.9613	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)

Sample Description	Sample ID	Mean Slope	Homogenous Groupings
2S3	084395	18.6	X
Camel SNUS Frost	084394	20.3	X
Copenhagen Long Cut	084456	23.8	XX
Ariva Wintergreen	084457	68.7	XXX
Mellow Sticks	084455	85.2	XX
Fresh Strips	084454	99.8	X
Fresh Orbs	084458	184	X

Schedule (ii)

Sample Description	Sample ID	Mean Slope	Homogenous Groupings
2S3	084395	13.6	X
Copenhagen Long Cut	084456	14.9	X
Camel SNUS Frost	084394	16.0	X
Ariva Wintergreen	084457	43.9	XX
Mellow Sticks	084455	55.6	X
Fresh Strips	084454	69.0	X
Fresh Orbs	084458	151	X

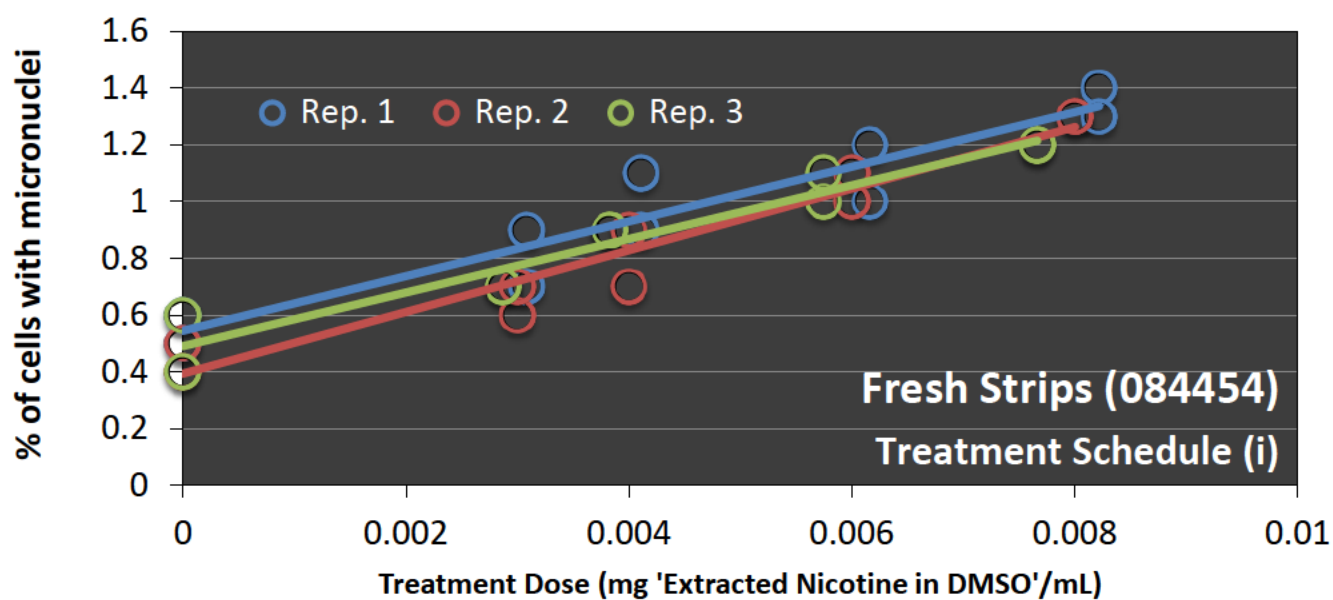
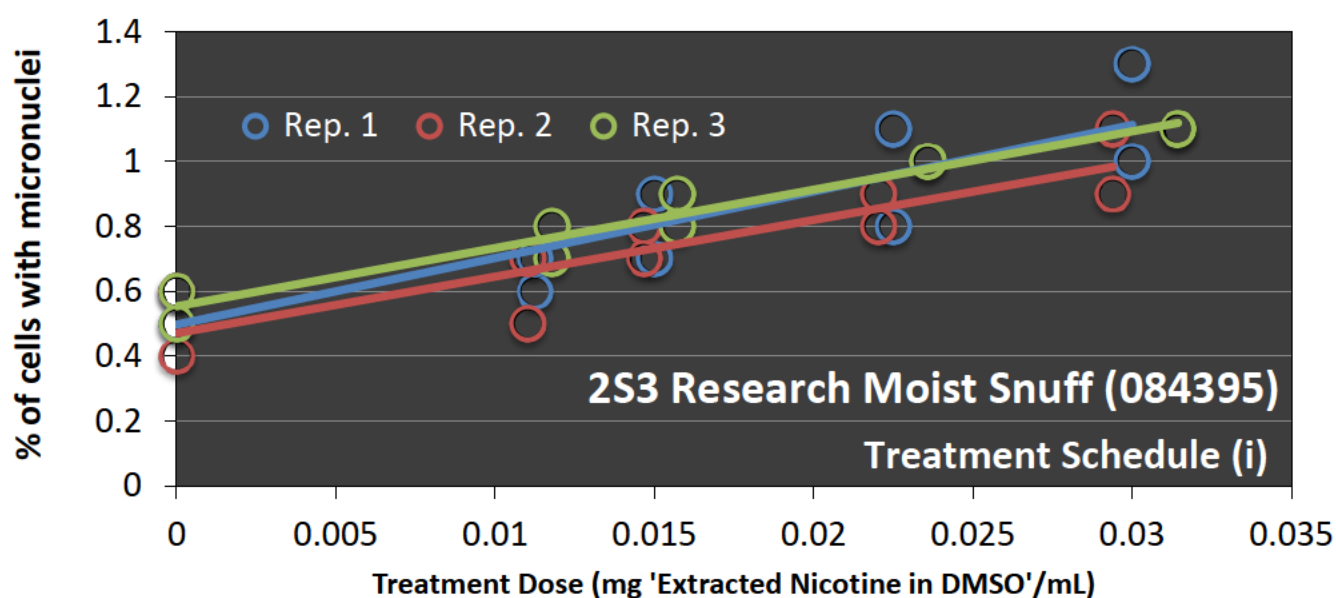
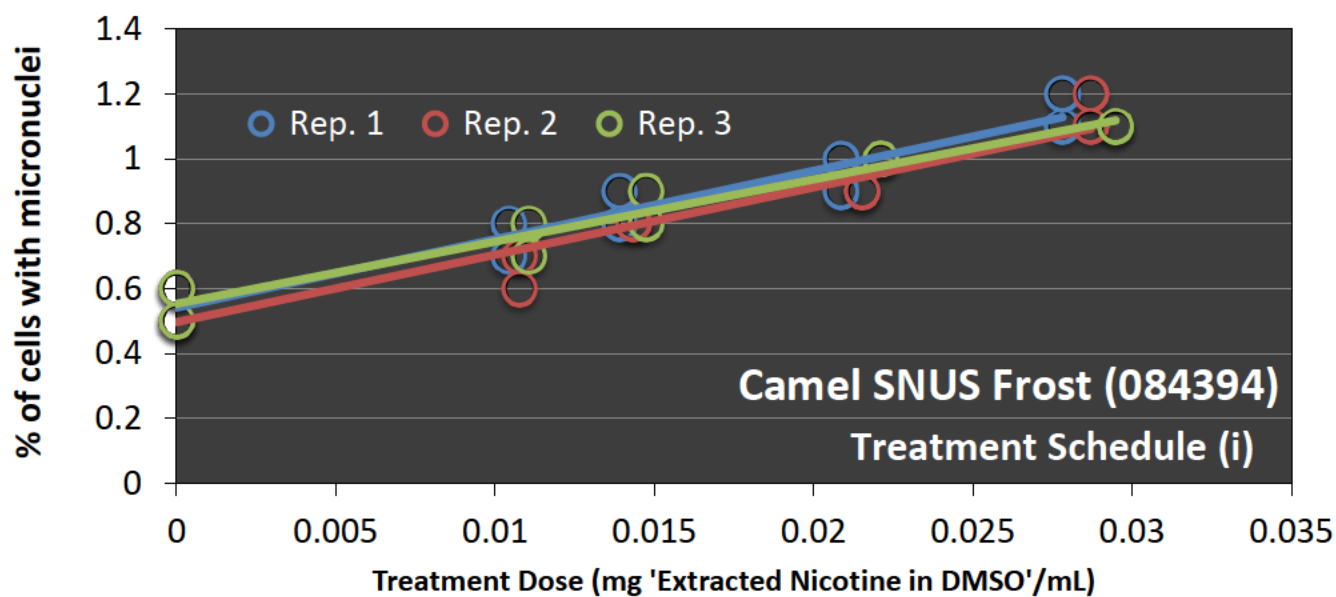
Pairwise T-test Comparisons of Mean 'Extracted Nicotine' Slope for Contrasts of Interest using Bonferroni-adjusted p-values

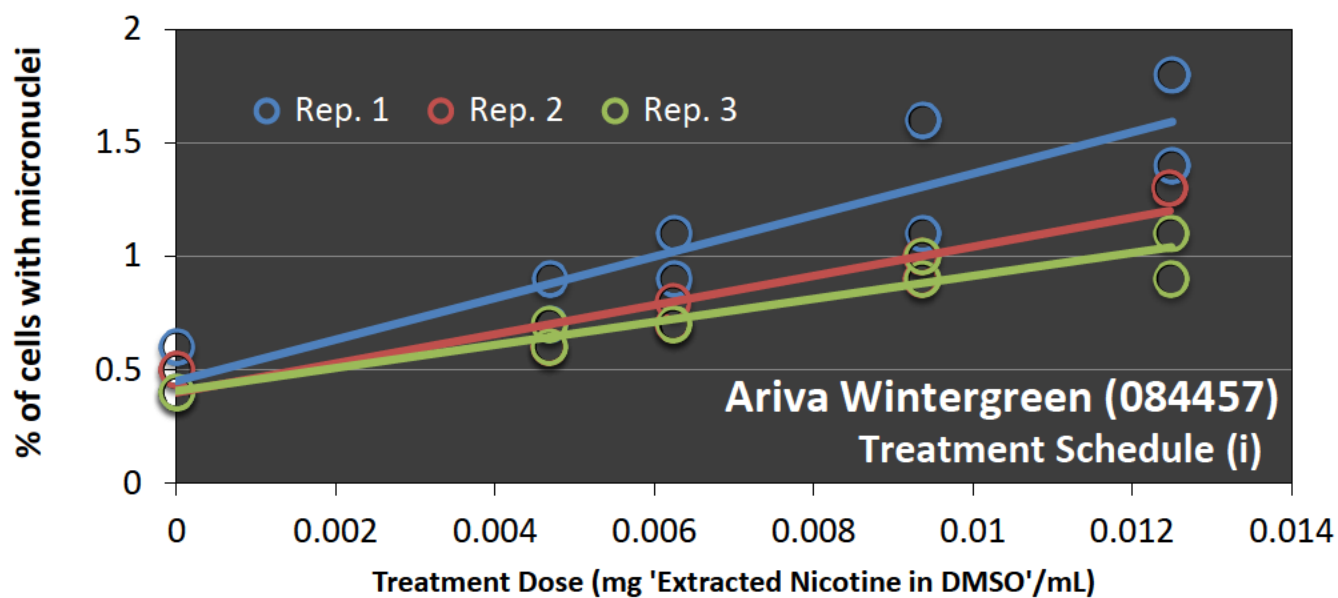
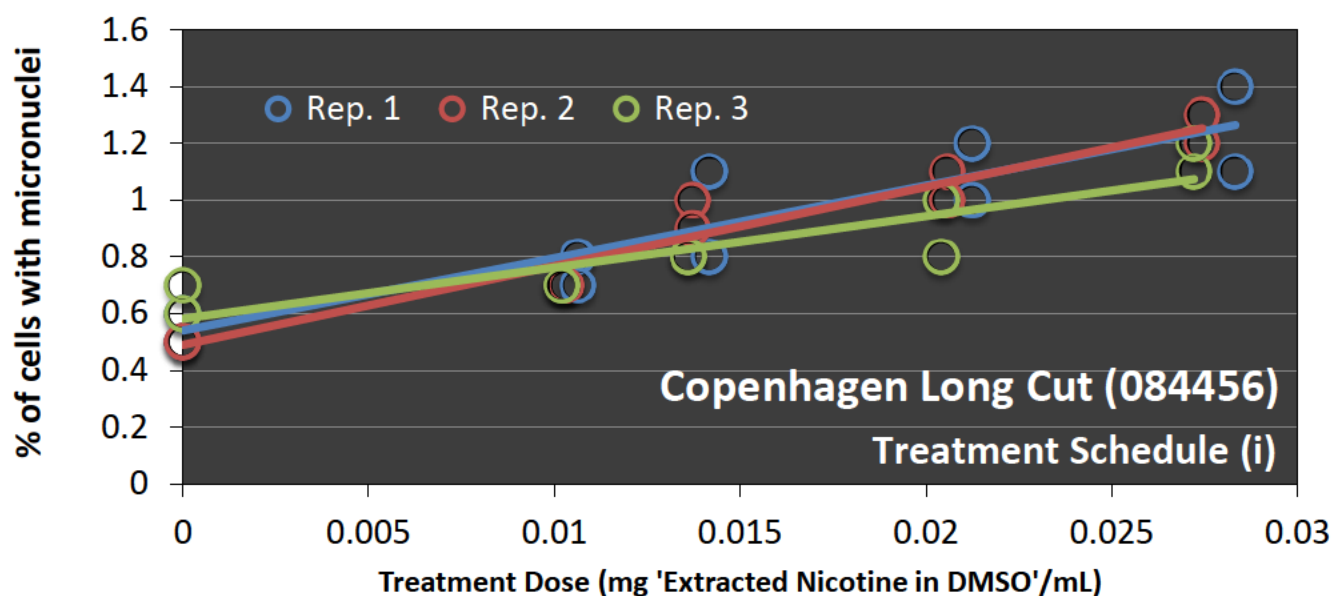
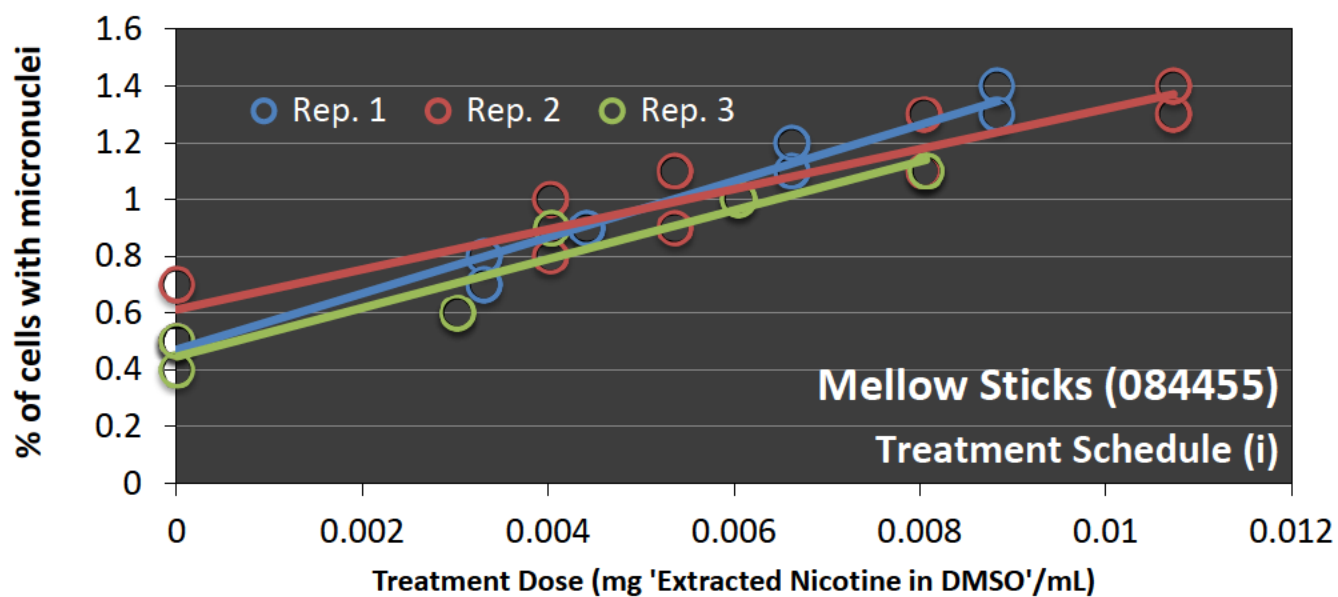
Pairwise T-Test Comparison	Schedule (i)			Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084395	1.5251	0.2019	not significant	1.2809	0.2694	not significant
084394 vs. 084454	17.6871	0.0001	significant	28.6353	0.0000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

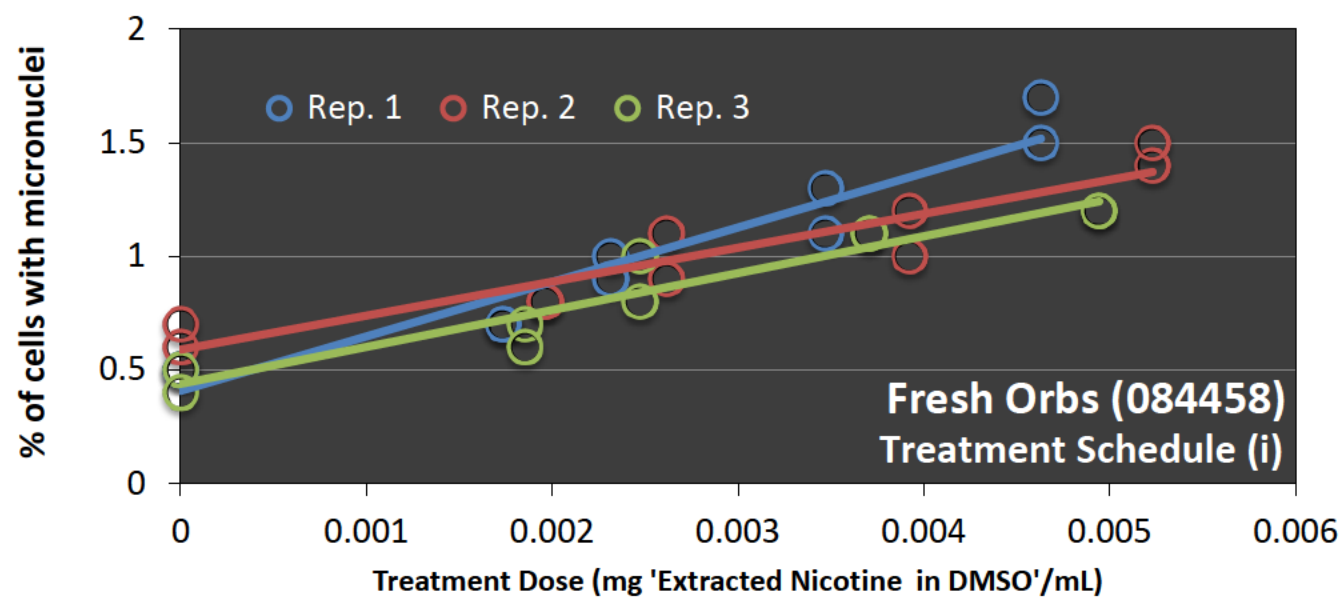
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'extracted nicotine' slope were detected between:

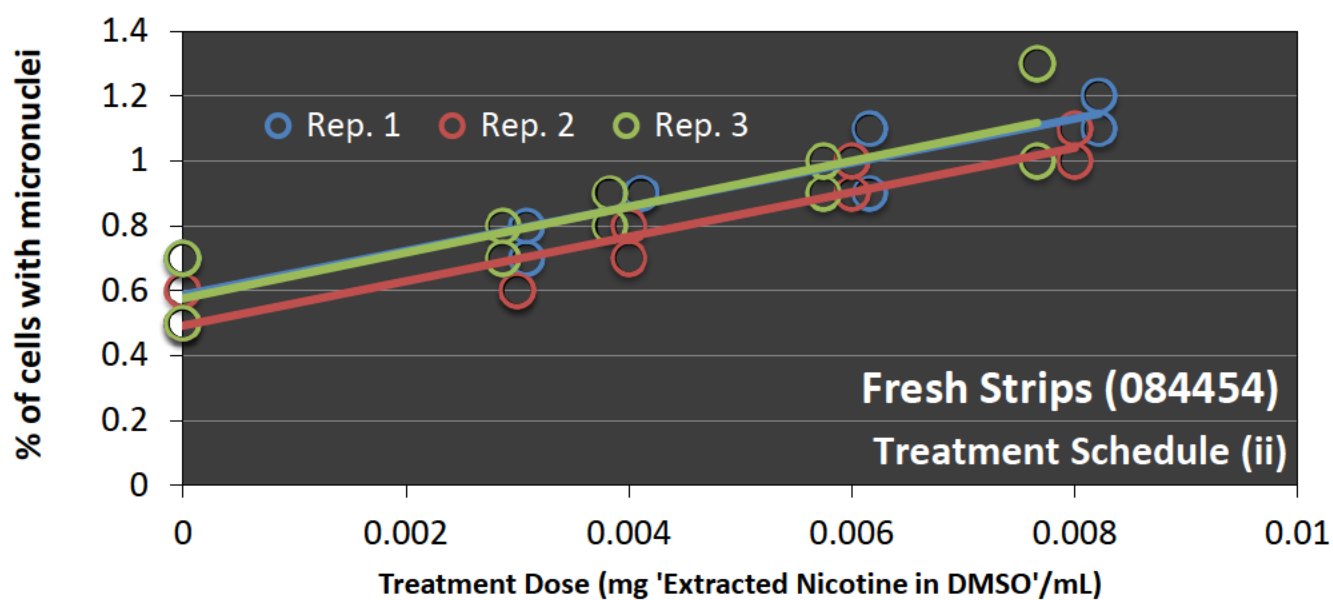
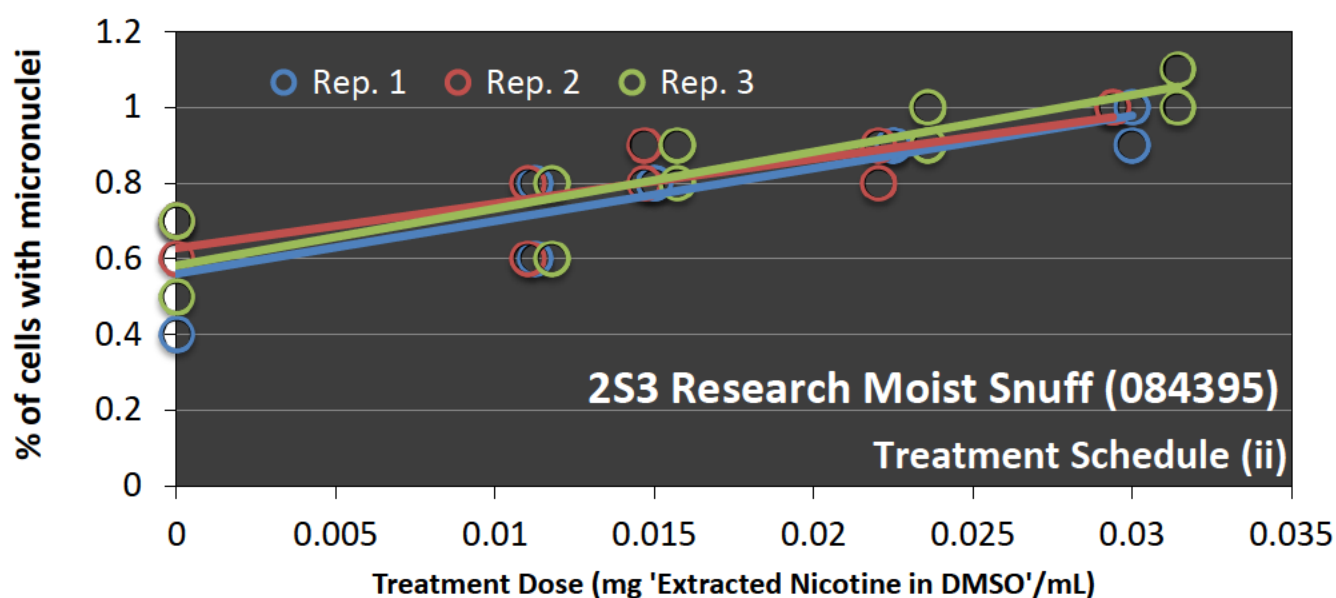
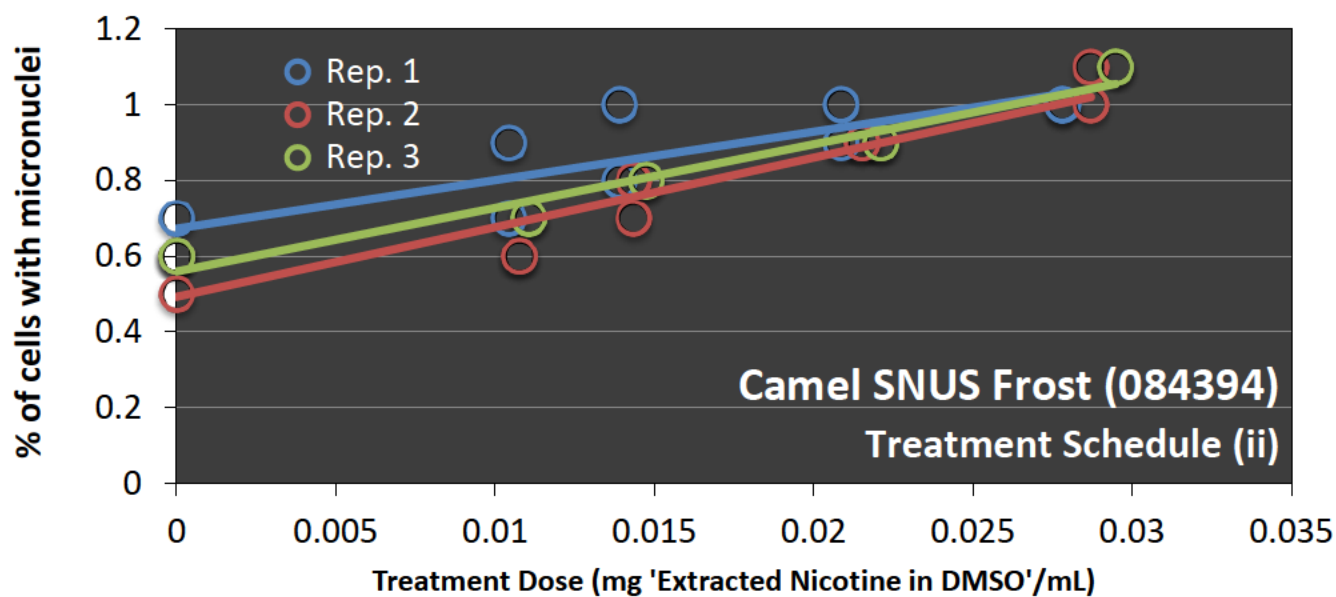
Fresh Strips (084454) as well as Mellow Sticks (084455) and each of {Camel SNUS Frost (084394), 2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456)} under treatment schedule (i).

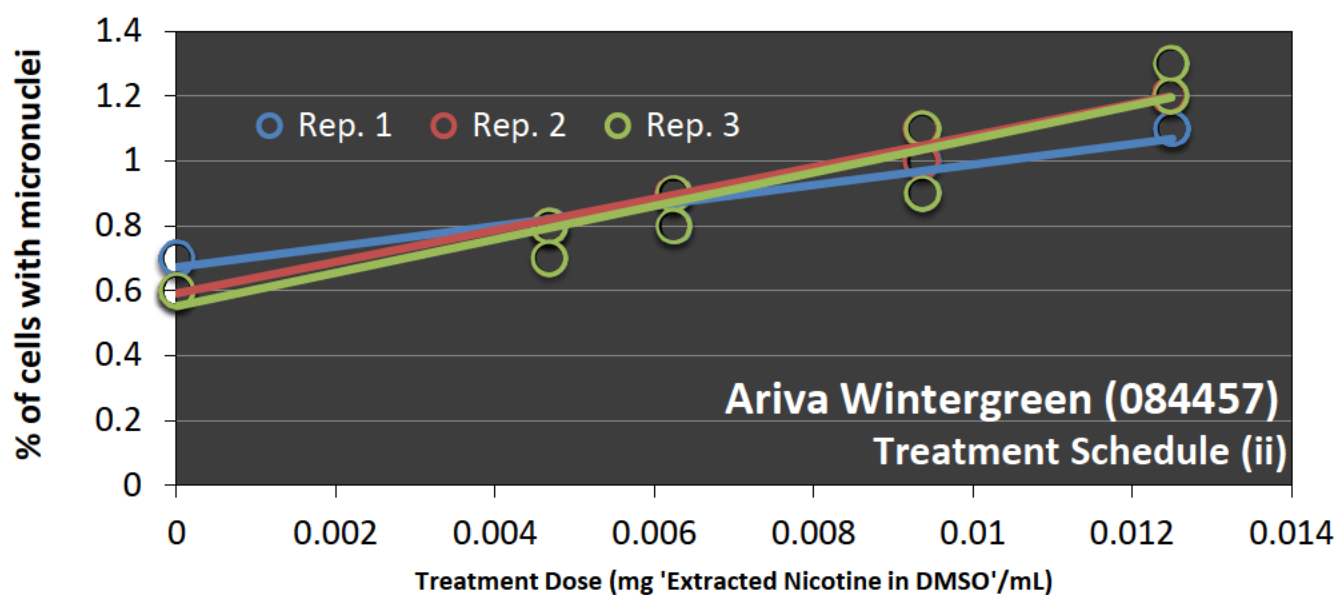
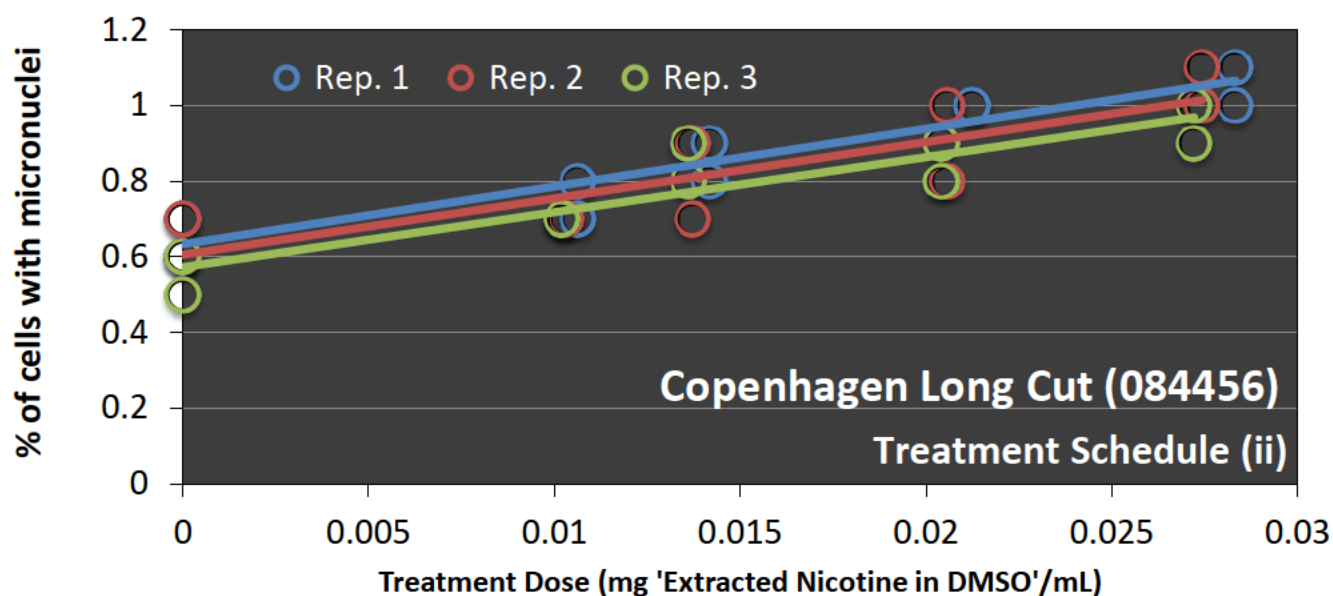
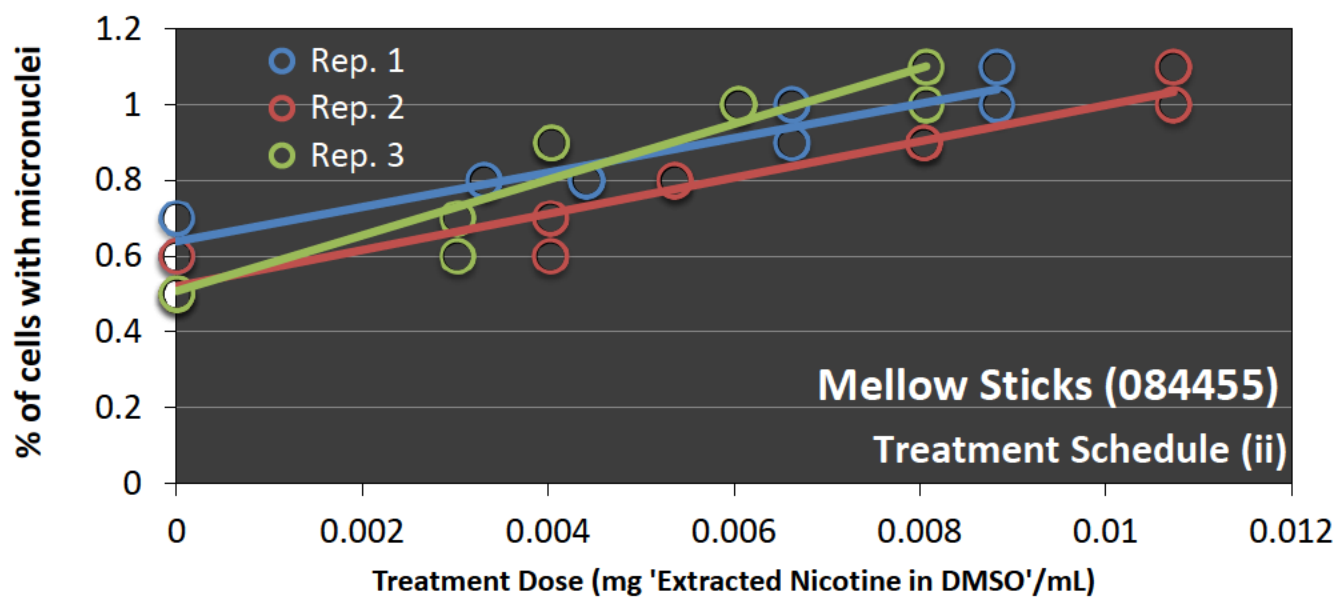
Fresh Strips (084454) as well as Fresh Orbs (084458) and each of {Camel SNUS Frost (084394), 2S3 Research Moist Snuff (084395), Copenhagen Long Cut (084456)} under treatment schedule (ii).

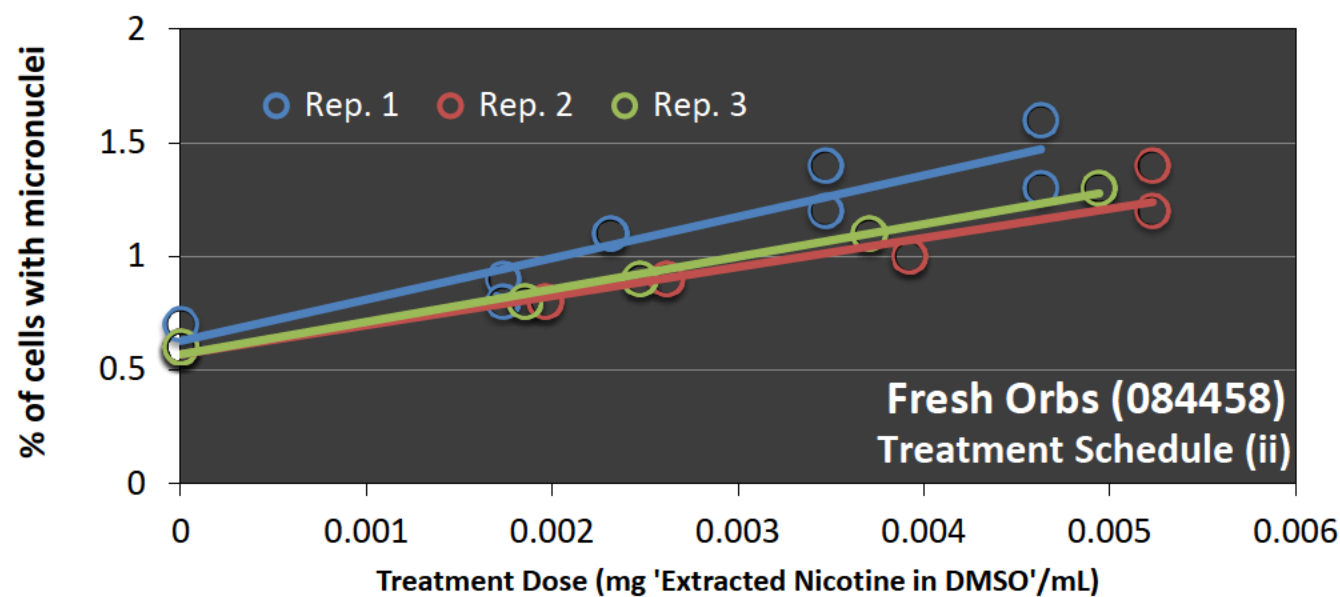


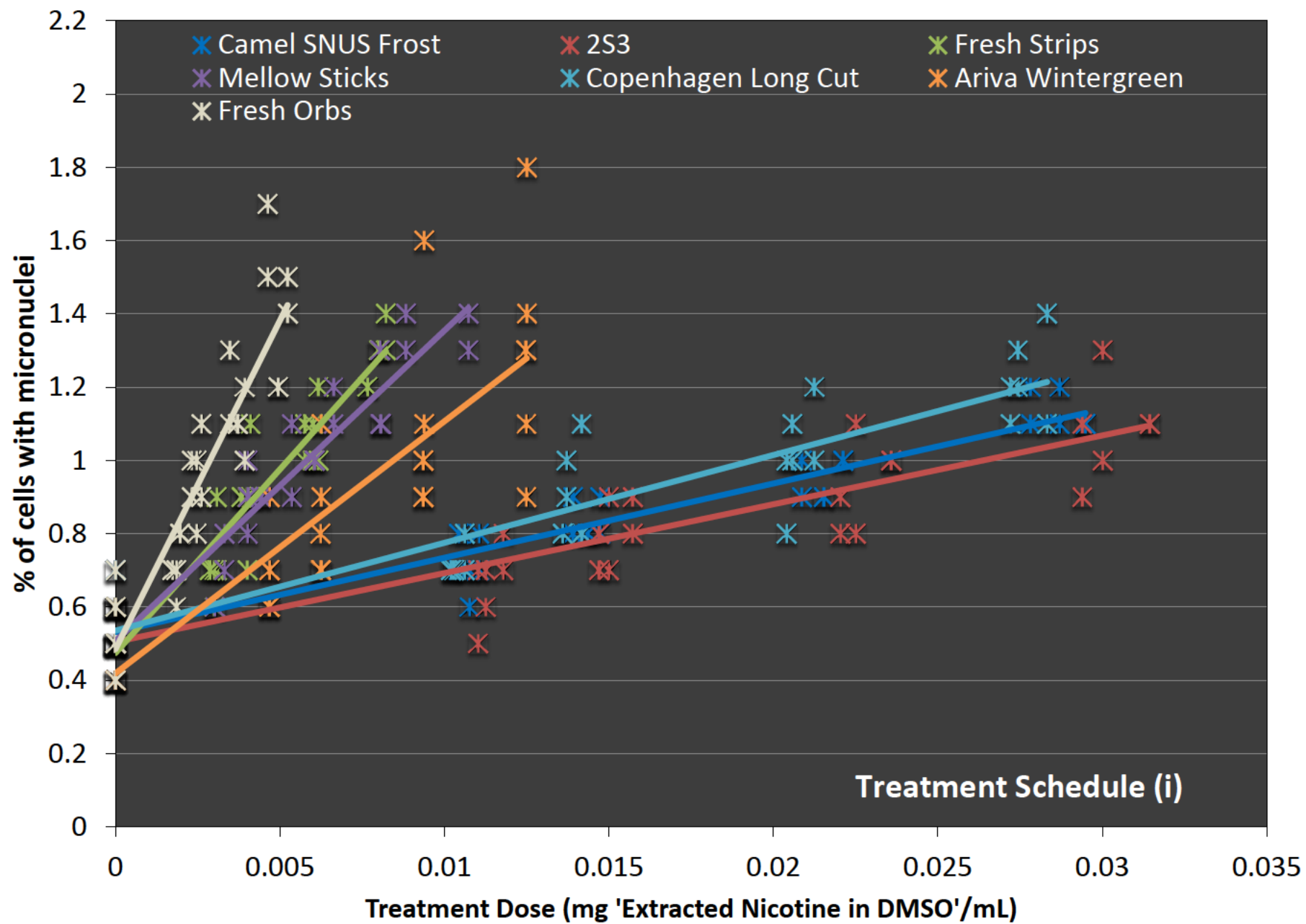


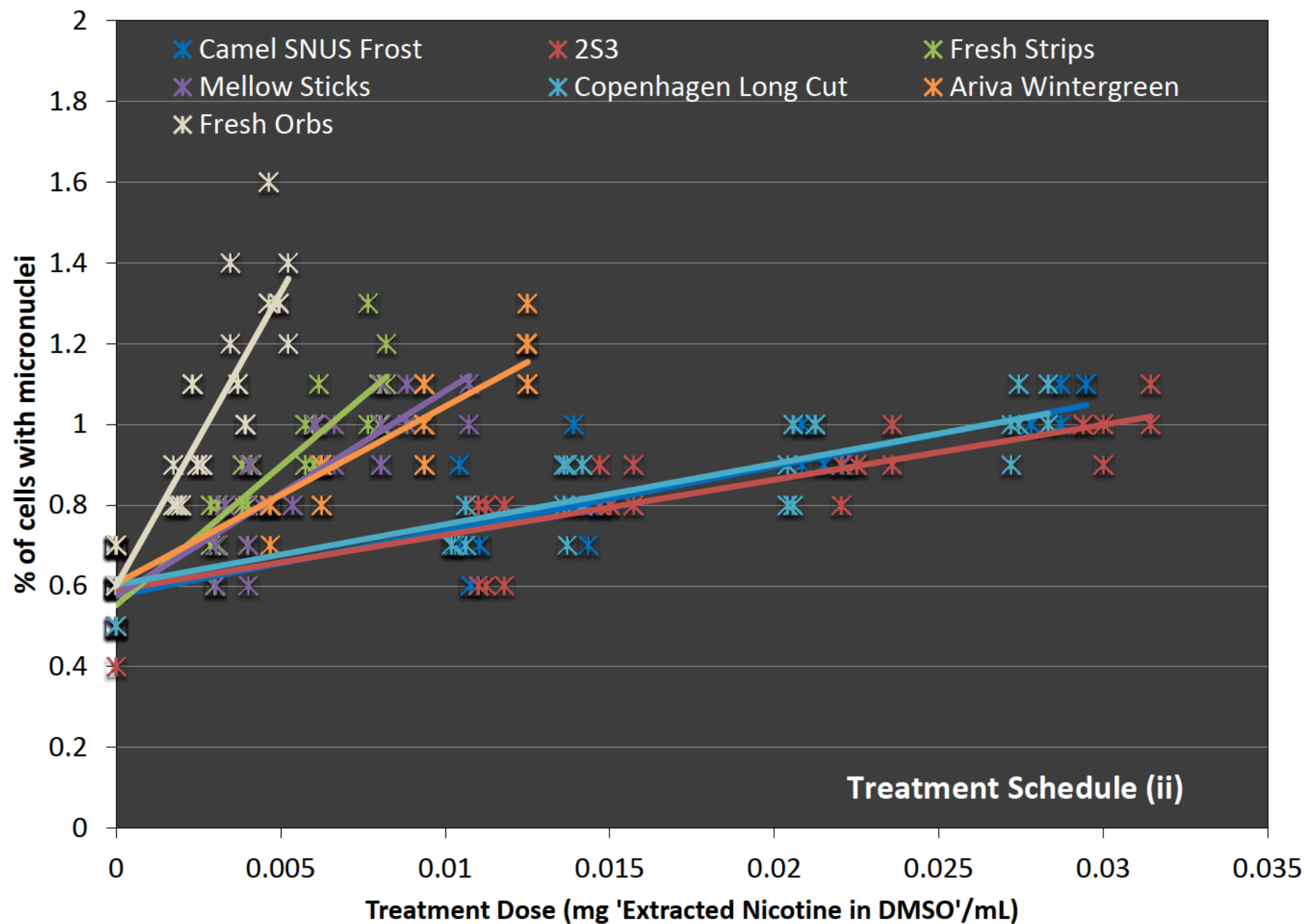












Slope Analysis of the Linear Portion of the Dose-Response Curve for Smokeless Tobacco [%MNC*/(mg 'Extracted Nicotine in DMSO'/mL)] and Smoked Tobacco [%MNC/(mg 'Nicotine in CSC'/mL)] Samples

			% MNC /(mg 'Nicotine in CSC'/mL) (KR 2R4F) or % MNC /(mg '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)	
			(mg 'Nic.'/mL)	slope	(mg 'Nic.'/mL)	slope	(mg 'Nic.'/mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084394	Camel SNUS Frost	0 - 0.028	21.1	0 - 0.029	20.8	0 - 0.029	19.2	20.3	0.594	17.8 - 22.9	0.001	significant
Schedule (i)	084395	2S3	0 - 0.03	20.5	0 - 0.029	17.5	0 - 0.031	18.0	18.6	0.940	14.6 - 22.7	0.003	significant
Schedule (i)	084396	KR 2R4F	0 - 0.013	120	0 - 0.014	108	0 - 0.014	104	111	4.9	90 - 132	0.002	significant
Schedule (i)	084454	Fresh Strips	0 - 0.008	96.3	0 - 0.008	109	0 - 0.008	94.5	99.8	4.45	80.6 - 119	0.002	significant
Schedule (i)	084455	Mellow Sticks	0 - 0.009	99.0	0 - 0.011	70.7	0 - 0.008	86.0	85.2	8.17	50.1 - 120	0.009	significant
Schedule (i)	084456	Copenhagen Long Cut	0 - 0.028	25.6	0 - 0.027	27.8	0 - 0.027	18.1	23.8	2.95	11.1 - 36.5	0.015	significant
Schedule (i)	084457	Ariva Wintergreen	0 - 0.013	91.3	0 - 0.012	64.2	0 - 0.012	50.6	68.7	11.9	17.3 - 120	0.029	significant
Schedule (i)	084458	Fresh Orbs	0 - 0.005	240	0 - 0.005	150	0 - 0.005	162	184	28.2	62.4 - 305	0.023	significant
Schedule (ii)	084394	Camel SNUS Frost	0 - 0.028	12.8	0 - 0.029	18.4	0 - 0.029	16.8	16.0	1.66	8.86 - 23.2	0.011	significant
Schedule (ii)	084395	2S3	0 - 0.03	13.9	0 - 0.029	11.8	0 - 0.031	15.0	13.6	0.952	9.46 - 17.7	0.005	significant
Schedule (ii)	084396	KR 2R4F	0 - 0.013	81.1	0 - 0.014	75.4	0 - 0.014	73.1	76.5	2.4	66.4 - 86.7	0.001	significant
Schedule (ii)	084454	Fresh Strips	0 - 0.008	68.0	0 - 0.008	68.5	0 - 0.008	70.6	69.0	0.817	65.5 - 72.5	0.000	significant
Schedule (ii)	084455	Mellow Sticks	0 - 0.009	45.5	0 - 0.011	47.8	0 - 0.008	73.6	55.6	8.98	17 - 94.3	0.025	significant
Schedule (ii)	084456	Copenhagen Long Cut	0 - 0.028	15.3	0 - 0.027	14.9	0 - 0.027	14.5	14.9	0.211	14 - 15.8	0.000	significant
Schedule (ii)	084457	Ariva Wintergreen	0 - 0.013	31.6	0 - 0.012	48.6	0 - 0.012	51.5	43.9	6.20	17.3 - 70.6	0.019	significant
Schedule (ii)	084458	Fresh Orbs	0 - 0.005	182	0 - 0.005	128	0 - 0.005	143	151	16.1	81.8 - 221	0.011	significant

* MNC = micronucleated cells

Cigarette smoke condensate (CSC) test sample with mg '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	67999.07	7	9714.15	24.42	0.000
Within Samples	6364.65	16	397.79		
Total (Corr.)	74363.72	23			

Schedule (ii)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	44641.31	7	6377.33	43.69	0.000
Within Samples	2335.27	16	145.95		
Total (Corr.)	46976.59	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).

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)

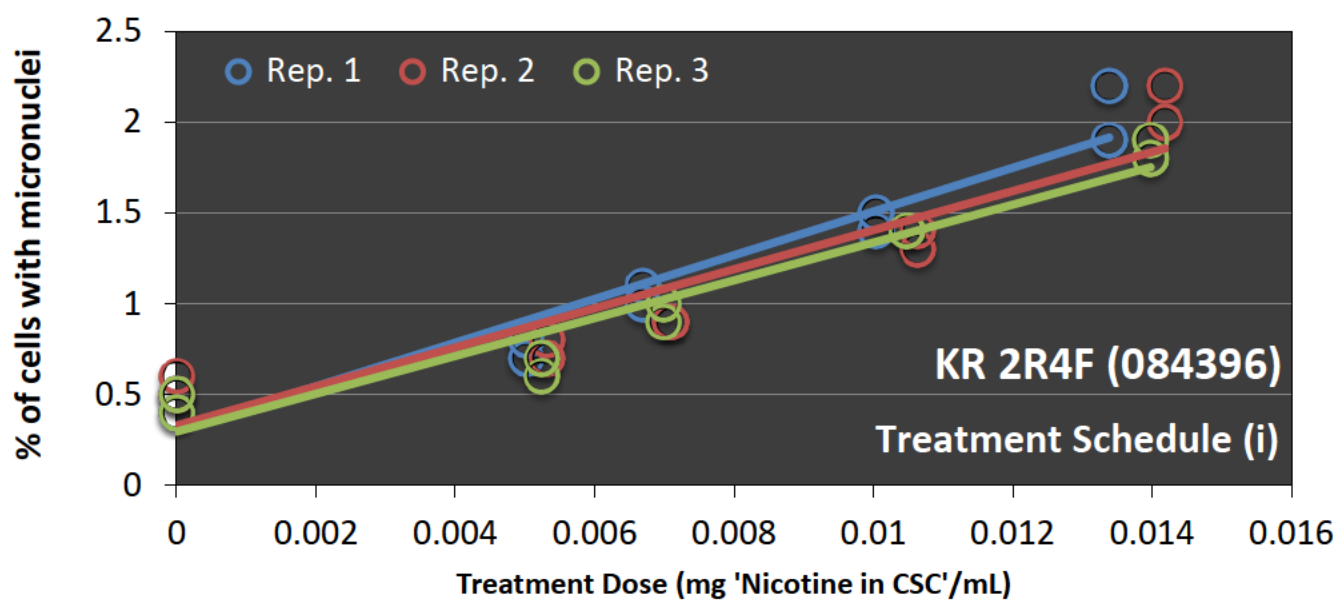
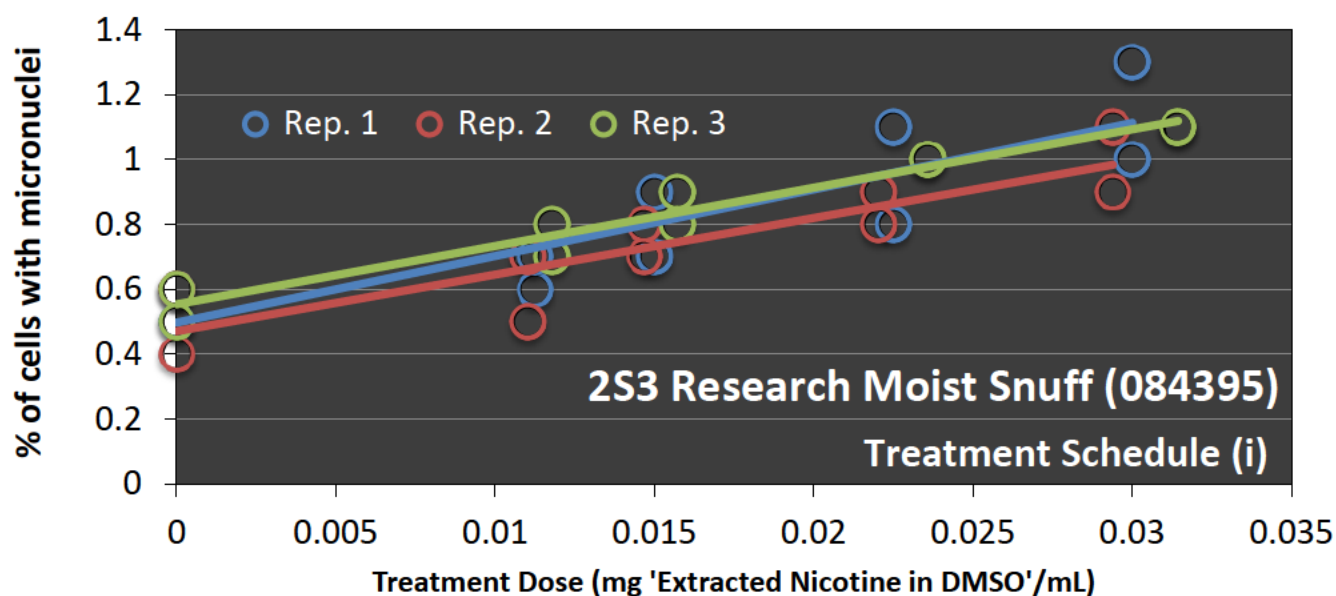
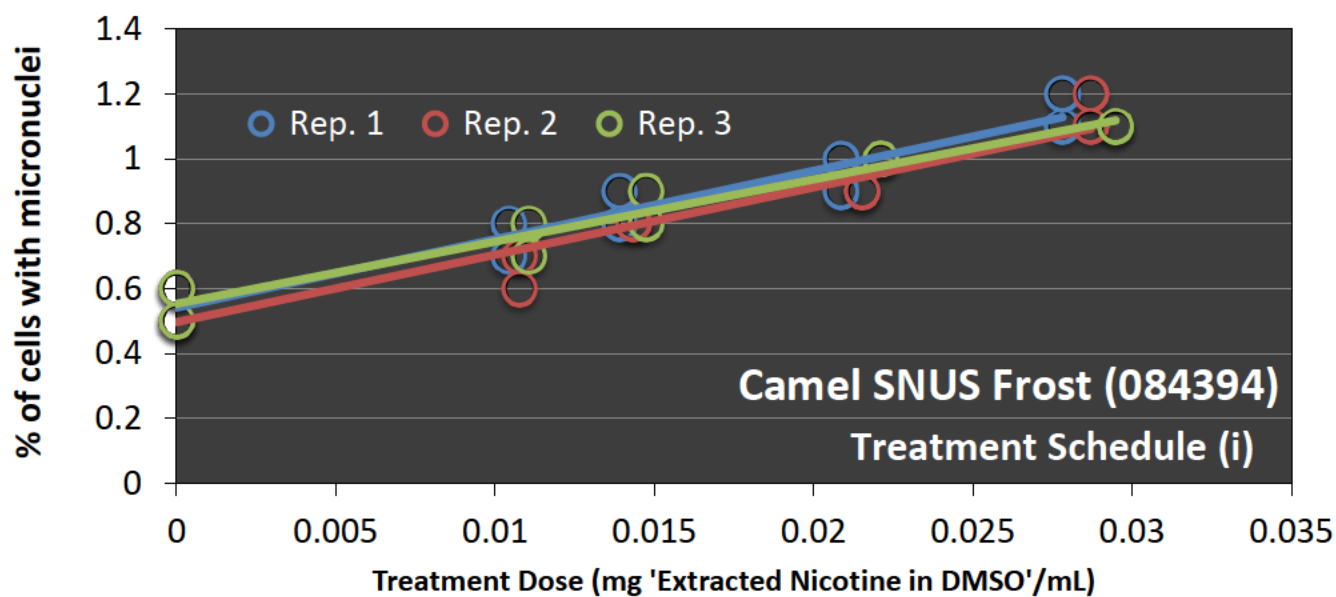
{Camel SNUS Frost (084394), 2S3 (084395), Copenhagen Long Cut (084456), Ariva Wintergreen (084457), Fresh Orbs (084458)}

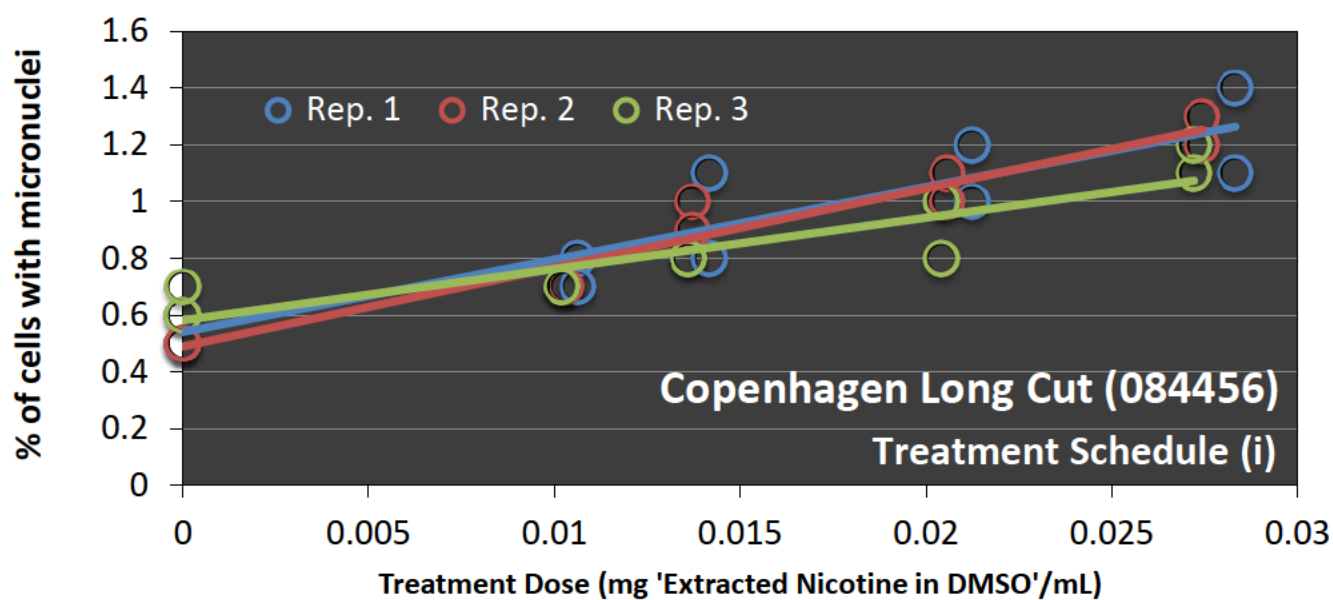
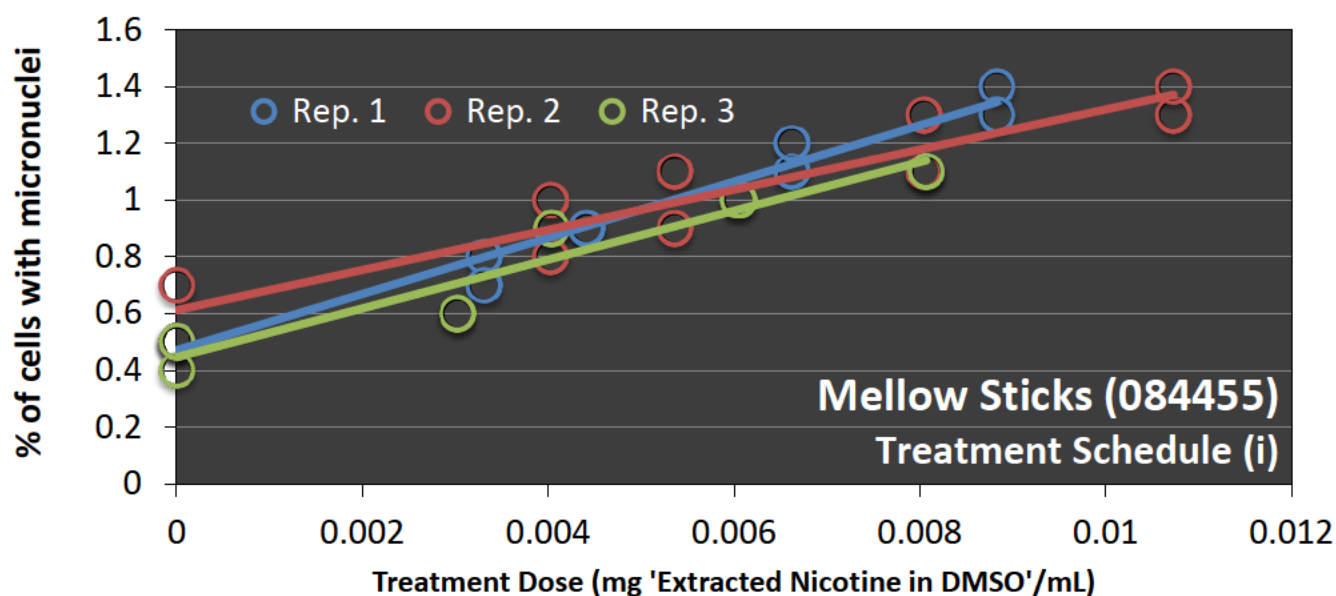
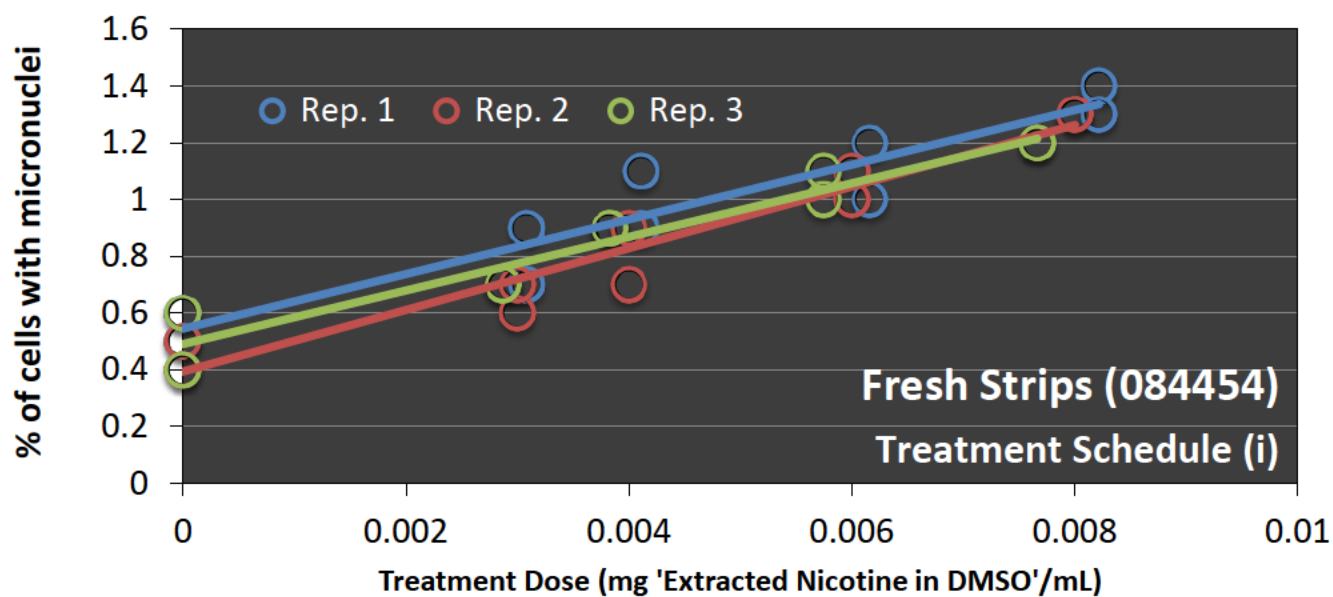
Pairwise T-test Comparisons of Smokeless Tobacco Mean 'Extracted Nicotine in DMSO' Slope to Control Brand KR 2R4F (084396) Mean 'Nicotine in CSC' Slope using Bonferroni-adjusted p-values

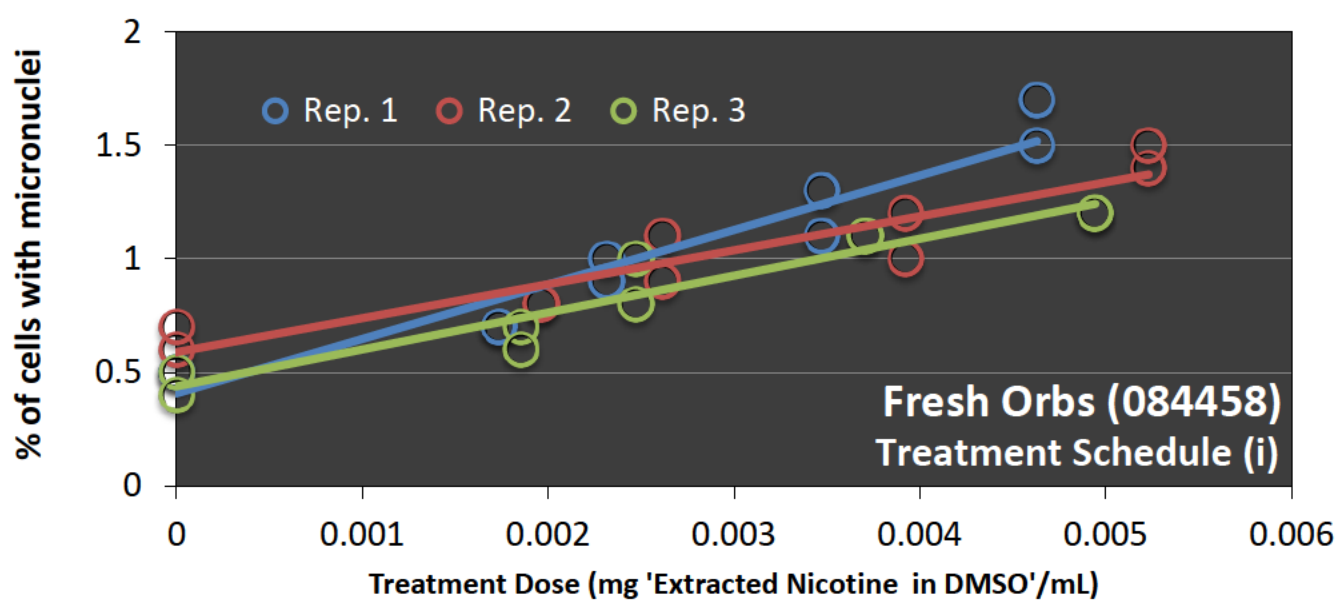
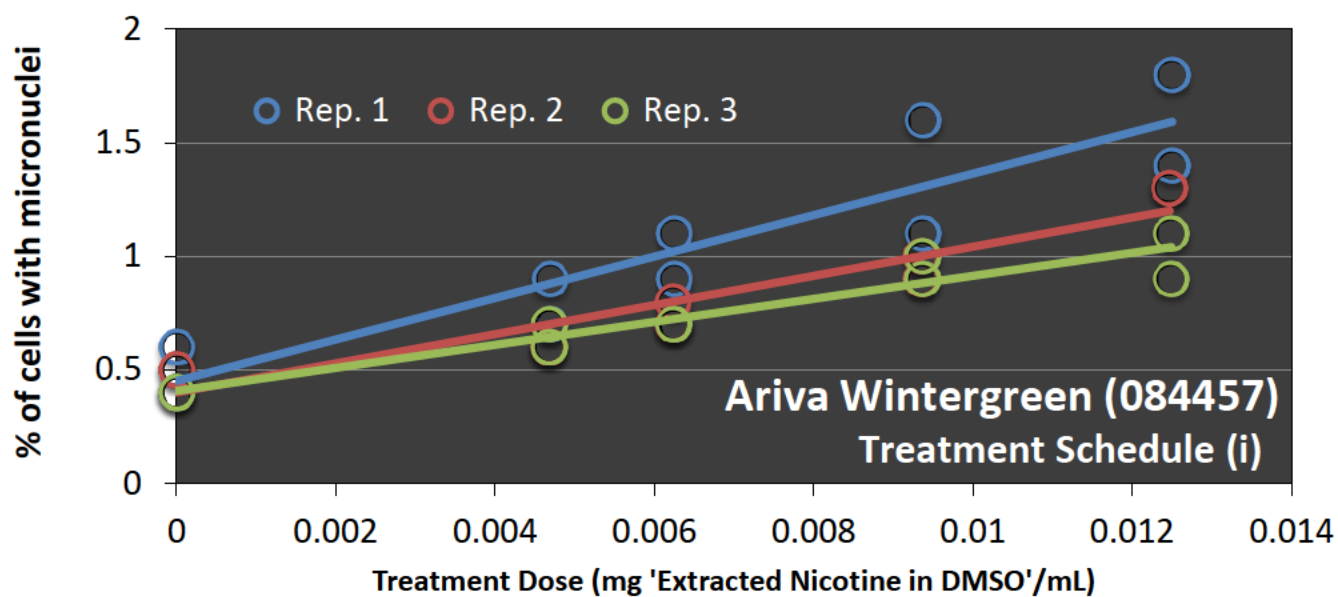
Pairwise T-Test Comparison	Schedule (ii)		
	t-statistic	p-value	significance at $\alpha = 0.05$
084394 vs. 084396	20.9526	3.1E-05	significant
084395 vs. 084396	24.7207	1.6E-05	significant
084454 vs. 084396	2.9980	0.0400	not significant
084455 vs. 084396	2.2482	0.0878	not significant
084456 vs. 084396	25.9795	1.3E-05	significant
084457 vs. 084396	4.9121	0.0080	not significant
084458 vs. 084396	4.5810	0.0102	not significant

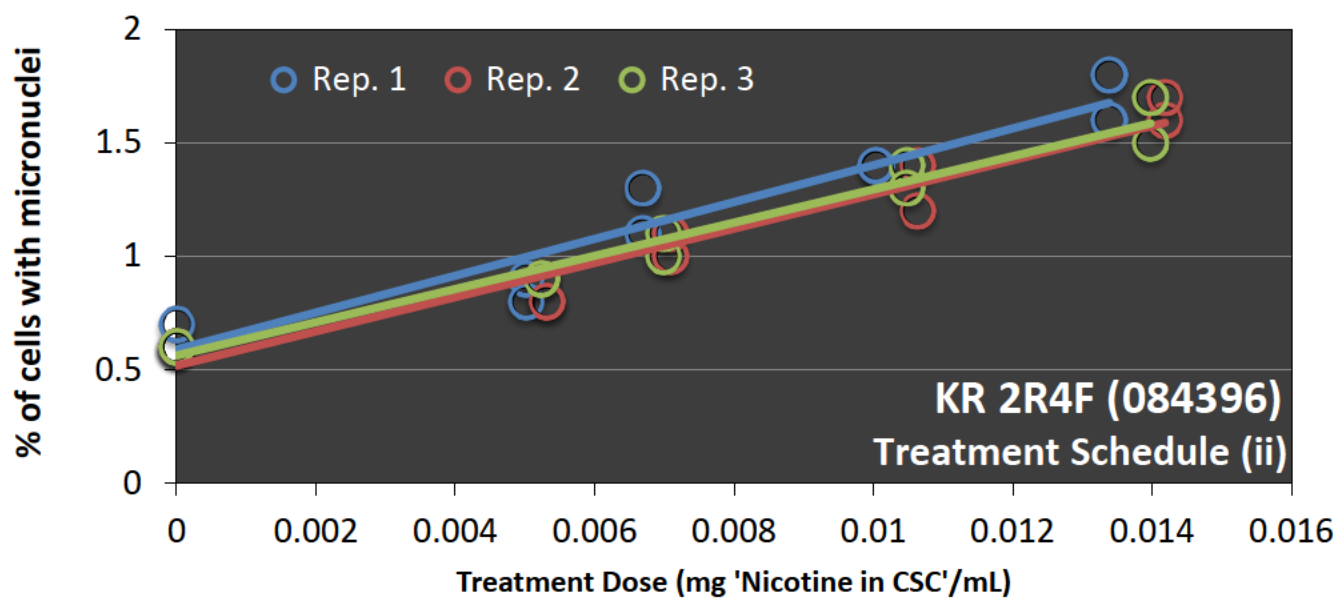
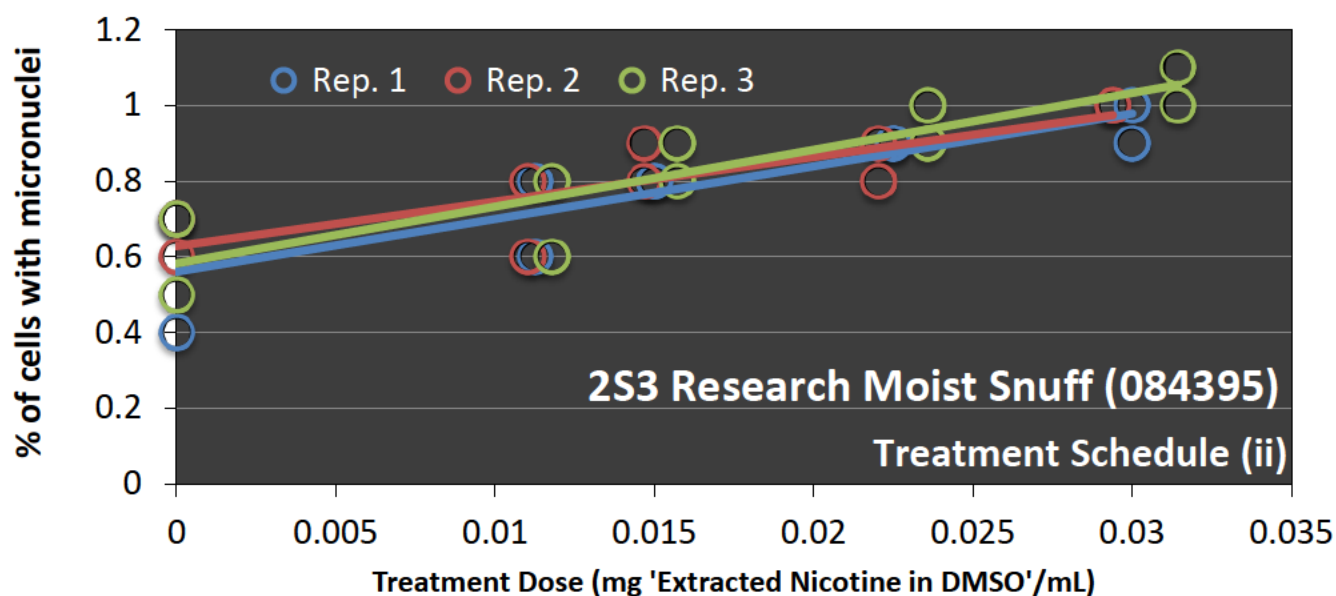
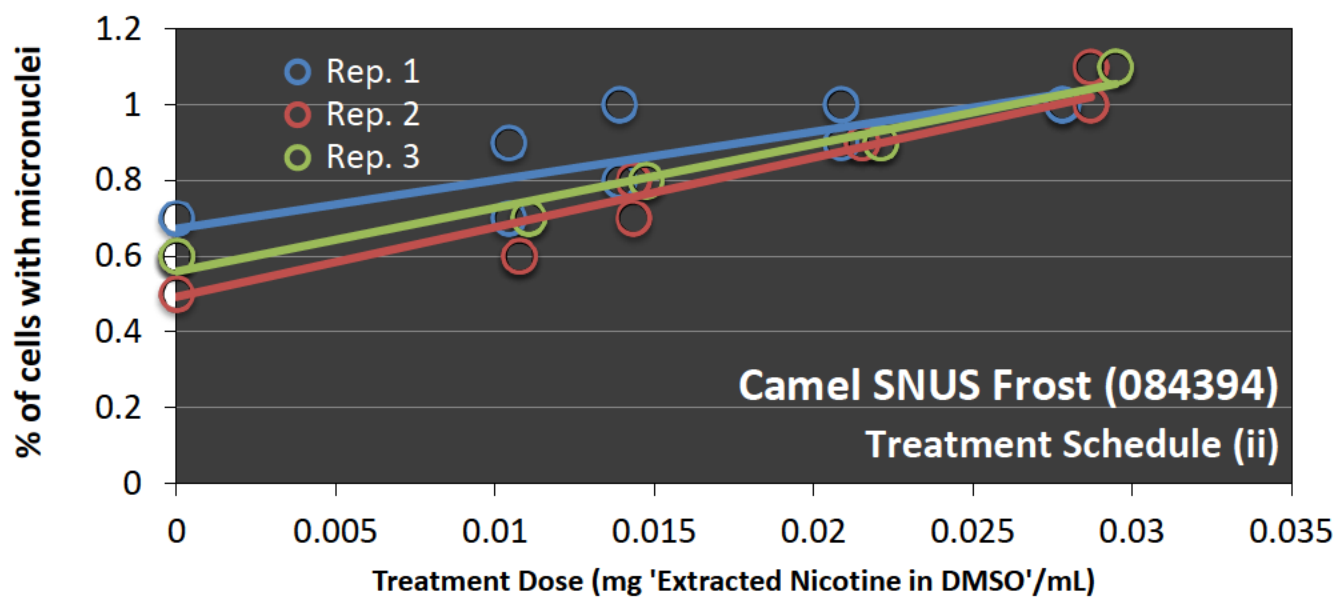
Pairwise t-test comparison p-values less than the Bonferroni-adjusted $\alpha = 0.05$ indicate that significant differences were detected between the mean 'nicotine in CSC' slope of the KR 2R4F (084396) smoked tobacco samples and the mean 'extracted nicotine in DMSO' slope of the following smokeless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

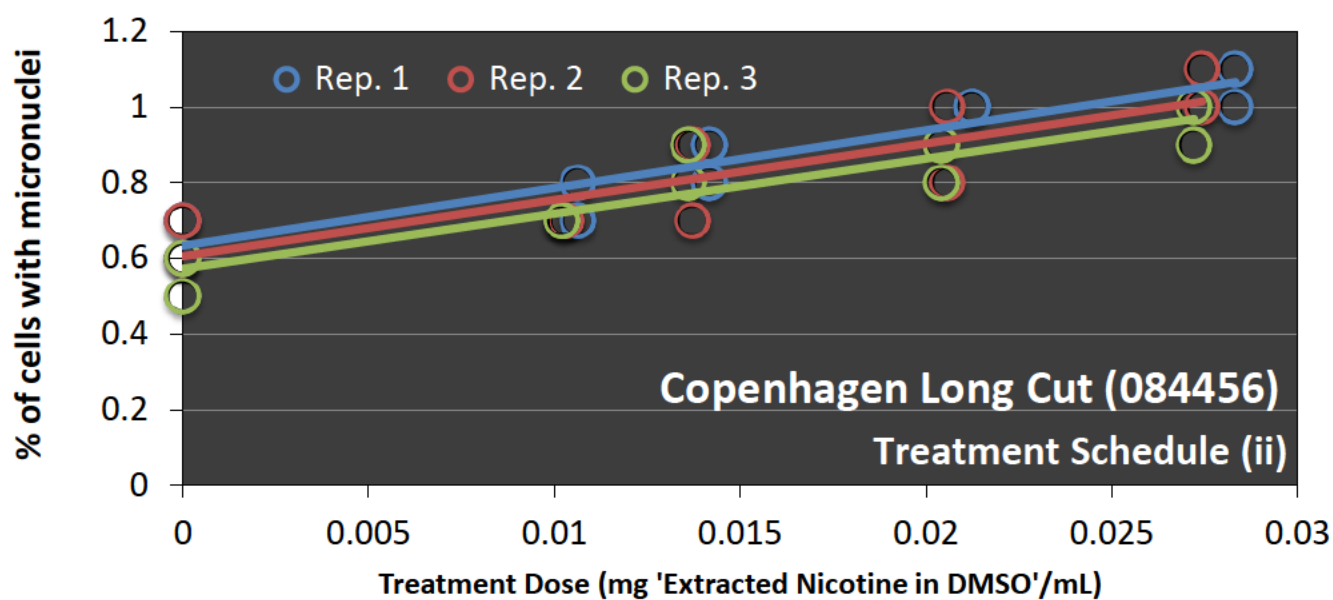
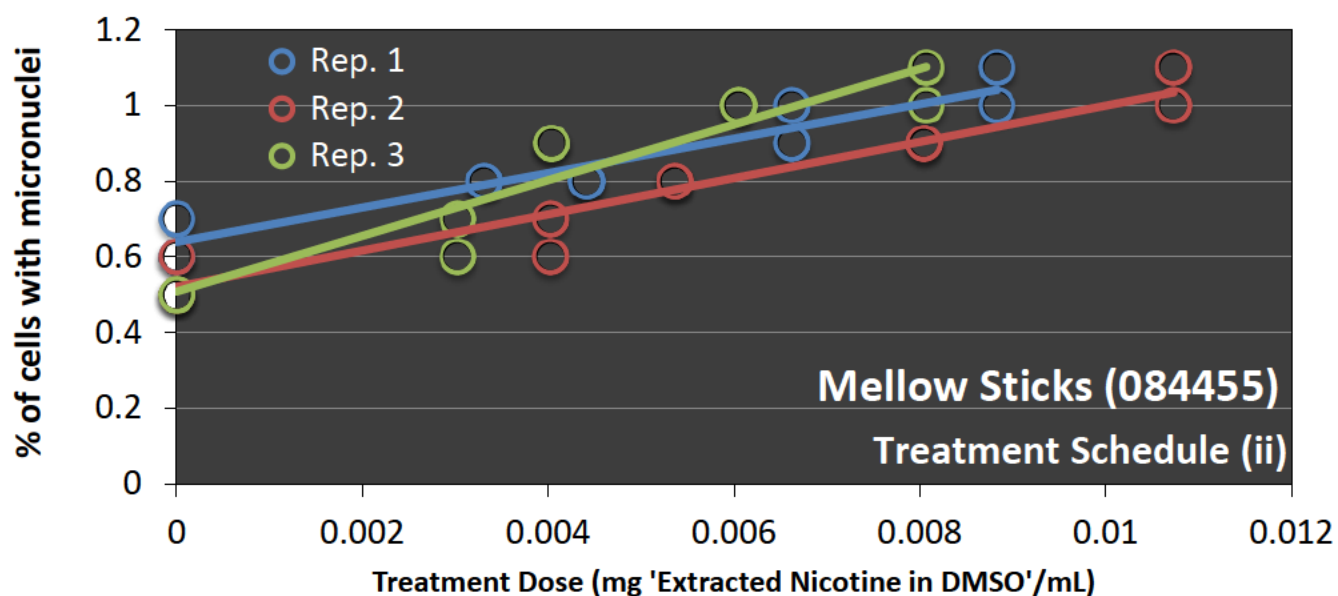
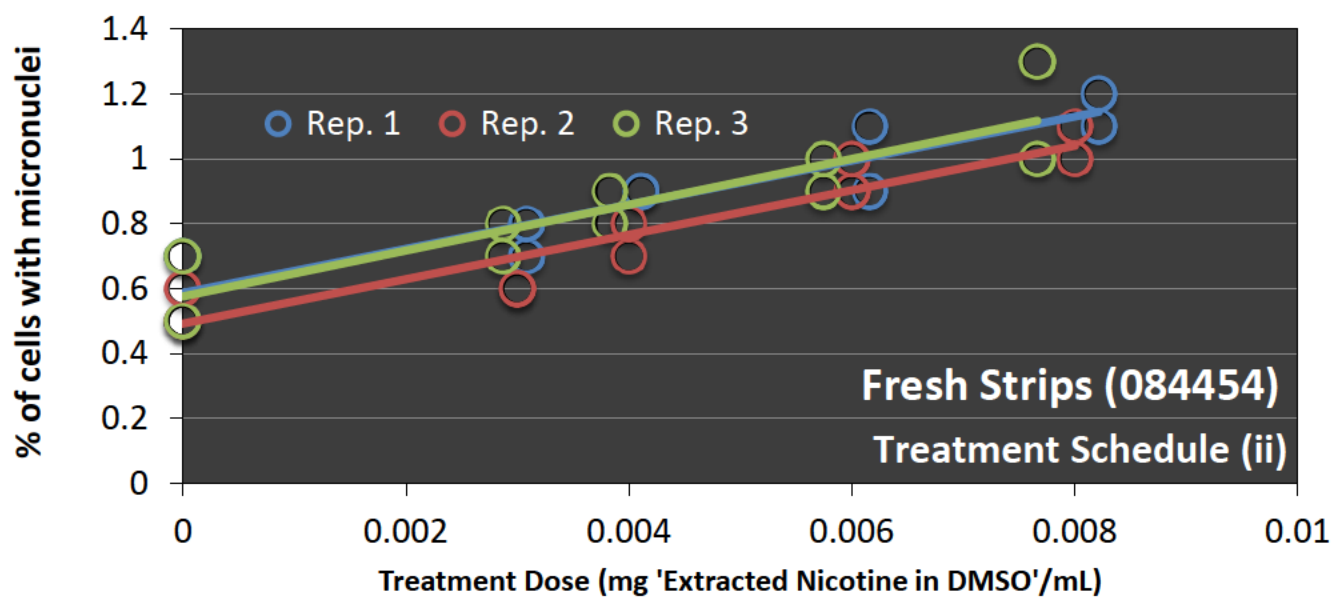
{Camel SNUS Frost (084394), 2S3 (084395), Copenhagen Long Cut (084456)}

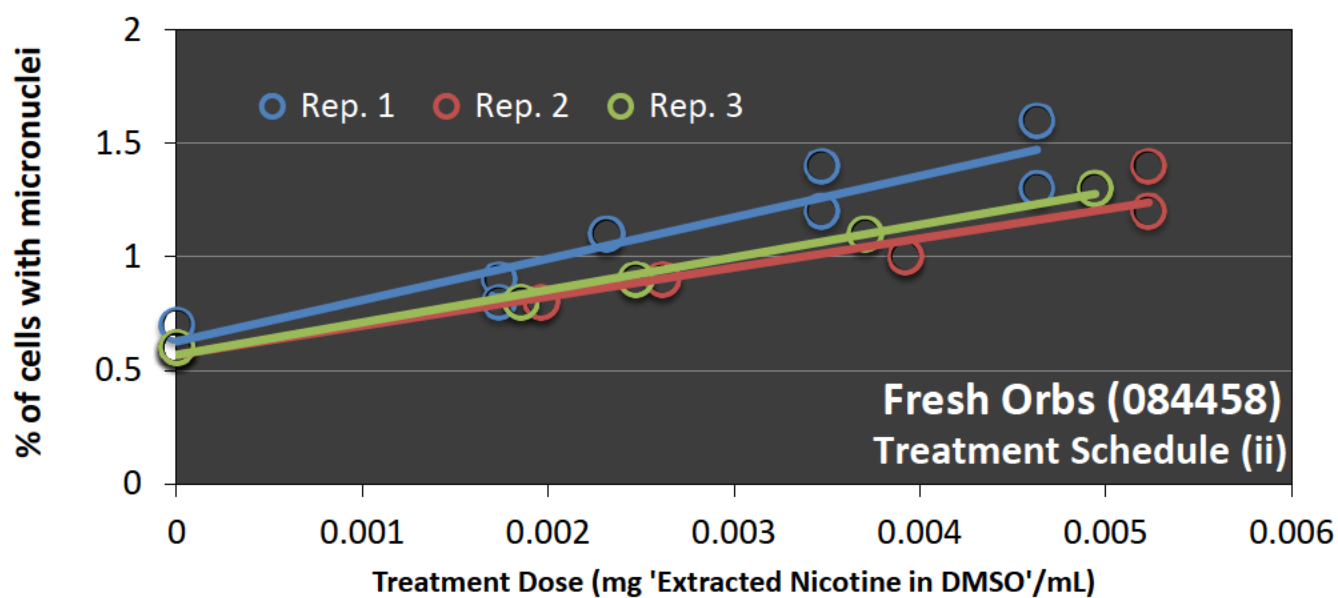
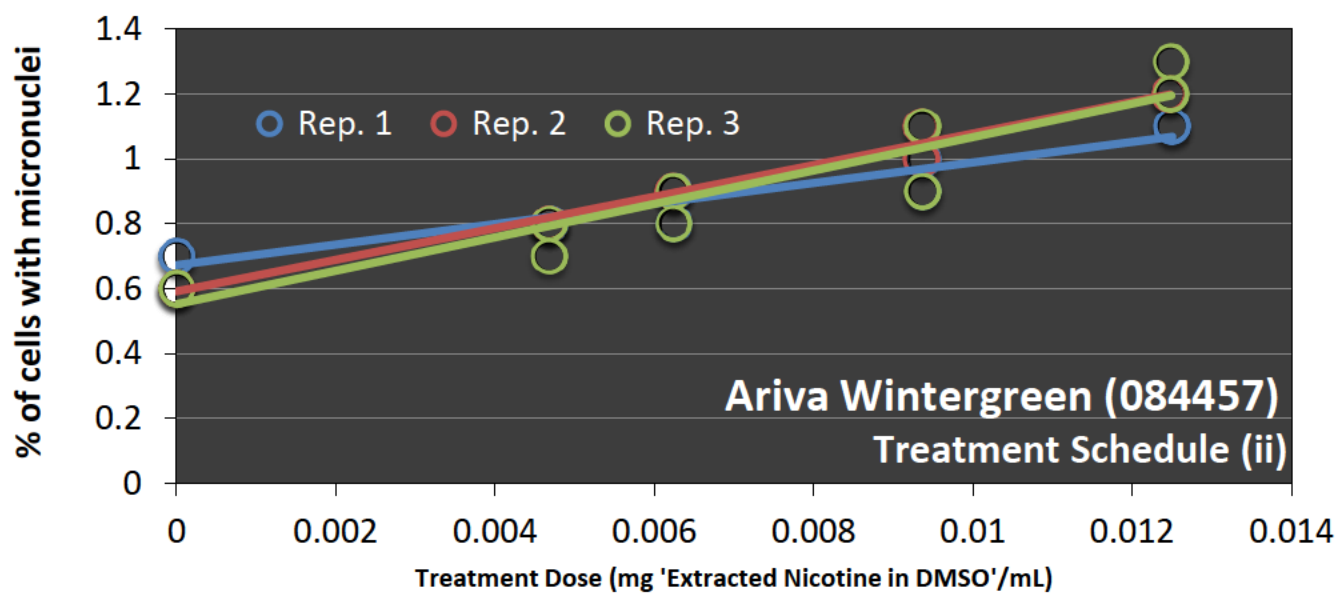


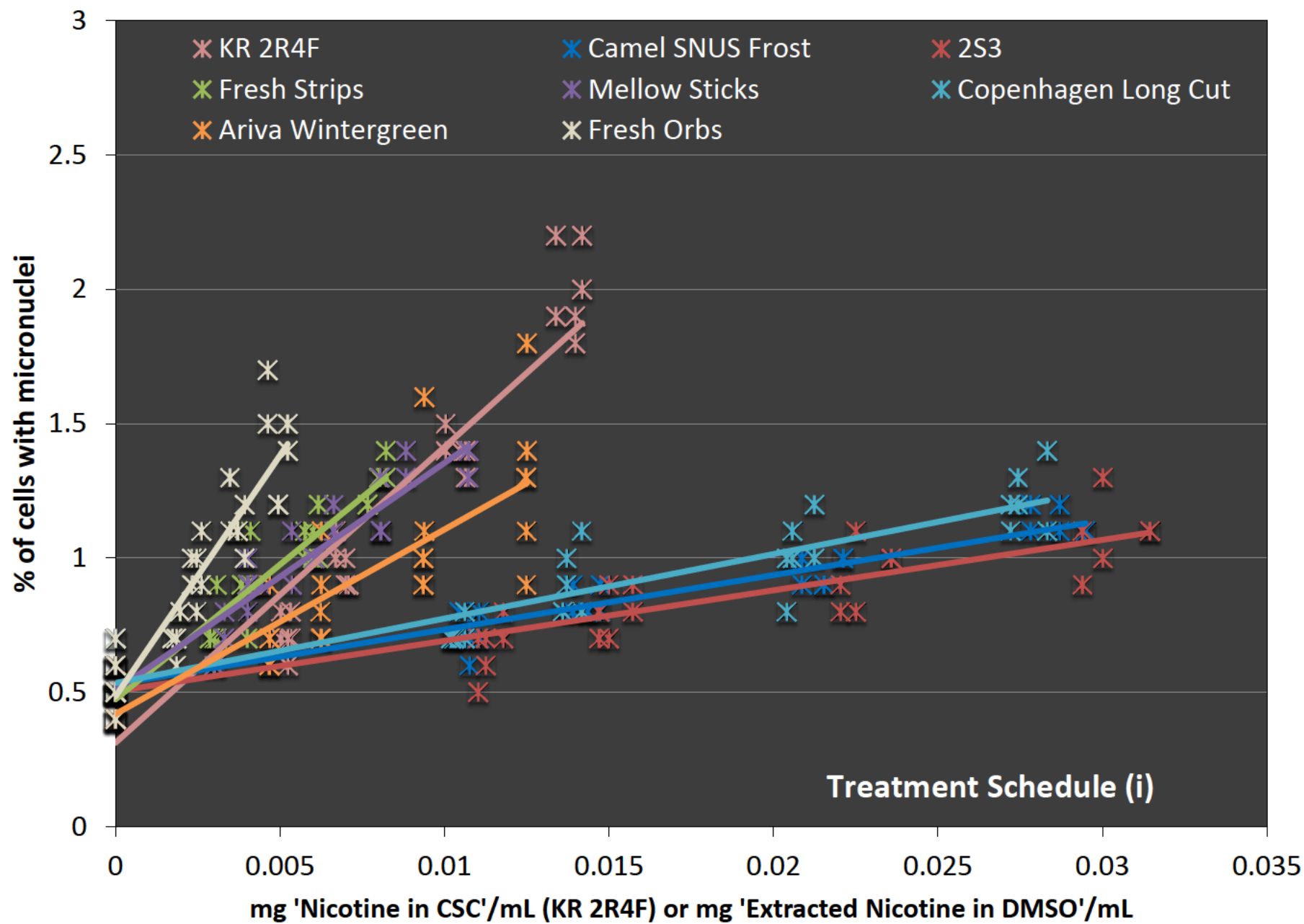


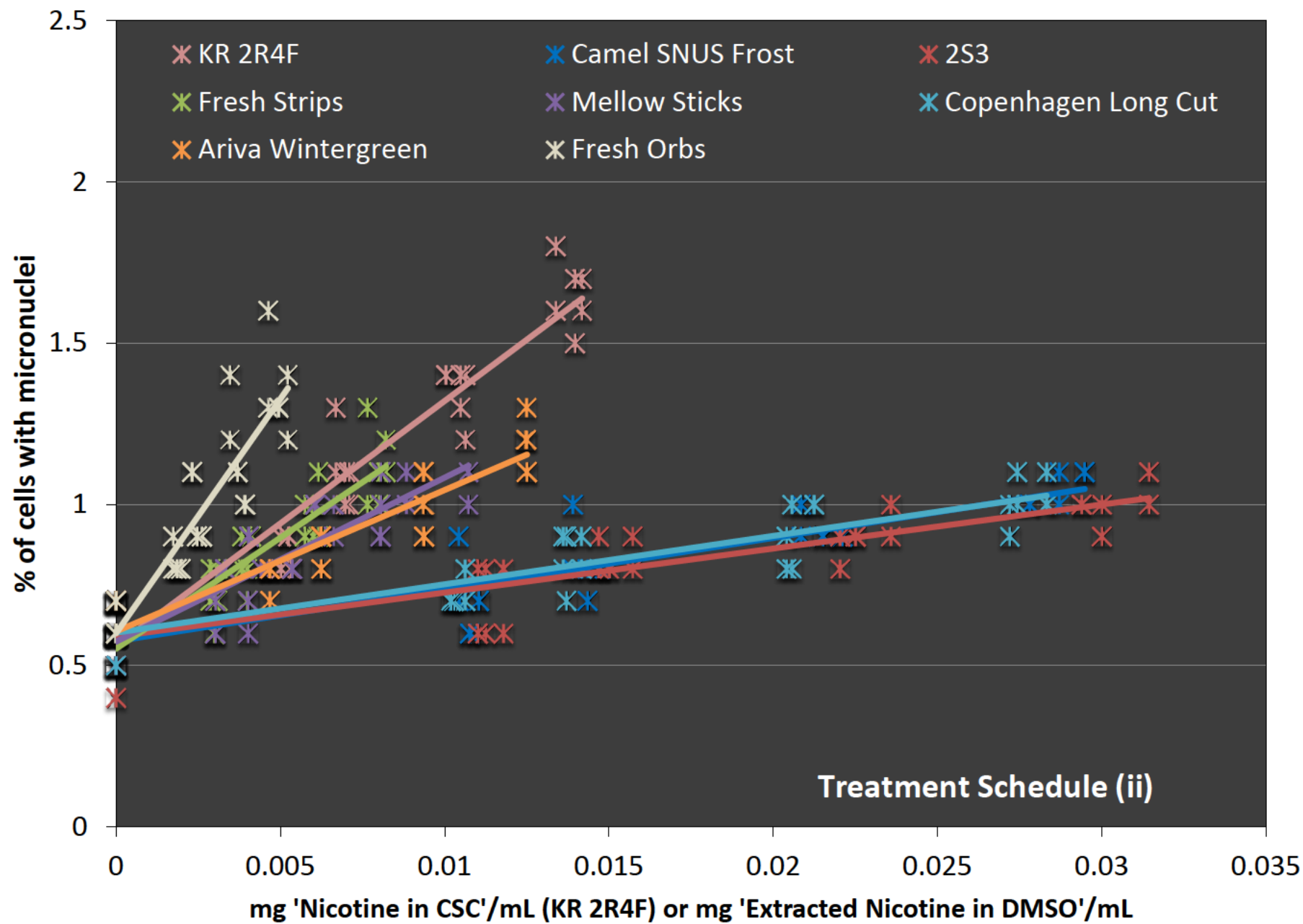












Slope Analysis of the Linear Portion of the Dose-Response Curve
[% of mononucleated cells with micronuclei/('Unit of Use'/mL)] (Unit of Use)

Treatment Schedule	Sample ID	Sample Description	% micronucleated cells/('Unit of Use'/mL)										
			Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate 'Unit of Use' Slope Estimates				
			Dose Range		Dose Range		Dose Range		Standard			t-test p-value (H ₀ : mean = 0)	
			('Unit'/mL)	slope	('Unit'/mL)	slope	('Unit'/mL)	slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084394	Camel SNUS Frost	0 - 0.0037	158	0 - 0.0037	161	0 - 0.0037	152	157	2	147 - 168	0.000	significant
Schedule (i)	084395	2S3	0 - 0.0009	692	0 - 0.0009	577	0 - 0.0009	636	635	33	492 - 777	0.003	significant
Schedule (i)	084454	Fresh Strips	0 - 0.0178	44.5	0 - 0.0178	48.9	0 - 0.0178	40.7	44.7	2.4	34.5 - 54.8	0.003	significant
Schedule (i)	084455	Mellow Sticks	0 - 0.0043	203	0 - 0.0043	176	0 - 0.0043	161	180	12	127 - 233	0.005	significant
Schedule (i)	084456	Copenhagen Long Cut	0 - 0.0009	814	0 - 0.0009	858	0 - 0.0009	552	742	95	331 - 1152	0.016	significant
Schedule (i)	084457	Ariva Wintergreen	0 - 0.0079	144	0 - 0.0079	101	0 - 0.0079	79.7	108	19	27 - 189	0.029	significant
Schedule (i)	084458	Fresh Orbs	0 - 0.0099	112	0 - 0.0099	79.2	0 - 0.0099	81.2	90.9	10.8	44.6 - 137	0.014	significant
Schedule (ii)	084394	Camel SNUS Frost	0 - 0.0037	96.2	0 - 0.0037	143	0 - 0.0037	134	124	14	63 - 185	0.013	significant
Schedule (ii)	084395	2S3	0 - 0.0009	469	0 - 0.0009	389	0 - 0.0009	530	463	41	286 - 639	0.008	significant
Schedule (ii)	084454	Fresh Strips	0 - 0.0178	31.4	0 - 0.0178	30.8	0 - 0.0178	30.4	30.9	0.3	29.7 - 32.1	0.000	significant
Schedule (ii)	084455	Mellow Sticks	0 - 0.0043	93.3	0 - 0.0043	119	0 - 0.0043	138	117	13	61.3 - 172	0.012	significant
Schedule (ii)	084456	Copenhagen Long Cut	0 - 0.0009	486	0 - 0.0009	460	0 - 0.0009	445	464	12	411 - 516	0.001	significant
Schedule (ii)	084457	Ariva Wintergreen	0 - 0.0079	49.8	0 - 0.0079	76.4	0 - 0.0079	81.1	69.1	9.7	27.3 - 111	0.019	significant
Schedule (ii)	084458	Fresh Orbs	0 - 0.0099	85.4	0 - 0.0099	67.7	0 - 0.0099	71.7	75.0	5.3	51.9 - 98	0.005	significant

One-Way ANOVA of Mean 'Unit of Use' Slope Estimates Among Test Samples

Schedule (i)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	1454272	6	242379	52.15	0.000
Within Samples	65064	14	4647		
Total (Corr.)	1519336	20			

Schedule (ii)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	636679	6	106113	106.64	0.000
Within Samples	13931	14	995		
Total (Corr.)	650610	20			

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

ANOVA Planned Comparison Tests of Mean 'Unit of Use' Slope for Contrasts of Interest using Bonferroni-adjusted p-values

Planned 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	73.62	0.0000	significant	172.91	0.0000	significant
084394 vs. 084454	4.09	0.0627	not significant	13.12	0.0028	not significant
084394 vs. 084455	0.17	0.6894	not significant	0.08	0.7762	not significant
084394 vs. 084456	110.23	0.0000	significant	173.78	0.0000	significant
084394 vs. 084457	0.78	0.3922	not significant	4.57	0.0506	not significant
084394 vs. 084458	1.42	0.2535	not significant	3.65	0.0766	not significant
084395 vs. 084454	112.40	0.0000	significant	281.31	0.0000	significant
084395 vs. 084455	66.78	0.0000	significant	180.61	0.0000	significant
084395 vs. 084456	3.68	0.0756	not significant	0.00	0.9742	not significant
084395 vs. 084457	89.55	0.0000	significant	233.72	0.0000	significant
084395 vs. 084458	95.47	0.0000	significant	226.83	0.0000	significant
084454 vs. 084455	5.91	0.0291	not significant	11.11	0.0049	not significant
084454 vs. 084456	156.78	0.0000	significant	282.41	0.0000	significant
084454 vs. 084457	1.30	0.2738	not significant	2.20	0.1599	not significant
084454 vs. 084458	0.69	0.4199	not significant	2.93	0.1091	not significant
084455 vs. 084456	101.83	0.0000	significant	181.50	0.0000	significant
084455 vs. 084457	1.67	0.2176	not significant	3.42	0.0857	not significant
084455 vs. 084458	2.56	0.1321	not significant	2.63	0.1272	not significant
084456 vs. 084457	129.55	0.0000	significant	234.73	0.0000	significant
084456 vs. 084458	136.66	0.0000	significant	227.83	0.0000	significant
084457 vs. 084458	0.09	0.7626	not significant	0.05	0.8238	not significant

Planned comparison p-values greater than bonferronni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'Unit of Use' slope were as follows under treatment schedules (i) and (ii):

Schedule (i)

Sample Description	Sample ID	Mean Slope	Homogenous Groupings
Fresh Strips	084454	44.7	X
Fresh Orbs	084458	90.9	X
Ariva Wintergreen	084457	108	X
Camel SNUS Frost	084394	157	X
Mellow Sticks	084455	180	X
2S3	084395	635	X
Copenhagen Long Cut	084456	742	X

Schedule (ii)

Sample Description	Sample ID	Mean Slope	Homogenous Groupings
Fresh Strips	084454	30.9	X
Ariva Wintergreen	084457	69.1	X
Fresh Orbs	084458	75.0	X
Mellow Sticks	084455	117	X
Camel SNUS Frost	084394	124	X
2S3	084395	463	X
Copenhagen Long Cut	084456	464	X

Unplanned Comparison Tests of Mean 'Unit of Use' Slope for Contrasts of Interest using Bonferroni-adjusted p-values

Unplanned 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	14.3657	0.0001	significant	7.8018	0.0015	significant
084394 vs. 084454	32.9417	0.0000	significant	6.5598	0.0028	not significant
084394 vs. 084455	1.8226	0.1424	not significant	0.3889	0.7172	not significant
084394 vs. 084456	6.1201	0.0036	not significant	18.1445	0.0001	significant
084394 vs. 084457	2.5845	0.0610	not significant	3.1968	0.0330	not significant
084394 vs. 084458	5.9935	0.0039	not significant	3.2403	0.0317	not significant
084395 vs. 084454	17.7552	0.0001	significant	10.5321	0.0005	significant
084395 vs. 084455	12.8742	0.0002	significant	8.0512	0.0013	significant
084395 vs. 084456	1.0571	0.3501	not significant	0.0198	0.9851	not significant
084395 vs. 084457	13.8106	0.0002	significant	9.3413	0.0007	significant
084395 vs. 084458	15.6008	0.0001	significant	9.3784	0.0007	significant
084454 vs. 084455	10.8712	0.0004	significant	6.6582	0.0026	not significant
084454 vs. 084456	7.2989	0.0019	significant	35.5799	0.0000	significant
084454 vs. 084457	3.3363	0.0289	not significant	3.9290	0.0171	not significant
084454 vs. 084458	4.1906	0.0138	not significant	8.2282	0.0012	significant
084455 vs. 084456	5.8366	0.0043	not significant	19.5802	0.0000	significant
084455 vs. 084457	3.1986	0.0329	not significant	2.9487	0.0420	not significant
084455 vs. 084458	5.4628	0.0055	not significant	2.9930	0.0402	not significant
084456 vs. 084457	6.5112	0.0029	not significant	25.3401	0.0000	significant
084456 vs. 084458	6.7735	0.0025	not significant	29.2606	0.0000	significant
084457 vs. 084458	0.7894	0.4740	not significant	0.5266	0.6263	not significant

Unplanned comparison p-values greater than bonferronni-adjusted $\alpha = 0.05$ indicate that significant differences in mean 'Unit of Use' slope were detected in the following cases:

Schedule (i):

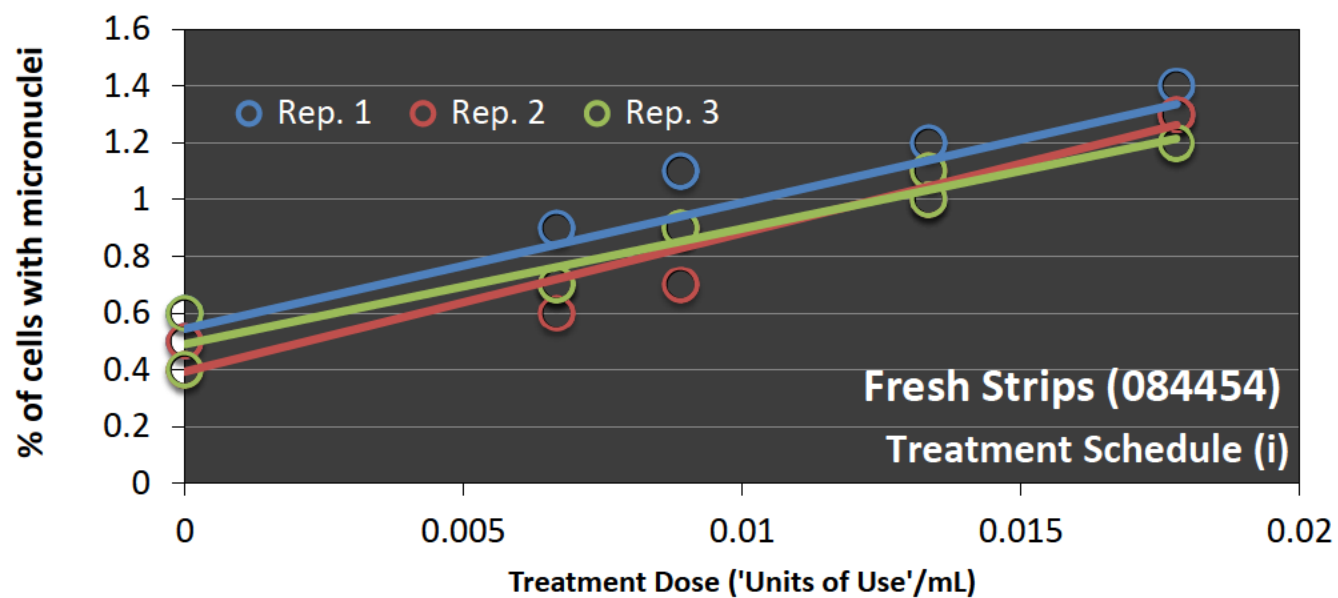
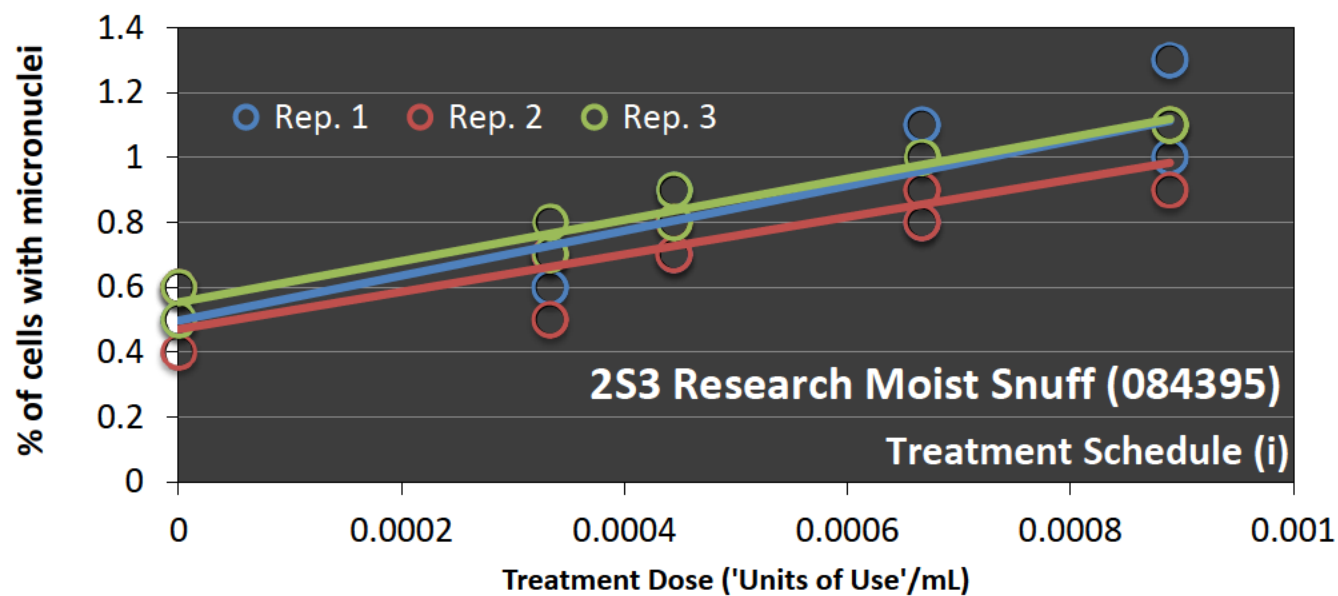
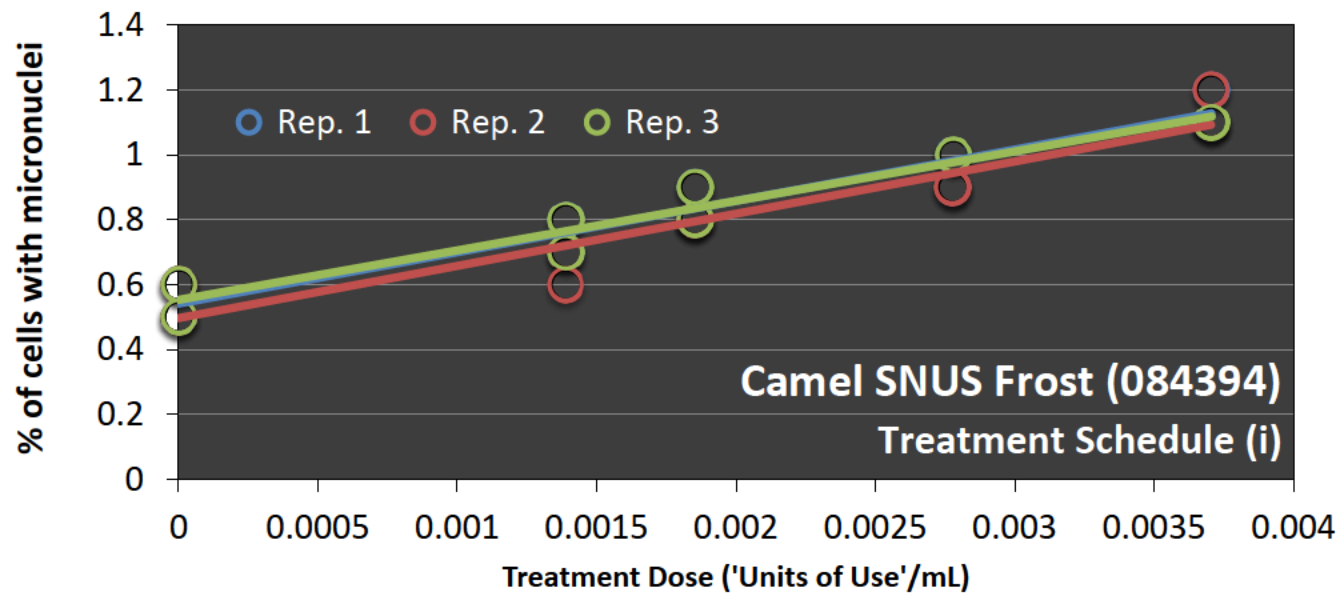
Fresh Strips (084454) and each of {Camel SNUS Frost (084394), Mellow Sticks (084455), 2S3 (084395), Copenhagen Long Cut (084456)}

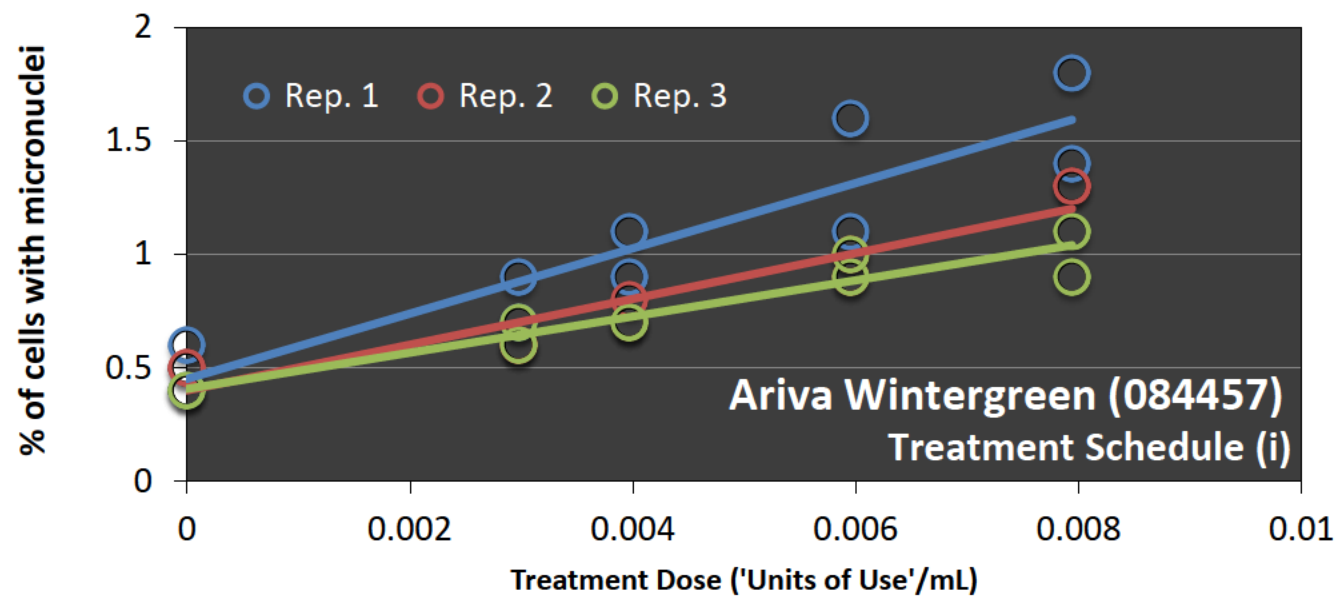
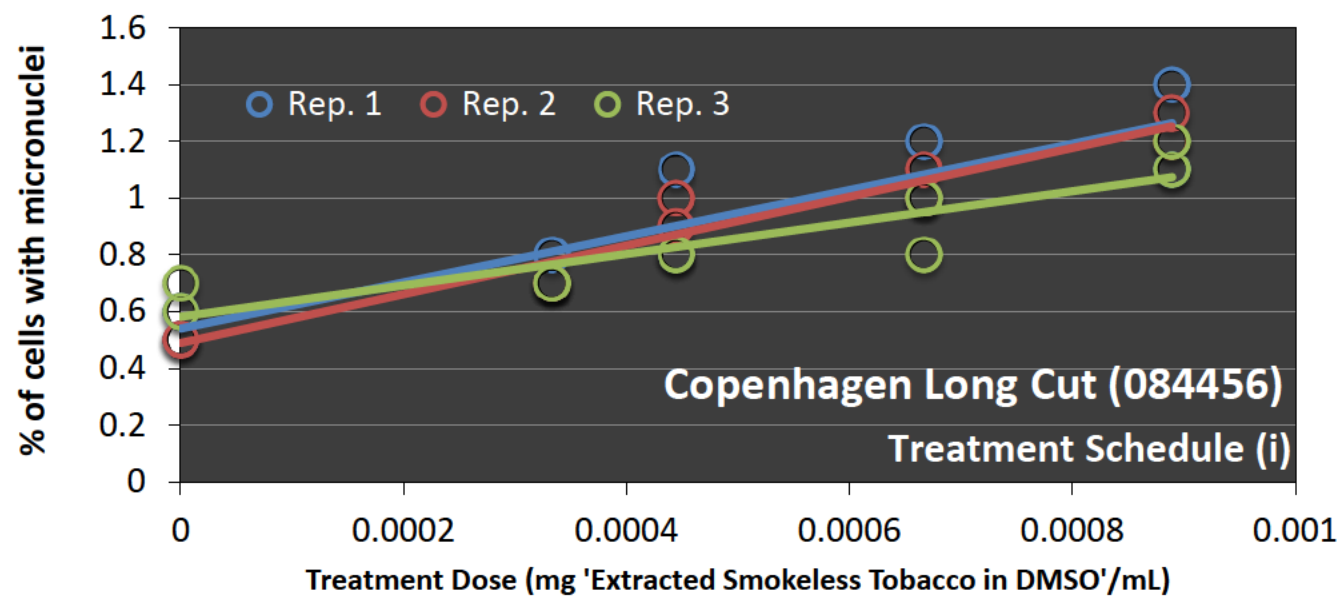
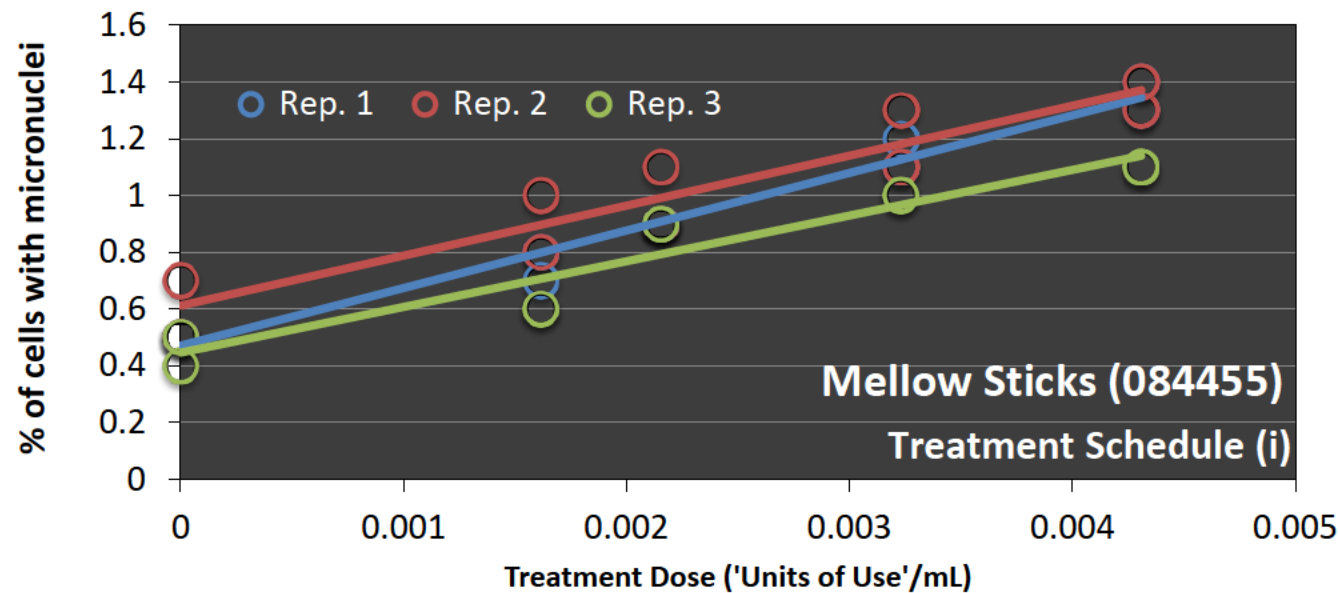
2S3 (084395) and each of {Fresh Orbs (084458), Ariva Wintergreen (084457), Camel SNUS Frost (084394), Mellow Sticks (084455)}

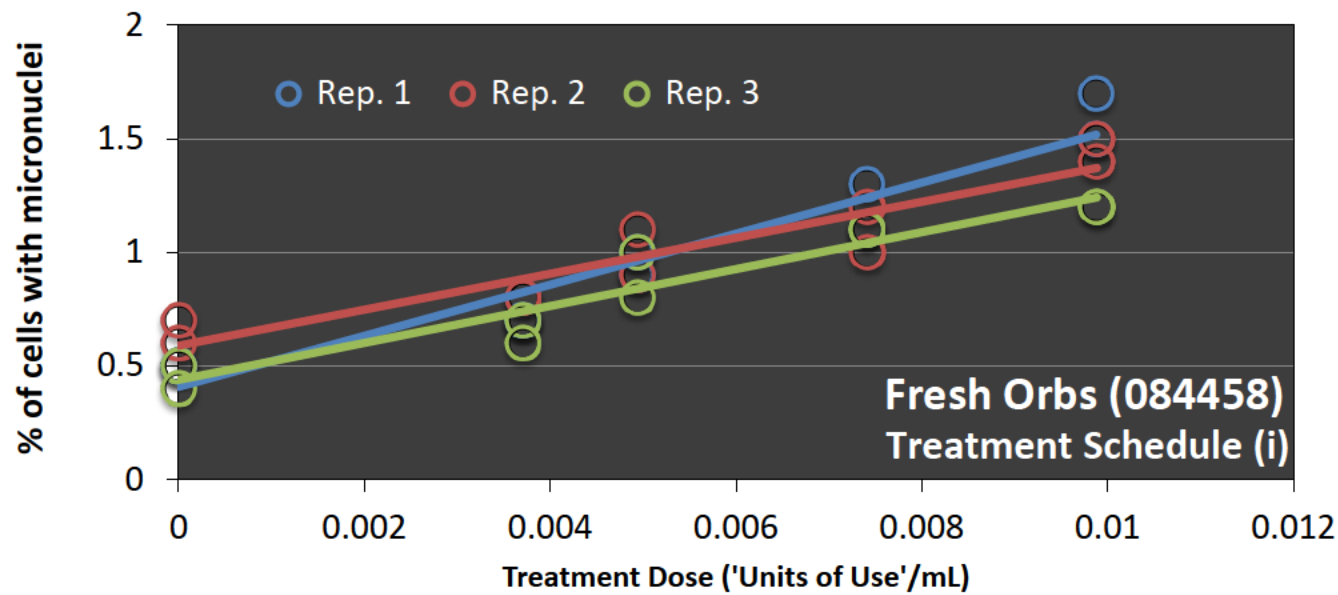
Schedule (ii):

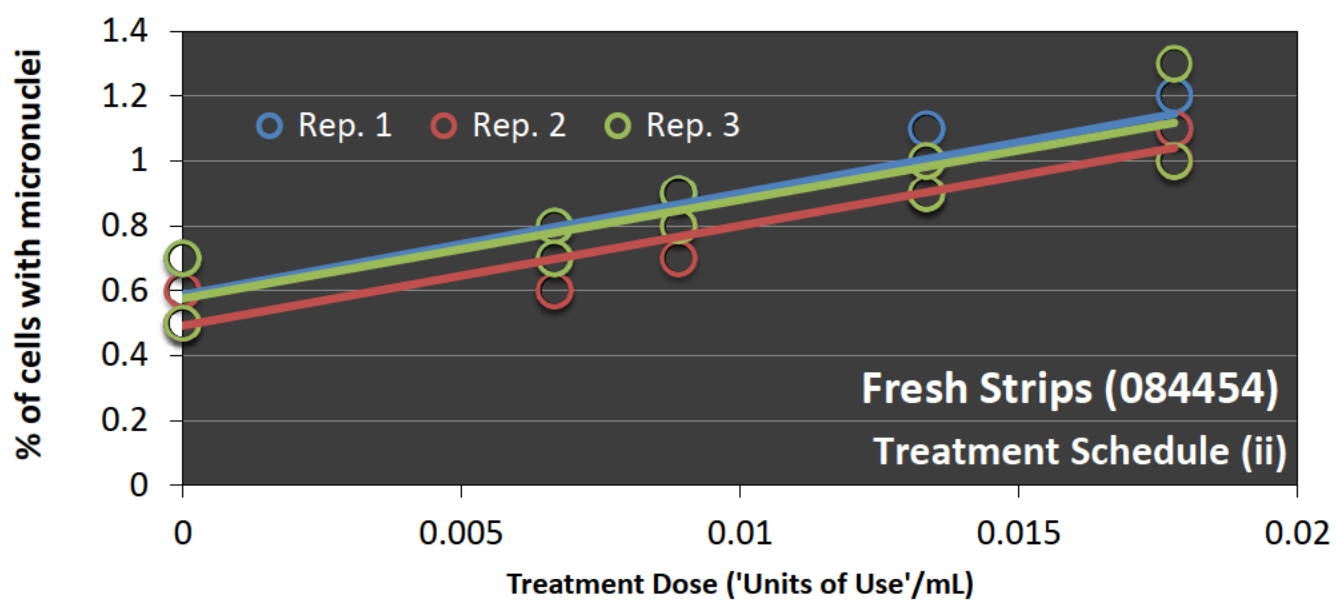
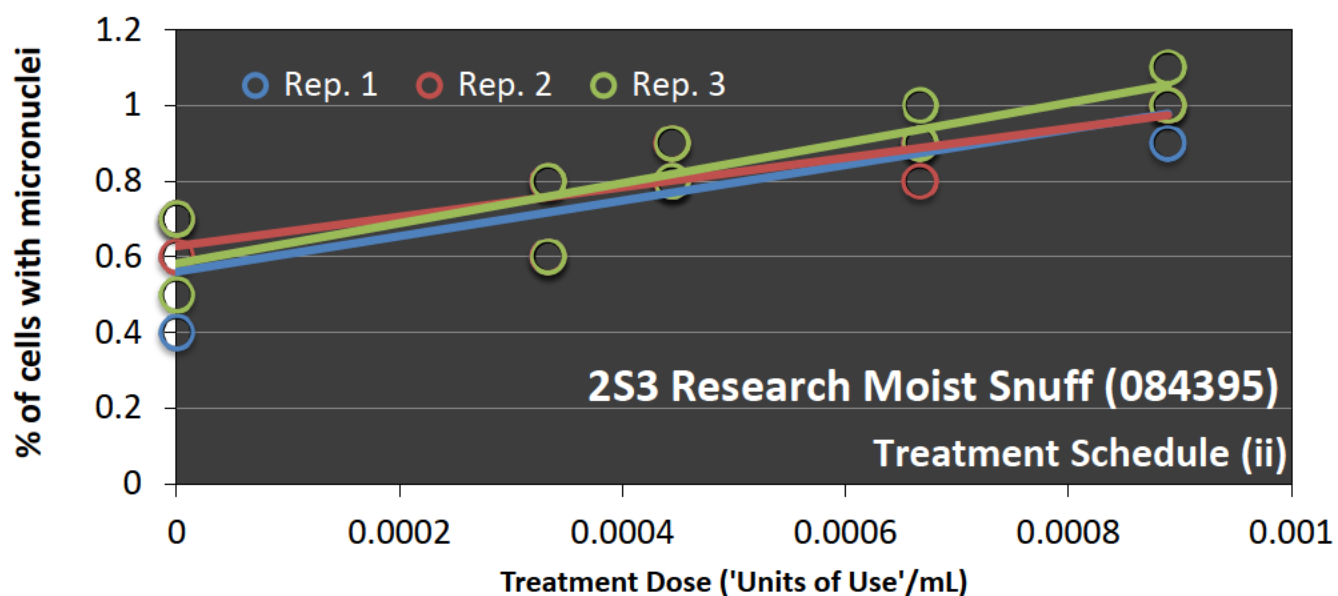
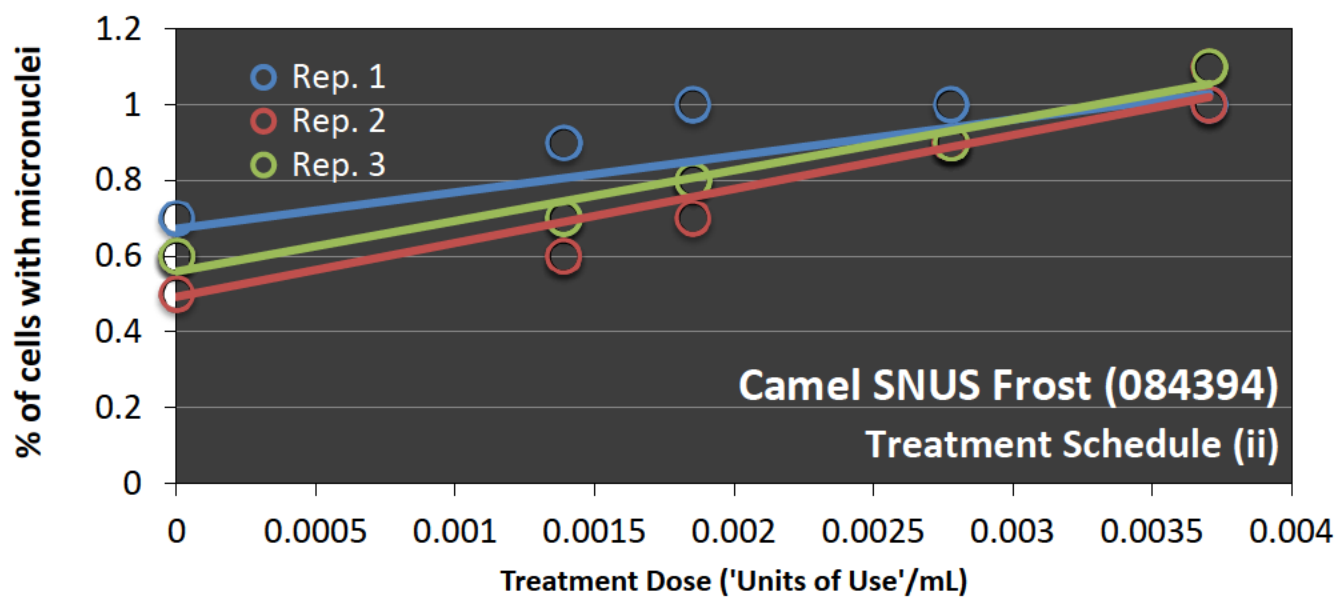
2S3 (084395) and Copenhagen Long Cut (084456) and each of {Camel SNUS Frost (084394), Mellow Sticks (084455), Fresh Orbs (084458), Ariva Wintergreen (084457), Fresh Strips (084454)}

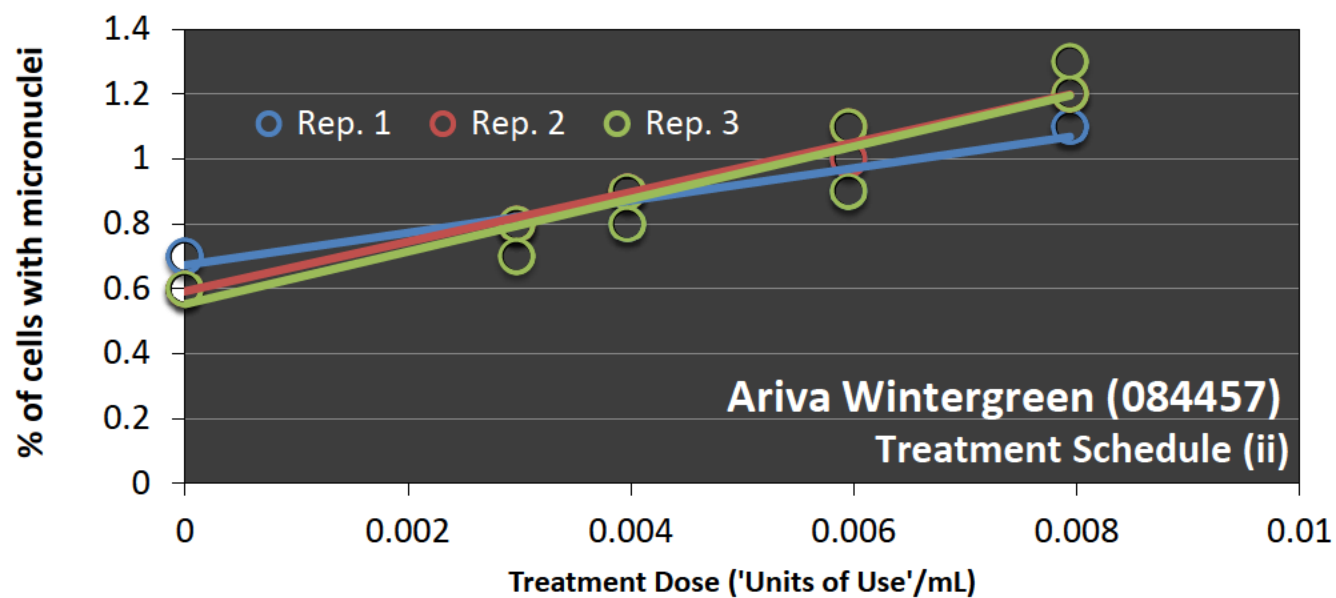
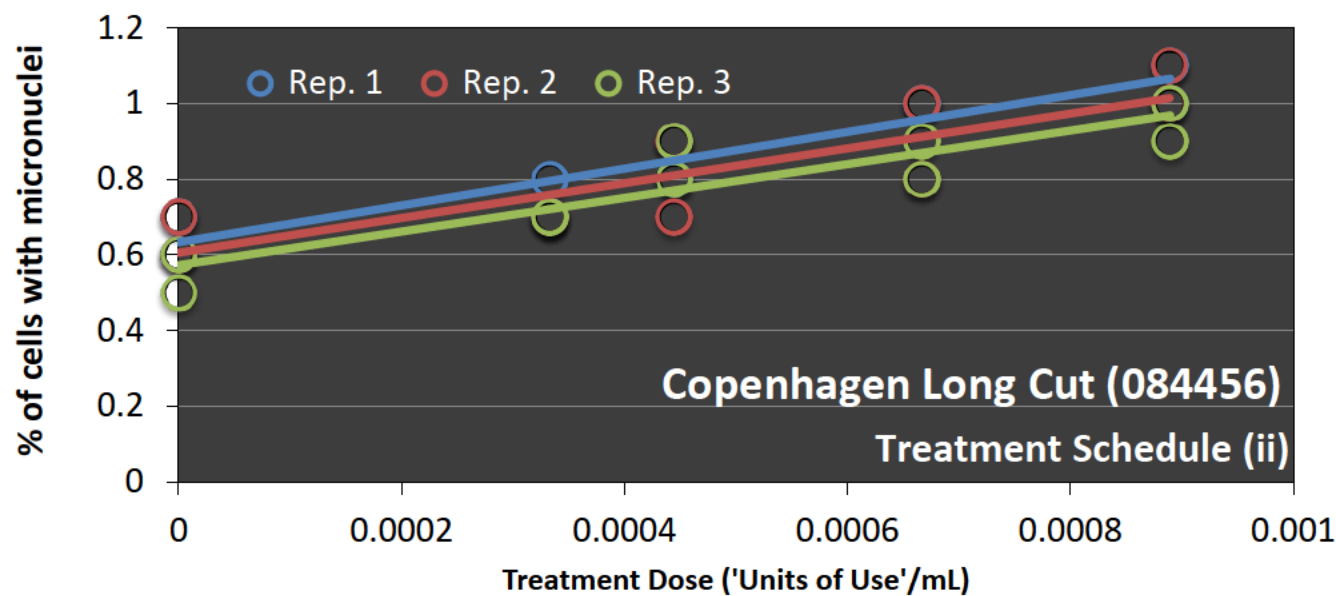
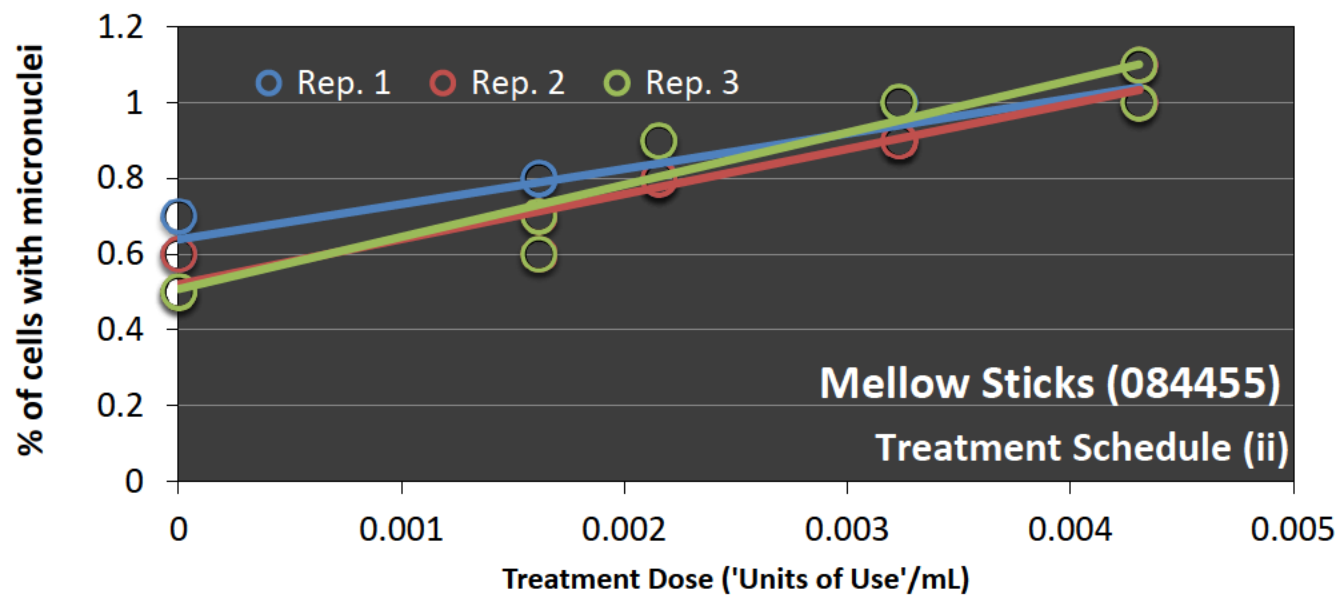
Fresh Strips (084454) and Fresh Orbs (084458)

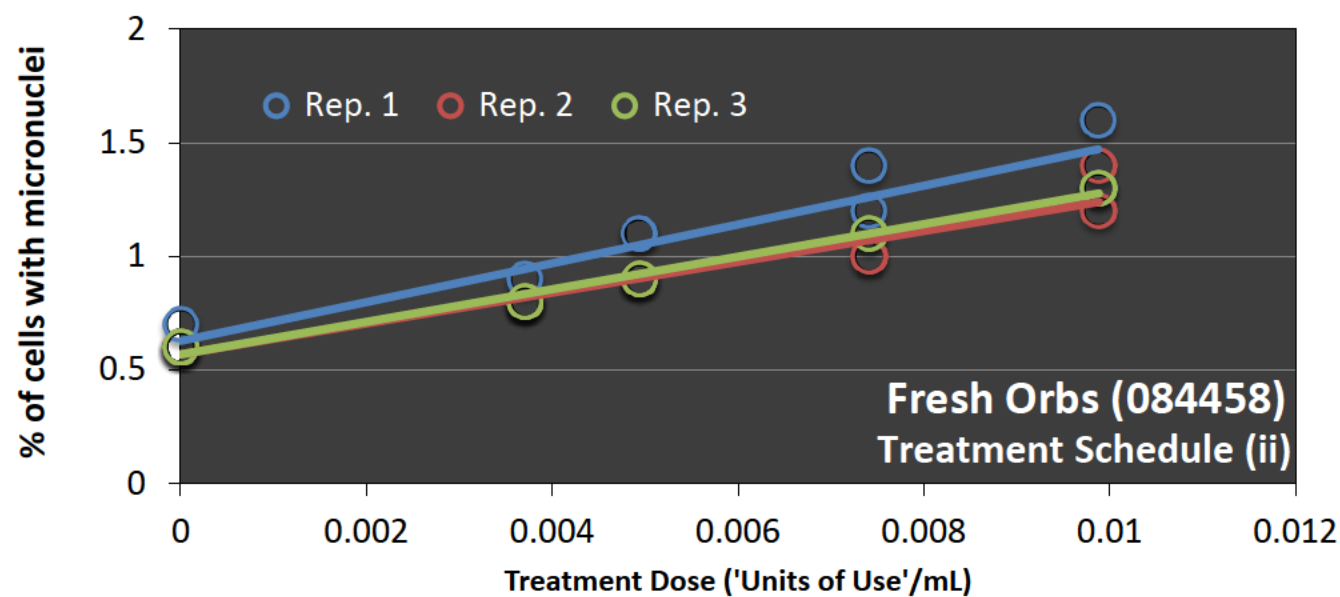


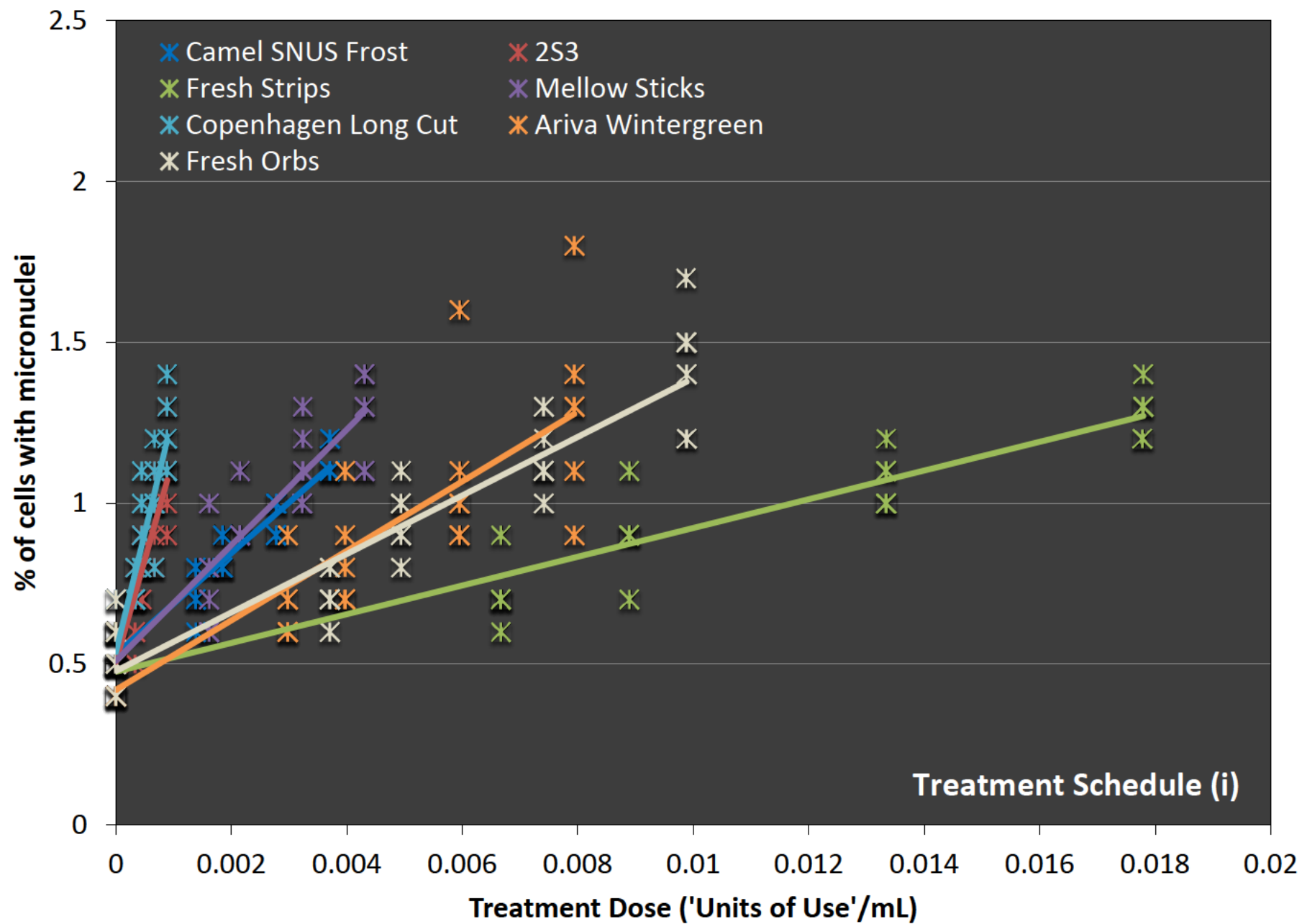


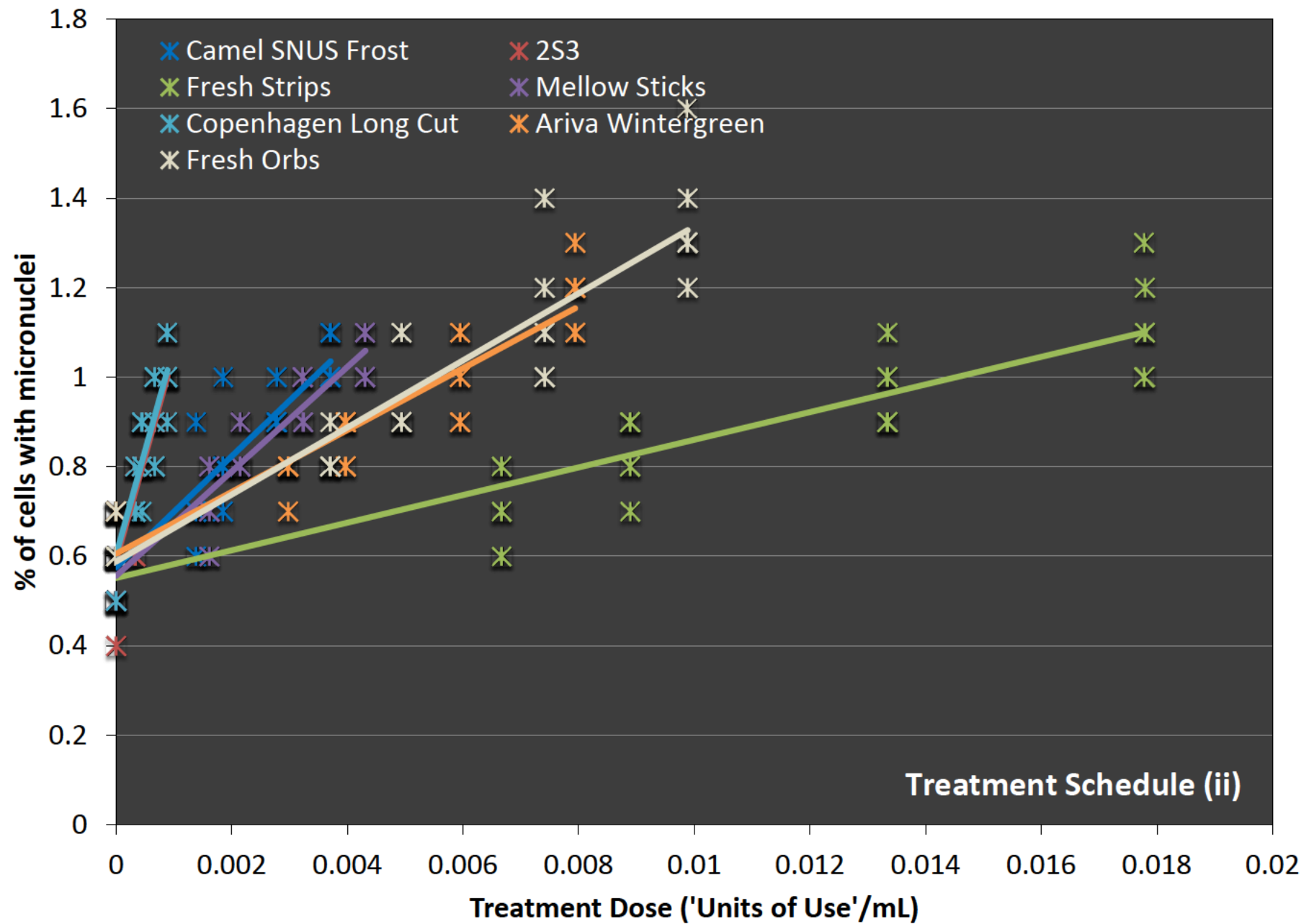












Treatment Schedule (ii)

Slope Analysis of the Linear Portion of the Dose-Response Curve for Smokeless Tobacco [%MNC*/('Unit of Use'/mL)] and Smoked Tobacco [%MNC/(cigarettes/mL)] Samples

Treatment Schedule	Sample ID	Sample Description	% micronucleated cells /(cigarettes/mL) (KR 2R4F) or % micronucleated cells/('Unit of Use'/mL)										
			Replicate 1		Replicate 2		Replicate 3		Statistics for Replicate 'Unit of Use' Slope Estimates				
			Dose Range ('Unit'/mL)		Dose Range ('Unit'/mL)		Dose Range ('Unit'/mL)		Standard		t-test p-value (H ₀ : mean = 0)		
				slope		slope		slope	Mean	Error	95% C.I.	p-value	significance
Schedule (i)	084394	Camel SNUS Frost	0 - 0.0037	158	0 - 0.0037	161	0 - 0.0037	152	157	2	147 - 168	0.000	significant
Schedule (i)	084395	2S3	0 - 0.0009	692	0 - 0.0009	577	0 - 0.0009	636	635	33	492 - 777	0.003	significant
Schedule (i)	084396	KR 2R4F	0 - 0.0182	88.3	0 - 0.0185	82.5	0 - 0.0191	76.0	82.3	3.5	67 - 97.5	0.002	significant
Schedule (i)	084454	Fresh Strips	0 - 0.0178	44.5	0 - 0.0178	48.9	0 - 0.0178	40.7	44.7	2.4	34.5 - 54.8	0.003	significant
Schedule (i)	084455	Mellow Sticks	0 - 0.0043	203	0 - 0.0043	176	0 - 0.0043	161	180	12	127 - 233	0.005	significant
Schedule (i)	084456	Copenhagen Long Cut	0 - 0.0009	814	0 - 0.0009	858	0 - 0.0009	552	742	95	331 - 1152	0.016	significant
Schedule (i)	084457	Ariva Wintergreen	0 - 0.0079	144	0 - 0.0079	101	0 - 0.0079	79.7	108	19	27 - 189	0.029	significant
Schedule (i)	084458	Fresh Orbs	0 - 0.0099	112	0 - 0.0099	79.2	0 - 0.0099	81.2	90.9	10.8	44.6 - 137	0.014	significant
Schedule (ii)	084394	Camel SNUS Frost	0 - 0.0037	96.2	0 - 0.0037	143	0 - 0.0037	134	124	14	63 - 185	0.013	significant
Schedule (ii)	084395	2S3	0 - 0.0009	469	0 - 0.0009	389	0 - 0.0009	530	463	41	286 - 639	0.008	significant
Schedule (ii)	084396	KR 2R4F	0 - 0.0182	59.5	0 - 0.0185	57.8	0 - 0.0191	53.4	56.9	1.8	49.1 - 64.8	0.001	significant
Schedule (ii)	084454	Fresh Strips	0 - 0.0178	31.4	0 - 0.0178	30.8	0 - 0.0178	30.4	30.9	0.3	29.7 - 32.1	0.000	significant
Schedule (ii)	084455	Mellow Sticks	0 - 0.0043	93.3	0 - 0.0043	119	0 - 0.0043	138	117	13	61.3 - 172	0.012	significant
Schedule (ii)	084456	Copenhagen Long Cut	0 - 0.0009	486	0 - 0.0009	460	0 - 0.0009	445	464	12	411 - 516	0.001	significant
Schedule (ii)	084457	Ariva Wintergreen	0 - 0.0079	49.8	0 - 0.0079	76.4	0 - 0.0079	81.1	69.1	9.7	27.3 - 111	0.019	significant
Schedule (ii)	084458	Fresh Orbs	0 - 0.0099	85.4	0 - 0.0099	67.7	0 - 0.0099	71.7	75.0	5.3	51.9 - 98	0.005	significant

* MNC = micronucleated cells

Cigarette smoke condensate (CSC) test sample with cigarettes/mL dose basis

One-Way ANOVA of Mean 'Unit of Use' Slope Estimates

Schedule (i)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	1556508	7	222358	54.62	0.000
Within Samples	65139	16	4071		
Total (Corr.)	1621646	23			

Schedule (ii)

Source	Sum of Squares	Degrees of Freedom	Mean Square	F-Ratio	P-Value
Among Samples	684414	7	97773	112.13	0.000
Within Samples	13951	16	872		
Total (Corr.)	698365	23			

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

ANOVA-Based Comparisons of Smokeless Tobacco Mean 'Unit of Use' Slopes to Control Brand KR 2R4F (084396) Mean 'Cigarette' 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	2.070	0.1695	not significant	7.783	0.0131	not significant
084395 vs. 084396	112	1.2E-08	significant	283	1.3E-11	significant
084454 vs. 084396	0.520	0.4810	not significant	1.167	0.2960	not significant
084455 vs. 084396	3.515	0.0792	not significant	6.151	0.0246	not significant
084456 vs. 084396	160	9.5E-10	significant	285	1.3E-11	significant
084457 vs. 084396	0.246	0.6270	not significant	0.255	0.6202	not significant
084458 vs. 084396	0.028	0.8699	not significant	0.559	0.4655	not significant

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

Treatment Schedules (i) and (ii)
{2S3 (084395), Copenhagen Long Cut (084456)}

Pairwise T-test Comparisons of Smokeless Tobacco Mean 'Unit of Use' Slope to Control Brand KR 2R4F (084396) Mean 'Cigarette' 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	17.37	0.0001	significant	4.691	0.0094	not significant
084395 vs. 084396	16.57	0.0001	significant	9.888	0.0006	significant
084454 vs. 084396	8.835	0.0009	significant	14.12	1.5E-04	significant
084455 vs. 084396	7.680	0.0015	significant	4.593	0.0101	not significant
084456 vs. 084396	6.903	0.0023	significant	33.08	5.0E-06	significant
084457 vs. 084396	1.346	0.2497	not significant	1.231	0.2857	not significant
084458 vs. 084396	0.7638	0.4875	not significant	3.190	0.0332	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 'cigarette' slope of the KR 2R4F (084396) smoked tobacco samples and the mean 'unit of use' slope of the following smokeless tobacco samples under each Treatment Schedule:

Treatment Schedule (i)
{Camel SNUS Frost (084394), 2S3 (084395), Fresh Strips (084454), Mellow Sticks (084455), Copenhagen Long Cut (084456)}

Treatment Schedule (ii)
{2S3 (084395), Fresh Strips (084454), Copenhagen Long Cut (084456)}

