PROGRAM BOOKLET AND ABSTRACTS

Volume 76

76th Tobacco Science Research Conference

September 24-27, 2023
Norfolk, Virginia USA

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76th Tobacco Science Research Conference

September 24-27, 2023
Norfolk, Virginia USA

Hosted by: Juul Labs, Inc

GENERAL PROGRAM

Sunday, September 24, 2023

2:00PM – 6:00PM	Registration	Presidential Foyer
2:00PM – 6:00PM	Speaker Ready Room	Madison
6:30PM – 9:30PM	Welcome Reception *Hosted by Juul Labs, Inc*	Off-site

Monday, September 25, 2023

7:30AM – 8:15AM	Session Chairs Breakfast	Franklin
7:30AM – 8:15AM	U.S. TAG: ISO/TC 126 Breakfast	Shangri-La
7:30AM – 5:15PM	Registration	Presidential Foyer
7:30AM – 5:00PM	Speaker Ready Room	Madison
8:00AM – 8:30AM	Morning Coffee	Presidential Foyer
8:30AM – 11:45 AM	Symposium Symposium Chair: Rana Tayyarah	Hampton Ballroom
9:45AM – 10:15AM	Coffee Break	Presidential Foyer
11:45AM – 12:45PM	Lunch	Norfolk Ballroom
12:45PM – 1:55PM	Poster Session	Presidential Foyer
1:55PM – 4:00PM	Session A: CDISC	Hampton I-IV
1:55PM – 4:00PM	Session B: e-Cigarette Chemistry	Hampton V-VIII
4:00PM – 4:20PM	Coffee Break	Presidential Foyer
4:20PM – 5:25PM	Session A: Toxicology, *in vitro*, Product Stewardship	Hampton I-IV
4:20PM – 5:45PM	Session B: Cigarette Chemistry	Hampton V-VIII

Tuesday, September 26, 2023

7:30AM – 5:00PM	Registration	Presidential Foyer
7:30AM – 5:00PM	Speaker Ready Room	Madison
8:00AM – 8:45AM	Morning Coffee	Presidential Foyer
8:45AM – 10:10AM	Session A: Regulatory & Public Health	Hampton I-IV
8:45AM – 10:10AM	Session B: Clinical, Behavioral & Perception Research	Hampton V-VIII

10:10AM – 10:30AM	Coffee Break	Presidential Foyer
10:30AM – 12:15PM	Session A: Regulatory & Public Health	Hampton I-IV
8:00AM – 12:15PM	Session B: e-Cigarette Chemistry	Hampton V-VII
12:15PM – 1:15PM	Lunch	Norfolk Ballroom
12:15PM – 2:00PM	Policy Committee Lunch	Tyler
1:00 PM – 2:10PM	Poster Session	Presidential Foyer
2:10PM – 3:35PM	Session A: Agronomy	Hampton I-IV
2:10PM – 3:35PM	Session B: Clinical, Behavioral & Perception Research	Hampton V-VII
3:35PM – 3:55PM	Coffee Break	Presidential Foyer
3:55PM – 4:35PM	Session A: Agronomy	Hampton I-IV
3:55PM – 4:55PM	Session B: Clinical, Behavioral & Perception Research	Hampton V-VII
5:00PM – 5:45PM	TSRC Business Meeting	Hampton I-IV
6:30PM – 10:00PM	Social Hour and Award Banquet	Marriott Ballroom

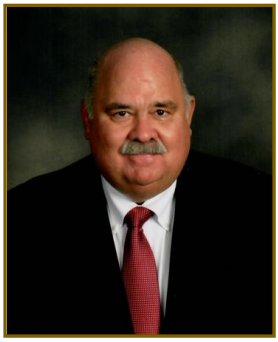
Wednesday, September 27, 2023

8:00AM – 2:00PM	Speaker Ready Room	Madison
8:00AM – 8:30AM	Morning Coffee	Presidential Foyer
8:45AM – 10:55AM	Joint Session: Symposium Panel – Assessment of ENDS Ingredients	Hampton I-IV
10:55AM – 12:00PM	Lunch	Presidential Foyer
12:00PM – 1:35PM	Session A: Symposium Panel – Exploring Risk Perceptions and Tobacco Use Behavior	Hampton I-IV
12:00PM – 1:05PM	Session B: Modern Oral, HTP, Other	Hampton V-VII

Adjourn

LIFETIME ACHIEVEMENT AWARD

J. Michael Moore, PhD



J. Michael Moore was born in the flue-cured tobacco production area of Kinston, NC, and grew up on a diversified farm in Jones County, NC. After graduating from Jones Senior High School in 1975, J. Michael attended NC State University and received a BS in Crop Science in 1979. Following graduation, he worked as County Extension Agent in Duplin County, NC, one of the largest flue-cured production counties at that time. During his time working as an agent in Duplin County, J. Michael completed a tobacco research project with field work on the Border Belt Research Station in Whiteville, NC and on-farms in Duplin County. Also, while working as an agent he completed classwork at NCSU resulting in a M.S. degree from NCSU in 1986 in Crop Science. Two semesters of full-time enrollment on campus in Raleigh, NC were made possible by the Philip Morris Fellowship.

In 1986, J. Michael began a Ph.D program at Virginia Tech, attending class in Blacksburg, VA and conducting field and laboratory research at the Southern Piedmont Research and Education Center in Blackstone, VA with a tobacco project with the support of a R.J. Reynolds assistantship. As he completed the Ph.D in Agronomy in 1989, he was hired as an Extension Agronomist for Tobacco by the University of Georgia and relocated to the University of Georgia Tifton Campus in Tifton, GA. As the UGA Tobacco Specialist, Dr. Moore conducts applied research, provides training of County Extension Agents, and assists county agents and growers with troubleshooting tobacco production problems. He continues in this position as the sole faculty member with a tobacco assignment with the university. As extension specialists from other departments have retired, Dr. Moore has added coverage of their subject matter areas as well as agronomy.

Since 2005, and the retirement of Dr. Ben Whitty, Tobacco Specialist for the University of Florida and with program support from Florida tobacco grower checkoff funds Dr. Moore has provided educational programs and troubleshooting services to Florida County Extension Agents and tobacco growers as well. Following the death of Dr. Dewitt Gooden, Clemson Tobacco Specialist, and with financial support for programming from the Clemson Extension Administration in 2015, and on a voluntary basis since then, Dr. Moore provided educational programming for County Extension Agents and growers in South Carolina until recent years when William J. Hardee, Clemson County Extension Agent, received an advanced degree and grew into the role of South Carolina Tobacco Specialist. Dr. Moore has lead the planning and presentation of Good Agricultural Practices (GAP) Training of all growers in Georgia, Florida and South Carolina since the beginning of this industry required training in 2012.

Dr. Moore's scientific contributions to the production of flue-cured tobacco including his efforts on MH residue reduction, barn heat exchanger retrofits and development of the Good Agricultural Practices (GAP) program are prime examples of his outstanding scientific contributions to the tobacco industry in the U.S. and abroad. His ability to take complex scientific data and make it relatable and applicable to tobacco growers has been a fixture across his career. His service to Tobacco Workers Conference, Tobacco Science Research Conference, and CORESTA has benefited the industry by highlighting the need for solid scientific inquiry at the field level.

Dr. Moore and his wife, Teresa, reside in Tifton, GA. They have two children, Brett, of Tifton, and Sandi (Joel) of Dawsonville, GA. The have three grandchildren, Ashlyn, Jayden and Bentleigh.

76TH TOBACCO SCIENCE RESEARCH CONFERENCE

MONDAY MORNING, SEPTEMBER 25, 2023
Symposium

8:30 AM **WELCOME REMARKS**
Gene Gillman, Juul Labs, Inc
76th TSRC Conference Chair

8:40 AM ***LOOKING FORWARD - THE CHALLENGES AND OPPORTUNITIES AHEAD FOR HARM REDUCTION.***
Rana Tayyarah, Labstat International Inc
76th Symposium Chair

8:45 AM Symposium Speaker - Brent Taylor; Altria Client Services, Richmond, VA, USA

9:15 AM Symposium Speaker - Todd Cecil; Food and Drug Administration, Washington, DC, USA

9:45 AM ***BREAK***

10:15 AM Symposium Speaker - Joe Murillo; Juul Labs, Inc, Washington, DC, USA

10:45 AM Symposium Speaker - Patricia Kovacevic; Cryomass Technologies Inc, Denver, CO, USA

11:15 AM Panel Discussion & Audience Q&A

11:45 AM ***LUNCH***

12:45 PM Poster Session

5 **CHEMICAL, PHARMACOLOGICAL, AND TOXICOLOGICAL ASSESSMENT OF 6-METHYLNICOTINE.** Andrew CHEETHAM[1], Susan Plunkett[1], Lynn McFadden[1], Mariano Scian[1], Sarah Marking[2], Bonne Coffa[2], Preston Campbell[2] and Stan Gilliland III[2]; [1]Enthalpy Specialty Labs, Richmond, VA, USA, [2]Consilium Sciences, Richmond, VA, USA

6 **IMOTINE™: A NOVEL NON-NICOTINE COMPOUND WITH CNS ACTIVITY.** Ed CARMINES[1], Manoj Misra[1] and Sam Benaim[2]; [1]Chemular, Hudson, MI, USA, [2]Novel Compounds, Cheyenne, WY, USA

7 **POTENTIAL ENVIRONMENTAL IMPACT OF USE AND DISPOSAL OF A MODERN ORAL NICOTINE POUCH PRODUCT.** Ed CARMINES; Chemular, Hudson, MI, USA

8 **EVALUATION OF THE POTENTIAL EXTRACTABLES FROM A CHUBBY GORILLA E-LIQUID BOTTLE.** Ed CARMINES[1], Lise Fraissinet[1] and Tom Barrett[2]; [1]Chemular Inc, Hudson, MI, USA, [2]Legend Technical Services, St. Paul, MN, USA

9 **APPLYING THE TOBACCO PRODUCT MANUFACTURING PRACTICES TO EXISTING MANUFACTURING PROCESSES.** Lillian ORTEGA, Lise Fraissinet, Randy Freund, Chris Woodruff and Kevin Burd; Chemular Inc, Hudson, MI, USA

10 **CLEARING THE MARKET OF ILLEGAL ENDS PRODUCTS BEGINS AT THE US PORTS.** Lillian ORTEGA, Kevin Burd and Bryan Burd; Chemular Inc, Hudson, MI, USA

11 **COMPARISON OF METALS CONTENT IN ENDS USING ICP-MS WITH TWO SEPARATE AEROSOL COLLECTION METHODS: FRITTED IMPINGERS AND FEP TUBING.** Donald STOGNER, Emma Willis, Jamil Gray, Carl J. Adams and Salem Chouchane; Eurofins Professional Scientific Services, Winston-Salem, NC, USA
Presented but no electronic file submitted

12 **Withdrawn**

13 **SIMULATION ANALYSIS OF STATISTICAL EQUIVALENCE TESTING OF HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS (HPHCS).** Qiwei LIANG, Joey Chen, David Cook, I. Gene Gillman and Ryan Black; Juul Labs, Inc,Washington, DC, USA

14 **FORMATION OF SMALL ORGANIC ACIDS DURING ENDS AEROSOL COLLECTION.** Joseph JABLONSKI and Andrew G. Cheetham; Enthalpy Specialty Labs, Richmond, VA, USA

15 **TOBACCO SPECIFIC NITROSAMINES AND NICOTINE DEGRADANTS: A METHOD FOR COMBINED ANALYSIS IN ENDS E-LIQUIDS AND AEROSOL.** Alexander PENNINGTON, Nancy Qian, Carol Perry, Dakota Hawkins and I. Gene Gillman; Juul Labs, Inc, Washington, DC, USA

16 **SURVEY OF METALS PRESENT IN THE E-LIQUID OF AGED CLOSE POD-BASED AND CIGALIKE ELECTRONIC-CIGARETTES FROM THE NORTH AMERICAN MARKET.** Prasad LAVISETTY, Darybelle Collins, David Cook, Kathy Humphries and I. Gene Gillman; Juul Labs, Inc, Washington, DC, USA

17 **A COMPARATIVE STUDY OF ENDS PARTICLE SIZE ANALYSIS WITH ELECTRICAL AND GRAVIMETRIC MEASUREMENTS OF DILUTED AND UN-DILUTED AEROSOLS.** Jake HENKIE, Angel Rodriguez-Lafuente, Amelia Mawdsley, Nathan Nguyen and Clark Robitaille; Labstat International Inc, Kitchener, ON, Canada

18 **METHODS FOR ANALYSIS OF SWEETENERS, FLAVOR COMPONENTS AND PROPYLENE GLYCOL IN NICOTINE POUCHES AND SALIVA SAMPLES.** Angel RODRIGUEZ-LAFUENTE, Kenneth Chalcraft, Rebecca Cornelius and Cosmin Stoicoiu; Labstat International Inc, Kitchener, ON, Canada
Presented but no electronic file submitted

19 **DESOLVATING INTRODUCTION SYSTEM TEMPERATURE OPTIMIZATION FOR LINEAR ZINC, CADMIUM, AND TIN CALIBRATIONS WITH TRIPLE QUAD ICP-MS FOR E-CIGARETTE AEROSOL ANALYSIS.** Naudia GRAY and R. Steven Pappas; Centers for Disease Control and Prevention, Atlanta, GA, USA

20 **AROMATIC AMINES IN THE MAINSTREAM SMOKE OF COMMERCIAL CIGARS.** Huihua JI, Zhenyu Jin, Laura Fenton, Stacey Slone and Bing Zhang; University of Kentucky, Lexington, KY, USA

21 **THE CONCENTRATIONS OF SELECTED TOXIC METALS IN THREE CATEGORIES OF COMMERCIAL CIGAR PRODUCTS.** Cynthia MCNEES, Priyanka Paul, Sanjay Joshi, Nicole Anderson and Solomon Kariuiki; University of Kentucky, Lexington, KY, USA
Presented but no electronic file submitted

22 **THE EFFECT OF DESIGN PARAMETERS ON YIELDS OF 33 HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS (HPHCS) IN MAINSTREAM SMOKE OF LARGE CIGARS.** Scott WASDO, Therese Ku, Samantha Reilly, Tianrong Chen and Charles Feng; United States Food and Drug Administration, Silver Spring, MD, USA

23 **Withdrawn**

24 **CARBONYL ANALYSIS OF CIGARETTE MAINSTREAM SMOKE BY BAG COLLECTION.** Bryan HEARN[1], Erica Lewis[1], Cody Sheppard[1], Clifford Watson[2] and Liza Valentin[2]; [1]Battelle Analytical Services, Atlanta, GA, USA, [2]Center for Disease Control, Atlanta, GA, USA

25 **CHANGE CONTROL CHALLENGES IN THE CONTEXT OF PMTA.** Lise FRAISSINET, Lillian Ortega, Randy Freund, Chris Woodruff and Bryan Burd; Chemular Inc, Hudson, MI, USA

26 **ELECTRONIC TRIAL MASTER FILE: AN IMPORTANT STEP IN DOCUMENTING CLINICAL TRIAL DATA USED TO SUPPORT A PREMARKET TOBACCO PRODUCT APPLICATION.** Jeff COFFIELD, Jason Henstock and Ken Szeliga; RAI Services Company, Winston-Salem, NC, USA

27 **PROMOTIONAL MATERIALS FOR A NOVEL HEATED TOBACCO CAPSULE SYSTEM INCREASE BEHAVIORAL INTENTIONS TO TRY AND USE IN ADULT SMOKERS BUT NOT IN NONUSERS, AND DO NOT IMPEDE QUIT INTENTIONS.** Diana MCKINNEY and Elizabeth Becker; Altria Client Services, Richmond, VA, USA
Presented but no electronic file submitted

28 **PROMOTIONAL MATERIALS FOR A NOVEL HEATED TOBACCO CAPSULE SYSTEM DO NOT ALTER RISK PERCEPTIONS.** Diana MCKINNEY and Elizabeth Becker; Altria Client Services, Richmond, VA, USA

29 **VITROCELL® HIGH THROUGHPUT EXPOSURE MODULE 2.0+: DEPOSITION OF WHOLE AEROSOL FROM TWO DIFFERENT TOBACCO PRODUCT TYPES.** Brian KEYSER[1], Robert Leverette[1], Kristen Jordan[1], Adam Seymour[2] and Michael Hollings[2]; [1]RAI Services Company, Winston-Salem, NC, USA, [2]Labcorp Early Development Laboratories, Harrogate, North Yorkshire, UK
Presented but no electronic file submitted

30 **THE CHANGING LANDSCAPE OF TOBACCO USE AND SWITCHING BEHAVIORS AMONG US ADULTS.** Yisha HE, Lai Wei, Raheema Muhammad-Kah and Edward Largo; Altria Client Services, Richmond, VA, USA

31 **AN ABUSE LIABILITY COMPARISON OF TEST AND REFERENCE TOBACCO AND MENTHOL FLAVORED E-LIQUIDS IN THE RELX INFINITY ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS).** Donald GRAFF[1], Mitch Nides[2] and Ryan G. N. Seltzer[3]; [1]Cheerain HK Limited, Hong Kong, China, [2]LA Clinical Trials, Burbank, CA, USA, [3]Safety in Numbers, Tucson, AZ, USA

32 **SUBJECTIVE EFFECTS ASSOCIATED WITH RELX INFINITY ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS) USE IN AN 8-WEEK SWITCHING STUDY OF ADULT SMOKERS.** Donald GRAFF[1], Yuli Xie[2] and Sabrina Ciric[2]; [1]Cheerain HK Limited, Hong Kong, China, [2]Celerion Inc, Lincoln, Nebraska, USA

33 **NON-CLINICAL TOXICOLOGICAL ASSESSMENT OF FLAVORED E-LIQUIDS AND CLOSED SYSTEM POD-BASED ENDS FLAVOR FORMULATIONS.** Manoj MISRA, Ed Carmines and Lise Fraissinet; Chemular Inc, Hudson, MI, USA

34 **COMPARATIVE QUANTITATIVE HEALTH RISK ASSESSMENT (QRA) OF A TEMPERATURE-REGULATED NICOTINE SALT-BASED CONNECTED ENDS PRODUCT WITH REFERENCE CIGARETTE: AEROSOL CANCER AND NON-CANCER RISKS.** Manoj MISRA, Ed Carmines and Lise Fraissinet; Chemular Inc, Hudson, MI, USA

35 **APPLICATION OF THE HUMAN HEALTH RISK ASSESSMENT PROCESS FOR THE EVALUATION OF ELECTRONIC CIGARETTES.** Autumn BERNAL[1], Charlene Liu[2], Charles Johnson[3] and Richard Young[3]; [1]Toxcreative, Laguna Hills, CA, USA, [2]RiskWise Soultions, Princton, NJ, USA, [3]Bibra Toxicology Advice & Consulting, Wallington, UK

36 **ABSTINENCE, RELAPSE, AND RELATIVE HARM PERCEPTIONS AMONG SMOKERS AND E-CIGARETTE USERS IN THE POPULATION ASSESSMENT OF TOBACCO AND HEALTH (PATH) STUDY.** Susan MARTELLE, Emery L. Ngamasana and Christie Powell; RAI Services Company, Winston-Salem, NC, USA

37 **A RANDOMIZED, SINGLE BLINDED, CROSS-OVER STUDY TO EVALUATE THE PHARMACOKINETIC PROFILES OF E-CIGARETTES WITH NICOTINE SALT FORMULATIONS IN UK ADULTS WHO USE E-CIGARETTES.** Yuki TAKESHIGE; JT International, Geneve, Switzerland

38 **ASSESSING THE RELATIONSHIP BETWEEN E-CIGARETTES RISK PERCEPTION, INTENTION TO QUIT CIGARETTES, AND CIGARETTE CONSUMPTION: A STRUCTURAL EQUATION MODEL.** Emery NGAMASANA; RAI Services Company, Winston-Salem, NC, USA
Presented but no electronic file submitted

39 **ANALYZING THE RELATIONSHIPS BETWEEN TOPOGRAPHY, E-LIQUID USAGE, AND PHARMACOKINETICS IN JUUL2 PROTOTYPE DEVICES.** Qiwei LIANG[1], Lonnie Rimmer[1], Joey Chien[1], Nicholas Goldenson[1], Ryan Black[1], Saul Shiffman[2] and Douglas Oliveri[3]; [1]Juul Labs, Inc, Washington, DC, USA, [2]PinneyAssociates, Bethesda, MD, USA, [3]Independent Consultant

40 **LEACHABLE TESTING TO EVALUATE EFFECT OF AN ALTERNATE TRANSPORT MODE ON ENDS POD INTEGRITY.** Felix AYALA-FIERRO, Harish Chevva, Qiwei Liang, Matthew Lyndon, David Cook and Michael J. Oldham; Juul Labs, Inc, Washington, DC, USA

MONDAY AFTERNOON, SEPTEMBER 25, 2023

		Session A ***CDISC*** ***Session Chair:*** *William A. "Allan" Rees*	***Session B*** ***e-Cigarette Chemistry*** *Session Chair: Karen Carter*
1:55 PM		Welcome Remarks	Welcome Remarks
2:00 PM	41	**FDA-CTP AND CDISC DEVELOP TOBACCO RELATED STANDARDS TO ACHIEVE EFFICIENCIES FOR ALL STAKEHOLDERS.** Chrissie CAI[1] and [2]Christine Connolly; [1]FDA Center for Tobacco Products, Beltsville, MD, USA, [2]CDISC, Austin, Texas, USA	46 **WORKFLOW ASSESSMENT OF POTENTIAL LEACHABLES IN AEROSOL FROM ENDS SYSTEMS.** Karen CARTER; Juul Labs, Inc, Washington DC, USA
2:20 PM	42	**CDISC DATA STANDARD.** William A. "Allan" REES; Altria Client Services, Richmond, VA, USA	47 **ANALYTICAL INVESTIGATION OF DATA DEFICIENT SIMULATED LEACHABLES IN ENDS PRODUCTS: CASE STUDY.** Cameron SMITH, Matthew Lyndon, Lena Jeong, Danielle Lehman, J. Brian Jameson, Harish Cheeva, Felix Ayala-Fierro, Karen Carter, David Cook and I. Gene Gillman; Juul Labs, Inc, Washington, DC, USA

2:25 PM	**SPEAKER** - Christine Connolly; CDISC, Austin, TX, USA	48	**FLAVORANT TRANSPORT PREDICTION FROM E-LIQUID MATRICES.** Bob MOISION, Laura Striepe, Vincent Nip and Huan Wang; Juul Labs, Inc, Washington, DC, USA
2:45 PM	**SPEAKER -** Chrissie CAI; Food and Drug Administration, Washington, DC, USA	49	**A MODEL OF THE TRANSFER OF SPECIES FROM THE E-LIQUID TO THE AEROSOL DURING VAPORIZATION IN AN ENDS PRODUCT.** David KANE, Gordon Holloway, Nagaraja Rao, Bob Moision, Venessa Tse and Norman Fraley; Juul Labs, Inc, Washington, DC, USA
3:05 PM	**SPEAKER -** Matthew HASSINK; Food and Drug Administration, Washington, DC, USA	50	**IDENTIFICATION OF AEROSOL COLLECTION RELATED UNKNOWNS IN NTA SAMPLES USING GC-ORBITRAP.** Laura STRIEPE,
3:25 PM	Panel Discussion & Audience Q&A	51	**THE MODULAR PUFF MACHINE (MPM): A NEW APPROACH TO PUFFING.** Nandita SINGH, Bob Moision, Johnathan Marquez, Scott Park and Tom Vo; Juul Labs, Inc, Washington, DC, USA

4:00 PM ***BREAK***

		Session A **Toxicology, *in vitro*,** **Product Stewardship** *Session Chair: Katarina Aleksa*		***Session B*** ***Cigarette Chemistry*** *Session Chair: Karl Wagner*
4:20 PM		Welcome Remarks		Welcome Remarks
4:25 PM	43	**LESSONS LEARNED FROM THE *IN VITRO/IN VIVO* TOXICOLOGICAL ASSESSMENT OF THE JUUL SYSTEM.** Michael OLDHAM[1], Pamela Heard[2], Leon F. Stankowski Jr.[2] and Guy Lalonde[1]; [1]Juul Labs, Inc, Washington, DC, USA, [2]Charles River Laboratories, Skokie, IL, USA	52	**HORWITZ-THOMPSON EQUATION AS A BENCHMARK FOR CORESTA COLLABORATIVE STUDY RESULTS.** Michael MORTON; Altria Client Services, Richmond, VA, USA
4:45 PM	44	**A QUANTITATIVE RISK ASSESSMENT APPROACH TO EVALUATE RELATIVE HEALTH RISKS OF ELECTRONIC CIGARETTES VS. COMBUSTIBLE CIGARETTES.** Charlene LIU[1], Autumn Bernal[2], Yilang Huang[3], Chuan Liu[4], Donald Graff[5] and Xingtao Jian[3]; [1]RiskWise Solution, Princeton, NJ, USA, [2]ToxCreative, Laguna Hills, CA, USA, [3]RELX Technology, Shenzhen, China, [4]Pinevale, Southampton, UK, [5]Cheerain HK Limited, Hong Kong	53	**EFFECT AND INFLUENCE OF PERFORATION METHODS FOR TIPPING PAPER ON THE CONTROL OF THE THERMAL ENERGY OF SMOKE FROM TOBACCO PRODUCTS.** Michael LINDNER[1], Cristina Rufener[2] and Tomas Bense[2]; [1] Tann Holding, Traun, Austria, [2]C.I.T. Montepaz, Montevideo, Uruguay

5:05 PM	45	**Withdrawn**	54	**Withdrawn**

5:25 PM			55	**Withdrwan**

ADJOURN

TUESDAY MORNING, SEPTEMBER 26, 2023

	Session A ***Regulatory & Public Health*** *Session Chair: Jessica Parker-Zdinak*	***Session B*** ***Clinical, Behavioral & Perception Research*** *Session Chair: Ian Fearon*
8:45 AM	Welcome Remarks	Welcome Remarks

8:50 AM 56 **UNDERSTANDING CONSUMERS' JOURNEY FROM CIGARETTES TO MODERN ORAL NICOTINE PRODUCTS.** Jessica PARKER-ZDINAK[1], Sarah Marking[2] and Andrew Joyce[2]; [1]Applied Research and Analysis Company, Richmond, VA, USA, [2]Consilium Sciences, Richmond, VA, USA

9:10 AM 57 **THE CASE FOR A REVISED ABUSE LIABILITY ASSESSMENT FRAMEWORK FOR TOBACCO PRODUCTS.** Andrea VANSICKEL; Altria Client Services, Richmond, VA, USA

65 **BEHAVIORAL INTENTIONS ASSESSMENT OF A DISPOSABLE E CIGARETTE AMONG ADULT CURRENT, FORMER, AND NON SMOKERS IN THE UNITED STATES.** Christopher RUSSELL[1], Willie J. McKinney[2] and Ian M. Fearon[3]; [1]Russell Burnett Research & Consultant, Glasgow, UK, [2]McKinney Regulatory Science Advisors, VA, USA, [3]whatIF? Consulting, Harwell, UK

66 **UNDERSTANDING THE SENSORY ATTRIBUTES UNDERLYING THE ACCEPTANCE OF E-CIGARETTE PRODUCTS, WITH THE AIM TO INCREASE THE ACCEPTANCE OF ALTERNATIVE SMOKING PRODUCTS.** Andrew LIVERMORE[1], Malori Comer[1] and Laurel Moller[2]; [1]Curion Insights, Red Wood City, CA, USA, [2]Curion Insights, Old Bridge, NJ, USA

9:30 AM 58 **STANDARDIZING THE EVALUATION OF APPROPRIATENESS FOR THE PROTECTION OF PUBLIC HEALTH IN PREMARKET TOBACCO PRODUCT APPLICATIONS.** Ryan SELTZER[1], Ding-Geng Chen[2] and [3]Ian M. Fearon; [1]Safety in Numbers, Tucson, AZ, USA, [2]Arizona State University, Phoenix, AZ, USA, [3]whatIF? Consulting Ltd, Harwell, UK

67 **ESTIMATING HUMAN PK PARAMETERS FOR ENDS PRODUCTS FROM CHEMICAL ANALYSES OF THEIR AEROSOLS.** Saul SHIFFMAN[1], Qiwei Liang[2], Georgios Karles[2] and Gal Cohen[3]; [1]PinneyAssociates, Pittsburg, PA, USA, [2]Juul Labs, Inc, Washington, DC, USA, [3]Intuitive Sciences, Tiburon, CA, USA

9:50 AM 59 **CORESTA TOBACCO HARM REDUCTION WORKSHOP OVERVIEW.** Jason FLORA[1] and Rob Stevens[2]; [1]Altria Client Services, Richmond, VA, USA, [2]RAI Services Company, Winston-Salem, NC, USA

68 **Withdrwan**

10:10 AM ***BREAK***

Session A
Regulatory & Public Health
Session Chair: Jessica Parker-Zdinak

Session B
e-Cigarette Chemistry
Session Chair: Brian Jameson

10:30 AM Welcome Remarks

Welcome Remarks

10:35 AM 60 **SUBSTANTIAL EQUIVALENCE OF TOBACCO PRODUCTS: ARE ALL TOBACCO PRODUCTS OF THE SAME TYPE AND CHARACTERIZING FLAVOR SUBSTANTIALLY EQUIVALENT? EXAMPLES OF EQUIVALENCE AND NONEQUIVALENCE AMONG WATERPIPE TOBACCOS.** John LAUTERBACH; Lauterbach and Associates, Deland, FL, USA

10:55 AM 61 **SWITCHING AWAY FROM CIGARETTES USING TOBACCO- AND MENTHOL-FLAVORED JUUL, AMONG ADULTS WHO SMOKE MENTHOL VS NON-MENTHOL CIGARETTES.** Arielle SELYA; PinneyAssociates, Pittsburg, PA, USA

69 **DETERMINATION OF GLYCIDOL IN E-LIQUID AND AEROSOL SAMPLES FOR ENDS PRODUCTS BY GC-MS.** David COOK, Beth Stump, Norman Fraley, Kathy Humphries, I. Gene Gillman and Brian Jameson; Juul, Labs, Inc, Washington, DC, USA

70 **SELECTED HPHC FORMATION IN JUUL2 NON-COMMERCIAL DEVICES AS A FUNCTION OF TEMPERATURE.** Hosna MOGADDEDI, I. Gene Gillman, Bob Moision, Nandita Singh, Venessa Tse, Kevin Pascual, Angela Huang, Valerie Schwartz and Sam Anderson; Juul Labs, Inc, Washington, DC, USA

11:15 AM 62 **MODELLING THE IMPACT OF AN ENDS FLAVOR BAN ON YOUTH USERS AND ADULT CURRENT SMOKERS IN THE UNITED STATES.** Andrea PATTON, Jyoti Goyal, Gabriel Barnard and Neil McKeganey; Centre for Substance Use Research, Glasgow, UK

11:35 AM 63 **EVOLUTION OF YOUTH TOBACCO USE: ANALYZING TRENDS IN E-CIGARETTE CONSUMPTION AND THE RISE OF CBD/THC CONTAINING DEVICES.** Mark CROSSWHITE; McKinney Regulatory Science Advisors, Henrico, VA, USA

11:55 AM 64 **ARE SMOKERS AND YOUNG PEOPLE OVER-SURVEYED? ADDRESSING CONCERNS ABOUT POSSIBLE RESPONDENT FATIGUE AND PRIMING EFFECTS IN PROBABILITY-BASED SAMPLING FOR REGULATORY SURVEY RESEARCH.** Christopher FLEURY, Victoria Hoverman and Abby Cohen; Ipsos-Insight, Washington, DC, USA

71 **GLYCIDOL IN ENDS: YIELD PATTERNS OVER POD LIFE AND MEASUREMENTS IN 35 NORTH AMERICAN MARKET PRODUCTS.** Brian JAMESON, Karen Carter, Candice Jongsma, Jiaming Wang, Austin L. Bates, Sifat Ullah, Cameron R. Smith, Lena N. Jeong, David K. Cook and I. Gene Gillman; Juul Labs, Inc, Washington, DC, USA

72 **ACCELERATED AGING OF PROPYLENE GLYCOL AND GLYCEROL.** Norman FRALEY, Lena Jeong, Matthew Lyndon, Anastasia Lioubmirov and I. Gene Gillman; Juul, Labs Inc, Washington, DC, USA

73 **ASSESSMENT OF FORMALDEHYDE AND ACETALDEHYDE FORMATION IN E-LIQUID AND DURING PUFFING OF AN ENDS PRODUCT.** Manali AGGRAWAL, Bob Moision, Katharine Pearce and Apurva Bhave; Juul Labs, Inc, Washington, DC, USA

12:15 PM ***LUNCH***

TUESDAY AFTERNOON, SEPTEMBER 26, 2023

1:00 PM Posters

74 **E-CIGARETTE REGULATORY NON-COMPLIANCE IN THE UK MARKETPLACE.** Malcolm SAXTON; Broughton Life Sciences, Earby, Lancashire, UK

75 **INNOVATIVE SOLUTION TO AN AGE-OLD PROBLEM- CONSIDERATIONS WHEN DEVELOPING AGE- GATED TECHNOLOGY.** Lillian ORTEGA, Lise Fraissinet, Ed Carmines, Bryan Burd and Kevin Burd; Chemular Inc, Hudson, MI, USA

76 **NICOTINE EXTRACTION FROM POLYPROPYLENE MODERN ORAL PACKAGING.** Owen BUSSEY, Cody Perry and Serban Moldoveanu; Reynolds American, Winston-Salem, NC, USA

77 **STABILITY EVALUATIONS OF TOBACCO-FREE NICOTINE-CONTAINING POUCH PRODUCTS.** Sawyer HUBBARD, Candice K. Cunningham and Nolan D. Spann; Reynolds American, Winston-Salem, NC, USA

78 **RAPID "MOISTURE" DETERMINATION AS AN ALTERNATIVE TO CRM76 FOR MODERN ORAL POUCHES.** Ian TINDALL; Cerulean, Milton Keynes, UK

79 **A COMPARISON OF HPHCS IN ON!® PLUS NICOTINE POUCHES TO HPHCS IN CIGARETTES, SMOKELESS TOBACCO INCLUDING SNUS AND AN ORAL NRT PRODUCT.** Regina BALLENTINE, John H. Miller IV, Cathy X. Jin, Jennifer H. Smith, Karl A. Wagner, Regina M. Ballentine, Hannah Grisevich, Chris K. Salmon, Michael S. Williams, Likun Yang, Richard W. Morgan, Vanessa Haase and Tim L. Danielson; Altria Client Services, Richmond, VA, USA

80 **QUANTITATIVE MEASUREMENT OF HPHCS IN 16 COMMERCIAL SMOKELESS TOBACCO PRODUCTS.** Selvin EDWARDS and Kenneth M. Taylor; Food and Drug Administration, Silver Springs, Maryland, USA
Presented but no electronic file submitted

81 **NICOTINE AND FREE- (UNPROTONATED) NICOTINE IN SEVERAL NOVEL SMOKELESS NICOTINE PRODUCTS: HERBAL SNUFF, TOOTHPICKS, LOZENGES, GUM, AND TOBACCO-FREE POUCHES.** Robert TYX, Hang Tran, Liza Valentin-Blasini and Clifford H. Watson; Centers for Disease Control and Prevention, Atlanta, GA, USA
Presented but no electronic file submitted

82 **METHOD MODIFICATIONS AND VALIDATION TO EXPAND SCOPE OF CRM No 95 TO ANALYZE SELECT AROMATIC AMINES IN HEATED TOBACCO PRODUCTS.** Nicholas MCCUTCHEON, Matt Melvin, Weiling Li, Regina Ballentine, Niti H. Shah and Yezdi Pithawalla; Altria Client Services, Richmond, VA, USA

83 **DETERMINATION OF AEROSOL MASS AND FIVE PRIMARY CONSTITUENTS IN AEROSOLS GENERATED FROM HEATED TOBACCO PRODUCTS.** Anthony BROWN[1], Sandra Ingram[2], Krystal Soler[2], Nick McCutcheon[1], Matt Melvin[1], Yezdi B. Pithawalla[1] and Weiling Li[1]; [1]Altria Client Services, Richmond, VA, USA, [2]Lancaster Professional Scientific Staffing, Richmond, VA, USA

84 **QUANTITATIVE DETERMINATION OF BENZO[A]PYRENE IN AEROSOL EMITTED BY HEATED TOBACCO PRODUCTS USING GAS CHROMATOGRAPHY-MASS SPECTROMETRY.** Suci INDRAYANI, Anggra Hardiansyah, Ari Wieliyani and Eka U. Mulyana; Filtrona Scientific Services, Surabaya, East Java, Indonesia
Presented but no electronic file submitted

85 **COMPARISON OF HPHCS IN AEROSOL GENERATED FROM A NOVEL HEATED TOBACCO CAPSULE (HTC) PROTOTYPE TO HPHCS IN CONVENTIONAL CIGARETTE SMOKE.** James A. SKAPARS, Weiling Li, Yezdi B. Pithawalla, Kyle W. Pfeiffer, Matt S. Melvin, Timothy L. Danielson; Altria Client Services, Richmond, VA, USA

86 **CREATING AN AI LLM TOBACCO DATABASE.** Kevin BURD[1] and Ryan Selby[2]; [1]Chemular Inc, Hudson, MI, USA, [2]Generative AI Solutions, Vancouver, BC, Canada

87 **EFFECT OF TIME IN THE PYROLYSIS OF HEET TOBACCO WITH SBA-15 FIBROUS AND SBA-15 PLATELETS.** Marbel BELTRÁN[1], Deseada Berenguer[1], Antonio Marcilla[1] and Michael Cairns[2]; [1]Alicante University, Alicante, Spain, [2]Strathclyde University, Scotland, UK

88 **IN VITRO CYTOTOXICITY AND MUTAGENICITY ASSESSMENT OF A NOVEL HEATED TOBACCO CAPSULE (HTC) PROTOTYPE IN COMPARISON TO COMBUSTIBLE CIGARETTES.** Utkarsh DOSHI, Britt Langston and K. Monica Lee; Altria Client Services, Richmond, VA, USA

89 **ON-DEVICE TOPOGRAPHY RECORDING IN A PROTOTYPE HEATED TOBACCO CAPSULE (HTC) SYSTEM.** Kevin BALL, Raymond Lau, Zack Blackmon, Jianmin Liu, Yezdi B. Pithawalla and Jeff Edmiston; Altria Client Services, Richmond, VA, USA

90 **CHARACTERIZATION OF NICOTINE PHARMACOKINETICS FROM USE OF A NOVEL HEATED TOBACCO CAPSULE PROTOTYPE IN ADULTS WHO SMOKE.** Jianmin LIU, Jingzhu Wang, Jeffery S. Edmiston, Raymond W. Lau and Yezdi B. Pithawalla; Altria Client Services, Richmond, VA, USA

91 **CIGARETTE REDUCTION AND SWITCHING BEHAVIOR BY MENTHOL CIGARETTE PREFERENCE AND MENTHOL HEATED TOBACCO PRODUCT USE AMONG ADULTS WHO SMOKE CIGARETTES.** Joshua KARELITZ, Hui Cheng, Elizabeth Becker and Jenna Leighty; Altria Client Services, Richmond, VA, USA

92 **TOBACCO USE, PERCEPTIONS, AND CHARACTERISTICS OF ADULTS WHO USE IQOS® IN THE UNITED STATES: FINDINGS FROM A CROSS-SECTIONAL STUDY.** Hui CHENG[1], Brendan Noggle[1], Andrea R. Vansickel[1], Edward G. Largo[1], Pierpaolo Magnani[2] and Annie Heremans[2]; [1]Altria Client Services, Richmond, VA, USA, [2]Philip Morris Products, Lausanne, Switzerland

93 **AN ASSESSMENT OF DEPENDENCE IN ADULT SMOKERS SWITCHING FROM COMBUSTIBLE CIGARETTES TO THE RELX INFINITY ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS) OVER 8 WEEKS.** Donald GRAFF[1] and Ian M. Fearon[2]; [1]Cheerain HK Limited, Hong Kong, China, [2]whatIF? Consulting Limited, Harwell, UK

94 **IN VITRO GENOTOXICITY EVALUATION OF JUUL ENDS, MARKETED ENDS, AND REFERENCE CIGARETTES.** Guy LALONDE[1], Christina Sulaiman[1], Pamela Heard[2], Vyom Sharma[2], Leon F. Stankowski, Jr.[2] and Michael Oldham[1]; [1]Juul Labs, Inc, Washington, DC, USA, [2]Charles River Labs, Skokie, IL, USA

95 **TOXICOLOGICAL POTENTIAL OF TWO JUUL ENDS PRODUCTS RELATIVE TO REFERENCE CIGARETTE 3R4F AND FILTERED AIR IN A 90-DAY NOSE-ONLY INHALATION TOXICITY STUDY.** Guy LALONDE[1], Rahat Wadhwa Desai[2] and Charles L. Gaworski[3]; [1]Juul Labs, Inc, Washington, DC, USA, [2]Syngenta Canada, Arva, ON, Canada, [3]Kozmin Consulting, Flat Rock, NC, USA

96 **A RELATIVELY LOW NICOTINE STRENGTH E-LIQUID THAT REDUCES THE URGE TO SMOKE AS MUCH AS CIGARETTES.** Ed CARMINES[1], Lise Fraissinet[1], Karen Carmines[1] and Naama Levy-Cooperman[2]; [1]Chemular Inc, Hudson, MI, USA, [2]Altreos Research Partners, Toronto, ON, Canada

97 **YOUTH UNDERESTIMATE THE HEALTH AND ADDICTION RISKS OF TOBACCO PRODUCTS.** Ed CARMINES[1], Lise Fraissinet[1] and Azure Steele[2]; [1]Chemular Inc, Hudson, MI, USA, [2]M/A/R/C Research, High Point, NC, USA

98 **Withdrawn**

99 **APPLICATION OF A RAPID IN VITRO TOXICOLOGICAL SCREENING (TOXTRACKER©) TO DETERMINE THE EFFECT OF FLAVORS IN SNUS PRODUCTS.** Ed CARMINES[1], Katarina Aleksa[2], Sean Oh[2], Manoj Misra[1], Bonnie Coffa[1] and Giel Hendriks[3]; [1]Chemular Inc, Hudson, MI, USA, [2]Labstat International Inc, Kitchener, ON, Canada, [3]Toxys, Leiden, Netherlands

100 **NEUTRAL RED UPTAKE TESTING OF ORAL NICOTINE PRODUCTS AFTER EXTRACTION WITH ARTIFICIAL SALIVA.** Mariano SCIAN, Emma Press, Jordan Jones, Lukas Braia, Lonneke Palmer, Joelle Carbonelle, Kirsten Lassiter and Lynn McFadden; Enthalpy Specialty Labs, Richmond, VA, USA

101 **EVALUATING SUBGINGIVAL MICROBIOME AFTER SWITCHING FROM CIGARETTES TO NICOTINE POUCHES.** Jianmin LIU[1], Jingzhu Wang[1], Jeffery S. Edmiston[1], Mohamadi A. Sarkar[1], Maria Gogova[1], Bruce Paster[2], Tsute Chen[2], Hatice Hasturk[2], Kimberly R. Milleman[3], Jeff L. Milleman[3] and Abbie L. Yoder[3]; [1]Altria Client Services, Richmond, VA, USA, [2]The Forsyth Institute, Cambridge, MA, USA, [3]Salus Research, Fort Wayne, IN, USA

102 **EFFECT OF ORAL NICOTINE PRODUCT USE ON CIGARETTE REDUCTION AND QUITTING IN A 6-MONTH PROSPECTIVE COHORT STUDY OF ADULT SMOKERS.** Elliott MCDOWELL[1], Jason N. Kennedy[1], Stacey A. Bell[1], Michael Feehan[1], Michelle Humphreys[1], Jessica Zdinak[2], Sarah Marking[3], Andrew Joyce[3], Rich Hill[4], Jo-Ann Quinn[4] and Chris Howard[4]; [1]Cerner Enviza, Kansas City, MO, USA, [2]Applied Research and Analysis Company, Richmond, VA, USA, [3]Consilium Sciences, Richmond, VA, USA, [4]Rogue Holdings, Jacksonville, FL, USA

103 **EFFECT OF FRUIT AND MINT FLAVORED ORAL NICOTINE PRODUCT USE ON CIGARETTE REDUCTION AND QUITTING IN A 6-MONTH PROSPECTIVE COHORT STUDY OF ADULT SMOKERS.** Jason KENNEDY[1], Elliott H. McDowell[1], Michael Feehan[1], Stacey A. Bell[1], Michelle Humphreys[1], Sarah Marking[2], Andrew Joyce[2], Jessica Zdinak[3], Rich Hill[4], Jo-Ann Quinn[4] and Chris Howard[4]; [1]Cerner Enviza, Kansas City, MO, USA, [2]Consilium Sciences, Richmond, VA, USA, [3]Applied Research and Analysis Company, Richmond, VA, USA, [4]Rogue Holdings, Jacksonville, FL, USA

104 **DESIGN AND EXECUTION OF A NON-SITE-BASED, PROSPECTIVE, MULTI-WAVE COHORT STUDY TO ASSESS PATTERNS OF ORAL NICOTINE PRODUCT USE OVER 6-MONTHS AND ASSOCIATED COMBUSTIBLE CIGARETTE REDUCTION AND QUITTING.** Stacey BELL[1], Michelle Humphreys[1], Michael Feehan[1], Elliott McDowell[1], Sarah Marking[2], Andrew Joyce[2], Jessica Zdinak[3], Richard Hill[4], JoAnn Quinn[4] and Chris Howard[4]; [1]Cerner Enviza, Kansas City, MO, USA, [2]Consilium Sciences, Richmond, VA, USA, [3]Applied Research and Analysis Company, Richmond, VA, USA, [4]Rogue Holdings, Jacksonville, FL, USA

105 **ASYNCHRONOUS ONLINE FOCUS GROUPS: QUALITATIVE RESEARCH ON REDUCED-RISK NICOTINE PRODUCTS WITH UNDERSERVED OR HARD-TO-REACH POPULATIONS.** Neil SHERWOOD[1] and Cheryl K. Olson[2]; [1]Neil Sherwood Consulting, Nyon, Vaud, Switzerland, [2]McKinney Regulatory Science Advisors, San Carlos, CA USA

106 **NON-TARGET ANALYSIS SURVEY OF TOBACCO-FREE NICOTINE POUCHES.** Jacqueline COLLINS and Alexandra M. Martin; Enthalpy Specialty Labs, Richmond, VA, USA

107 **ABUSE LIABILITY ASSESSMENT OF VELO NICOTINE POUCHES IN COMPARISON TO COMBUSTIBLE CIGARETTES AND NICOTINE GUM.** Milly KANOBE, Christie Y. Powell, Sarah A. Ayoku, Alison G. Gibson, Melissa A. Tapia, Kristen G. Jordan, Makena Patrudu, Brian M. Keyser, Jeffrey W. Coffield and Sarah A. Baxter-Wright; RAI Services Company, Winston-Salem, NC, USA

108 **OPTIMIZATION OF SEEDING DENSITY OF PRIMARY HUMAN GINGIVAL FIBROBLASTS FOR IN VITRO TOXICITY TESTING.** Xuefei CAO[1], Utkarsh Doshi[1], Kyeonghee M. Lee[1] and Manoochehr Khazaee[2]; [1]Altria Client Services, Richmond, VA, USA, [2]Eurofins Lancaster Laboratories, Lancaster, PA, USA

	Session A ***Agronomy*** *Session Chair: Rana Tayyarah*	***Session B*** ***Clinical, Behavioral & Perception Research*** *Session Chair: Preston Campbell*
2:10 PM	Welcome Remarks	Welcome Remarks

2:15 PM 109 **INFLUENCES OF GENETICS AND NITROGEN APPLICATION RATE TO FLUE-CURED TOBACCO AGRONOMIC CHARACTERISTICS AND CHEMICAL CONSTITUENTS.**
Matthew VANN; NC State University, Raleigh, NC, USA

2:35 PM 110 **POTENTIAL ULTRA-LOW NICOTINE LIMIT IN TOBACCO – CAN WE MEET IT?**
Anne FISHER[1], Colin Fisher[1], Barunava Patra[1], Huihua Ji[1], Jeffrey Kinney[1], Shengming Yang[2] and Stacey Slone[1]; [1]University of Kentucky, Lexington, KY, USA, [2]US Department of Agriculture, Fargo, ND, USA

115 **SWITCHING AWAY FROM CIGARETTES ACROSS 24 MONTHS AMONG US ADULT SMOKERS WHO PURCHASED THE JUUL SYSTEM.**
Nicholas GOLDENSON[1], Saul Shiffman[2], Gem M. Le[1] and Ryan A. Black[1]; [1]Juul Labs, Inc, Washington, DC, USA, [2]PinneyAssociates, Pittsburgh, PA, USA

116 **COMPARING ADULT SMOKERS WHO SWITCHED TO JUUL VS CONTINUING SMOKERS: BIOMARKERS OF EXPOSURE AND OF POTENTIAL HARM AND RESPIRATORY SYMPTOMS.**
Saul SHIFFMAN[1], Douglas R. Oliveri[2], Nicholas I. Goldenson[2], Qiwei Liang[2], Ryan A. Black[2] and Snigdha Mishra[2]; [1]PinneyAssociates, Bethesda, MD, USA, [2]Juul Labs, Inc, Washington, DC, USA

2:55 PM	111	**Withdrawn**	117	**UTILIZING REAL-WORLD TOPOGRAPHY DATA TO DEFINE SMOKE MACHINE PUFFING REGIMEN FOR ENDS.** Robert UNDERLY and Randy Weirdman; RAI Services Company, Winston-Salem, NC, USA
3:15 PM	112	**Withdrawn**	118	**DESIGN OF A RANDOMIZED MULTI-SITE, OPEN-LABEL, 8-WEEK, ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS) ACTUAL USE STUDY.** Mandara SHETTY; British American Tobacco, Southampton, Hampshire, UK
3:35 PM		***BREAK***		
3:55 PM	113	**Withdrawn**	119	**SWITCHING EXCLUSIVELY FROM SMOKING TO USING GLO RESULTS IN SIGNIFICANT, SUBSTANTIAL REDUCTIONS IN EXPOSURE TO CIGARETTE SMOKE TOXICANTS.** Nathan GALE, David Azzopardi, Mike McEwan, Filimon Meichanetzidis and Senthil Vel; B.A.T. (Investments) Ltd, Southampton, UK

4:15 PM 114 **Withdrawn**

120 **APPLYING FACTOR ANALYSIS TO UNDERSTAND PRODUCT DIFFERENCES OBSERVED IN CLINICAL STUDIES.** Yisha HE, Jingzhu Wang, Lai Wei, Raheema Muhammad-Kah, Jeffery Edmiston and Edward Largo; Altria Client Services, Richmond, VA, USA

4:35 PM 121 **EVALUATING ORAL HEALTH AFTER SWITCHING FROM CIGARETTES TO NICOTINE POUCHES.** Jianmin LIU[1], Jingzhu Wang[1], Jeffery S. Edmiston[1], Mohamadi A. Sarkar[1], Maria Gogova[1], Kimberly R. Milleman[2], Jeffery L. Milleman[2] and Abigail L. Yoder[2]; [1]Altria Client Services, Richmond, VA, USA, [2]Salus Research, Fort Wayne, IN, USA

ADJOURN

WEDNESDAY MORNING, SEPTEMBER 27, 2023

Joint Session
Symposium Panel: Assessment of ENDS Ingredients
Session Chair: Michael Oldham

8:45 AM Session Welcome Remarks

8:50 AM 122 **A TIERED APPROACH TO ENDS INGREDIENT ASSESSMENT.** Irene ABRAHAM; JT International, Geneva, Switzerland

9:05 AM 123 **ESTABLISHING AN ENDS IN VITRO AND IN VIVO INGREDIENT ASSESSMENT STRATEGY USING A TOOLBOX APPROACH.** Florence VONMOOS and Karsta Luettich; Philip Morris Products, Neuchatel, Switzerland

9:20 AM 124 **A PRODUCT STEWARDSHIP ASSESSMENT STRATEGY FOR E-LIQUIDS.** Liam SIMMS; Imperial Brands, Bristol, UK

9:35 AM 125 **NEW ASSESSMENT METHODS FOR ENDS INGREDIENTS.** Arno GUTLEB; Invitrolize, Belvaux, Luxembourg

9:55 AM 126 **EVALUATION OF SYNTHETIC COOLING AGENTS WS-3 AND WS-23 IN 90-DAY INHALATION TOXICITY STUDIES IN SPRAGUE DAWLEY RATS.** Richard SAVORY; B.A.T. (Investments) Ltd, Southampton, UK

10:10 AM 127 **TOXICOLOGICAL ASSESSMENT OF ELECTRONIC NICOTINE DELIVERY SYSTEMS USING SEVERAL 2D AND 3D IN VITRO CYTOTOXICITY AND GENOTOXICITY ASSAYS.** Robert LEVERETTE; RAI Services Company, Winston-Salem, NC, USA

10:25 AM Panel Discussion & Audience Q&A

10:55 AM ***LUNCH***

Session A
Symposium Panel: Exploring Risk Perceptions and Tobacco Use Behavior
Session Chair: Elizabeth Becker

12:00 PM Welcome Remarks

12:05 PM 128 **PERCEPTIONS OF NICOTINE AND TOBACCO PRODUCTS IN THE US ADULT POPULATION – A LATENT CLASS ANALYSIS.** Hui CHENG, Sade Jones and Joshua Karelitz; Altria Client Services, Richmond, VA, USA

12:20 PM 129 **AN EXPLORATION ON RELATIVE HARM PERCEPTIONS OF PORTIONED ORAL NICOTINE PRODUCTS AMONG POTENTIALLY VULNERABLE POPULATIONS.** Christie POWELL[1], Red Thaddeus D. Miguel[2] and Isabella Steffensen[2]; [1]RAI Services Company, Winston-Salem, NC, USA, [2]Thera-Business Consulting, Ottawa, ON, Canada

Session B
Modern Oral, HTP, Other
Session Chair: Karl Wagner

Welcome Remarks

132 **NICOTINE EXTRACTION FROM POLYPROPYLENE MODERN ORAL PACKAGING.** Owen BUSSEY, Cody Perry and Serban Moldoveanu; Reynolds American, Winston-Salem, NC, USA

133 **DETECTION OF THE PRESENCE OF TOBACCO IN TEA BASED HEAT-NOT-BURN SMOKING DEVICES.** Serban MOLDOVEANU; Reynolds American, Winston-Salem, NC, USA

12:35 PM 130 **THE EFFECTS OF A MODIFIED-RISK CLAIM FOR AN ENDS PRODUCT TO INCREASE SMOKERS' BEHAVIORAL INTENTIONS TO USE THE PRODUCT ARE COMPLETELY MEDIATED BY THE CLAIM'S EFFECTS ON RISK PERCEPTIONS.** Saul SHIFFMAN[1], Stacey McCaffrey[2] and Ryan Black[2]; [1]PinneyAssociates (consultant to Juul Labs, Inc), Bethesda, MD, USA and University of Pittsburgh, Pittsburg, PA, USA, [2] Juul Labs, Inc, Washington, DC, USA

12:50 PM 131 Omitted

1:05 PM Panel Discussion & Audience Q&A

1:35 PM ***Adjourn***

134 **PUFF-BY-PUFF CHEMICAL CHARACTERIZATION OF HEATED TOBACCO AEROSOL.** Kaitlyn SUSKI, Brad Ingebrethsen, Raj Rao, Josh Kurzman and Emily Dong; Juul Labs, Inc, Washington, DC, USA

135 **HOW FLUFFY IS YOUR PACK?** JOHN LAUTERBACH; Lauterbach and Associates, Deland, FL, USA

136 **DEVELOPMENT OF CERTIFIED REFERENCE CIGARS REPRESENTING THREE PRODUCT CATEGORIES.** Ruth MCNEES, Huihua Ji, Stacey Slone, Brent Shelton, Matt Craft, JT Hall, Orlando Chambers and Ling Yuan; University of Kentucky, Lexington, KY, USA

ABSTRACTS

SYMPOSIUM - LOOKING FORWARD - THE CHALLENGES AND OPPORTUNITIES AHEAD FOR HARM REDUCTION. Rana TAYYARAH; Labstat International Inc, Kitchener, ON, Canada

In the year since TSRC marked its Diamond Jubilee, we have seen an unprecedented level of activity concerning regulatory mile-markers and challenges in the tobacco industry. In the United States, the FDA Center for Tobacco Products has issued decisions on nearly 26 million Pre-market Tobacco Product Applications, most of which have been refuse to accept (RTA) letters or marketing denial orders (MDO). The Reagan-Udall Foundation's report on its independent evaluation of CTP was released with significant criticism and opportunity recommendations for the center. Internationally, we continue to see simultaneous advocacy for and warnings against combustible-alternative nicotine products. With the potential confusion for the consumer due to this 'mixed messaging,' there has been an uptick in demand for an increased focus on the voice of the consumer and public education campaigns. In this past year, flavors, menthol in particular, synthetic nicotine, enforcement against illegal products, and potential nicotine limits have been striking and volatile topics. With these complex issues in mind, we have invited experts and stakeholders to share insights from multiple perspectives on the challenges, progress, and ongoing opportunities for tobacco and tobacco products regulations. Brent Taylor (Altria Client Services) will share insights from recent consumer research. Todd Cecil (FDA-CTP) will provide an update from the perspective of a regulator. Joe Murillo (Juul Labs, Inc) will discuss regulatory challenges from the perspective of the manufacturer. Finally, Patricia Kovacevic (Cryomass Technologies Inc) will discuss key cases and path forward concepts from a legal viewpoint.

5. CHEMICAL, PHARMACOLOGICAL, AND TOXICOLOGICAL ASSESSMENT OF 6-METHYLNICOTINE. Andrew CHEETHAM[1], Susan Plunkett[1], Lynn McFadden[1], Mariano Scian[1], Sarah Marking[2], Bonne Coffa[2], Preston Campbell[2] and Stan Gilliland III[2]; [1]Enthalpy Specialty Labs, Richmond, VA, USA, [2]Consilium Sciences, Richmond, VA, USA

There is interest in nicotine-related alkaloids for both recreational use and pharmaceutical applications such as smoking cessation and central nervous

system disorders conditions such as Parkinson's, Tourette's, ADHD. Nicotine is one of many alkaloids produced by the tobacco plant (*Nicotiana tabacum* species) and more recently synthesized for commercial use. The compound 6-methylnicotine (CAS# 101540-79-8) has been identified as a nicotine analog of interest based on its chemical structure, sensorial properties, and commercial availability. Chemical, pharmacological, and toxicological assessments were conducted on 6-methylnicotine and compared to pharmaceutical grade (*S*)-nicotine. Samples of 6-methylnicotine analyzed included both freebase and salt forms, as well as in e-liquid formulations containing propylene glycol (PG) and vegetable glycerin (VG) for use in an electronic nicotine delivery system (ENDS). Chemical analysis confirmed the sample was 6-methylnicotine, racemic, and ~98% pure utilizing ^{1}H NMR, chiral UPLC-UV, and GC-MS, respectively. The aerosol transfer efficiency of 6-methylnicotine was similar to that of nicotine (82.5 ± 2.9 % vs. 85.6 ± 0.6 % for freebase forms). The QSAR computational pharmacology of 6-methylnicotine is similar in potency and binding affinity to that of (S)-nicotine in *in vivo* and *ex vivo* models. Conventional *in vitro* toxicology testing (Neutral Red and Ames) demonstrated 6-methylnicotine salt e-liquid formulations have similar cellular cytotoxicity and mutagenicity to the analogous (*S*)-nicotine salt e-liquid formulation. The totality of available evidence indicates that 6-methylnicotine has comparable chemical, pharmacological, and toxicological properties to the more widely used nicotine.

6. IMOTINE™: A NOVEL NON-NICOTINE COMPOUND WITH CNS ACTIVITY. Ed CARMINES[1], Manoj Misra[1] and Sam Benaim[2]; [1]Chemular Inc, Hudson, MI, USA, [2]Novel Compounds, Cheyenne, WY, USA

Imotine™ ((S)-3-(N-Methylpyrollidino)-6-methyl-pyridine Benzoate; CAS 5861225-70-7) is a new non-nicotine compound that is reported to have Central Nervous System activity similar to nicotine. Imotine exists as the s-isomer. The compound is not manufactured from nicotine and does not contain any nicotine nor tobacco specific nitrosamine impurities. Analysis of the pure material did not reveal any chemicals of toxicologic concern. The pKa1 and pKa2 are reported to be 8.26 and 3.75 (respectively) as compared to 8.04 and 2.91 for nicotine. The compound is reported to be about 2.6 times more potent than s-nicotine on a molar basis in a mouse LD50 study. The compound is reported to have a similar affinity (K_i= 1.8 nM) for rat brain nicotinic acetylcholinergic receptors (nAChRs) as nicotine (K_i= 1.26 nM). Specific receptor binding data using [3H](-)-nicotine in rat brain (minus cerebellum) preparations containing nAchR alpha4-beta2

subunits showed a K_i of 1.8 nM compared to a K_i= of 2nM for nicotine. It has been concluded that the activity of Imotine is related to its structure and lipophilicity. Nicotine and nicotine analogues are being researched in clinical trials for possible benefit in treating smoking addiction, Alzheimer's disease, Parkinson's disease, ADHD, depression, anxiety, and schizophrenia. Imotine may prove an effective agent for some of these diseases.

7. POTENTIAL ENVIRONMENTAL IMPACT OF USE AND DISPOSAL OF A MODERN ORAL NICOTINE POUCH PRODUCT. Ed CARMINES; Chemular Inc, Hudson, MI, USA

An environmental assessment is required for all new tobacco products. This assessment includes determining the impact of manufacturing, use, and disposal of the product. A new category of pouched tobacco products generally known as modern oral nicotine products has become popular. They do not contain any tobacco leaf material and are generally made with microcellulose granulates, binders, flavors, and nicotine. The granular material is enclosed in a fleece pouch. The consumer places the pouch between the lip and gum for buccal absorption of the nicotine. After the pouch is depleted, the consumer is instructed to dispose of the used pouch in the trash. Reasonable worst case disposal scenarios were modeled to evaluate if a used pouch was disposed of in publicly owned wastewater treatment systems, in home septic systems, or as litter on the ground. Additional potential releases of nicotine to the environment during product use from human excretion were also modeled. The FDA approach established for human drugs and biologics was applied to quantify the anticipated effect of residual nicotine in the pouch on the environment. The calculations compared the Expected Introduction Concentration to the established de minimis concentration of 1 microgram per liter or 1 part per billion. The results of the various worst case scenario calculations showed the estimated nicotine concentrations are not expected to exceed the de minimis threshold under any of the scenarios and therefore the use and disposal of the product is not likely to significantly impact the environment.

8. EVALUATION OF THE POTENTIAL EXTRACTABLES FROM A CHUBBY GORILLA E-LIQUID BOTTLE. Ed CARMINES[1], Lise Fraissinet[1] and Tom Barrett[2]; [1]Chemular Inc, Hudson, MI, USA, [2]Legend Technical Services, St. Paul, MN, USA

Leachable materials in product packaging present a possible hazard to consumers. Toxic materials may migrate out of the packaging into the e-liquid product and be inhaled by the consumer during use of the product. The classical approach to evaluating the potential of packaging material chemicals to migrate into the product is first to perform an extraction study using model solvent systems, and if materials are found at levels of toxicological concern, then a leachables study is performed throughout the shelf life of thel product to confirm if the packaging material has the potential to migrate into the product during intended storage and use. The Product Quality Research Institute ("PQRI") Leachables and Extractables Working Group's recommended approach was followed to evaluate a Chubby Gorilla e-liquid bottle. Specifically, the bottle and cap were tested using the USP 1663 method (Assessment of Extractables Associated with Pharmaceutical Packaging/Deliver Systems). Samples were extracted with aqueous solutions at pH 5.2 and 9.5 and a 50/50% solution of isopropanol and deionized water. The solutions were analyzed by GC/MS (volatiles and semi-volatiles), LC/MS (non-volatiles) and ICP/MS (metals). The bottle and caps did not appear to have the potential to leach materials of toxicological concern above the Safety Concern Threshold (SCT) or Toxicological Threshold of Concern (TTC). Under the conditions of use, the bottle was deemed acceptable as a packaging container for e-liquids.

9. APPLYING THE TOBACCO PRODUCT MANUFACTURING PRACTICES TO EXISTING MANUFACTURING PROCESSES. Lillian ORTEGA, Lise Fraissinet, Randy Freund, Chris Woodruff and Kevin Burd; Chemular Inc, Hudson, MI, USA

On March 8, 2023, the US Food and Drug Administration announced proposed Tobacco Product Manufacturing Practice (TPMP) requirements for manufacturers of finished and bulk tobacco products. The agency is not unaccustomed to requiring FDA regulated product manufacturers to comply with manufacturing standards as other commodities regulated by FDA have done so for decades. These proposed requirements will help protect public health by minimizing or preventing contamination, incorporating traceability down to the ingredients, reducing additional risks to the users and non-users and ensure product conformity and consistency. The tobacco product category is very diverse ranging from cigarette, smokeless and ENDs, to dissolvable, heated tobacco products, cigars and many more products all with distinct design parameters and manufacturing processes. According to the agency, tobacco

manufacturers over the years have incorporated some elements of quality management systems to support their manufacturing processes (based on previous inspections of the establishments). As the proposed TPMP rule undergoes the rulemaking process, it provides ample time for tobacco manufacturers to either establish and implement a Quality Management System (QMS) that will comply with all requirements in the proposed TPMPs or conduct a robust assessment of the current QMS in place with a gap analysis to ensure compliance with future TPMPs. The poster will provide an overview of the proposed TPMP requirements highlighting the differences between existing GMPs, identify the keys to successfully conducting a gap analysis of manufacturing processes and the proposed TPMP and discuss best practices for implementing changes to manufacturing processes to comply with the TPMP rule.

10. CLEARING THE MARKET OF ILLEGAL ENDS PRODUCTS BEGINS AT THE US PORTS. Lillian ORTEGA, Kevin Burd and Bryan Burd; Chemular Inc, Hudson, MI, USA

The FDA's compliance and surveillance efforts are in place to ensure that regulated industry and regulated tobacco products are following the laws designed to protect the public's health and to prevent tobacco use by minors. However, millions of illegal ENDS products are on the U.S. market today and being sold at retail establishment to underage purchasers daily. According to 2022 National Youth Tobacco Survey (NYTS) in 2022, about 1 in 10 or more than 2.5 million U.S. middle and high school students currently used e-cigarettes. The most used devices among the current users were disposables (55.3%), followed by prefilled/refillable pods or cartridges (25.2%) and nearly 85% used flavored e-cigarettes. The agency has not authorized any flavored ENDS products to date. Many of the illegal ENDS products such as flavored disposables or prefilled/refillable pods have not complied with the premarket requirements prior to importing and/or selling in the US. Most ENDS products are manufactured outside of the US and outside of the agency's inspection surveillance activities. Importers are required to ensure the tobacco products imported or offered for import comply with all the applicable requirements under the FD&C Act. According to the U.S Department of Commerce's Census Bureau consumption imports of vapor product devices (ENDS) rose from 2016's $204.1 million to over $513.1 million in 2022 and the estimated forecast for 2023 is over $620 million. Strengthening the surveillance activities such as

conducting physical examinations, requiring proof of compliance with Tobacco Control Act upon entry and increase the number of random screenings at the ports of entry and International Mail Facilities will reduce the number of illegal products and protect public health by making only authorized products available.

11. COMPARISON OF METALS CONTENT IN ENDS USING ICP-MS WITH TWO SEPARATE AEROSOL COLLECTION METHODS: FRITTED IMPINGERS AND FEP TUBING. Donald STOGNER, Emma Willis, Jamil Gray, Carl J. Adams and Salem Chouchane; Eurofins Professional Scientific Services, Winston-Salem, NC, USA

Analytical evaluation of metals in electronic nicotine delivery systems (ENDS) is critical for the assessment of ENDS products. The collection method is important in that it should be able to collect all the aerosol produced without introducing contamination. Collection methods such as quartz pads contribute high background levels of the elements of interest, particularly chromium, and are therefore not suitable for trace level analysis. Therefore, we have assessed two alternative collection techniques, Fritted Impingers and fluorinated ethylene propylene (FEP) tubing, both of which produce little to no contribution of the elements of interest. The Fritted Impinger traps the metals and ENDS aerosol in an acidic aqueous solution, while the FEP tubing physically traps the ENDS aerosol through aerosol condensation in the looped tubing. During method development the Fritted Impingers and the FEP tubing gave similar results. The work was performed on a Perkin Elmer Inductively Coupled Plasma Mass Spectrometry (ICP-MS) instruments (NexION 300, 350, and 2000) with a radio frequency (RF) power of 1600. The elements were also analyzed using three modes: standard, dynamic reaction cell (DRC), and kinetic energy discrimination (KED). Standard mode is when no reaction gas is added, DRC is when ammonia gas is introduced and KED is when helium gas is introduced. This method uses Germanium-74, Gallium-71, Indium-115, Bismuth-209 as internal standards. Beryllium, manganese, cobalt, nickel, copper, zinc, arsenic, cadmium, tin, barium, lead, chromium, vanadium, and selenium were validated. The results of the method validation and the comparative data of the collection techniques will be reported.

12. Withdrawn

13. SIMULATION ANALYSIS OF STATISTICAL EQUIVALENCE TESTING OF HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS (HPHCS). Qiwei LIANG, Joey Chen, David Cook, I. Gene Gillman and Ryan Black; Juul Labs, Inc, Washington, DC, USA

Published reviews by the Center for Tobacco Products (CTP) suggest levels of harmful and potentially harmful constituents (HPHCs) in tobacco products are important considerations in the review of tobacco product applications by the agency. Statistical equivalence testing has been proposed by CTP as an approach for demonstrating the equivalence of HPHC levels between two tobacco products. To account for analytical method variability/measurement error, the Important Analytical Difference (IAD) was defined for various HPHCs by CTP. Recently, the approach of total error probability has also been proposed.

A simulation study was conducted to explore the impact of various combinations of statistical factors on the statistical power to demonstrate statistical equivalence. Specifically, the study used the statistical equivalence testing approach recommended by CTP and examined the aerosol nicotine levels of two prototype JUUL products. The statistical factors considered in the study included IAD (4% to 20%), coefficient of variation (CV) (5% to 30%), Type I error (10% to 30%), and expected differences (0% to 10%). With various combinations of these factors, the study generated 36 tables with the statistical power values for demonstrating equivalence under various scenarios. Although 80% power is required by FDA to demonstrate equivalence, smaller power values were observed in many scenarios. For example, in the scenario with 4% IAD, n=20, 10% Type I error rate, 5% CV and zero expected difference, only 61.2% power was achieved. The study findings highlight the importance of the statistical factors when designing equivalence studies and the potential consequences of not achieving adequate power. Simulation analysis may also be needed in examining the approach of total error probability.

14. FORMATION OF SMALL ORGANIC ACIDS DURING ENDS AEROSOL COLLECTION. Joseph JABLONSKI and Andrew G. Cheetham; Enthalpy Specialty Labs, Richmond, VA, USA

To reduce the risks associated with combustible nicotine products, efforts have focused on the production of non-combustible alternatives such as electronic nicotine delivery systems (ENDS). At the 75th TSRC, we presented our findings

into potential ketene generation through thermal degradation of ester flavorants during ENDS aerosol generation. As part of this, we observed the creation of products formed from reactive species generated by propylene glycol (PG) and glycerol (VG), speculating that these species may have been small organic acids (SOA). Here we present our findings in a study looking at SOA generation from PG, VG, and select ester flavorants.™

Model e-liquids were vaped under regular-to-moderate experimental conditions (0.7–1.8 Ω coils, 12–75 W power setting, 55/3/30 puff regime) using the CORESTA recommended device (Aspire Nautilus™ tank system with an Evolv™ Reference Mod DNA 75 Color battery), collected in puff blocks to dryness, and analyzed using ion chromatography. Generally, the amount of SOA produced was dependent on the power setting and collection duration/puff block. PG and VG both contributed to the formation of acetic acid (0.112–8.07 μg/puff & 0.207–86.3 μg/puff, respectively) and formic acid (0.122–0.713 μg/puff & 0.229–5.43 μg/puff respectively). VG was shown to be primarily responsible for the formation of propionic acid (ND–11.2 μg/puff). At higher power settings, acrylic acid was also observed at levels up to 2.46 μg/puff along with conversion of ester flavorants to their corresponding acid to varying degrees. Though not on the FDA's published HPHC list, these acids have associated hazards that warrant further investigation into their production and effects of long-term exposure.

15. TOBACCO SPECIFIC NITROSAMINES AND NICOTINE DEGRADANTS: A METHOD FOR COMBINED ANALYSIS IN ENDS E-LIQUIDS AND AEROSOL. Alexander PENNINGTON, Nancy Qian, Carol Perry, Dakota Hawkins and I. Gene Gillman; Juul Labs, Inc, Washington, DC USA

Electronic Nicotine Delivery System (ENDS) e-liquids typically comprise the main components; nicotine, propylene glycol, glycerine, and flavouring compounds. US Pharmacopeia (USP) grade nicotine is commonly used during the formulation of these ENDS e-liquids, and USP-grade nicotine requires single impurities to be less than 0.5% and total impurities to be less than 1%. Known impurities of nicotine include the nicotine degradants, nornicotine, myosmine, cotinine, anatabine, anabasine, nicotine-n-oxide, and β-nicotyrine, and the tobacco specific nitrosamines (TSNAs) NNN and NNK. Together, these TSNA impurities and nicotine degradants include carcinogenic and respiratory irritants reportable to the FDA under Section

904(a)(3) of the Federal Food, Drug, and Cosmetic Act. Published methods used for quantitation of these sets of compounds include either GC/MS or LC/MS and separate the quantitation of TSNAs and nicotine degradants. Utilizing LC-MS/MS instrumentation in multiple reaction monitoring (MRM) mode with the Acquity UPLC trifunctionally bonded BEH C18 column, a combined analysis method was developed and utilized for the quantitation of TSNA impurities and nicotine degradants in e-liquids and trapped ENDS aerosol. Electrospray ionization (ESI) using a low fragmentation voltage of 50V, focusing all detection through the MRM mode, allowed for an instrument analysis range of ~30-3000 ng/mL for all nicotine degradants and ~0.2-100 ng/mL for TSNAs. Retention time of all compounds fall between 2.5-9 min in a total 14-minute single injection, creating an overall savings of analysis time. This combined analysis method for TSNAs and nicotine degradants shows a detection range equivalent to that of published methodologies with the added benefit of increased throughput, waste reduction, reduced sample collection time and direct data correlation of related nicotine constituents.

16. SURVEY OF METALS PRESENT IN THE E-LIQUID OF AGED CLOSE POD-BASED AND CIGALIKE ELECTRONIC-CIGARETTES FROM THE NORTH AMERICAN MARKET. Prasad LAVISETTY, Darybelle Collins, David Cook, Kathy Humphries and I. Gene Gillman; Juul Labs, Inc, Washington, DC, USA

Electronic nicotine delivery systems (ENDS) aerosolize a nicotine containing e-liquid, which aerosol is inhaled during product use. The e-liquid is contained within the ENDS which is the container closure system. During prolonged storage, the e-liquid has the potential to corrode metal components, such as the heating element, resulting in metals leaching into the e-liquid. The objective of this study was to analyze levels of metals in the e-liquids of North American market ENDS products stored for more than 24 months at ambient temperature. The study included 27 samples comprising several brands, flavors, and batches of both closed pod and cigalike ENDS devices. Samples were analyzed using CORESTA Recommended Method No. 98 which was validated in-house for a range of metals. The method's limits of detection (LODs), expressed in µg/g, were 0.007 (Chromium), 0.007 (Nickel), 0.008 (Copper), 0.007 (Cadmium) and 0.007 (Lead), 0.088 (Zinc), 0.015 (Iron), 0.005 (Antimony), 0.005 (Tin). The method's limit of quantitation (LOQ) was 0.05

µg/g for all the metals except 0.5 µg/g for Zinc and Iron. Nickel, copper, and zinc were observed in most of the e-liquids in the range of 0.051 to 298.771µg/g, 0.051 to 351.810 µg/g, and 0.589 to 184.306 µg/g respectively. Lead, chromium, iron, antimony, and tin were observed in some of the e-liquids in the range of 0.231 to 21.183 µg/g, 0.05 to 13.252 µg/g, 0.1 to 46.430 µg/g, 0.064 to 1.119 µg/g and 0.1 to 1.85 µg/g, respectively. Cadmium was not detected for all liquids. The data demonstrate that some metals can leach into e-liquids following prolonged storage at ambient temperature. Further, the results indicate that the amount of leaching varies among manufacturers and formulations.

17. A COMPARATIVE STUDY OF ENDS PARTICLE SIZE ANALYSIS WITH ELECTRICAL AND GRAVIMETRIC MEASUREMENTS OF DILUTED AND UN-DILUTED AEROSOLS. Jake HENKIE, Angel Rodriguez-Lafuente, Amelia Mawdsley, Nathan Nguyen and Clark Robitaille; Labstat International Inc, Kitchener, ON, Canada

Particle size analysis of emissions has emerged as an important physical property for the health and safety evaluation of electronic nicotine delivery systems (ENDS) within this product category and for comparison with other product categories, including traditional combustibles. Although particle size measurement has been conducted with gravimetric cascade impactor instruments for decades, more recently developed electrical low-pressure impactors (ELPIs) electrostatically charge incoming aerosol particles to enable live electrical readouts of particle flux between filter stages, providing more sensitive and timely data collection. In fact, the high sensitivity of these modern measurement techniques requires volumetric dilution of ENDS aerosols for optimal performance. This contrasts with the capabilities of gravimetric cascade impactors which can capture and measure undiluted aerosols.

To investigate the equivalency of experimental aerosol properties between different puff generation and measurement techniques, a comparative study was conducted using electronic cigarettes as the test products. Puff profiles were generated using either a dual syringe pump engine or a 2-stage flow dilution apparatus and analyzed by either a traditional gravimetric cascade impactor or ELPI+ instrument, respectively, with differing numbers of impactor stages and stage cut sizes. Results were compared principally based on mass median aerodynamic diameter (MMAD), count median aerodynamic diameter (CMAD) and geometric standard deviation (GSD), with multiple calculation methods explored. We find no statistically significant difference between these reported

aerosol metrics based on puff generation and measurement combinations explored in this study. However, the obtained MMAD, CMAD and GSD values from a given data set are shown to be relatively sensitive to the calculation method used and emphasize the need to clearly define and justify particle size reporting methods.

18. METHODS FOR ANALYSIS OF SWEETENERS, FLAVOR COMPONENTS AND PROPYLENE GLYCOL IN NICOTINE POUCHES AND SALIVA SAMPLES. Angel RODRIGUEZ-LAFUENTE, Kenneth Chalcraft, Rebecca Cornelius and Cosmin Stoicoiu; Labstat International Inc, Kitchener, ON, Canada

Modern oral nicotine products are becoming increasingly popular alternatives to smoking however the palatability is largely related to added flavorants which may have high chemical diversity. Furthermore, in clinical studies the measurement of remnant flavors in used products and in saliva during use are often critical for understanding the bioavailability of product components and the overall expected usage timeframe. In this study, a comprehensive strategy was developed and validated to quantify two non-volatile artificial sweeteners plus fourteen volatile flavor components in unused and used smokeless pouch products as well as in saliva for application in support of clinical trials. Analysis of artificial sweeteners required two independent LC-ESI-MS/MS injections using reversed phase and HILIC separation prepared from a single aqueous extract. The volatile flavor components were analyzed by GC-MS using an ethanol-based extract. Each method developed in this study demonstrates analytical characteristics well suited for clinical trial use in both matrices including low saliva volume requirements, low or sub-ppm limits of quantification, as well as good specificity and linearity. The development process, methodology, and exemplary validation results will be discussed.

19. DESOLVATING INTRODUCTION SYSTEM TEMPERATURE OPTIMIZATION FOR LINEAR ZINC, CADMIUM, AND TIN CALIBRATIONS WITH TRIPLE QUAD ICP-MS FOR E-CIGARETTE AEROSOL ANALYSIS. Naudia GRAY and R. Steven Pappas; Centers for Disease Control and Prevention, Atlanta, GA, USA

Toxic metals in e-cigarette aerosols are generally derived from corrosion of device components rather than from the source e-liquid. Therefore, toxic metal

concentrations in the aerosols are often at trace levels, requiring an analytical method with high sensitivity for metals at low concentrations in aerosols from these devices. Aerosol is collected as previously described following ISO Standard 20768 puff regimen with a fluoropolymer condensation tube. Calibration standards are prepared in a 2% v/v nitric acid, 1% v/v hydrochloric acid, and 0.25% v/v hydrofluoric acid matrix. Higher sensitivity is achieved by using an Apex™ HF desolvating introduction system with "Triple Quad" Inductively Coupled Plasma-Mass Spectrometry (ICP-MS; Agilent, Santa Clara, CA) for the analysis of chromium, nickel, copper, zinc, cadmium, tin, and lead in aerosols. The Apex™ is designed with a heated cyclonic spray chamber followed by a peltier-cooled condenser to reduce solvent load and plasma interferences. However, occasional problems with zinc, cadmium, and tin calibration linearity were observed when the Apex system was operated at the default temperature of 140 °C. This temperature is above the boiling point of zinc nitrate hexahydrate (105-131 °C), cadmium nitrate tetrahydrate (132 °C), and tin(IV) chloride (114 °C) species which could occur in the presence of nitrate and chloride anions in the dilute acid solvents. If zinc, cadmium, or tin are in these forms, inconsistent analyte loss may occur from boiling. The new generation Apex permitted decreased spray chamber temperature, which rendered calibrations for zinc, cadmium, and tin consistently linear at 100 °C, improving calibration and quality control results. A summary of results from analysis of e-cigarette aerosols with low metal concentrations using the improved temperature-controlled system are presented.

20. AROMATIC AMINES IN THE MAINSTREAM SMOKE OF COMMERCIAL CIGARS. Huihua JI, Zhenyu Jin, Laura Fenton, Stacey Slone and Bing Zhang; University of Kentucky, Lexington, KY, USA

Aromatic amines are a class of carcinogenic compounds in tobacco smoke that are listed on the FDA list of harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke. Six aromatic amines yields (1-aminonaphthalene (1-AN), 2-aminonaphthalene (2-AN), 3-aminobiphenyl (3-ABP), 4-aminobiphenyl (4-ABP), ortho-toluidine (o-TOL), o-anisidine (o-ANI)) in the mainstream smoke from 23 commercial filtered cigars, 16 cigarillos, and 11 large cigars were determined with the solid-phase microextraction-coupled to gas chromatography triple quadrupole mass spectrometry (SPME headspace GC–MS/MS) method. The commercial cigars were smoked under Cooperation

Centre for Scientific Research Relative to Tobacco (CORESTA) Recommended Method 64 using a linear cigar smoke machine. The aromatic amine yields in the mainstream smoke from 50 commercial cigars show high variation within and between the products. The averages of each aromatic amine yield in the filtered cigars, cigarillos, and large cigars are 108, 371, and 623 ng/cigar for o-TOL; 6, 14, and 22 ng/cigar for o-ANI; 65, 114, and 174 ng/cigar for 1-AN; 25, 59, and 87 ng/cigar for 2-AN; 6, 17, and 27 ng/cigar for 3- ABP; 8, 11, and 17 ng/cigar for 4-ABP, respectively. The relationship between aromatic amine and total particulate matter (TPM) was evaluated. On a per cigar basis, the aromatic amines have a good linear response with TPM. On a per mass of TPM basis, the ratios of aromatic amines and TPM were consistent.

21. THE CONCENTRATIONS OF SELECTED TOXIC METALS IN THREE CATEGORIES OF COMMERCIAL CIGAR PRODUCTS. Cynthia MCNEES, Priyanka Paul, Sanjay Joshi, Nicole Anderson and Solomon Kariuiki; University of Kentucky, Lexington, KY, USA

Smoking is considered to be a primary cause of preventable death, with major attention focused on cigarettes. While cigarette sales have declined over the last two decades, cigars have gained popularity resulting in increased sales. However, very little data is available on harmful and potentially harmful constituent (HPHC) concentrations in cigars. With cigar use rising, further research on product characteristics is necessary. In this study, we analyzed a selection of commercially available cigars using inductively coupled plasma-optical emission spectroscopy (ICP-OES) to determine the concentrations of arsenic, cadmium, cobalt, chromium, nickel, and lead. The cigars tested represented three product categories: large machine-made cigars, cigarillos, and filtered cigars. The metals of interest were quantified and a high content of arsenic, cadmium, and nickel, which are considered Group 1 carcinogens for humans, was observed in all cigar groups. Products in the filtered cigar category had the highest variability for samples tested, while products in the large cigar category had the highest concentrations of chromium and nickel. The analysis of the multiple cigar categories show that the presence of select toxic metals in the filler material at levels sufficient enough to warrant additional research to elucidate the potential health impact these analytes have on consumers. Given the concentrations of toxic metals in the cigar products tested, the mainstream smoke inhaled by consumers while smoking may possibly contain these harmful constituents.

22. THE EFFECT OF DESIGN PARAMETERS ON YIELDS OF 33 HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS (HPHCS) IN MAINSTREAM SMOKE OF LARGE CIGARS. Scott WASDO, Therese Ku, Samantha Reilly, Tianrong Chen and Charles Feng; United States Food and Drug Administration, Silver Spring, MD, USA

The effect of design parameters on a large cigar's mainstream smoke yields of harmful and potentially harmful constituents (HPHCs) is relatively unstudied. Furthermore, available chemical analysis research on large cigars has focused on tar and a limited number of HPHCs (e.g., nicotine, carbon monoxide, benzo[a]pyrene and select carbonyls) and many recognized smoke HPHCs have been largely overlooked. To bridge this gap, the smoke yields of 33 HPHCs were measured in 10 large cigar brands using the Canadian Intense regimen (55 mL puff volume, 30 sec puff frequency, 2 sec puff duration, 100% vent block, if applicable) to produce mainstream smoke. HPHC yields were plotted against the cigars' design parameters (total cigar weight, tobacco filler weight, length, circumference, pressure drop, and estimated density and volume) and analyzed using simple linear regression. The influence of each design parameter on individual HPHC yields was evaluated using the plots' slopes and correlation coefficients (R2), and P values were used to ensure that the slopes were significant. Cigar length, product mass, tobacco mass, and estimated volume were positively correlated to smoke yields of several classes of HPHCs including tobacco alkaloids (anabasine and nornicotine), carbonyls (acetone, methyl ethyl ketone, and propionaldehyde), and volatile and semi-volatile organic compounds (ethyl benzene, styrene, benzofuran, and furan). In the present study, in general, tobacco rod density and cigar circumference did not consistently correlate to any class of HPHCs and pressure drop did not correlate with any individual HPHC yields.

23. Withdrawn

24. CARBONYL ANALYSIS OF CIGARETTE MAINSTREAM SMOKE BY BAG COLLECTION. Bryan HEARN[1], Erica Lewis[1], Cody Sheppard[1], Clifford Watson[2] and Liza Valentin[2]; [1]Battelle Analytical Services, Atlanta, GA, USA, [2]Center for Disease Control, Atlanta, GA USA

Most previous methods for quantitatively determining carbonyl levels in mainstream cigarette smoke used impingers for sample collection. We present a

simplified method using disposable Tedlar® bags, rather than impingers, to collect mainstream smoke. Conceptionally, we think of this as an "asynchronous disposable impinger" method because we perform in-bag derivatization after smoking. Results from our new approach shows that the bag contributes minimally to background or artifact formation and the derivatization reaction proceeds efficiently for all target analytes.

We compared results from our new approach to the older impinger methods to demonstrate equivalency. Parallel calibration curves were generated from the derivatization of the unreacted carbonyls in Tedlar bags as well as in glassware. The maximum slope difference between the curves for all analytes was equal to or lower than 9%.

Our new, robust method provided comparable results to prior existing methods that use impingers. All our carbonyl measurements for 3R4F and CM6 reference cigarettes fell within the reported confidence limits reported from a CORESTA 2012 collaborative study for both ISO and CI regimens. Similarly, seven of eight measurements of carbonyls for the 1R6F reference cigarette fell within the published limits from the University of Kentucky Center for Tobacco Reference Products Certificate of Analysis 1R6F (2016). Our simplified method produces less chemical waste, has higher throughput, and has a linear range suitable for measuring wide range of carbonyl yields from both ISO and Intense machine smoking regimens.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC. Use of trade names is for identification only and does not imply endorsement by the CDC.

25. CHANGE CONTROL CHALLENGES IN THE CONTEXT OF PMTA. Lise FRAISSINET, Lillian Ortega, Randy Freund, Chris Woodruff and Bryan Burd; Chemular Inc, Hudson, MI, USA

Product changes are an integral part of quality improvement and innovation, whether it is for design improvement, supply chain constraints, product standard compliance or business requirements. Navigating the regulatory landscape when product changes are needed is a challenge when changes may potentially result in the product being considered a new tobacco product. Section 910(a)(1)(B) of the FD&C Act states that new tobacco products include those that are new because they have been rendered new

through any modification (including a change in design, any component, any part, or any constituent, including a smoke constituent, or in the content, delivery or form of nicotine, or any other additive or ingredient) of a tobacco product where the modified product was commercially marketed in the U.S. on February 15, 2007.

The FDA has classified minor and major amendments in terms of their impact on the review process, but guidance is vague in terms of classification of changes themselves and how to report those changes. The FDA provides examples in the PMTA Final Rule, PMTA ENDS guidance and the proposed TPMP rule. The aim of this work is to propose a systematic classification of the changes, establish how to address change requests, change assessment, then change order via Good Change Control Practices and how it should be reported to the FDA.

The approach is based on multiple FDA guidance documents and regulations on product changes and when to report to the FDA that have been implemented across regulated industries:

- Deciding When to Submit a 510(k) for a Change to an Existing Device
- Changes to an Approved NDA or ANDA
- Applications for Premarket Review of New Tobacco Products

26. ELECTRONIC TRIAL MASTER FILE: AN IMPORTANT STEP IN DOCUMENTING CLINICAL TRIAL DATA USED TO SUPPORT A PREMARKET TOBACCO PRODUCT APPLICATION. Jeff COFFIELD, Jason Henstock and Ken Szeliga; RAI Services Company, Winston-Salem, NC, USA

Before introducing a new tobacco product to the US market, companies are required to submit a Premarket Tobacco Product (PMTA) application to the FDA and receive authorization. This application comprises data generated across multiple scientific disciplines to collectively demonstrate that the product is appropriate for the protection of public health. Clinical trial data is key to this scientific evidence as it directly represents potential risks and benefits of new tobacco product use in humans. Clinical studies are often lengthy endeavors with potentially large numbers of subjects and study conditions conducted across multiple study sites. These studies produce vast quantities of documentation including every record associated with each subject's participation in the trial. All

this information must be tracked, verified, and stored in a way that is easily accessible upon request, as per regulatory requirements. For clinical trials, regulatory compliance may be maintained through implementation of an electronic trial master file (eTMF) process. Our company has used eTMF for the past ten years to simplify clinical trial documentation management, including tracking, maintaining, and storing data and documents related to clinical study conduct. This secure database ensures all records associated with the clinical trial are managed in compliance with FDA regulations promulgated under good clinical practice (GCP), HIPPA and FDA 21CFR Part 11. Moreover, the archived eTMF documents are retrieval-ready in human-readable electronic formats for regulatory applications, inspections, or review.

Over the past few years, use of eTMF has helped facilitate rigorous quality standards for clinical research studies within the tobacco industry and provided substantiation of clinical evidence supporting applications that have resulted in receipt of FDA Marketing Granted Orders for a selection of new tobacco products.

27. PROMOTIONAL MATERIALS FOR A NOVEL HEATED TOBACCO CAPSULE SYSTEM INCREASE BEHAVIORAL INTENTIONS TO TRY AND USE IN ADULT SMOKERS BUT NOT IN NONUSERS, AND DO NOT IMPEDE QUIT INTENTIONS. Diana MCKINNEY and Elizabeth Becker; Altria Client Services, Richmond, VA, USA

Heated tobacco products may offer a reduced risk alternative to adults 21+ who smoke cigarettes (AS) and are unable or unwilling to quit. We conducted an online quantitative experimental study evaluating the effect of promotional materials on behavioral intentions for a novel heated tobacco capsule system (HTC) among adults who use and do not use tobacco. The study included 4,511 U.S. adults, who were either current AS, adults who used other tobacco products (OTP), or adult nonusers (NU) who did not currently use any tobacco. The study oversampled for ages 21-24 and included a cohort of underage adults aged 18-20. Participants were randomly assigned to view either the prototype HTC concept with a portfolio of potential promotional materials (Test) or prototype concept only (Control) and completed surveys measuring behavioral intentions. Participants could re-visit the materials throughout the study. AS 21+ who viewed the promotional materials reported significantly higher intentions to try, use and switch to the HTC product than those who did not view the promotional materials. No significant impact on intentions to try and use the HTC product

was observed among adults 21-24 and among underage adults who used tobacco. Both NU 21+ and underage adult NU reported low intentions to try and use the HTC product, and exposure to promotional materials did not impact intentions. The promotional materials did not impact quit intentions among AS or OTP for any age group. These results suggest that, in context of the proposed promotional materials, the novel HTC product may facilitate transition of AS 21+ to a smoke-free future, while having minimal impact on NU and underage individuals.

28. PROMOTIONAL MATERIALS FOR A NOVEL HEATED TOBACCO CAPSULE SYSTEM DO NOT ALTER RISK PERCEPTIONS. Diana MCKINNEY and Elizabeth Becker; Altria Client Services, Richmond, VA, USA

Heated tobacco products may offer a reduced risk alternative to adults 21+ who smoke cigarettes (AS) and are unable or unwilling to quit. We conducted an online quantitative experimental study evaluating the effects of promotional materials on risk perceptions for a novel heated tobacco capsule system (HTC) among adults who use and do not use tobacco. The study included 4,511 U.S. adults, who were either current AS, adults who used other tobacco products (OTP), or adult nonusers (NU) who did not currently use any tobacco. The study oversampled for ages 21-24 and included a cohort of underage adults aged 18-20. Participants were randomly assigned to view either the prototype HTC concept with a portfolio of potential promotional materials (Test) or prototype concept only (Control) and completed surveys measuring risk perceptions. Participants could re-visit the materials throughout the study. Adults who used tobacco (AS and OTP) and NU accurately perceived using HTC as less risky than using cigarettes or dual use, and riskier than using nicotine replacement therapies or quitting all tobacco. Exposure to promotional materials did not affect relative risk perceptions of HTC (except in OTP group). Across seven health outcomes related to tobacco use, absolute risk perceptions (likelihood of risk) of the HTC ranged from 39-86% (100% = extremely likely) and were unaffected by exposure to promotional materials. Absolute risk perceptions were higher among NU compared to tobacco users. These results suggest that, in the context of the proposed promotional materials, tobacco users and NU appropriately perceive that the novel HTC is not risk-free. Appropriate understanding of risks may facilitate the transition of AS 21+ to HTC, leading towards a smoke-free future.

29. VITROCELL® HIGH THROUGHPUT EXPOSURE MODULE 2.0+: DEPOSITION OF WHOLE AEROSOL FROM TWO DIFFERENT

TOBACCO PRODUCT TYPES. Brian KEYSER[1], Robert Leverette[1], Kristen Jordan[1], Adam Seymour[2] and Michael Hollings[2]; [1]RAI Services Company, Winston-Salem, NC, USA, [2]Labcorp Early Development Laboratories, Harrogate, North Yorkshire, UK

The continued development of exposure systems provides a means to conduct *in vitro* assessment of freshly generated whole aerosol from both heated tobacco products (HTP) and electronic nicotine delivery systems (ENDS). A challenge with such exposure systems is ensuring sufficient sample throughput for *in vitro* toxicological studies in a timely manner. Vitrocell has developed high throughput whole smoke/aerosol exposure modules designed to deliver up to seven doses of whole smoke/aerosol plus a clean air control concurrently onto 12mm or 24mm Transwell® inserts. Initial characterization of this exposure system was conducted using a series of experiments designed to assess the delivery of whole aerosol from a commercially available HTP or ENDS. A Vitrocell VC1/7 smoking robot was used to deliver aerosol generated under ISO 20788:2018 regimen (55 mL puff, 2 sec puff duration, 30 sec puff interval) or a modified ISO 20768:2018 (55 mL puff, 3 sec puff duration, 30 sec puff interval, with a 60 sec pause every 10 puffs) for HTP or ENDS, respectively, to the exposure modules. Aerosol concentrations were controlled using serial dilution airflows ranging from 0 (undiluted) to 4 L/min and the deposition was quantified using aerosol photometers and chemical analysis (e.g., glycerol) of PBS traps within the modules. Intra-experimental free glycerol deposition was largely within ±15% for both module and product types. Free glycerol vs. photometer area under the curve linear regression R^2 values were >0.8 for all experiments. Overall, the Vitrocell 48 2.0+ exposure module will be a useful tool to increase sample throughput for the *in vitro* toxicological assessment of freshly generated whole aerosols from different tobacco product types.

30. THE CHANGING LANDSCAPE OF TOBACCO USE AND SWITCHING BEHAVIORS AMONG US ADULTS. Yisha HE, Lai Wei, Raheema Muhammad-Kah and Edward Largo; Altria Client Services, Richmond, VA, USA

Objectives: With the emergence of e-vapor and novel oral nicotine products, the adult tobacco use landscape has been changing drastically in recent years. It's important to understand the evolving tobacco landscape and transitions from smokeable to smokefree tobacco products to support harm reduction strategies.

Methods: Using National Health Interview Survey (NHIS) 2016 to 2021 datasets,

we characterized current adult (21 years of age or older) tobacco consumers (ATCs) into smokeable (cigarettes and cigars) and smokefree (e-vapor and smokeless tobacco products) groups. For adults who had ever smoked 100 cigarettes lifetime (lifetime cigarette smokers), we further studied their switching behaviors by inhalable (e-vapor) versus oral (smokeless tobacco products) use.

Results: From 2016 to 2021, the total ATC population has decreased from 48.5 million to 43.4 million. Among ATCs, we observed a decreasing proportion of exclusive smokeable users (74.6% to 66.2%) and an increasing proportion of exclusive smokefree users (13.0% to 21.7%). Among ATCs who were lifetime cigarette smokers (36 million in 2021), 65.7% remained exclusive smokeable users and 15.1% became exclusive smokefree product users (defined as 'switched lifetime adult cigarette smokers'). The switched lifetime adult cigarette smoker population has increased from 3.8 million in 2016 to 5.4 million in 2021, where 71.4% were current e-vapor users.

Implications: The prevalence of exclusive smokefree products usage has been increasing while exclusive use of smokeable products has been declining. A growing proportion of lifetime adult cigarette smokers have switched to exclusive smokefree product use. Our analysis may be limited by the lack of assessments of novel tobacco products (e.g., nicotine pouches) in NHIS surveys. Adding these assessments to national surveys is critical to keep pace with the changing landscape.

31. AN ABUSE LIABILITY COMPARISON OF TEST AND REFERENCE TOBACCO AND MENTHOL FLAVORED E-LIQUIDS IN THE RELX INFINITY ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS). Donald GRAFF[1], Mitch Nides[2] and Ryan G. N. Seltzer[3]; [1]Cheerain HK Limited, Hong Kong, China, [2]LA Clinical Trials, Burbank, CA, USA, [3]Safety in Numbers, Tucson, AZ, USA

Reference and test tobacco and menthol flavored e-liquids (4% nicotine) used with the RELX Infinity ENDS (a closed 2 mL pod with a ceramic/metal coil atomizer) were evaluated in a randomized, two-arm, cross-over study of adult closed-system ENDS users to determine whether within-category flavor differences may raise unique concerns for abuse liability.

Subjects were assigned to a study arm (tobacco or menthol, n = 20 per arm)

based on their preferred usual flavor and randomized to the order they received reference and test e-liquids. Each product was used at home for 14 days during which subjects documented use daily. Subjects returned to the clinic for additional study activities, including a 5-minute ad libitum product use and 30 minutes of blood sampling for nicotine concentration measurement, product use measurements (puffing topography and pod weight change), subjective measures assessments, and safety and tolerability reporting.

No statistically significant or clinically meaningful differences in the number of pods used per day during the 14-day ambulatory periods were observed between test and reference formulations for either e-liquid flavor. In addition, the amount of e-liquid consumed per day during the ambulatory periods and clinic sessions was comparable between formulations for both e-liquid flavors. Furthermore, a 5-minute use of the test and reference tobacco and menthol flavored products resulted in comparable levels of nicotine uptake (Cmax and AUC0-30) and a similar time to reach the maximum concentration (Tmax). There were no remarkable differences between the test and reference formulations for either e-liquid flavor for the subjective or safety measures assessed.

These data suggest that the prototype and test formulations of each flavor are unlikely to exhibit unique concerns for abuse liability compared to the prototype formulations.

32. SUBJECTIVE EFFECTS ASSOCIATED WITH RELX INFINITY ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS) USE IN AN 8-WEEK SWITCHING STUDY OF ADULT SMOKERS. Donald GRAFF[1], Yuli Xie[2] and Sabrina Ciric[2]; [1]Cheerain HK Limited, Hong Kong, China, [2]Celerion Inc, Lincoln, Nebraska, USA

Changes in a panel of subjective effects questionnaires in cohorts of smokers who switched from combustible cigarettes to the RELX Infinity ENDS were evaluated in an 8-week, randomized, parallel-cohort study of adult smokers.

Subjects smoked their own-brand cigarettes through the baseline visit and were randomized to receive a RELX Infinity ENDS with a tobacco or

menthol flavored e-liquid based on their own-brand combustible cigarette flavor, both e-liquid flavors, or to continue smoking. Subjects returned to the clinic every 2 weeks to complete questionnaires, including the Questionnaire of Smoking Urges-Brief (QSU), Penn State (Electronic) Cigarette Dependence Index (PS(E)CDI), Minnesota Tobacco Withdrawal Scale-Revised (MTWS-R), modified Product Evaluation Scale (mPES), and Future Intent to Use Questionnaire (FIU), along with other endpoint assessments.

A total of 194 subjects were randomized and 170 subjects completed the study, including 150 who switched to the RELX Infinity ENDS. Compared to baseline, all cohorts switching to the RELX Infinity ENDS experienced significant decreases in QSU factor scores and MTWS-R and PSECDI total scores by Week 2, with scores continuing to be lower than baseline through Week 8. mPES Satisfaction, Psychological Reward, and Relief subscale responses tended to be higher at baseline compared to post-baseline, although directional and statistically significant differences varied across time points and cohorts. Intent to purchase the RELX ENDS tended to increase slightly over time along with a lower intent to smoke following the study compared to intent at baseline.

These data support the potential for the RELX Infinity ENDS to provide a substitute for cigarettes, including the ability to reduce withdrawal symptoms and urges to smoke, produce satisfaction and relief, and generate reinforcing effects which would stimulate continued use by smokers.

33. NON-CLINICAL TOXICOLOGICAL ASSESSMENT OF FLAVORED E-LIQUIDS AND CLOSED SYSTEM POD-BASED ENDS FLAVOR FORMULATIONS. Manoj MISRA, Ed Carmines and Lise Fraissinet; Chemular Inc, Hudson, MI, USA

The aerosol from various market flavored e-liquids and pod-based ENDS flavor formulations (tobacco, menthol and non-tobacco) were evaluated for their potential in vitro toxicity.

A closed system pod-based temperature-regulated ENDS device and a open tank ENDS (Aegis Mini Mod with a Nautilus Aspire tank and a Nautilus BVC 1.8 Ohms, non-mesh coil) were used to generate the aerosols. All e-liquids were

nicotine-salt of 50 mg/mL concentrations. The formulations were vaped following CRM81 non-intense puffing conditions and aerosol collected mass (ACM) was prepared using an ethanol extraction methodology. Progressive doses of ACM were tested in the in vitro toxicological assays. The cytotoxicity was assessed by the neutral red uptake in vitro assay in BALBc/3T3 cells (OECD, TG 129). The mutagenicity was assessed by bacteria reverse mutation assay (OECD TG 471) using 5 tester strains of (TA98, TA100, TA102, TA1535, and TA1537) in the presence and absence of rat liver S9 fraction metabolic activation system. The genotoxicity was assessed by MN assay (OECD TG 487) in human lymphoblast TK6 cells.

Under the experimental conditions and based on the established criteria for evaluation of various assays, no aerosol mediated cytotoxicity, mutagenicity or genotoxicity was observed in any of the tested flavors. EC50 for all aerosols could not be calculated for any assay because the lack of dose-response. This in vitro toxicological analysis of aerosol generated either with pod-based temperature-regulated ENDS device and an open tank ENDS with three different flavors (tobacco, menthol and non-tobacco,) containing nicotine-salt at 50 mg/mL did not induce cytotoxic, mutagenic or genotoxic response.

34. COMPARATIVE QUANTITATIVE HEALTH RISK ASSESSMENT (QRA) OF A TEMPERATURE-REGULATED NICOTINE SALT-BASED CONNECTED ENDS PRODUCT WITH REFERENCE CIGARETTE: AEROSOL CANCER AND NON-CANCER RISKS.
Manoj MISRA, Ed Carmines and Lise Fraissinet; Chemular Inc, Hudson, MI, USA

The Glas G² ENDS is a temperature-regulated nicotine salt pre-filled disposable pod connected system (Glas system). This work adopted the QRA approach to evaluate and present a comparison of reduced exposure (selective HPHCs) and corresponding potential cancer and non-cancer risks for the Glas G² system with tobacco, menthol and non-tobacco-non-menthol formulations in comparison to the reference cigarette (3R4F) machine smoked/vaped under non-intense and intense puffing conditions.

Exposure concentrations (EC) were estimated assuming a lifetime continuous exposure using the equations.

3R4F cigarette: $AC \times CPD \times ED \times EF / DIR \times AT$

Glas ENDS: $AC \times (PC \times PV) \times ED \times EF / DIR \times AT$

where EC, exposure concentration; AC, analyte concentrations under non-intense and intense conditions; CPD, cigarettes per day (20 for 3R4F); E, exposure duration (64.4 years); EF, exposure frequency (365 days); DIR, daily inhalation rate (20 m3/day); AT, averaging time (25550 days); PC, puff count (worst-case 400 puffs), and PV, puff volume (Glas: 0.055 L non-intense and 0.11 L intense and 3R4F: 0.035 L ISO non-intense and 0.055 L Heal Canada intense).

Non-cancer risks were quantified using the hazard quotient (HQ) approach and cancer risks were estimated by calculating the incremental lifetime cancer risk (ILCR), utilizing non-cancer and cancer toxicity values issued by government agencies or published in peer-reviewed literature.

Data revealed that, the modelling of exposure to HPHCs in Glas ENDS products aerosols lead to a marked reduction when compared to the smoke from 3R4F reference cigarette at both non-intense and intense vaping conditions, indicating the potential for significant reduced (>99%) non-cancer and cancer health hazard risks.

35. APPLICATION OF THE HUMAN HEALTH RISK ASSESSMENT PROCESS FOR THE EVALUATION OF ELECTRONIC CIGARETTES.

Autumn BERNAL[1], Charlene Liu[2], Charles Johnson[3] and Richard Young[3]; [1]Toxcreative, Laguna Hills, CA, USA, [2]RiskWise Soultions, Princton, NJ, USA, [3]Bibra Toxicology Advice & Consulting, Wallington, UK

Electronic cigarettes (e-cigarettes) aerosolize a nicotine-containing e-liquid that is inhaled by the consumer. Compared to combustible cigarette smoke, e-cigarettes typically produce significantly lower levels of inhaled toxicants. The aerosol mixture delivered to the consumer from an e-cigarette contains several components, such as e-liquid ingredients, thermal decomposition/reaction products, and device-derived materials. Exposure to this inhaled mixture is not without health risks that must be evaluated. The human health risk assessment process provides a systematic approach to evaluate the potential adverse effects associated with chemical exposures. However, a comprehensive risk assessment framework for evaluating e-cigarettes has not previously been developed due to the complex nature of the aerosol mixture, variability of toxicological data for

the inhaled ingredients (e.g., nicotine, excipients, and flavoring compounds), thermal decomposition/reaction products (e.g., harmful and potentially harmful constituents and non-targeted analytes), and device-derived materials (e.g., leachables), as well as a lack of accepted standards. The objective of this work is to propose a suitable and pragmatic risk assessment process that can be adopted to evaluate the health effects potentially caused by exposure to e-cigarette aerosol mixtures. The framework presented here considers the variability in toxicological data and toxicological prioritization for each aerosol component to incorporate appropriate analytical characterization methods, tools for hazard identification and dose-response assessment, best practices for exposure estimation, and regulatory standards for quantitative and/or qualitative risk characterization approaches. Overall, with consideration of other sources of nonclinical data, a systematic, weight-of-evidence risk assessment process is established for the whole aerosol. This comprehensive framework is the first to be presented for any tobacco product and can be utilized to support risk assessment standardization, product development, regulatory submissions, and inform regulatory decisions.

36. ABSTINENCE, RELAPSE, AND RELATIVE HARM PERCEPTIONS AMONG SMOKERS AND E-CIGARETTE USERS IN THE POPULATION ASSESSMENT OF TOBACCO AND HEALTH (PATH) STUDY. Susan MARTELLE, Emery L. Ngamasana and Christie Powell; RAI Services Company, Winston-Salem, NC, USA

Objectives: Nearly 30 million adults in the United States smoke, and of those wanting to quit, most individuals report multiple quit attempts. In the current study, we examine how abstinence and relapse patterns differ between cigarette smokers and e-cigarette users in PATH adult datasets, with the goal of understanding how harm perceptions influence these behaviors.

Methods: We identified the longest abstinence period prior to relapse in samples of current smokers and current vapor product users at Wave 4 who abstained from using their product at Wave 5. Abstinence was defined as either:

A) Self-reported time since last use of the product among Wave 5 former smokers or former vapor product users, or

B) Self-reported time since one abstained from smoking (or vaping) because he/she wanted to quit until the time he/she relapsed into the same product

among Wave 5 current smokers or current vapor product users.

Kaplan-Meier and Cox proportional hazard models were used in the analysis. Analyses were adjusted for sociodemographic variables – sex, age groups, race, and education – and perception of e-cigarettes harm relative to cigarettes.

Preliminary Results: The final sample included 1,554 Wave 5 abstainers with valid data:

- 1,131 abstained from cigarettes during wave 5 (14.31%, n=160 relapsed into cigarettes)
- 522 abstained from e-cigarettes during wave 5 (2.86%, n=12 relapsed into e-cigarettes)

We will explore how perceptions of e-cigarette harm relative to cigarettes affects abstinence and relapse in the two user groups, which has implications for public health by informing tobacco product policy and regulations.

37. A RANDOMIZED, SINGLE BLINDED, CROSS-OVER STUDY TO EVALUATE THE PHARMACOKINETIC PROFILES OF E-CIGARETTES WITH NICOTINE SALT FORMULATIONS IN UK ADULTS WHO USE E-CIGARETTES. Yuki TAKESHIGE; JT International, Geneve, Switzerland

When an organic acid combines with a freebase nicotine, it forms a nicotine salt. Recently e-liquids marketed as containing nicotine salts have become popular and it appears that nicotine in salts form can provide a sensorial experience that some adult consumers perceive as more enjoyable and satisfying versus freebase nicotine e-liquids.

Here, we evaluated nicotine pharmacokinetic (PK) profiles and subjective effects following single and multiple *ad libitum* use of an e-cigarette (eDNC3) with two e-liquid pods, one with and one without organic acid. A randomized, single blinded, cross-over study was conducted in 20 healthy UK adults who use e-cigarettes.

Results showed that the C_{max} of plasma nicotine was approximately 53% greater following single *ad libitum* use and 58% greater following multiple *ad libitum* use of eDNC3 with e-liquids containing nicotine salts than freebase nicotine,

while AUC was approximately 20% greater following single *ad libitum* use of eDNC3 with e-liquids containing nicotine salts than freebase nicotine. The differences in these PK parameters ($C_{max\text{-}single}$, $C_{max\text{-}multiple}$ and AUC) between the eDNC3 e-liquids with nicotine salts versus freebase nicotine were associated with an increase in the consumed amount of e-liquid corresponding to nicotine consumption. No notable differences were observed between the eDNC3 e-liquids with nicotine salts versus freebase nicotine for any of the subjective effects measured in this study and there were no marked changes or clinically significant findings in the safety data obtained.

These results indicate that use of e-liquid with nicotine salt formulations, made by adding organic acid, leads to an increase in nicotine uptake compared to freebase nicotine e-liquid, and these differences may be explained by increased consumption of e-liquid.

38. ASSESSING THE RELATIONSHIP BETWEEN E-CIGARETTES RISK PERCEPTION, INTENTION TO QUIT CIGARETTES, AND CIGARETTE CONSUMPTION: A STRUCTURAL EQUATION MODEL.

Emery NGAMASANA; RAI Services Company, Winston-Salem, NC, USA

Background: It remains unclear whether appraisal of e-cigarettes risk relative to cigarettes could influence current smokers' intentions to quit cigarettes, which in turn could impact cigarette consumption. This project demonstrates that misperception or miscommunication about the harmfulness of e-cigarettes relative to cigarettes may hinder tobacco harm reduction efforts.

Methods: We postulate that e-cigarette perception of harmfulness influences cigarette consumption directly and indirectly through intentions to quit cigarettes. Data from the five initial waves of PATH adults were used to identify baseline cigarette smokers. A structural equation model simultaneously estimated: (1) e-cigarette risk perception as a function of baseline characteristics, (2) the effect of e-cigarettes' risk perception on intentions to quit cigarettes, (3) the effect of e-cigarettes' risk perception on cigarettes consumption with intentions to quit cigarettes as a mediating factor.

Results: The sample included 6,366 adult cigarette smokers. A unit increase in the perception of e-cigarettes harmfulness relative to cigarette was associated with 1.7 (p-value: 0.036) reduced points on the quit intentions scale at wave 4.

Subsequently, a unit increase in cigarette quit intentions at wave 4, was associated with 0.18 (p-value: 0.001) reduction in CPD at wave 5, whereas a unit increase in e-cigarette risk perception at wave 4 was associated with 1.1 (p-value: <0.001) increase in CPD at wave 5.

Conclusion: The effect of e-cigarette risk perception on cigarette reduction is partially mediated through intentions to quit cigarettes. Findings suggest that beliefs that e-cigarettes are as harmful or more harmful than cigarette may lead to continued or higher cigarette consumption. A public health goal should address the public misperception of e-cigarettes harmfulness relative to cigarettes.

39. ANALYZING THE RELATIONSHIPS BETWEEN TOPOGRAPHY, E-LIQUID USAGE, AND PHARMACOKINETICS IN JUUL2 PROTOTYPE DEVICES. Qiwei LIANG[1], Lonnie Rimmer[1], Joey Chien[1], Nicholas Goldenson[1], Ryan Black[1], Saul Shiffman[2] and Douglas Oliveri[3]; [1]Juul Labs, Inc, Washington, DC, USA, [2]PinneyAssociates, Bethesda, MD, USA, [3]Independent Consultant

The latest JUUL2 prototypes come equipped with a new feature that enables it to record puffing typography parameters during product use. In a recent pharmacokinetic study involving 37 participants, two new prototype products were tested under both *ad libitum* and controlled use conditions, and the recorded data including device ID, puff count, puff duration and inter-puff intervals were downloaded from the devices after the study completion. As the weight change of JUUL2 pods, calculated as the difference between the pre-use weight and post-use weight, and PK parameters were also measured in the same study, the key question now is to what extent the device topography parameters correlate with pod weight change and PK parameters.

The device IDs were linked with the study subject numbers (without use of personal information). Descriptive statistics for the topography parameters were provided. Total puff duration was identified as a significant contributor to the variability in both pod weight change and AUC for Product I. Specifically, total puff duration accounted for 86% and 70% of the variability in pod weight change and 23% and 26% of the variability in AUC in the *ad libitum* and controlled conditions, respectively. For Product II, total puff duration was also found to

significantly influence the variability in pod weight change and AUC, accounting for 82% and 46% of the variability in pod weight change and 56% and 33% of the variability in AUC in the two study conditions, respectively. The strong correlation between total puff duration and pod weight change is a good indication of the usefulness of the new feature.

40. LEACHABLE TESTING TO EVALUATE EFFECT OF AN ALTERNATE TRANSPORT MODE ON ENDS POD INTEGRITY. Felix AYALA-FIERRO, Harish Chevva, Qiwei Liang, Matthew Lyndon, David Cook and Michael J. Oldham; Juul Labs, Inc, Washington, DC, USA

The JUUL® System is a pre-filled, closed pod Electronic Nicotine Delivery System (ENDS) that delivers nicotine via an inhalable aerosol. The pod is considered the container closure system since it contains the e-liquid. Simulated leachable studies were used to support an alternate mode of pod transportation by comparing chemical leachable profiles and conducting a toxicological risk evaluation when differences were noted.

Simulated leachable studies were conducted on empty pods shipped by air and ocean, during winter and summer, and subsequently filled with neutral flavor-free e-liquid. To identify volatile and non-volatile organic leachable compounds semi-quantitative methods (GC-MS & LC-MS with +/- ion mode) were used while quantitative methods (ICP-MS) were used to identify metals. Leachables were reported based on method-specific analytical evaluation threshold calculated with a dose-based threshold of 1.5 µg/day. Shipping mode differences were determined based on percent change (>100%) for non-targeted organic compounds and p-value <0.05 for metals. Risk assessment using (Q)SAR to detect alerts for toxicological endpoints including mutagenicity and sensitization, then chemical-specific permissible daily exposures (PDE) or TTC for Cramer Class-derived thresholds for inhalation exposures were used to calculate a margin-of-exposure (MOE).

Comparing results of transportation modes and seasons indicated that levels of only a few compounds were changed, showed statistical difference, or were uniquely identified in ocean shipped pods. None that exceeded the acceptable change were classified as mutagenic or sensitizers. Risk assessment resulted in MOEs greater than unity indicating no toxicological concerns. None of the

statistically significant increases in metals (Fe, Cu, Ni, Zn) exceeded USP <232> relevant inhalation PDE limits. Overall, the risk assessment indicated minimal impact from ocean shipping on pod quality and integrity when compared to air shipping.

41. FDA-CTP AND CDISC DEVELOP TOBACCO RELATED STANDARDS TO ACHIEVE EFFICIENCIES FOR ALL STAKEHOLDERS. Chrissie CAI[1] and [2]Christine Connolly; [1]FDA Center for Tobacco Products, Beltsville, MD, USA, [2]CDISC, Austin, Texas, USA

The FDA Center for Tobacco Product's mission is to protect Americans from tobacco-related disease and death by regulating the manufacture, distribution, and marketing of tobacco products and by educating the public, especially young people, about tobacco products and the dangers their use poses to themselves and others. To achieve this mission CTP performs science-based application review in addition to compliance outreach, enforcement, regulation and guidance formulation and other product regulation activities.

This presentation will describe work as part of the collaborative project commenced by CTP and CDISC to develop nonclinical and clinical data standards for tobacco studies to speed regulatory review and decision making. Innovative approaches to standardization developed as part of this project will be discussed and include a hybrid implementation guide structure, new domains, and terminology.

42. CDISC DATA STANDARD. William A. "Allan" REES; Altria Client Services, Richmond, VA, USA

Clinical Data Interchange Standards Consortium (CDISC), in collaboration with the FDA's Center for Tobacco Products (CTP), is developing non-proprietary, consensus-based data standards for tobacco product submissions, including pre-market (e.g. PMTA and SE) and 904(a) submissions. Data standards are in development by the Tobacco Implementation Guide (TIG) team, composed of members from FDA-CTP and industry, using the CDISC standards development process. Through this program, we are excited to bring application-based tobacco data standards forward with the support of FDA-CTP and believe users will benefit from a deeper understanding of this program.

In 2022, FDA sponsored a grant to create data standards for tobacco product submissions; CDISC is facilitating the development of the standards and plan to publish the TIG v1.0 in late Fall 2023. The TIG will describe how to implement CDISC standards for the collection, representation, and exchange of tobacco product data with focus on implementation for common use cases in tobacco product submissions. Use cases are composed of concepts identified by CDISC TIG v1.0 team as important in the context of tobacco product studies. Use cases specifically addressed in the TIG are:

- Product Description refers to concepts used to characterize tobacco products including product specifications, HPHCs, stability and ingredient listing.

- Nonclinical refers to concepts used to identify potential risks and effects on biological processes for tobacco products via in vitro and in vivo nonclinical studies.

- Product Impact on Individual Health refers to concepts used to assess the impact of tobacco products on individuals.

- Product Impact on Population Health refers to concepts used to assess the impact of tobacco products on populations of individuals.

Data standards for each use case are developed in separate workstreams composed of subject matter experts from FDA-CTP and industry.

43. LESSONS LEARNED FROM THE IN VITRO/IN VIVO TOXICOLOGICAL ASSESSMENT OF THE JUUL SYSTEM. Michael OLDHAM[1], Pamela Heard[2], Leon F. Stankowski Jr.[2] and Guy Lalonde[1]; [1]Juul Labs, Inc, Washington, DC, USA, [2]Charles River Laboratories, Skokie, IL, USA

Juul Labs, Inc (JLI) evaluated the toxicological risks of the JUUL System with Virginia Tobacco (VT) and Menthol (ME) JUULpods using standard toxicological assays as part of our product stewardship program. These assays were conducted and interpreted consistent with internationally recognized guidelines. Ultimately, the results of these studies were included in JLI's 2020 Premarket Tobacco Product Application (PMTA) for the JUUL System. JLI received a Marketing Denial Order (MDO) in June 2022 for the JUUL System although the product remains on the market under enforcement discretion while

the MDO undergoes administrative review. The purpose of this presentation is to share JLI's in vitro toxicological assessment of the JUUL System in light of our recent MDO.

JLI conducted the standard battery of in vitro toxicological assays recommended by CORESTA; Neutral Red cytotoxicity assay, Ames mutagenicity assay, and micronucleus (MN) assay for genotoxicity per OECD guidelines on e-liquid and aerosol condensates collected using two puffing regimens. Results of the neutral red and AMES assays were negative for all JUULpod variants tested (VT 3.0% and 5.0% nicotine and ME 3.0% and 5.0% nicotine). In the MN assay, VT 5.0% and ME 5.0% e-liquids yielded positive results and the VT 3.0% aerosol condensate yielded positive results using manual counting. To determine the biological significance of these in vitro results, an in vivo MN and in vivo comet assay (nasal, lung and liver tissue) per OECD guidelines on VT 3.0% and ME 5.0% was performed. Aerosol exposures utilized the maximum tolerated dose. All MN and comet assays for both VT 3.0% and ME 5.0% were negative. JLI concluded on the weight of evidence, that JUUL System aerosols were not genotoxic.

44. A QUANTITATIVE RISK ASSESSMENT APPROACH TO EVALUATE RELATIVE HEALTH RISKS OF ELECTRONIC CIGARETTES VS. COMBUSTIBLE CIGARETTES. Charlene LIU[1], Autumn Bernal[2], Yilang Huang[3], Chuan Liu[4], Donald Graff[5] and Xingtao Jian[3]; [1]RiskWise Solution, Princeton, NJ, USA, [2]ToxCreative, Laguna Hills, CA, USA, [3]RELX Technology, Shenzhen, China, [4]Pinevale, Southampton, UK, [5]Cheerain HK Limited, Hong Kong

Electronic cigarettes (e-cigarettes) heat a nicotine-containing e-liquid that could significantly reduce the number and levels of inhaled toxicants compared to combustible cigarettes. A framework for assessment of potential health risk of e-cigarette aerosol emissions can support regulatory evaluation and inform regulatory decisions of whether an e-cigarette product meets regulatory agency requirements. This quantitative risk assessment (QRA) approach evaluated relative cancer and noncancer health risks associated with the use of RELX Infinity Tobacco compared with Kentucky 1R6F reference cigarettes and Vuse Alto Golden Tobacco. The e-cigarette aerosol samples were analyzed for the U.S. Food and Drug Administration recommended harmful and potentially harmful constituents (HPHCs) and target constituents under both non-intense and intense puffing regimens. Machine-generated HPHC yields for 1R6F reference

cigarette mainstream smoke were obtained from the literature. Toxicity reference values for HPHCs and target constituents were obtained from regulatory and public health agency databases. Exposure concentrations were estimated under "typical " and "heavy" scenarios by utilizing exposure parameters specific to adult tobacco product consumers and standard default exposure parameters for human health risk assessment. The potential health risks associated with inhalation of HPHC and target constituent emissions from e-cigarettes and combustible cigarettes for adult consumers were assessed and compared by integrating the exposure and the dose-response assessments into quantitative estimates of health hazards and cancer risk. The QRA results indicated that estimated risks of vaping RELX and comparator e-cigarette products for cancer and respiratory, cardiovascular, reproductive and developmental toxicity were at least 97% lower than those of cigarette smoking. This study demonstrates that QRA is a practical tool for evaluating relative health risks of e-cigarettes to support regulatory submissions and inform regulatory decisions. In addition, this study adds to the body of evidence that e-cigarettes have the potential for substantial reduction in toxicant exposure and associated health risk compared to combustible cigarettes.

45. Withdrawn

46. WORKFLOW ASSESSMENT OF POTENTIAL LEACHABLES IN AEROSOL FROM ENDS SYSTEMS. Karen CARTER; Juul Labs, Inc, Washington, DC, USA

Leachables are substances that have the potential to transfer to a product from its container closure system. For Electronic Nicotine Delivery Systems (ENDS), leachables may transfer from all materials that contact the e-liquid. Leachable substances from materials in contact with e-liquid may subsequently transfer to the aerosol and be inhaled by the user. There is no specific guidance for conducting leachable studies on ENDS, there is general guidance for inhaled drug products (United States Pharmacopeia, Chapters 1663 & 1664; ISO-10993-18, Product Quality Research Institute - Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, etc.). Herein, we present a workflow for the analysis of leachable compounds in ENDS. To illustrate the workflow's applicability, we present a case study using the JUUL2 pod-based ENDS system. First, leachable compounds were assessed for closed JUUL2 pods filled with non-commercial base e-liquid formulation (propylene

glycol/glycerin/nicotine/benzoic acid). Results for the initial analyses performed using GC-MS and LC-MS (+/- mode) provided a list of 29 organic compounds including potential leachables and nicotine related compounds. After long-term 12-month ambient storage of JUUL2 pods, e-liquid formulation was re-analyzed to investigate the migration of substances over time which provided a list of 12 previously and 24 newly identified compounds. Finally, to better understand potential exposure to leachable compounds, aerosol was collected from the aged pods using non-intense and intense puffing. Results indicated 11/18 of the organic compounds identified in the GC-MS analysis of the e-liquid transferred to aerosol while only 5/30 of the organic compounds identified in the LC-MS analysis transferred. Under GC/MS evaluation, non-nicotine related compounds transferred to aerosol; whereas LC/MS aerosol transfer was exclusively nicotine related compounds. This work supports the observation that larger compounds have limited transfer efficiencies into the aerosol.

47. ANALYTICAL INVESTIGATION OF DATA DEFICIENT SIMULATED LEACHABLES IN ENDS PRODUCTS: CASE STUDY. Cameron SMITH, Matthew Lyndon, Lena Jeong, Danielle Lehman, J. Brian Jameson, Harish Cheeva, Felix Ayala-Fierro, Karen Carter, David Cook and I. Gene Gillman; Juul Labs, Inc, Washington, DC, USA

Leachable investigations are routinely undertaken across a range of sectors, including Electronic Nicotine Delivery Systems (ENDS), to determine if any chemicals from the container closure system can migrate or leach into a product. In general, leachable study conditions and analytical protocols are fairly straightforward, however, risk assessment of the analytical results can be challenging and may require additional data. Herein, we present a case study of the analytical investigation of two leachable compounds with little, if any, toxicological information (data deficient) that were found in simulated leachable studies using JUULpods filled with flavorless base formulation (PG/VG/nicotine/benzoic acid). Because no commercial reference standards for the two data deficient leachable compounds were available, nor any reasonable synthetic route possible due to the compounds' molecular size and structural complexity, an analytical approach was needed to determine whether these two data deficient leachable compounds identified in aged e-liquid from JUULpods transfer to the aerosol. LC-MS/MS analysis using ESI negative mode confirmed that molecular mass and fragmentation patterns for each leachable compound in

e-liquid were consistent with proposed structures and compound rationalizations reported in simulated leachable studies. Upon e-liquid confirmation, aerosol was collected from aged JUULpods in order to determine the transfer efficiency of leachable compounds from e-liquid to aerosol. Aerosol collected from aged JUULpods did not contain any detectable levels of either leachable compound, and transfer efficiency from e-liquid to aerosol was experimentally determined to be < 2%. The novel analytical approached used in this case study provided experimentally determined exposure estimates on two data deficient leachable compounds to support risk assessment and the observation that larger compounds have limited transfer efficiencies into the aerosol.

48. FLAVORANT TRANSPORT PREDICTION FROM E-LIQUID MATRICES. Bob MOISION, Laura Striepe, Vincent Nip and Huan Wang; Juul Labs, Inc, Washington, DC, USA

The two most common solvent carriers used in e-cigarettes, glycerol (VG) and polyethylene glycol (PG), are highly polar molecules that can form extensive hydrogen bonding networks. High polarity solvent matrices can create an inhospitable environment for many of the flavoring compounds used in e-cigarettes which are generally less polar relative to VG and PG. As PG and VG often form 90% or more of an e-liquid formulation, such polarity mismatches can result in non-ideal behavior and can potentially play a role in the relative transport of these molecules into and out of the e-liquid matrix. While the chemistry adage that “like dissolves like” can be used to qualitatively describe the solvation of molecules with disparate properties, several parameterized solvation methodologies can be used to quantify and predict solvent/solute interactions. Hansen Solubility Parameters (HSP) is one such approach that uses three parameters, dispersion (δD), polarity (δP), and hydrogen bonding (δH), to describe solvent/solute interactions. In e-liquid formulations, HSP can be used to determine the relative solubility of common e-cigarette flavorants and deviation from ideal behavior in mixtures of VG and PG. In this work HSP calculations are used to predict the relative transport characteristics of a variety of flavor analytes from proxy e-liquids in a sealed system from the e-liquid matrix into the gas phase as well as predicting the transport of flavor analytes from the headspace into e-liquid matrix. GC-Headspace at 40 °C and liquid GC-

MS measurements were used to provide experimental verification. Flavorants with HSP distances from VG greater than ~22 $MPa^{1/2}$ showed lower affinities to transfer from the headspace into VG relative to PG.

49. A MODEL OF THE TRANSFER OF SPECIES FROM THE E-LIQUID TO THE AEROSOL DURING VAPORIZATION IN AN ENDS PRODUCT.

David KANE, Gordon Holloway, Nagaraja Rao, Bob Moision, Venessa Tse and Norman Fraley; Juul Labs, Inc, Washington, DC, USA

Electronic nicotine delivery systems (ENDS) that vaporize an e-liquid to produce an aerosol are observed experimentally to transfer nicotine, glycerol, and propylene glycol to the aerosol at concentrations nearly proportional to their e-liquid concentration. However, because vaporization is the primary mechanism for transfer of compounds to the aerosol, proportional transfer (PT) does not occur for larger, less volatile compounds under similar conditions.

This report presents a model for e-liquid vaporization in ENDS based on the energy and mass balance in the vaporization region (VR), the heated area at the interface between the e-liquid and air. In the VR, e-liquid components are vaporized at rates proportional to their equilibrium vapor pressures and concentrations. The model demonstrates that initially vaporization rates for the e-liquid components are not proportional to their e-liquid concentrations, but over time within a puff, and over successive puffs, the VR concentrations of the less volatile components increase, resulting in higher vaporization rates and eventually leading to PT. For the major e-liquid components this occurs within 0.1-0.3s, while for less volatile and dilute compounds it takes significantly longer to reach PT, and in some cases it will not occur before the ENDS runs out of e-liquid.

A series of polyethylene glycols (PEG) with 4-8 repeating units has been used to test the model. The model predicts nearly 100% transfer for the major constituents and accurately predicts the measured device mass loss. The model also predicts a decrease in transfer efficiency due to decreasing vapor pressure for the PEGs, from 98% for PEG4 to 54% for PEG8 in qualitative agreement with the experimentally observed trend. This work supports the observation that larger compounds have limited transfer efficiencies into the aerosol.

50. IDENTIFICATION OF AEROSOL COLLECTION RELATED UNKNOWNS IN NTA SAMPLES USING GC-ORBITRAP. Laura STRIEPE, Bob Moision, Vincent Nip, Brian Jameson and Lena Jeong; Juul Labs, Inc, Washington, DC, USA

As presented at the 75th TSRC, GC-MS non-targeted analysis (NTA) of JUUL ENDS aerosolized samples showed the presence of three unknown peaks ranging in concentration from 10-300 µg/g which also appeared sporadically at much lower concentration in blank measurements and were not detected in the e-liquid. This work focuses on the identification of the unknown compounds using a GC-Orbitrap instrument. The original experimental data was collected on a single quadrupole mass spectrometer with an electron impact (EI) source and could not provide unambiguous identification of the unknown compounds. Collected aerosol samples were subjected to additional analysis using an Orbitrap mass spectrometer. The Orbitrap has higher mass resolution relative to the single quadrupole mass spectrometer which allows for the molecular formula of analyzed compounds to be determined, greatly reducing the number of possible identifications. In addition, the Orbitrap used in this analysis has a chemical ionization (CI) source which produces less fragmentation relative to an EI source. The combination of high mass resolution EI and CI was successfully employed to provide provisional identities of the unknown compounds as long chain benzoates. The tentative identifications were subsequently verified as the predicted long chain benzoates by comparing the original unknown GC and MS signals to chemical standards. For the highest concentration of the three original unknown peaks, dodecyl-benzoate, Hovoglass filter pads were found to have ~2-5 µg/pad. The addition of benzoic acid to the pad extract solution was found to increase the detected concentration of dodecyl-benzoate to 21-35 µg/pad indicating a possible reaction between benzoic acid and hydrocarbons in the filter pad was responsible for the observed unknowns.

51. THE MODULAR PUFF MACHINE (MPM): A NEW APPROACH TO PUFFING. Nandita SINGH, Bob Moision, Johnathan Marquez, Scott Park and Tom Vo; Juul Labs, Inc, Washington, DC, USA

The Juul Labs, Inc designed and developed Modular Puff Machine (MPM) is a contemporary alternative to traditional puff (i.e. aerosol collection) machines from manufacturers such as Borgwaldt and Cerulean. Traditional puff machines use a piston to draw a specified volume of air in a given amount of time through

an e-cigarette/heated tobacco device and in-line sample collection equipment (e.g. filter pads and impingers). The MPM uses a mass flow controller connected to a vacuum source and employs flow control to establish puffing volumes and profiles. The MPM has several advantages over conventional puff machines, including its ability to draw large puff volumes, modularity in that the MPMs can be operated as independent single units or cooperatively in groups as large as twelve, user interface customization that can streamline and simplify workflows, over-the-air firmware updates for fleetwide bug fixes and feature updates, the ability to stream device and puff machine data directly to the cloud for subsequent analysis of individual puff profiles or machine performance, device charging between puffs as well as between tests, and user-defined "flushing puffs" that can move static aerosols in tubing onto filter pads or for subsequent analysis. This work focuses on comparing collected aerosols on both an MPM and traditional puff machines to investigate the impact of adding variable resistances such as filter pads and impingers into the flow path. Delivery of major e-liquid constituents (in mg/puff) was found to be comparable for glycerol (Borgwaldt: 3.7±0.2; MPM: 3.8±0.3), propylene glycol (Borgwaldt: 4.6±0.3; MPM: 4.8±0.2) and nicotine (Borgwaldt: 0.30±0.04; MPM: 0.28 ±0.02). Select carbonyls (formaldehyde, acetaldehyde, and acrolein) were also measured on both types of puff machines and found to be equivalent.

52. HORWITZ-THOMPSON EQUATION AS A BENCHMARK FOR CORESTA COLLABORATIVE STUDY RESULTS. Michael MORTON; Altria Client Services, Richmond, VA, USA

The Horwitz Equation is intended to approximate the relationship between the variability of an analytical method and the analyte concentration. The equation was developed by William Horwitz and colleagues to provide a benchmark for the reproducibility standard deviation in collaborative studies. It is sometimes referred to as the Horwitz trumpet because it predicts that as the concentration of the analyte decreases, the relative variability of the analytical method tends to be larger. Michael Thompson has more recently suggested refinements to the equation to make it better fit low concentration analytical results and that refined version is referred to as the Horwitz-Thompson (HT) equation. In this presentation, I compare numerous CORESTA Recommended Method collaborative study results involving 17 tobacco and tobacco product analytes and 23 smoke analytes to

the HT equation. Overall, there is great variation around the predicted variability, but for traditional unburned tobacco and tobacco products, the CORESTA results are generally in line with the HT equation. For mainstream cigarette smoke, the results were normalized to the approximate cigarette tobacco weight of one gram per cigarette. Interestingly, with that normalization, the smoke analytes in the µg or mg per cigarette range tend to have greater variability than predicted by the HT equation whereas the analytes in the ng per cigarette range tended to have less variability than predicted by the HT equation. These data support the use of the HT equation as a rough benchmark for what to expect with unburned tobacco and tobacco product analytical results but suggest that the use may be more limited for smoke.

53. EFFECT AND INFLUENCE OF PERFORATION METHODS FOR TIPPING PAPER ON THE CONTROL OF THE THERMAL ENERGY OF SMOKE FROM TOBACCO PRODUCTS. Michael LINDNER[1], Cristina Rufener[2] and Tomas Bense[2]; [1] Tann Holding, Traun, Austria, [2]C.I.T. Montepaz, Montevideo, Uruguay

Perforation of tipping paper is mainly relevant for adjusting the ventilation level of a combustible filter cigarette to achieve specific smoke deliveries. Moreover, the dynamic smoke flow underneath the tipping paper and inside the filter plug undergoes essential interaction with the stream of ambient air penetrating through the perforation area of the paper thus generating significant impact of diluted cigarette smoke on the human sense of taste. With the successful market launch of next generation products, which include all kinds of e-vapor items as well as heated tobacco products (HTPs), particular physical properties of smoke moved closer into the focus of scientific research activities. Hereby, the temperature of the aerosol generated by HTPs represents a typical example of a parameter which requires special attention in terms of its control and optimization. The purpose of the present study is to determine experimentally the temperature of the mainstream smoke of combustible filter cigarettes made with tipping paper comprising different perforation methods (electrostatic, laser and plasma perforation) and selected permeability levels. Physical and geometrical aspects of these individual perforation types serve as basis for a numerically derived dynamic smoke flow simulation model which is applied to evaluate and confirm the correlation

between the measured mainstream smoke temperature and the smoke flow characteristics. With the gained results, possible options will be outlined for projecting the conclusions onto HTPs in order to lower the thermal energy of the created aerosol through the effect of filter ventilation.

54. Withdrawn

55. Withdrawn

56. UNDERSTANDING CONSUMERS' JOURNEY FROM CIGARETTES TO MODERN ORAL NICOTINE PRODUCTS. Jessica PARKER-ZDINAK[1], Sarah Marking[2] and Andrew Joyce[2]; [1]Applied Research and Analysis Company, Richmond, VA, USA, [2]Consilium Sciences, Richmond, VA, USA

The Rogue Switching Context Study examined the use of Rogue modern oral nicotine products (Lozenge, Gum, and Pouch) and the impact on switching behaviors among adult cigarette smokers. This qualitative research was conducted as part of the Rogue Longitudinal Switching Study, a larger quantitative study. The research objective was to provide context on how adult smokers use Rogue products to reduce their cigarette usage or to switch completely from combustible cigarettes. A total of 78 participants participated in one of 16 one-hour focus groups over the course of the six-month study. Discussions centered on understanding the factors that contribute to adult smokers' journey from cigarettes to a noncombustible product lower on the continuum of risk, such as Rogue Pouch, Lozenge, or Gum. Findings from this research are unique as they highlight the individual differences associated with switching that are specific to the Rogue product portfolio, consisting of diverse flavors and forms. Findings to be discussed in this presentation include how the choice of flavors helped adult smokers to quit smoking or reduce cigarette consumption, how the variety of forms were used in different situations or times of day, and the importance of regular, daily use of Rogue products to effectively switch.

57. THE CASE FOR A REVISED ABUSE LIABILITY ASSESSMENT FRAMEWORK FOR TOBACCO PRODUCTS. Andrea VANSICKEL; Altria Client Services, Richmond, VA, USA

For new or modified risk tobacco product applications, the U.S. Food and Drug

Administration (FDA) recommends tobacco product manufacturers provide an abuse liability assessment (ALA) of their products to inform the likelihood that product use will lead to addiction and repeated or sporadic use that results in undesirable consequences. The typical approach to tobacco product ALA stemmed from the methods and framework used to evaluate pharmaceutical products, with primary outcomes derived from clinical laboratory studies that assess subjective effects (e.g., liking and satisfaction) and nicotine delivery. While this approach has been successful in meeting FDA recommendations, recent data reveal opportunities to reevaluate the tobacco ALA framework. Controlled, clinical conditions do not necessarily reflect nicotine delivery under real world conditions or likelihood of product use and existing subjective measures often do not differentiate products within the same category, even when products vary by nicotine level or flavor, making it difficult to infer the likelihood that product use would lead to addiction and undesirable consequences. This presentation will describe a potential revised ALA framework that would rely foremost on data from actual use and topography studies, including tobacco use patterns, subjective responses, and product use intentions. These data along with nicotine pharmacokinetic data can serve as inputs to models that predict resultant nicotine and toxicant exposure and infer the likelihood that the product would serve to displace more harmful tobacco use behaviors. This framework represents a more relevant and fulsome tobacco product ALA that prioritizes information inclusive of product preferences and real-world usage patterns, which better describes whether individuals would use the product in a way that would result in undesirable consequences relative to other tobacco products.

58. STANDARDIZING THE EVALUATION OF APPROPRIATENESS FOR THE PROTECTION OF PUBLIC HEALTH IN PREMARKET TOBACCO PRODUCT APPLICATIONS. Ryan SELTZER[1], Ding-Geng Chen[2] and [3]Ian M. Fearon; [1]Safety in Numbers, Tucson, AZ, USA, [2]Arizona State University, Phoenix, AZ, USA, [3]whatIF? Consulting Ltd, Harwell, UK

Behavioral surveys for Premarket Tobacco Product Applications (PMTAs) for novel non-combustible tobacco products are intended to show that the benefits to smoking cessation outweigh the risks of youth initiation and use among nicotine non-users. We developed a statistical approach to quantify this risk-benefit balance. This optimization algorithm is created by calculating a

composite score based on multiple survey responses and then using this score to predict the likelihood of using or intending to use a product. We accessed behavioral survey data from the 2017 IQOS PMTA. A principal components analysis was run on 26 questions that indicate perceptions of health and addiction risk. A two-factor model was revealed based on the derived scree plot and Eigen values of 21.71 and 1.06. Factor scores were calculated and summed for each respondent to create a composite risk score. This risk score was then used to predict likelihood of IQOS use and intention to use IQOS. We demonstrate models varying in survey response patterns in which IQOS use for adult cessation benefit is more likely than the risk of youth initiation and in which youth initiation risk is more likely than adult cessation benefit. This method is intended to objectively assess a product's Appropriateness for the Protection of Public Health (APPH) and offer explicit criterion on which the FDA can evaluate APPH of a product in a PMTA. Knowledge of these factors can provide direction on what areas of youth use and smoking cessation need to be addressed to improve the risk-benefit balance. This approach can help clarify what information should be collected in PMTAs and guide efforts to standardize the regulation and review process.

59. CORESTA TOBACCO HARM REDUCTION WORKSHOP OVERVIEW. Jason FLORA[1] and Rob Stevens[2]; [1]Altria Client Services, Richmond, VA, USA, [2]RAI Services Company, Winston-Salem, NC, USA

In June 2022, CORESTA held a Science Day in Paris, France. Presenters included tobacco harm reduction (THR) experts within and outside of the CORESTA membership. Topics covered included the role of nicotine in harm reduction, misperceptions on the harm of nicotine, the challenges and opportunities of harm reduction substantiation, innovation and harm reduction of alternative products, and supply chain integrity. Through guidance from the CORESTA Board and with what we learned from Science Day, a workshop was developed and executed in April 2023, in Antibes, France, to develop insights into how CORESTA can advance the science related to THR. A diverse group of participants were selected by the CORESTA delegates (approximately 70 participants attended), and the workshop was designed to address the following objectives: 1) Identify key areas where CORESTA can advance the science related to THR; 2) Create actionable objectives to advance the key areas of science related to THR; and 3) Develop a recommendation for the infrastructure by which to accomplish the actionable objectives. In this presentation, we will

provide an overview of the outcomes of the THR Workshop, progress to date, and next steps.

60. SUBSTANTIAL EQUIVALENCE OF TOBACCO PRODUCTS: ARE ALL TOBACCO PRODUCTS OF THE SAME TYPE AND CHARACTERIZING FLAVOR SUBSTANTIALLY EQUIVALENT? EXAMPLES OF EQUIVALENCE AND NONEQUIVALENCE AMONG WATERPIPE TOBACCOS. John LAUTERBACH; Lauterbach and Associates, Deland, FL, USA

Many adults who use tobacco products are unaware of differences among the brand-styles of the tobacco products they use or even differences in their preferred brand-style. For example, there is little in the peer-reviewed literature that tells us how far we can change the tobacco blend, nontobacco ingredients, processing, and fabrication parameters for a brand-style of conventional combustible cigarettes before a statistically significant number of consumers of that brand will notice the difference in the smoking properties of the cigarette. There are numerous other tobacco products for which there are little data on how changes in blend, nontobacco ingredients, processing, and fabrication parameters can affect consumer sensory responses. Waterpipe tobacco (WPT) is one such product type. WPT's are mixtures of glycerol, sugar syrups, tobacco, flavors, and in some cases, colorants. Tobacco is < 30% and nicotine is < 0.2% by weight in final products. The remainder is glycerol (VG), sugar syrups, flavors, and other solvents such as propylene glycol (PG), triacetin, ethanol. Literature reports show preferences for some flavors over others [e.g., fruits (particularly apple), candy, mint >> spice, tobacco]. Since many manufacturers offer similar products, and they may only differ in flavor composition, but bear the same flavor name, deciding what products are essentially equivalent requires a combination of physical (particle size distribution, optical microscopy) and chromatographic analyses for tobacco type (flue-cured, dark air-cured, burley) levels of VG, PG, sugars, and flavors. Examples with data and conclusions on equivalence will be provided for the followings cases: same flavor name, but different blends and manufacturers; same flavor name, but different manufactures; and same tobacco type, different trade-name flavors, and different manufacturers, but same tobacco type.

61. SWITCHING AWAY FROM CIGARETTES USING TOBACCO- AND MENTHOL-FLAVORED JUUL, AMONG ADULTS WHO SMOKE

MENTHOL VS NON-MENTHOL CIGARETTES. Arielle SELYA; PinneyAssociates, Inc, Pittsburg, PA, USA

In May 2022, FDA issued a proposed rule to ban menthol in cigarettes. The agency - based on a review of internal and external analyses - projects that a menthol cigarette ban will save as many as 654,000 lives over forty years, in part from existing menthol cigarette users switching to less harmful nicotine products. These analyses assume a risk continuum policy framework that supports the increased and sustained use of less harmful tobacco products. However, the impacts of a menthol ban in cigarettes may depend on the availability of non-tobacco flavors in other tobacco products.

62. MODELLING THE IMPACT OF AN ENDS FLAVOR BAN ON YOUTH USERS AND ADULT CURRENT SMOKERS IN THE UNITED STATES. Andrea PATTON, Jyoti Goyal, Gabriel Barnard and Neil McKeganey; Centre for Substance Use Research, Glasgow, UK

Objectives: Following publication of the 2022 National Youth Tobacco Survey, highlighting the level of youth use of Menthol flavored ENDS, further enforcement of all non-tobacco flavors, including Menthol, is a current topic of regulatory debate.

1. To determine what flavors youth and adult current smokers reported using in an e-cigarette in the past 30 days

2. To estimate the number of youth and adult current smokers who have used an ENDS in the past 30-days who, post implementation of a flavor ban, may exit vaping

Methods: An online questionnaire was administered to probability-based samples of youth and adults in the United States, recruited through Ipsos' KnowledgePanel® in June 2022.

Participants' use of ENDS flavors in the past 30 days was categorized into the following groups: (1) Tobacco only; (2) Tobacco and Menthol; (3) Tobacco and Other Flavors; (4) Menthol only; (5) Menthol and Other Flavors; (6) Other Flavors only; and (7) Tobacco and Menthol and Other Flavors. A weighted percentage and estimated weighted number of persons was calculated for each of the seven flavor groups.

A flavor ban scenario was modelled where FDA bans all e-liquid flavors except tobacco.

Results: If FDA banned all flavors except Tobacco, for every 1% that used a flavor other than Tobacco in the past 30 days and, following the flavor ban, did not migrate to Tobacco, then an estimated 4,142 youth may exit vaping and an estimated 25,143 adult current smokers may exit vaping.

Implications: Changes to policy restricting e-liquid flavor choice must strike the correct balance between mitigating risk to youth against the potential benefit to adult smokers who use e-cigarettes to reduce their cigarette consumption or switch.

63. EVOLUTION OF YOUTH TOBACCO USE: ANALYZING TRENDS IN E-CIGARETTE CONSUMPTION AND THE RISE OF CBD/THC CONTAINING DEVICES. Mark CROSSWHITE; McKinney Regulatory Science Advisors, Henrico, VA, USA

The Centers for Diseases Control and Prevention (CDC) is a Federal Agency whose mission is to protect America from health, safety, and security threats, both foreign and in the US. For approximately the last 25 years, the CDC has been conducting the National Youth Tobacco Survey (NYTS) to provide national data on long-term, intermediate, and short-term indicators key to the design, implementation, and evaluation of comprehensive tobacco prevention and control programs. These data are also used by the US Department of Health and Human Services to compare progress toward the *Healthy People 2030* goals.

Since 1999, the NYTS questions have evolved to address an ever-changing tobacco use landscape. Initially, there were no questions regarding electronic cigarette use, but as that format increased in popularity, questions regarding electronic cigarettes were added to the NYTS. Partly based on NYTS data, in 2018 the US Department of Health and Human Services Surgeon General declared youth vaping an “epidemic”, following which State and Federal agencies acted quickly to start to mitigate the epidemic. Over the last few years, the survey questions are continuing to evolve and now the CDC is including questions on the NYTS to collect data on the use electronic cigarettes containing CBD and THC. In this presentation we use NYTS data to show trends in tobacco related e-cigarette youth use leading up the 2018

epidemic and compare those data to current trends in CBD and THC related e-cigarette youth use.

64. ARE SMOKERS AND YOUNG PEOPLE OVER-SURVEYED? ADDRESSING CONCERNS ABOUT POSSIBLE RESPONDENT FATIGUE AND PRIMING EFFECTS IN PROBABILITY-BASED SAMPLING FOR REGULATORY SURVEY RESEARCH. Christopher FLEURY, Victoria Hoverman and Abby Cohen; Ipsos-Insight, Washington, DC, USA

Tobacco and nicotine product manufacturers pursuing the PMTA and MRPTA pathways are expected to submit product-specific perceptions, behavior, and intentions data with their applications. The mission-critical importance of these submissions makes the quality of the data especially important. Many companies chose to invest in probability based panels for their surveys, even though this approach is more costly than standard non-probabilistic or "opt-in" online consumer panels to ensure greater representativeness and higher data quality. Yet, probability-based survey sample is a finite resource, especially among certain key audiences of relevance to regulatory research, namely adult smokers, youth, and young adults. This raises the concern that the same pool of panelists is potentially being oversurveyed for this critical regulatory research, and that exposure to multiple questionnaires of this nature may shape respondents' subsequent responses.

Our paper uses blinded internal data from the probability-based Ipsos KnowledgePanel® to assess:

1. How often panelists have been surveyed for regulatory surveys in recent years; this will be assessed overall, as well as among key subgroups of panelists likely to be targeted for this type of research.
2. The degree of consistency across comparable outcome measures of particular regulatory interest (e.g., intention to try, awareness, risk perception, claims comprehension) among the same respondents re-surveyed at different times with certain response patterns potentially indicating that exposure to the first survey influenced answers to the later one.

We will also discuss the general advantages of using probability-based sample for regulatory research, citing examples of how KnowledgePanel® estimates track with national tobacco prevalence benchmarks.

65. BEHAVIORAL INTENTIONS ASSESSMENT OF A DISPOSABLE E CIGARETTE AMONG ADULT CURRENT, FORMER, AND NON SMOKERS IN THE UNITED STATES. Christopher RUSSELL[1], Willie J. McKinney[2] and Ian M. Fearon[3]; [1]Russell Burnett Research & Consultance, Glasgow, UK, [2]McKinney Regulatory Science Advisors, VA, USA, [3]whatIF? Consulting, Harwell, UK

Modelling the public health effects of e-cigarettes requires estimates of the likelihood that different individuals and population subgroups will start using e-cigarettes and subsequently transition to and from combustible cigarette use. To begin to generate input values for modelling efforts, this study assessed adults' behavioral intentions in relation to a disposable e-cigarette: BIDI® Stick.

An online questionnaire assessed intentions to try and use a BIDI® Stick regularly in 11 flavor variants among U.S. nationally representative samples of adult (21+years) Non-Smokers (n=2,284), Current Smokers (n=2,391), Former Smokers (n=2,241), and Young Adult (21-24 years) Non-Smokers (n=1,140) of combustible cigarettes following exposure to product information and images. Current Smokers rated their intentions to use a BIDI® Stick to partially or completely replace cigarettes.

Positive intention to try a BIDI® Stick at least once was, for each flavor variant, highest among Current Smokers (22.4-28.1%), lower among Former Smokers (6.0-9.7%) and Non-Smokers (3.4-5.2%), and lowest among Never-Smokers (1.0-2.4%). Among Current Smokers, Former Smokers, and Non-Smokers, trial and regular use intentions were lowest among E-Cigarette Non-Users and E-Cigarette Never-Users. Approximately 23.6% of Current Smokers reported an intention to use a BIDI® Stick in at least one flavor to completely switch from cigarettes and/or to reduce cigarette consumption.

Low trial and regular use intentions suggest U.S. adults who do not currently smoke cigarettes and/or use e-cigarettes are unlikely to initiate use of the BIDI® Stick e-cigarette. Trial and regular use intentions are highest among

adults who currently smoke cigarettes and/or use e-cigarettes. A moderate proportion of Current Smokers may try using a BIDI® Stick e-cigarette as a partial or complete replacement for combustible cigarettes.

66. UNDERSTANDING THE SENSORY ATTRIBUTES UNDERLYING THE ACCEPTANCE OF E-CIGARETTE PRODUCTS, WITH THE AIM TO INCREASE THE ACCEPTANCE OF ALTERNATIVE SMOKING PRODUCTS. Andrew LIVERMORE[1], Malori Comer[1] and Laurel Moller[2]; [1]Curion Insights, Red Wood City, CA, USA, [2]Curion Insights, Old Bridge, NJ, USA

An important component of Harm Reduction strategies is to transition smokers to products presenting a lower risk of disease. However, to achieve this transition, smokers must find these products to be sensorially acceptable. The objectives of the current research were to understand the sensorial attributes of e-cigarettes that underlie consumers perception of the product, to uncover those attributes that are important to (or drive) acceptance, to identify consumer segments that have different drivers of acceptance, and to uncover opportunities for modifying products to better meet consumer needs.

To achieve this, Curion used their multistep Product Optimization (PROP) methodology. This involved using our trained descriptive (QDA) panel to create a sensory profile of products within the e-cig category. Vapers/smokers (390) then rated their opinion of 16 selected products. Multivariate statistical analysis integrated the sensory and consumer data to uncover the sensory attributes having the highest positive and negative impact on consumer acceptance. Results revealed three distinct consumer segments with different patterns of sensory attributes underlying their acceptance. Segments 1 and 3 preferred lighter products and acceptance was driven by either nutty or sweet brown notes, while a third segment preferred bold traditional flavors- a pattern that is not uncommon across categories. These findings were used to identify opportunities to modify products to better address the acceptance of harm reduced products.

67. ESTIMATING HUMAN PK PARAMETERS FOR ENDS PRODUCTS FROM CHEMICAL ANALYSES OF THEIR AEROSOLS. Saul SHIFFMAN[1], Qiwei Liang[2], Georgios Karles[2] and Gal Cohen[3]; [1]PinneyAssociates, Pittsburg, PA, USA, [2]Juul Labs, Inc, Washington, DC, USA, [3]Intuitive Sciences,

Tiburon, CA, USA

Evaluating the nicotine uptake from ENDS products in pharmacokinetic (PK) studies is an important part of evaluating their performance, bearing both on their 'abuse liability' and their potential to help smokers switch away from smoking. However, human PK studies are very time- and resource-intensive, and the amount of nicotine absorbed by users should logically be highly related to the nicotine uptake from the aerosol. We evaluated whether ENDS products' C_{max} (ng/mL, "nicotine uptake") could be predicted from their "nicotine yield," defined as the mass of nicotine per puff (mg/puff) in machine puffing. Specifically, we statistically modeled the relationship between nicotine yield and nicotine uptake in human PK studies, considering both non-intense and intense puffing regimens in assessing nicotine yield, and both controlled and ad libitum puffing regimens in assessing nicotine uptake. We used meta-analytic (meta-regression) statistical methods with conditions within PK studies as the units of analysis. Data on nicotine yield under non-intense puffing conditions and nicotine uptake under controlled puffing conditions included 31 study conditions, comprising 945 observations of individual users' C_{max} values. C_{max} was highly predictable from nicotine yield. The correlation between yield under non-intense puffing and nicotine uptake under controlled puffing was 0.89. Results were similar for ad-libitum puffing (r=0.88), but weaker for nicotine yields measured under intense puffing (r=0.82, r=0.62, for controlled and ad libitum puffing, respectively), likely because human users do not typically puff in this way. Thus, ENDS products' C_{max} (and, by extension, AUC) is highly predictable from nicotine mass per puff measured under non-intense machine puffing conditions. This relationship can facilitate product testing during development, and may be a suitable substitute for human clinical PK measurements.

68. Withdrawn

69. DETERMINATION OF GLYCIDOL IN E-LIQUID AND AEROSOL SAMPLES FOR ENDS PRODUCTS BY GC-MS. David COOK, Beth Stump, Norman Fraley, Kathy Humphries, I. Gene Gillman and Brian Jameson; Juul, Labs, Inc, Washington, DC, USA

Glycidol, a thermal degradant of glycerol, is a proposed addition to the established U.S. Food and Drug Administration (FDA) Harmful or Potentially Harmful Constituents (HPHC) and is also listed for consideration within the

FDA Guidance for Premarket Tobacco Product Application for Electronic Nicotine Delivery Systems (ENDS). Due to its chemical instability, Glycidol is a challenging compound to analyze and, at present, no standardized method exists for the determination of this compound.

The objective of this work was to develop and validate a stable, sensitive, and selective method for the determination of glycidol in e-liquid and aerosol samples utilizing a derivatization methodology via gas chromatography-mass spectrometry (GC-MS). This new method involves an aliquot of e-liquid and/or collection of trapped aerosol onto a Cambridge Filter Pad (CFP) followed by extraction using acetone spiked with deuterated glycidol as an internal standard. The extraction solution is then transferred to a vial containing p-Toluenesulfonyl chloride and concentrated Hydrogen Bromide (HBR) to form the Bromo-p-toluenesulfonate derivative followed analysis via GC-MS.

The calibration range was from 10 ng/mL to 800 ng/mL, with a quantification (LOQ) equivalent to 180 ng/g for e-liquids and 250 ng/collection for aerosols. All requirements for method validation were met including specificity, accuracy, precision, repeatability, robustness, and stability. An assessment of whole pod glycidol measurements were conducted on nine commercially available disposable ENDS products using the ISO 20768 standard puffing regime. Results of these samples ranged from 1.64 to 329 ng/puff. In conclusion, this method is deemed fit for purpose to accurately determine trace amounts of glycidol in both e-liquids and aerosol samples.

70. SELECTED HPHC FORMATION IN JUUL2 NON-COMMERCIAL DEVICES AS A FUNCTION OF TEMPERATURE. Hosna MOGADDEDI, I. Gene Gillman, Bob Moision, Nandita Singh, Venessa Tse, Kevin Pascual, Angela Huang, Valerie Schwartz and Sam Anderson; Juul Labs, Inc, Washington, DC, USA

Harmful and potentially harmful constituents (HPHCs), such as aldehydes, can form in electronic nicotine delivery system (ENDS) aerosols due to overheating during aerosol production. Overheating may result from imprecise temperature control of the heating element used to aerosolize ENDS e-liquids. JUUL2 is a next-generation ENDS device engineered with active temperature control that maintains a consistent temperature during e-

liquid heating and aerosolization, minimizing formation of low-level thermally-generated HPHCs. This study focuses on the formation of HPHCs as a function of temperature.

Selected HPHCs formed in the aerosol produced by non-commercial JUUL2 devices were studied as a function of vaporization temperature. A range of temperature setpoints (247°C, 271°C, 296°C, and 321°C) were created by altering the device firmware. An e-liquid formulation consisting of a 50:50 PG:VG blend with 4% nicotine with equimolar benzoic acid was used in these studies. The samples were analysed for PG, VG, nicotine via GC-FID, carbonyls by LC-MS, and glycidol by GC-MS.

The results demonstrated a three-fold increase in Total Aerosol Mass (TAM) as the temperature increased from 247°C to 296°C, then remained constant at 9 mg/puff when the temperature was further increased to 321°C. Similar trends were observed for PG, VG, and nicotine levels. Carbonyls and glycidol exhibited a four-fold and eight-fold increase, respectively, as the temperature increased. The data exhibited low variance (<5%), indicating consistent device performance throughout the study. The study suggests that increasing the temperature set-point in the device beyond the level typically found in commercial JUUL2 devices had minimal impact on the per-puff delivery of nicotine. Additionally, the levels of HPHCs detected in the aerosol were lower than those typically found in combustion during the use of conventional cigarettes.

71. GLYCIDOL IN ENDS; YIELD PATTERNS OVER POD LIFE AND MEASUREMENTS IN 35 NORTH AMERICAN MARKET PRODUCTS. Brian JAMESON, Karen Carter, Candice Jongsma, Jiaming Wang, Austin L. Bates, Sifat Ullah, Cameron R. Smith, Lena N. Jeong, David K. Cook and I. Gene Gillman; Juul Labs, Inc, Washington, DC, USA

Glycidol is a group 2A carcinogen and is proposed for inclusion in FDA's list of harmful or potentially harmful constituents. FDA recommends assessment of glycidol in its Guidance for Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (ENDS). Glycidol is present in combustible cigarette (CC) and ENDS aerosol, but due to chemical instability, accurate quantitation of glycidol in product aerosol is difficult. In this study, a recently developed analytical method for glycidol was leveraged

to determine the glycidol yield of a range of products representing the majority of North American ENDS market.

First, aerosol glycidol measurements were conducted on 50-puff block collections at the beginning, middle, and end of pod life for several ENDS products to determine the variability of glycidol yield over pod life. Most ENDS showed increasing yield of glycidol from beginning to end puff blocks. Some ENDS also showed a high level of replicate-to-replicate variability in glycidol yield, suggesting inconsistency of glycidol yield between individual pods.

Subsequently, glycidol measurements were conducted by analyzing whole pod aerosol from a total of 35 unique combinations of devices and formulations, including nine closed pod-based devices, four open pod-based devices, and one cigalike device. All 35 test articles contained quantifiable levels of glycidol. Using the ISO 20768 standard puffing regime, glycidol levels in closed devices ranged from 24 to 8200 ng/mg nicotine, representing between a 98% decrease and an 620% increase compared to 1R6F CC. In open systems, glycidol levels ranged from 9 to 1900 ng/mg Nicotine, representing between a 99% decrease and an 68% increase compared to 1R6F CC.

72. ACCELERATED AGING OF PROPYLENE GLYCOL AND GLYCEROL. Norman FRALEY, Lena Jeong, Matthew Lyndon, Anastasia Lioubmirov and I. Gene Gillman; Juul Labs, Inc, Washington, DC, USA

The United States Food and Drug Administration (FDA) Family Smoking Prevention and Tobacco Control Act empowered the FDA to protect public health by regulating the manufacturing, distribution, and marketing of tobacco products. In its guidance for Premarket Tobacco Product Applications for electronic nicotine delivery systems (ENDS), FDA recommends that applicants evaluate chemical changes in their product over its shelf-life and provide complete product characterization. Compounds commonly used in the e-liquids of ENDS, such as propylene glycol (PG) and glycerin (VG) have the potential to degrade through oxidation, acidification, or radical processes during storage, resulting in new compounds. Because these new compounds may potentially transfer into the aerosol, resulting in

consumer exposure, it is necessary to identify them as part of product characterization.

A semi-quantitative gas chromatography-mass spectrometry (GC-MS) based non-targeted analysis (NTA) screening method was utilized for chemical characterization. The aim of this work was to characterize degradants arising from PG and VG during storage and build a custom mass spectral database of known degradants, in addition to the NIST database, for an improved compound identification. A simplified e-liquid of PG/VG (60/40 w/w 1.6% nicotine 1.2% benzoic acid) without flavor ingredients was conditioned at high temperature (100° C) to accelerate the potential reaction processes.

This presentation will include examples of PG- and VG-related compounds in simplified e-liquid formulations, such as propylene glycol acetate, 2,4-dimethyl-1,3-dioxolane-2-methanol, or hydroxyacetone. Because PG and VG are used as e-liquid carriers across the ENDS industry, the results of these studies will expand foundational knowledge and improve the ease of NTA identification generally.

73. ASSESSMENT OF FORMALDEHYDE AND ACETALDEHYDE FORMATION IN E-LIQUID AND DURING PUFFING OF AN ENDS PRODUCT. Manali AGGRAWAL, Bob Moision, Katharine Pearce and Apurva Bhave; Juul Labs, Inc, Washington, DC, USA

The production of carbonyls during use of an electronic nicotine delivery system (ENDS) is of high concern, and several carbonyls appear in FDA's list of suggested analytes for ENDS testing. Therefore, close monitoring of the levels and sources of carbonyls is of prime importance. Production of carbonyls is generally associated with the thermal degradation of e-liquid components during the heating and aerosolization process, but carbonyls can also form in the e-liquid. The carbonyls present in the aerosols are hypothesized to come from two sources - the carbonyls formed in the e-liquid and those produced during aerosolization. In this work, we study the formation of carbonyls in e-liquids after exposure to accelerated storage conditions (40 °C at 60% RH) to determine its relative contribution. Standard carbonyl analysis using DNPH complexation followed by LC-MS detection was employed to determine the carbonyl content of the e-liquid and aerosolized e-liquid prior to accelerated storage (T=0) and after 30 days of accelerated storage (T=30). At the T=0 timepoint formaldehyde was found to originate primarily due to the aerosolization process (0.010 ± 0.02 μg/mg) and not from the e-liquid (0.0014 ± 0.0005 μg/mg). At the T=30 timepoint, after e-liquid formaldehyde measurements were subtracted from the

puffed measurements, the resulting contribution from the aerosolization process was found to be similar to those at T=0, 0.011 ± 0.05 µg/mg, despite the T=30 puffed formaldehyde levels ranging from 0.010 to 0.049 µg/mg. For formaldehyde, adding the T=0 aerosolization values to the T=30 e-liquid measurements was found to be a good predictor for the puffed values at T=30 (r2 = 0.96). For acetaldehyde, the contribution due to aerosolization was found to increase from T=0 (0.0022 ± 0.0006 µg/mg) to T= 30 (0.0044 ± 0.0023 µg/mg). When the T=0 aerosolized values and the T=30 values are added, it resulted in an underprediction of the T=30 values by about 10%. As the collection of aerosolized carbonyl samples is labor intensive, this work suggests that direct testing of e-liquids in accelerated storage may offer a rapid screening approach for e-liquid stability.

74. E-CIGARETTE REGULATORY NON-COMPLIANCE IN THE UK MARKETPLACE. Malcolm SAXTON; Broughton Life Sciences, Earby, Lancashire, UK

A strong and growing body of science now exists, showing that switching from conventional, combustible cigarettes to e-cigarettes significantly reduces a user's exposure to harmful and potentially harmful constituents (HPHCs). While this evidence has been accepted by some health bodies, notably in the UK, where the place of e-cigarettes in smoking cessation is official health advice, many regions of the world still view e-cigarettes as a potential health and addiction issue.

An area of particular recent concern in convincing consumers, health professionals, and regulators of the benefits of switching to e-cigarettes is the perception that a not insignificant number of products available to consumers fail to comply with the regulatory requirements of markets for which they are on sale.
To investigate this perception, Broughton Life Sciences analyzed a cross-section of the disposables market in the UK to determine which products were in compliance with the UK's relatively light-touch Tobacco and Related Products Regulations (TRPR).

For the products selected from the market, their registration with the MHRA was confirmed, and analytically, liquid fill volume and nicotine concentration were measured to determine whether the products were in compliance with the TRPR stipulation of less than a maximum of 2 mL of liquid and nicotine concentration of no more than 20 mg/mL.

The data presented will show the scale of the issue in the UK market of non-compliant disposable e-cigarette products, and we will present a potential test package that should be undertaken to ensure products are compliant, which will allow the industry to show that it is serious in giving consumer well-control products as an alternative to conventional cigarettes.

75. INNOVATIVE SOLUTION TO AN AGE-OLD PROBLEM-CONSIDERATIONS WHEN DEVELOPING AGE-GATED TECHNOLOGY. Lillian ORTEGA, Lise Fraissinet, Ed Carmines, Bryan Burd and Kevin Burd; Chemular Inc, Hudson, MI, USA

According to the National Youth Tobacco Survey, over 3 million U.S. youth reported using a commercial tobacco product in 2022. The most commonly used tobacco product in middle and high school aged students are e-cigarettes with 85% using flavored (i.e., menthol, mint, clove or spice, alcoholic drinks, candy, fruit, chocolate, or any other flavor other than tobacco) e-cigarettes. The FDA's Premarket Tobacco Application (PMTA) authorization decisions are based on a public health standard that considers the risks and benefits of the product on the population. To date, the agency has not authorized any flavored e-cigarettes and has denied millions of applications due to lack of evidence demonstrating an added benefit to adult smokers that outweighs the substantial risk of youth initiation and use of flavored e-cigarette products. The tobacco industry has few options to provide evidence that e-cigarette products benefit adult smokers and outweigh the risk of youth initiation and use, one potential option is age verification technology built into the tobacco product. Tobacco manufacturers are considering and, in some cases, have developed technology to solve a problem that predates the Family Prevention and Tobacco Control Act keeping tobacco products out of the hands of minors. This presentation offers viewpoints based on the agency's approach to medical device software technology, including insight on ISO standards for software development, addressing risk versus benefit through ENDS software design parameters restricting youth access without defined endpoints and lessons learned from Actual User Study of E-cigarette age gating technology.

76. NICOTINE EXTRACTION FROM POLYPROPYLENE MODERN ORAL PACKAGING. Owen BUSSEY, Cody Perry and Serban Moldoveanu; Reynolds American, Winston-Salem, NC, USA

Many nicotine pouch products are sold in polypropylene packaging and over time nicotine can be absorbed into the packaging. This packaging can be recycled but there may be regulatory limits on the level of absorbed nicotine in some countries. This research describes two methods for nicotine extraction and quantitation from polypropylene modern oral packaging in support of recycling claims in the United Kingdom. The first extraction method included a 48-hour Soxhlet methanol extraction with an extraction efficiency of 89%. The second method included a 2-hour microwave methanol extraction demonstrating an equivalent efficiency. The extraction efficiency of each method was determined using pyrolysis GCMS of a reference piece of plastic from each sample before and after extraction. The quantitation method for the extract used liquid chromatography with ultraviolet detection. Experimental formulations were used for a comparison study between the Soxhlet and microwave extraction techniques. Samples tested included some with nicotine formulations ranging from 4 mg to 10.9 mg per pouch and 3 to 12 months in age. Data showed levels not exceeding 0.095% nicotine by mass of the plastic which was well below the threshold of 0.25% nicotine in the recyclability claims.

77. STABILITY EVALUATIONS OF TOBACCO-FREE NICOTINE-CONTAINING POUCH PRODUCTS. Sawyer HUBBARD, Candice K. Cunningham and Nolan D. Spann; Reynolds American, Winston-Salem, NC, USA

Regarding the stability endpoints to support a PMTA submission, Tobacco-Free Nicotine-Containing Pouch Products (TFNCPPs) are generally grouped with other smokeless tobacco products - the same stability endpoints are required by the FDA to support a company's proposed shelf life. The objective of this presentation is to demonstrate, using different TFNCPPs and packaging types, that the stability endpoints required by the FDA for smokeless tobacco products are specific to products that contain tobacco leaf and may be less relevant for TFNCPPs. Four distinct packages and four styles of Velo-branded products were tested for aerobic microbial count, yeast count, mold count, TSNA, and water activity across several stability studies. The results will be presented, and statistical comparisons made, where possible, to demonstrate, for TFNCPPs specifically, the endpoints required by FDA for evaluating stability over time are unaffected by different packaging styles.

78. RAPID "MOISTURE" DETERMINATION AS AN ALTERNATIVE TO

CRM76 FOR MODERN ORAL POUCHES. Ian TINDALL; Cerulean, Milton Keynes, UK

Moisture content is a key parameter in the manufacture of modern oral pouches, a growing area of alternative nicotine delivery. Many of the modern oral pouches emerging onto the market have high levels of moisture (30% – 50%) as a design parameter. CORESTA has developed an oven volatiles method, CRM76, which takes over 3.5 hrs to complete a measurement and so is of little practical use when considering manufacturing feedback control. The most rapid oven method takes ~10 minutes to perform.

To provide faster feedback alternative methods based upon a microwave cavity were explored and found unsatisfactory as the response curve of the cavity showed a point of inflexion at around 35% moisture resulting in uncertainty and insensitivity to moisture content above 25% moisture.

A further alternative based on the electrical properties of the pouch, using contact resistance, was developed. Correlation between CRM76 and contact resistance was possible with a simple procedure. Using a "generic" moisture curve ±5% accuracy could be routinely obtained for a sample of 8 pouch types, and where specific curves based on pouch type are adopted the accuracy with respect to CRM76 becomes ±2%. Pouch to pouch variability is clearly seen with individual pouch moisture SD of between 0.2% and 4% that is dependent upon brand. Limitations of the method are noted, the method is unsuitable for pouches with less than 10% moisture and the correlation is with oven volatiles not true water content. Finally the need for pouch type specific curves may be a function of the pH of the pouch.

79. A COMPARISON OF HPHCS IN ON!® PLUS NICOTINE POUCHES TO HPHCS IN CIGARETTES, SMOKELESS TOBACCO INCLUDING SNUS AND AN ORAL NRT PRODUCT. Regina BALLENTINE, John H. Miller IV, Cathy X. Jin, Jennifer H. Smith, Karl A. Wagner, Regina M. Ballentine, Hannah Grisevich, Chris K. Salmon, Michael S. Williams, Likun Yang, Richard W. Morgan, Vanessa Haase and Tim L. Danielson; Altria Client Services, Richmond, VA, USA

on!® PLUS nicotine pouches (on!® PLUS NPs) are smoke-free tobacco products intended for adults aged 21 years or older who use smokeless tobacco (ST) or who dual use ST and cigarettes. on!® PLUS NPs are a new type of oral tobacco-

derived nicotine (OTDN) product that has a soft-feel and does not contain cut, ground, powdered or leaf tobacco. To receive market authorization in the United States, the U.S. Food and Drug Administration (FDA) must determine if on!® PLUS NPs are appropriate for the protection of public health (APPH). To inform an APPH determination, we characterized the levels of harmful and potentially harmful constituents (HPHCs) for on!® PLUS NPs.

In this study, we measured HPHCs in on!® PLUS NPs from the FDA's ST abbreviated list, recognizing that these products do not meet the statutory definition of an ST product. This approach was considered appropriate as there is no FDA specific guidance for reporting HPHCs for OTDN products. The HPHCs on FDA's ST abbreviated list include nicotine, NNN, NNK, B[a]P, acetaldehyde, formaldehyde, crotonaldehyde, cadmium and arsenic. In this work we compared the ST HPHCs in on!® PLUS NPs to commercially available tobacco products including cigarettes, smokeless tobacco, OTDN pouches and a nicotine replacement therapy product. Nicotine, formaldehyde and acetaldehyde were the only HPHCs that have quantifiable values in on!® PLUS NPs. Except for nicotine, the HPHCs measured in on!® PLUS NPs demonstrated a 91% reduction compared to traditional smokeless tobacco and 99% reduction compared to cigarettes. Additionally, a toxicological risk assessment of the HPHCs present at measurable levels in on!® PLUS NPs were below levels of toxicological concern.

80. QUANTITATIVE MEASUREMENT OF HPHCS IN 16 COMMERCIAL SMOKELESS TOBACCO PRODUCTS. Selvin EDWARDS, Matthew Hassik, Kenneth M. Taylor and An Vu; Food and Drug Administration, Silver Springs, Maryland, USA

Smokeless tobacco products expose adult and youth tobacco users to various addictive and carcinogenic constituents that can cause long-term nicotine dependence and oral cancers. In this study, nicotine, benzo[a]pyrene (B[a]P), N′-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), acetaldehyde, crotonaldehyde, formaldehyde, moisture, and pH levels in 16 smokeless tobacco products were measured on a wet-weight basis (wwb). In addition, change in analytical variability with increasing replicate measurements was assessed. Total nicotine in the products varied from 6.2 to 35.5mg/g. The percentage of total nicotine in the unprotonated form ranged from 0.1 to 62%; whereas moisture content varied from 7.4 to 57%. The quantities of harmful and

potentially harmful constituents (HPHCs) ranged from 0.46–179.9 ng/g for B[a]P, 270–12206 and 81–20716 ng/g for NNN and NNK, respectively, and 0.33-6.85 and 0.13–5.67 μg/g for acetaldehyde and formaldehyde, respectively. This study shows wide variation in smokeless tobacco product HPHC quantities. The results also show that analytical variability stabilizes after seven replicate measurements.

81. NICOTINE AND FREE- (UNPROTONATED) NICOTINE IN SEVERAL NOVEL SMOKELESS NICOTINE PRODUCTS: HERBAL SNUFF, TOOTHPICKS, LOZENGES, GUM, AND TOBACCO-FREE POUCHES. Robert TYX, Hang Tran, Liza Valentin-Blasini and Clifford H. Watson; Centers for Disease Control and Prevention, Atlanta, GA, USA

Nicotine is a highly addictive ingredient in tobacco products which often results in dependence with associated negative health effects. Heavy focus has been on reducing the prevalence of smoking, and while traditional smoking has seen a decline in the United States, the use of other tobacco products is increasing. Several newly introduced nicotine delivery products, some in non-traditional forms, have recently appeared on U.S. markets. These include nicotine-containing pouches, lozenges, toothpicks, chewing gums, and tobacco-free herbal snuff. Many of these products come in flavored forms, potentially suggesting a marketing shift towards younger users. Thus, it is crucial to assess the composition of these products to assist regulatory authorities in their decision-making process. Nicotine, pH, free-nicotine, and moisture content was analyzed for 70 commercial products of several product types. Statistical comparisons of chemical analyses were performed between product groups. Lozenges had the lowest total nicotine content, while nicotine pouches had the highest pH and total nicotine. Free nicotine, as a percentage of the total nicotine, was also highest for nicotine pouches and the lowest in nicotine lozenges. Higher strength-advertised products had higher nicotine content than lower strength products, but in all cases where numbers were stated, nicotine content was measured as less than the stated amount. In conclusion, the nicotine strength and availability varied by product types, often with a range of nicotine available. Nicotine levels on the packages were generally accurate and no products had nicotine higher than advertised. Nicotine toxicity based on the levels of nicotine and pH (and therefore, free-nicotine), flavor abundance, and the benevolent appearance of the products may be of some concern to regulatory authorities.

82. METHOD MODIFICATIONS AND VALIDATION TO EXPAND SCOPE OF CRM No 95 TO ANALYZE SELECT AROMATIC AMINES IN HEATED TOBACCO PRODUCTS. Nicholas MCCUTCHEON, Matt Melvin,

Weiling Li, Regina Ballentine, Niti H. Shah and Yezdi Pithawalla; Altria Client Services, Richmond, VA, USA

Heated Tobacco Products (HTPs) constitute a growing product category, as evidenced by increasing commercialization of products such as IQOS, glo, and PLOOM in markets worldwide. HTPs contain a tobacco substrate that is heated to low temperatures (<350°C), as opposed to burning it in a conventional cigarette. Heating tobacco in an HTP prevents high temperature pyrolysis and combustion reactions and reduces generation of harmful and potentially harmful constituents (HPHCs), such as aromatic amines (AAs), which include 1-Aminonaphthalene (1-NA), 2-Aminonaphthalene (2-NA) and 4-Aminobiphenyl (4-ABP). Due to significantly lower concentrations of AAs in HTPs, CORESTA recommended method (CRM N° 95) was modified to be fit for the determination of these low-level AAs in HTPs. For this new HTP method, several changes were made to processes in CRM N° 95, such as changing the solvent system from dichloromethane to toluene, implementing a new derivatization procedure, and lowering the limit of quantification. The method was validated using a novel heated tobacco capsule (HTC) prototype, consisting of a durable hand-held battery-operated device (BVR 3.2) and a disposable tobacco-containing capsule which is inserted into the device. The method validation data demonstrated conformance to acceptance criteria with percent recoveries for all analytes in the matrix being between 75% and 125% and all repeatability measurements having %RSD ≤ 20%. In addition, the concentrations of AAs in aerosols of the novel HTC prototype were significantly lower than those in cigarette smoke. Considering the absence of standardized methods for HTPs, the results of our validation study show the suitability and reliability of this modified method in measuring and reporting of AAs in HTPs.

83. DETERMINATION OF AEROSOL MASS AND FIVE PRIMARY CONSTITUENTS IN AEROSOLS GENERATED FROM HEATED TOBACCO PRODUCTS. Anthony BROWN[1], Sandra Ingram[2], Krystal Soler[2], Nick McCutcheon[1], Matt Melvin[1], Yezdi B. Pithawalla[1] and Weiling Li[1]; [1]Altria Client Services, Richmond, VA, USA, [2]Lancaster Professional Scientific Staffing, Richmond, VA, USA

In 2021, CORESTA conducted a proficiency study for the determination of aerosol mass, propylene glycol, glycerin, and nicotine in aerosols generated from heated tobacco products (HTPs) to determine and recommend a suitable method to

measure these components. Due to most laboratories using similar methodology based on ISO 24199 (CRM 84) and ISO 20778 (intense puffing regime), the study was considered to be a proficiency and a collaborative study. However, the study did not include the determination of two additional primary HTP aerosol constituents, water and menthol. Our efforts focused on expanding the method scope to include the two additional constituents. The sample trap was modified to include a Cambridge pad followed by an impinger to capture the breakthrough of water and menthol, which ranged from 15% to 30%. The modified method was validated using a novel heated tobacco capsule (HTC) prototype, which consists of a durable hand-held battery-operated device and a disposable tobacco-containing capsule that is inserted into the device. Method modifications and validation results for the determination of propylene glycol, glycerin, nicotine, water, and menthol from the HTC prototypes will be presented. The mean sample recoveries for all analytes were 86.2% - 103.0%. The %RSD of repeatability for each day were ≤ 14.6% for all samples. The %RSD of intermediate precision over 3 days was ≤ 9.0%. These method validation elements all met their pre-determined acceptance criteria. This validation data demonstrates that the modified method is suitable and reliable for measuring aerosol mass and the five primary constituents in aerosols generated by HTPs.

84. QUANTITATIVE DETERMINATION OF BENZO[A]PYRENE IN AEROSOL EMITTED BY HEATED TOBACCO PRODUCTS USING GAS CHROMATOGRAPHY-MASS SPECTROMETRY. Suci INDRAYANI, Anggra Hardiansyah, Ari Wieliyani and Eka U. Mulyana; Filtrona Scientific Services, Surabaya, East Java, Indonesia

Heated tobacco products (HTPs) are tobacco products that heat tobacco-filled sticks wrapped in paper to generate a nicotine-containing aerosol using an electronic device. Based on the FDA's list, 93 analytes are defined as harmful and potentially harmful constituents (HPHCs) found in tobacco smoke and tobacco product. Twenty analytes have a mandatory reporting requirement, including Benzo[a]pyrene for the polycyclic aromatic hydrocarbons (PAHs) group. This study presents a quantitative determination method for analyzing Benzo[a]pyrene in aerosol emitted from HTPs using Gas Chromatography-Mass Spectrometry (GC/MS). Benzo[a]pyrene is a highly carcinogenic compound found in tobacco smoke. The developed method can serve as a reliable tool for assessing the impact of HTPs aerosol on human health and for regulatory purposes. Aerosols are collected using a linear smoking machine with a Cambridge filter

holder containing 44-mm filter pads under the Health Canada Intense regime. Smoke yields are extracted using cyclohexane, followed by an SPE clean-up using NH_2 cartridges and evaporated before analyzed by GC/MS using a selective PAH column. The validation demonstrated reliable support based on parameters such as selectivity, accuracy, precision, linearity, and LOD/LOQ.

85. COMPARISON OF HPHCS IN AEROSOL GENERATED FROM A NOVEL HEATED TOBACCO CAPSULE (HTC) PROTOTYPE TO HPHCS IN CONVENTIONAL CIGARETTE SMOKE. James A. SKAPARS, Weiling Li, Yezdi B. Pithawalla, Kyle W. Pfeiffer, Matt S. Melvin, Timothy L. Danielson; Altria Client Services, Richmond, VA, USA

Heated Tobacco Products (HTP) contain a tobacco substrate that is heated to low temperatures (below 350°C), resulting in an inhalable nicotine-containing aerosol. The objective of this work is to compare concentrations of select harmful and potentially harmful constituents (HPHCs) in the aerosols generated by a novel heated tobacco capsule (HTC) prototype to their corresponding concentrations in smoke generated from conventional cigarettes (University of Kentucky 1R6F Certified Reference Cigarette). The HTC prototype consists of a hand-held battery-operated device (BVR 3.2) and a disposable tobacco-containing capsule that is inserted into the device. The selection criteria employed to identify the 50+ HPHCs, compared across the HTC prototype and conventional cigarettes, will be discussed. Comparisons of the HPHC data will be presented on a per unit and normalized per nicotine basis. Data presented will demonstrate significant reductions (80-99%) for most HPHC chemical classes such as carbonyls, volatile organic compounds, aromatic amines, carbon monoxide, and polycyclic aromatic hydrocarbons in the aerosols generated from the HTC prototype compared to cigarette smoke. The significant reduction in HPHCs substantiates that heating tobacco in the HTC prototype prevents high temperature pyrolysis and combustion reactions that occur when tobacco is burned in a conventional cigarette. The data indicates that Adults 21+ who smoke (AS) should significantly reduce their exposure to HPHCs by switching to use of the HTC prototype.

86. CREATING AN AI LLM TOBACCO DATABASE. Kevin BURD[1] and Ryan Selby[2]; [1]Chemular Inc, Hudson, MI, USA, [2]Generative AI Solutions, Vancouver, BC, Canada

In the rapidly evolving landscape of tobacco regulation, staying abreast of the latest research, policies, and legal developments is paramount for regulatory

professionals. The vast and continuously expanding body of literature on tobacco products presents a unique challenge in accessing, organizing, and harnessing the information available. We propose the establishment of an Artificial Intelligence (AI)-driven Large Language Model (LLM) database specifically tailored to support regulatory professionals in navigating and leveraging published literature on tobacco products. The AI LLM database aims to address the gaps and inefficiencies in accessing and utilizing tobacco products literature by leveraging the power of machine learning and natural language processing techniques. We will provide an overview of the key components and benefits of the proposed database, highlighting its potential to revolutionize the way regulatory professionals engage with tobacco products literature. The AI LLM database will offer a solution by employing advanced algorithms to curate, categorize, and analyze the extensive literature on tobacco products. The database can identify patterns, detect trends, and uncover relationships within the literature, providing regulatory professionals with a deeper understanding of tobacco products' legal, scientific, and public health aspects. Such insights can assist in developing effective regulatory frameworks, evaluating the impact of existing policies, and identifying areas for further research. By harnessing the power of AI, machine learning, and natural language processing, the proposed database has the potential to transform how regulatory professionals access, analyze and utilize published literature. This innovative tool can enhance decision-making, facilitate evidence-based policy development, and support the continuous advancement of tobacco regulation in an increasingly complex and dynamic landscape.

87. EFFECT OF TIME IN THE PYROLYSIS OF HEET TOBACCO WITH SBA-15 FIBROUS AND SBA-15 PLATELETS. Marbel BELTRÁN[1], Deseada Berenguer[1], Antonio Marcilla[1] and Michael Cairns[2]; [1]Alicante University, Alicante, Spain, [2]Strathclyde University, Scotland, UK

The effect of two mesoporous SBA-15 catalysts with fibrous and platelet morphologies on the toxicity of HNB tobacco aerosols has been studied in laboratory experiments using blends of 25 wt% SBA-15 catalysts and 75 wt% Heet Tobacco. TGA and PY/GC/MS experiments under inert and oxidizing atmospheres were studied. Additionally, smoking experiments were run with mixtures of Heet tobacco and fibrous SBA-15.

Kinetic parameters have been obtained by the simultaneous correlation of the

TGA results at the four heating rates studied. Both catalysts provoked reductions in the intensity of the first DTG peak.

The PY/GC/MS results confirmed significant overall reductions in the quantity of volatiles evolved under both atmospheres, which were assigned mainly to aldehydes, nicotine and glycerol. Under oxidative atmosphere larger overall reductions observed are attributed mainly to the oxidation of glycerol. Lower amounts of many chemical families were obtained when using the SBA-15 Fiber blend as compared to the Platelet blend.

TGA and PY/GC/MS experiments showed that heating rates and pyrolysis times do influence the volatiles evolved. Higher heating rates lead to the decomposition occurring at slightly higher temperatures in TGA. PY/GC/MS experiments showed higher reductions at low pyrolysis times, with both catalysts under both atmospheres. The lower reductions obtained at high pyrolysis times were relatively uniform between both catalysts under inert atmosphere, however under oxidative conditions, the SBA-15 Platelets became dramatically less effective.

Smoking experiments with different contents of the SBA-15 Fiber blend showed a larger than 60 % reduction of toxic compounds for the 25 wt% SBA-15/Fiber blend, thus drastically reducing the toxicity of this already reduced toxicity smoking product.

88. IN VITRO CYTOTOXICITY AND MUTAGENICITY ASSESSMENT OF A NOVEL HEATED TOBACCO CAPSULE (HTC) PROTOTYPE IN COMPARISON TO COMBUSTIBLE CIGARETTES. Utkarsh DOSHI, Britt Langston and K. Monica Lee; Altria Client Services, Richmond, VA, USA

Heated tobacco products (HTPs), that do not burn tobacco, may contain fewer harmful and potentially harmful constituents (HPHCs) than combustible cigarettes and hence offer a potentially reduced risk alternative to adults (age 21+) who smoke cigarettes and are unable or unwilling to quit. We conducted toxicological assessments of a novel heated tobacco capsule (HTC) prototype which consists of a durable hand-held battery-operated device (BVR 3.2) and a disposable tobacco-containing capsule that is inserted into the device. Capsules containing different prototype tobacco blend variants were evaluated using standardized in vitro mutagenicity (Ames) and cytotoxicity (Neutral Red

Uptake-NRU) assays and results were compared, on a per nicotine basis, to those obtained from testing combustible reference cigarettes (3R4F and 1R6F). The mainstream smoke/aerosol samples were generated under the Health Canada Intense (HCI) smoking regime and both total particulate matter (TPM) and gas-vapor phase (GVP) were collected and subjected to toxicological assessments. In the Ames assay, TPMs from cigarettes were mutagenic in bacterial strains TA98, TA100 and TA1537 in presence of S9, whereas TPMs from all HTC prototype blend variants were not mutagenic even when tested at concentrations greater than the assay recommended maximum of 5 mg/plate. The GVP fraction from both combustible cigarettes and prototype HTCs were negative for mutagenicity in the Ames assay. In the NRU assay, both TPM and GVP from cigarette showed concentration dependent toxicity in lung A549 cells, whereas TPM and GVP from prototype HTCs showed substantially lower cytotoxicity (greater than 70% reduction compared to cigarette smoke). Overall, HTC prototype blend variants consistently demonstrated significantly lower toxicity potential than cigarette smoke.

89. ON-DEVICE TOPOGRAPHY RECORDING IN A PROTOTYPE HEATED TOBACCO CAPSULE (HTC) SYSTEM. Kevin BALL, Raymond Lau, Zack Blackmon, Jianmin Liu, Yezdi B. Pithawalla and Jeff Edmiston; Altria Client Services, Richmond, VA, USA

Puff topography (PT) includes measures of inhaled tobacco product use behaviors, facilitating understanding of consumer use behavior, exposure to toxicants, and product abuse liability. PT methods traditionally include video capture and external topography devices. Such external devices are affixed to the product (typically via mouthpiece) potentially limiting naturalistic PT data under real-world extended use conditions. Furthermore, the mouthpiece may alter normal puffing behavior and sensory experience of study participants. Needed now is an unobtrusive method of measuring PT that can allow for natural puffing behavior and sensory experience. We present an on-device PT recording tool within a prototype heated tobacco capsule (HTC) system, which measures PT parameters (i.e., flow rate, puff duration, and inter-puff interval) without affecting the product use experience.

We will present PT data generated during a nicotine pharmacokinetics (PK) study on a novel HTC prototype to demonstrate applicability and validity of our on-device PT tool. The HTC prototype consists of a durable hand-held battery-

operated device (BVR 3.2) and a disposable tobacco-containing capsule that inserts into the device. PT data were collected from adults who smoke (ages 21+) from two separate product trials during the PK study (2-hour periods & single session, both *ad-libitum*) will be shared. Across the four prototype HTC capsule variants evaluated, mean puff volumes ranged from approximately 48 to 61 mL, mean puff durations ranged from 2.0 to 2.4 secs, and mean inter-puff intervals ranged from 16 to 20 secs. On-device puff topography is a valid and unobtrusive way to collect detailed puff data to better understand consumer product use.

90. CHARACTERIZATION OF NICOTINE PHARMACOKINETICS FROM USE OF A NOVEL HEATED TOBACCO CAPSULE PROTOTYPE IN ADULTS WHO SMOKE. Jianmin LIU, Jingzhu Wang, Jeffery S. Edmiston, Raymond W. Lau and Yezdi B. Pithawalla; Altria Client Services, Richmond, VA, USA

Heated tobacco products (HTPs) may offer a potentially reduced-risk alternative to adults 21+ who smoke cigarettes (AS) and are unable or unwilling to quit. In this study, we characterized the nicotine pharmacokinetics (PK) and subjective measures of a novel heated tobacco capsule (HTC) prototype in AS. The HTC prototype consists of a hand-held battery-operated device and a disposable tobacco-containing capsule that is inserted into the device. We conducted a randomized, crossover study to characterize nicotine PK of prototype capsules containing menthol and non-menthol tobacco blend variants, relative to the subject's usual brand cigarette (UBC) in 20 menthol and 24 non-menthol AS. To facilitate acclimation with the novel HTC prototype, subjects were allowed to use up to 5 capsules for each prototype tobacco blend variant during a product trial, and up to 2 capsules for each prototype the day prior to the PK session. The PK assessments were conducted during a single use session of the HTC prototype or UBC. Subjects also completed questionnaires on "urges to smoke", "craving cigarettes", and rated the products for "pleasant" and "satisfying" using visual analog scales (VAS). The non-baseline adjusted average plasma nicotine C_{max} values ranged from ~13-18 ng/ml for the HTC prototypes and were ~24 and ~19 ng/ml for menthol and non-menthol UBCs, respectively. The "pleasant" and "satisfying" VAS scores for the prototype non-menthol HTCs used in this study were statistically significantly lower compared to the UBC. Reductions in "craving a cigarette" were significantly lower for the prototype menthol HTC compared to UBC.

Overall, the nicotine uptake during use of the HTC prototypes suggests they have the potential to be acceptable substitutes for cigarettes.

91. CIGARETTE REDUCTION AND SWITCHING BEHAVIOR BY MENTHOL CIGARETTE PREFERENCE AND MENTHOL HEATED TOBACCO PRODUCT USE AMONG ADULTS WHO SMOKE CIGARETTES. Joshua KARELITZ, Hui Cheng, Elizabeth Becker and Jenna Leighty; Altria Client Services, Richmond, VA, USA

Objectives: Heated tobacco products (HTPs) deliver nicotine with significantly lower toxicant levels relative to combustible cigarettes. Availability of a portfolio of HTPs (i.e., menthol and non-menthol versions) may help adults who smoke reduce consumption of or completely switch away from combustible cigarettes. We examined whether smoking reduction or switching is associated with menthol versus non-menthol HTP stick use or menthol/non-menthol cigarette preference.

Methods: In a six-week open-label study of HTP, adults ages 21-64 (n=615) who smoked cigarettes and were not planning to quit were offered free choice of a portfolio of HTPs (one non-menthol and two menthol varieties) to use at home ad-libitum. Menthol/non-menthol cigarette preference was assessed upon study entry (374 menthol; 241 non-menthol). HTP and cigarette use were measured daily.

Results: At Week 6, there was a statistically significantly greater reduction in cigarettes per day among menthol versus non-menthol smokers (-77% vs -61%). Similarly, a significantly greater proportion of menthol versus non-menthol smokers completely switched from cigarettes to HTP (47% vs 30%). Most participants—regardless of menthol cigarette preference—used menthol HTP sticks in Week 6 (93% of menthol smokers; 63% of non-menthol smokers). We observed a significant interaction between baseline menthol cigarette preference and proportion of menthol HTP stick use at Week 6 on the likelihood of switching at end of study. Non-menthol smokers were significantly more likely to switch when using menthol HTP. However, menthol smokers had consistent levels of switching.

Implications: Menthol HTP use was associated with switching and cigarette

reduction. Continued availability of menthol HTPs may offer harm reduction potential for adults who smoke and are not interested in quitting, regardless of preference for menthol or non-menthol cigarettes.

92. TOBACCO USE, PERCEPTIONS, AND CHARACTERISTICS OF ADULTS WHO USE IQOS® IN THE UNITED STATES: FINDINGS FROM A CROSS-SECTIONAL STUDY. Hui CHENG[1], Brendan Noggle[1], Andrea R. Vansickel[1], Edward G. Largo[1], Pierpaolo Magnani[2] and Annie Heremans[2]; [1]Altria Client Services, Richmond, VA, USA, [2]Philip Morris Products, Lausanne, Switzerland

Background: IQOS®, a smoke-free heated tobacco product, was introduced in the United States (US) in 2019 and was authorized by the US Food and Drug Administration as a modified risk tobacco product (MRTP) in 2020. The aim of this study was to describe selected sociodemographic characteristics of adults who used IQOS® (AUI), tobacco use patterns relevant to IQOS® use (e.g., tobacco use history, exclusive and dual use, switching from cigarette smoking, etc.), risk perceptions of IQOS®, and understanding of IQOS® MRTP messages among AUI.

Methods: The IQOS® cross-sectional Postmarket Adult Consumer Study was a study of AUI aged 21 and older, recruited from an IQOS® consumer database via direct mail and emails. Participants completed the online survey between September and November 2021.

Results: A total of 645 current and 43 former AUI who had used at least 100 IQOS® HeatSticks prior to the assessment completed the survey. Of the 688 participants, 61% were males; 73% were non-Hispanic white; the mean age was 45. The vast majority (99%) of AUI had ever smoked combusted cigarettes before first trying IQOS®. At the time of assessment, 49% were smoking after an average of one year of IQOS® use. Among those who were still smoking, 83.6% smoked fewer cigarettes compared to before first trying IQOS®. Among all AUI, over 80% had never used a cessation treatment or had not used it in the past 12 months. Approximately 80% of AUI had correct understanding of the MRTP message.

Conclusions: This study is the first to provide evidence that IQOS® can help individuals who smoke completely switch away from cigarettes or to reduce smoking in the US.

93. AN ASSESSMENT OF DEPENDENCE IN ADULT SMOKERS SWITCHING FROM COMBUSTIBLE CIGARETTES TO THE RELX INFINITY ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS) OVER 8 WEEKS. Donald GRAFF[1] and Ian M. Fearon[2]; [1]Cheerain HK Limited, Hong Kong, China, [2]whatIF? Consulting Limited, Harwell, UK

The Penn State Cigarette/Electronic Cigarette Dependence Index was used to evaluate dependence in subjects who switched from combustible cigarettes to the RELX Infinity ENDS in an 8-week, randomized, parallel-cohort study of adult smokers.

All subjects smoked their own-brand cigarettes through baseline and were randomized to use an Infinity ENDS with a prototype tobacco or menthol flavored e-liquid based on their own-brand combustible cigarette flavor, both flavored e-liquids, or to continue smoking. Subjects returned to the clinic every 2 weeks to complete the questionnaire and other study assessments. Responses to the questionnaires were used to calculate total scores (range 0-20) that were indexed to dependence level (not, low, medium, high).

Of the 150 subjects who completed the study in the Infinity ENDS cohorts, 73 were classified at baseline as having a “medium” dependence level, 58 as “high,” and 19 as “low”. Compared to baseline PSCDI mean total scores, PSECDI mean total scores for the Infinity ENDS cohorts were statistically significantly lower by Week 2 and continued to be approximately 20%-30% lower at Week 8. Reductions in craving, urge, and feelings of irritability and nervousness/restlessness, were the primary contributors for the observed differences. By Week 8, PSECDI total scores were lower than baseline PSCDI total scores in 67% of the completers while 23% experienced an increase and 11% experienced no change in total score. Furthermore, a greater percentage experienced a decrease in dependence level (49%) than experienced an increase (10%) or no change (41%).

Smokers switching from combustible cigarettes to the Infinity ENDS reported being less dependent on the ENDS product. Additional analyses are ongoing to identify potential factors which may predict dependence on Infinity ENDS products.

94. IN VITRO GENOTOXICITY EVALUATION OF JUUL ENDS, MARKETED ENDS, AND REFERENCE CIGARETTES. Guy LALONDE[1], Christina Sulaiman[1], Pamela Heard[2], Vyom Sharma[2], Leon F. Stankowski, Jr.[2] and Michael Oldham[1]; [1]Juul Labs, Inc, Washington, DC, USA, [2]Charles River Labs, Skokie, IL, USA

In vitro toxicology studies are a critical component of regulatory submissions of electronic nicotine delivery system (ENDS) products.

Ames assays and micronucleus (MN) by flow cytometry assays using e-liquid and aerosol condensates produced under non-intense and intense puffing conditions were used to evaluate the mutagenic and genotoxic potential of nine JUUL ENDS products, eleven marketed ENDS products, and two reference cigarettes, 3R4F and 1R6F.

Completed studies indicate that all JUUL products tested negative in both the Ames and MN assays, for both e-liquid and aerosol condensates produced under non-intense and intense puffing conditions (one product is still pending). Of the eleven marketed ENDS tested, three showed positive results (one in the Ames assay and two in the MN assay) and one showed equivocal results when e-liquids were tested. When aerosol condensates were tested, one showed positive results in the Ames assay under intense conditions and one showed an equivocal result in the MN assay under non-intense conditions. Condensates from the reference cigarettes 3R4F and 1R6F tested positive in the Ames and MN assays under all conditions, except for the 3R4F non-intense condensate in the MN assay, which showed equivocal results.

In conclusion, these studies indicated that, under the test conditions, the JUUL products assayed were not found to be mutagenic or genotoxic. In contrast, five of the eleven marketed ENDS were either positive or equivocal

in one of the genotoxicity assays. Reference cigarettes 3R4F and 1R6F were positive in both assays. These results emphasize the importance of in vitro toxicology testing for ENDS products to evaluate the differences in genotoxicity responses observed in the Ames and MN assays among marketed ENDS products.

95. TOXICOLOGICAL POTENTIAL OF TWO JUUL ENDS PRODUCTS RELATIVE TO REFERENCE CIGARETTE 3R4F AND FILTERED AIR IN A 90-DAY NOSE-ONLY INHALATION TOXICITY STUDY. Guy LALONDE[1], Rahat Wadhwa Desai[2] and Charles L. Gaworski[3]; [1]Juul Labs, Inc, Washington, DC, USA, [2]Syngenta Canada, Arva, ON, Canada, [3]Kozmin Consulting, Flat Rock, NC, USA

Electronic nicotine delivery systems (ENDS) are increasingly recognized as one alternative along a spectrum of risk reduction alternatives for those who would otherwise continue to smoke cigarettes. The potential toxicity of two marketed JUUL ENDS products: JUUL Device and JUULpods in Virginia Tobacco (VT3) and Menthol (ME3) flavors at 3.0% nicotine concentrations was assessed in a 90-day rodent inhalation study performed in general accordance with OECD 413 and compared to that of reference cigarette 3R4F and of a Filtered Air (FA) control. Target aerosol mass exposure concentrations [0 µg/L (FA), 250 µg/L for 3R4F, and 1400 µg/L for VT3 and ME3] were achieved in the respective exposure groups. Systemic exposure was confirmed with plasma concentrations of propylene glycol, nicotine and cotinine. Mean body weight reductions, with corresponding reductions in food consumption, were more pronounced in 3R4F than VT3 and ME3 animals and in males compared to females. At the end of exposures, 3R4F animals showed evidence of pulmonary inflammation in an increase in mean body weight-normalized lung weights, in bronchoalveolar lavage fluid analysis (elevated lactate dehydrogenase, pro-inflammatory cytokines and neutrophils) and in histopathology (minimal to marked histopathological changes throughout the respiratory system). In contrast, ME3 and VT3 exposed animals showed minimal to mild squamous metaplasia of the larynx. In conclusion, despite exposure to 5.5x higher aerosol mass concentrations and up to 2x higher plasma nicotine and cotinine levels, JUUL ME3 and VT3

product aerosols resulted in significantly less toxicity compared to 3R4F smoke.

96. A RELATIVELY LOW NICOTINE STRENGTH E-LIQUID THAT REDUCES THE URGE TO SMOKE AS MUCH AS CIGARETTES. Ed CARMINES[1], Lise Fraissinet[1], Karen Carmines[1] and Naama Levy-Cooperman[2]; [1]Chemular Inc, Hudson, MI, USA, [2]Altreos Research Partners, Toronto, ON Canada

A pharmacokinetic and pharmacodynamic evaluation of a new 3 and 6 mg/ml nicotine e-liquid (OG Blue from Liquid Labs LLC) was conducted comparing the products to own brand cigarettes and 2 mg nicotine gum. The randomized, open label, crossover clinical study was completed in 27 smokers to measure nicotine plasma levels and subjective effects of product use. Subjects used the products under controlled conditions and blood was collected prior to and for up to 180 minutes following use. The ability of the products to satisfy the urge to smoke over the short term was assessed using the "Urges to Smoke" question in the Tobacco/Nicotine Withdrawal Questionnaire (TNWQ), and positive effects were assessed using the "Is the product 'Pleasant' right now?" question in the Direct Effects of Product Questionnaire (DEPQ); both were administered as 100-point VAS. Peak (Cmax) and overall (AUC) nicotine exposure for the 2 e-liquids was less than the 2 mg nicotine gum and significantly lower than own-brand cigarettes. Overall, the 3 mg/ml and 6 mg/ml products were rated to be similarly pleasant and effective in reducing the urge to smoke compared with own-brand cigarette, despite significantly lower nicotine exposure.

97. YOUTH UNDERESTIMATE THE HEALTH AND ADDICTION RISKS OF TOBACCO PRODUCTS. Ed CARMINES[1], Lise Fraissinet[1] and Azure Steele[2]; [1]Chemular Inc, Hudson, MI, USA, [2]M/A/R/C Research, High Point, NC, USA

Perception and intention studies are required by the FDA to assess new tobacco products. These studies are generally conducted as surveys of smokers, former smokers and non-smokers across the United States. A group of 21 up to 25 year olds is over sampled to more accurately estimate the impact the product might have on young never smokers. Approximately 4500 subjects are routinely included in the study. An attempt is made to match the U.S. Census to make sure that all potential users are represented. Study participants are shown labels of

the new products and asked about their perceptions of the health and addiction risks using validated questionnaires. In our approach we first show participants different types of tobacco products including cigarettes, smokeless tobacco, e-cigarettes, and nicotine replacement therapy products and assess where on the health and addiction continuum the participants place the products. When compared to the never users in the general population, young participants (legal age up to 25 years of age) consistently underestimate the health and addiction risks associated with the various tobacco products. Current smokers also underestimate the risks while former smokers perceive the risks consistent with the general population. The overall general population order of perceived health risks is cigarettes > e-cigarette = smokeless tobacco > NRT. Depending on the study populations, vapor users tend to perceive e-cigarettes to have less health risks than smokeless tobacco. Smokeless tobacco users generally perceive the health risk of smokeless to be less than e-cigarettes. The new modern oral nicotine pouch products are perceived to have health risk equivalent to NRT.

98. RAPID IN VITRO TOXICOLOGICAL SCREENING USING TOXTRACKER TO DETERMINE THE EFFECT OF REPEATED FREEZE/THAW OF COMBUSTIBLE CIGARETTE EXTRACT. Katarina ALEKSA[1], Sean Oh[1], Ed Carmines[2], Manoj Misra[2], Bonnie Coffa[2] and Giel Hendrik[3]; [1]Labstat International Inc, Kitchener, ON, Canada, [2]Chemular Inc, Hudson MI, USA, [3]Toxys, Leiden, Netherlands

Combustible cigarette extracts (CCE) are stored at -80°C to preserve sample integrity. Sample shipping and repeated freeze/thaw cycles prior to testing may lead to changes in the chemical composition through the formation of ice-water interfaces, phase separation, pH induced changes and chemical degradation may produce inaccurate results in chemistry and in *in vitro* toxicological assays. We sought to determine the impact of repeated freeze/thaw on CCE at the DNA level using the stem cell based ToxTracker© reporter assay.

Combustible reference cigarettes (1R6F) (n=3) were smoked (Health Canada standard regime). Particulate phase (PP), gas-vapor phase (GVP) and the 1:1 combined phase (PP+GVP)] were collected and evaluated in the ToxTracker© assay. Samples were tested within 1hr of sample generation or after 3 freeze/ thaw cycles. Cells were incubated for 24hr (both +/- S9). Green-fluorescence protein (GFP) reporter gene induction and cytotoxicity was assessed using flow cytometry.

Fresh PP (-S9) samples induced a 35-fold increase in Srxn1(indicative of oxidative stress) and a 10-fold increase in Ddit3 (indicative of protein damage) at 200 µg/mL; addition of S9 decreased Srxn1 to 12-fold GFP-induction in fresh PP. GFP-induction was not observed in fresh GVP samples. Fresh PP+GVP (+S9), induced Srxn1 and Blvrb (indicative of oxidative stress) 10 and 4-fold, respectively at 200 µg/mL and no effect on Ddit3. Sample freeze and thaw decreased Srxn1 from 35 to 20-fold while Ddit3 increased from 10 to 21-fold (-S9). No significant difference between fresh (+S9) and freeze/thaw (+S9) for PP or PP+GVP samples was observed.

This data indicates that sample freeze/thawing can alter *in vitro* toxicity results in the ToxTracker© assay. A "fresh" sample should be used for the ToxTracker© assay to eliminate unintended potential sample manipulation effects. This allows for the test system to be treated with a sample that more closely resembles the chemical profile produced immediately after sample collection and representative of normal smoking behavior.

99. APPLICATION OF A RAPID IN VITRO TOXICOLOGICAL SCREENING (TOXTRACKER©) TO DETERMINE THE EFFECT OF FLAVORS IN SNUS PRODUCTS. Ed CARMINES[1], Katarina Aleksa[2], Sean Oh[2], Manoj Misra[1], Bonnie Coffa[1] and Giel Hendriks[3]; [1]Chemular Inc, Hudson MI, USA, [2]Labstat International Inc, Kitchener, ON, Canada, [3]Toxys, Leiden, Netherlands

Snus is an oral tobacco derived nicotine product that is sold in flavored pre-packages. Snus is traditionally sold as tobacco flavored. The potential impact of flavors on toxicity is unknown. Regulatory assays such as Ames, neutral red uptake (NRU), and *in vitro* micronucleus (ivMN) have not been traditionally used to differentiate the possible toxicological impact of the different flavor systems. ToxTracker is a stem cell-based reporter assay that provides mechanistic insights into the mode-of-action of products.

The objective of this study was to utilize ToxTracker to determine if the toxicity of different snus flavors can be differentiated and if they have different reporter gene induction profiles. The CORESTA snus reference product CRP 2.1 and 3 different flavored (traditional, menthol, and wintergreen from the same brand) commercially available snus products were extracted with DMSO and concentrations (up to 1.6 µg/mL) applied to each of the six reporter cell lines (+/- S9) in the ToxTracker assay. Reporter gene (GFP) induction and

cytotoxicity were assessed by flow cytometry following a 24 hr incubation. The induction profile for all products tested, including CRP 2.1, showed a 3 to 4-fold induction of the Ddit3 reporter gene in the absence of S9 indicating that the products could potentially damage proteins. Among flavor assessment, a 2-fold increase in the Srxn1 (indicator for oxidative stress) reporter gene was observed only with the wintergreen snus product in the absence of metabolic activation. However, there was no reporter gene induction in the presence of metabolic activation. None of the concentrations tested has an impact on cellular cytotoxicity indicating that the doses were not toxic, and the concentration range could be increased.

This preliminary work suggests that under the tested experimental conditions, ToxTracker is capable of distinguishing the effect of wintergreen flavor compared to traditional or menthol flavor.

100. NEUTRAL RED UPTAKE TESTING OF ORAL NICOTINE PRODUCTS AFTER EXTRACTION WITH ARTIFICIAL SALIVA.
Mariano SCIAN, Emma Press, Jordan Jones, Lukas Braia, Lonneke Palmer, Joelle Carbonelle, Kirsten Lassiter and Lynn McFadden; Enthalpy Specialty Labs, Richmond, VA, USA

Oral nicotine-containing products have become popular as reduced harm product alternatives in comparison to other products such as cigarettes. In this study, a market map of oral products was conducted using the Neutral Red Uptake Assay (NRU) and mouse fibroblast BALBc/3T3 cells. Market available products were purchased from various stores and extracted with artificial saliva using a standardized extraction method where products were extracted to generate a 1:10 w/v extract. The final extract was assumed to have a 100 mg/ml concentration. All extracts were tested for sterility prior to NRU testing. The types of oral nicotine products tested included nicotine pouches, tobacco pouches, and snuff, which included mint and fruit flavors of various market products. NRU assays were conducted following OECD guidelines. BALBc/3T3 cells were exposed to 8 different concentrations of extract (0.1, 0.5, 1, 2, 4, 6, 8, 10 mg of product/mL). The vehicle concentration did not exceed 10% of the dosing volume. Osmolarity and pH were measured in all dosing solutions. Many of the nicotine products tested were not considered cytotoxic under the conditions of the assay based on accepted guidelines. However, several tested products resulted in < 70%

viability at one or more doses tested. In particular, some products containing cinnamon were found to be significantly more cytotoxic compared to other products tested. Nicotine content in the extracts was measured using an in-house method. As reduced harm products become more common and available to the public, it is important to understand these products' cytotoxic potential. The work presented here highlights Enthalpy Analytical's capability for extraction and testing of oral nicotine products. Although BALBc/3T3 cells may not be the ideal model cell line, and perhaps using an oral epithelium derived cell line may be more suitable, the data presented here shows that most oral nicotine products tested did not induce cytotoxicity.

101. EVALUATING SUBGINGIVAL MICROBIOME AFTER SWITCHING FROM CIGARETTES TO NICOTINE POUCHES. Jianmin LIU[1], Jingzhu Wang[1], Jeffery S. Edmiston[1], Mohamadi A. Sarkar[1], Maria Gogova[1], Bruce Paster[2], Tsute Chen[2], Hatice Hasturk[2], Kimberly R. Milleman[3], Jeff L. Milleman[3] and Abbie L. Yoder[3]; [1]Altria Client Services, Richmond, VA, USA, [2]The Forsyth Institute, Cambridge, MA, USA, [3]Salus Research, Fort Wayne, IN, USA

Completely switching from cigarette smoking to oral tobacco-derived nicotine products, like nicotine pouches, presents a harm reduction opportunity for adult smokers who are unable or unwilling to quit using tobacco. The objective of this study was to compare subgingival microbiome profiles in adult smokers who switched from cigarette smoking (CS) to using on!® nicotine pouches (NPs) in a single-center, randomized, open-label, parallel-group study. Adult smokers with moderate gingivitis were randomly assigned into NP (n=88) and CS (n=61) groups at baseline. Subgingival plaque was collected by curettes from two separate sites with the highest gingival inflammation determined by modified gingival index and bleeding at baseline. Sampling was repeated at 12- and 24-weeks from the same sites. The V1-V3 regions of 16S rDNA were sequenced using the Illumina platform. Alpha (Shannon and Simpson indices) and beta diversities, differential abundance with bias control, and LefSe analyses were determined. In NP users, no statistically significant changes were observed in alpha and beta diversities at both 12- and 24-weeks compared to baseline. However, using LefSe analysis, health-associated species, e.g., *Rothia aeria, Streptococcus cristatus, Kingella oralis, species of Neisseria* and *Haemophilus*, became

more predominant while relative abundances of putative pathogens, e.g., *Fusobacterium, Saccharibacteria TM7* and *Prevotella* spp. declined at both time points. In the continued smoking group, no statistically significant changes were observed in alpha or beta diversities at 12- or 24-weeks compared to baseline. In these smokers, using differential abundance analysis, one *Capnocytophaga* specy was statistically higher ($p<0.05$) at 24 weeks compared to baseline while some, albeit low abundance, differences using LefSe were observed over time.

102. EFFECT OF ORAL NICOTINE PRODUCT USE ON CIGARETTE REDUCTION AND QUITTING IN A 6-MONTH PROSPECTIVE COHORT STUDY OF ADULT SMOKERS. Elliott MCDOWELL[1], Jason N. Kennedy[1], Stacey A. Bell[1], Michael Feehan[1], Michelle Humphreys[1], Jessica Zdinak[2], Sarah Marking[3], Andrew Joyce[3], Rich Hill[4], Jo-Ann Quinn[4] and Chris Howard[4]; [1]Cerner Enviza, Kansas City, MO, USA, [2]Applied Research and Analysis Company, Richmond, VA, USA, [3]Consilium Sciences, Richmond, VA, USA, [4]Rogue Holdings, Jacksonville, FL, USA

The Rogue® Longitudinal Switching Study assessed oral nicotine product use and switching behaviors among 1,863 adult cigarette smokers in the U.S. over 6 months. The study determined the associations between use of Rogue® Nicotine Products (RNP) and cigarette reduction and quitting. Participants were provided their choice of RNP Pouch (6mg), Gum (4mg), and/or Lozenge (4mg) in 14 flavors and were free to use or not use the products at their discretion. Combustible Cigarette (CC), and other tobacco and nicotine product (TNP) use were assessed at enrollment, and again (along with RNP use) at 1-, 2-, 4-, and 6-month intervals. Among 1,393 participants who completed the study, RNP use was associated with a statistically significant reduction in CC use at 6-months, with 720 participants reducing their cigarettes per day (CPD) by 25-99% (51.7%, $p<0.001$) and 524 participants reducing by 50-99% (37.6%, $p<0.001$). RNP use was also significantly associated with CC quitting, with 185 participants (13.3%, $p<0.001$) quitting at 6-months after baseline. Participants who used more RNP per day smoked fewer cigarettes than those who used less RNP ($p<0.001$), both overall and for each RNP form (pouch, gum, and lozenge). This study conducted in a near real-world setting, provides evidence that switching to use of RNP may have beneficial effects in helping CC users significantly reduce or quit smoking.

103. EFFECT OF FRUIT AND MINT FLAVORED ORAL NICOTINE PRODUCT USE ON CIGARETTE REDUCTION AND QUITTING IN A 6-MONTH PROSPECTIVE COHORT STUDY OF ADULT SMOKERS. Jason KENNEDY[1], Elliott H. McDowell[1], Michael Feehan[1], Stacey A. Bell[1], Michelle Humphreys[1], Sarah Marking[2], Andrew Joyce[2], Jessica Zdinak[3], Rich Hill[4], Jo-Ann Quinn[4] and Chris Howard[4]; [1]Cerner Enviza, Kansas City, MO, USA, [2]Consilium Sciences, Richmond, VA, USA, [3]Applied Research and Analysis Company, Richmond, VA, USA, [4]Rogue Holdings, Jacksonville, FL, USA

The Rogue® Longitudinal Switching Study prospectively assessed the association between predominant fruit and mint flavored oral Rogue® Nicotine Product (RNP) use and switching behavior from combustible cigarettes (CC) among 1,863 adult smokers in the U.S. over 6 months. Participants were provided their choice of RNP Pouch (6mg), Gum (4mg), and/or Lozenge (4mg) in a variety of fruit and mint flavors and were free to use or not use the products at their discretion. Predominant fruit or mint flavor use was defined as >50% of RNP use of that flavor during the past 30 days across all forms. Among 1,393 participants who completed the study, there were a greater number of predominant mint users than fruit users (N=732, 52.6% vs. N=577, 41.4%). At study conclusion, similar proportions of fruit and mint users reduced cigarettes per day by more than 50% (38.8% vs. 39.3%, p=0.85), defined by CC use in the past 30 days. Fruit users were significantly more likely to quit smoking (15.4% vs 11.6%, p=0.044), defined by any CC use in the past 30 days. The number of RNP flavors used, both fruit and mint, was associated with significantly increased percent CC reduction and increased odds of significantly reducing or quitting smoking ($p<0.001$ for both). This study provides evidence that both fruit and mint flavored RNP products may have beneficial effects in helping CC users significantly reduce or quit smoking and that availability of a greater number of flavors may provide additional beneficial effects in a near-real world setting.

104. DESIGN AND EXECUTION OF A NON-SITE-BASED, PROSPECTIVE, MULTI-WAVE COHORT STUDY TO ASSESS PATTERNS OF ORAL NICOTINE PRODUCT USE OVER 6-MONTHS AND ASSOCIATED COMBUSTIBLE CIGARETTE REDUCTION AND QUITTING. Stacey BELL[1], Michelle Humphreys[1], Michael Feehan[1], Elliott McDowell[1], Sarah Marking[2], Andrew Joyce[2], Jessica Zdinak[3], Richard Hill[4], JoAnn Quinn[4] and Chris Howard[4]; [1]Cerner Enviza, Kansas City, MO, USA, [2]Consilium Sciences, Richmond, VA, USA, [3]Applied Research and Analysis Company, Richmond, VA, USA, [4]Rogue Holdings, Jacksonville, FL, USA

The Rogue® Longitudinal Switching Study determined the association between the use of oral Rogue® Nicotine Products (RNP) in varying flavors and forms (pouches, gum, or lozenges) and reduction and quitting behaviors among adult combustible cigarette (CC) smokers, in a near real-world setting over 6-months. To minimize participant burden and ensure wider geographical representation, a site-based design was not used. Rather a cohort of participants received RNP through the mail and completed periodic online assessments of their use behaviors of RNP, CC, and other tobacco and nicotine products (TNP). A total of 1,863 adult smokers in the U.S. were recruited and enrolled from a third-party consumer database. Age-verified participants were e-mailed a web survey link to self-report their current CC and other TNP use in a Baseline survey. For each month of the 6-month actual use period, participants completed an online product ordering form in which they selected their choice of currently marketed RNP for their personal use. Selected products were shipped directly from the sponsor. Participants completed online follow-up surveys to report their CC, other TNP, and RNP use at 1-month, 2-months, 4-months, and 6-months after Baseline. A total of 1,393 participants completed the final survey, resulting in a 74.8% retention rate at 6-months. Other study processes were executed successfully, including the approaches used for online age-verification, product shipping, adverse event reporting, and e-incentives for subject participation. The study showed that TNP switching research for oral products can be conducted effectively leveraging online survey completion and remote (mail) product distribution.

105. ASYNCHRONOUS ONLINE FOCUS GROUPS: QUALITATIVE RESEARCH ON REDUCED-RISK NICOTINE PRODUCTS WITH UNDERSERVED OR HARD-TO-REACH POPULATIONS. Neil SHERWOOD[1] and Cheryl K. Olson[2]; [1]Neil Sherwood Consulting, Nyon, Vaud, Switzerland, [2]McKinney Regulatory Science Advisors, San Carlos, CA USA

Objectives: New technologies provide alternatives to traditional in-person focus groups for Tobacco Product Perception and Intention (TPPI) studies, allowing inclusion of a diverse range of population subgroups and reducing logistical challenges. We present two nicotine product studies that used an online data collection platform to conduct asynchronous online focus groups.

Methods: We used the QualBoard platform to collect data for two projects in situations where in-person focus groups would be difficult or impossible: One

conducted during the COVID-19 epidemic, the other involving retirement-age adults ordering online.

Results: In Study 1 (pouched product), important information emerged on how women perceive smokeless tobacco products and their users, and on ways to package and inform about a novel smokeless product to overcome strong negative preconceptions and to encourage trial.

Study 2 (e-cigarette), on older adult use of a cigarette-like vaping product, revealed key drivers of use (including a sensorimotor experience similar to a cigarette, and a zero-nicotine option).

Implications: Online focus groups are a flexible tool that affordably and safely enables greater participant diversity in qualitative research. This approach rapidly provides a wealth of in-depth information on language, images and situations that can promote or discourage trial and switching from cigarettes to reduced-risk nicotine alternatives, especially those sold primarily online. It also enables the development of valid survey questions.

106. NON-TARGET ANALYSIS SURVEY OF TOBACCO-FREE NICOTINE POUCHES. Jacqueline COLLINS and Alexandra M. Martin; Enthalpy Specialty Labs, Richmond, VA, USA

In the continuing quest for Reduced Harm Nicotine Delivery products, there has been an increase in the types of products available to the consumer. Many of these products are not regulated and there is little information available to evaluate the reduced harm potential.

One of these product classes is Tobacco-Free Nicotine Pouches (TFNP). In 2022 we presented results of target compound analysis of a selection of these products. In this work, we have expanded the original scope to include Non-Targeted Analysis of a cross section of flavored products readily available on the market.

Products of varying flavor descriptions were extracted into ethanol and analyzed using GCMS full scan with MassHunter deconvolution, followed by spectral matching using the NIST 2017 MS library.

There was not always overlap between products as far as the flavor profiles were concerned. For example, there were four cinnamon flavored products and, although most contained high levels of cinnamaldehyde, as expected, one of the products also contained significant levels of coumarin and butylated hydroxy toluene (BHT). Furthermore, some compounds found in many of the products at low levels, were found at high levels in other products. Benzyl alcohol and benzyl salicylate, for example, were observed in low levels across many products (< 2 µg/g), and were found at approximately 400 µg/g in at least one product. Although many of the compounds identified are considered natural flavors, they could be considered mild irritants when present at high levels.

Guidelines to determining best practices should be established, and screening of products in tandem with toxicological evaluation must be performed to ensure the use of these products does, in fact, reduce potential harm.

107. ABUSE LIABILITY ASSESSMENT OF VELO NICOTINE POUCHES IN COMPARISON TO COMBUSTIBLE CIGARETTES AND NICOTINE GUM. Milly KANOBE, Christie Y. Powell, Sarah A. Ayoku, Alison G. Gibson, Melissa A. Tapia, Kristen G. Jordan, Makena Patrudu, Brian M. Keyser, Jeffrey W. Coffield and Sarah A. Baxter-Wright; RAI Services Company, Winston-Salem, NC, USA

Velo Nicotine Pouches are portioned oral nicotine products containing tobacco-derived, pharmaceutical-grade nicotine rather than tobacco leaf. Because these pouches neither contain tobacco leaf nor are combusted, exposure to harmful and potentially harmful constituents from smoke generated with combusted tobacco products is significantly reduced. Subjective and nicotine pharmacokinetics (PK) measures taken over the course of product use provide a framework for abuse liability (AL) assessment of tobacco and nicotine products as well as information on adoption potential for a new tobacco product. This study evaluated elements of AL of a subset of Velo Nicotine Pouches (Velo Mini Pouch Cool Mint and Velo Mini Pouch Modern Traditions, each in 4 and 8 mg nicotine) compared to high (combustible cigarette [CC]) and low (nicotine gum) AL comparators. Smokers and smokers who also use smokeless tobacco products were enrolled and participated in daily Test Sessions during which they used one product per session based on their randomized product use sequence. Study results show that most subjective measures of Velo Mini Pouches were

significantly lower compared to CC and generally lower than or similar to nicotine gum. Plasma nicotine uptake in the first 15 minutes for Velo Mini Pouches was significantly lower compared to CC. All nicotine PK parameters for the 4 mg nicotine products were not significantly different compared to nicotine gum. For the 8 mg nicotine products, these parameters were significantly higher than nicotine gum. The results of this study support the conclusion that Velo Mini Pouches have a low AL, and that these products provide levels of nicotine that may enable some adult cigarette smokers to transition away from smoking to use of Velo Mini Pouches.

108. OPTIMIZATION OF SEEDING DENSITY OF PRIMARY HUMAN GINGIVAL FIBROBLASTS FOR IN VITRO TOXICITY TESTING. Xuefei CAO[1], Utkarsh Doshi[1], Kyeonghee M. Lee[1] and Manoochehr Khazaee[2]; [1]Altria Client Services, Richmond, VA, USA, [2]Eurofins Lancaster Laboratories, Lancaster, PA, USA

Human gingival fibroblasts (HGFs), the predominant resident cells of the gingival connective tissue, are capable of self-renewal and secreting inflammatory molecules when stimulated and thus play a key role in the remodeling and disease development in periodontal tissues. Therefore, it is a physiologically relevant in vitro model for assessing the potential effects of tobacco and nicotine products on oral health. In this test system qualification study, we determined seeding densities of HGFs in 24- and 96-well tissue culture plates that would reach the target confluency of 70-80% after 24 or 48 h of culture to avoid the adverse effects from over confluency. HGFs were seeded at densities up to 160K cells/cm2 per well and cell number was measured using a hemocytometer (in 24-well plate) and proliferation measured using MTT assay (in 96-well plate) after 24 and 48 h of culture. Cell number increased linearly at seeding densities up to 60K cells/cm2 and plateaued at higher seeding densities 24 h after plating. Cell proliferation curves at both timepoints as measured by MTT assay were similar and absorbance almost doubled at seeding densities up to 30K cells/cm2. At seeding densities higher than 30K/cm2, HGFs proliferated at a slower rate, resulting in a slower increase in MTT absorbance and lower absorbance at 48 h compared to 24 h; microscopic evaluation did not reveal obvious cell death, although cells appeared more aggregated in some areas of the wells. These findings suggest that HGFs may have undergone growth

arrest possibly caused by contact inhibition at high seeding densities. Seeding densities in the range of 20K to 30K cells/cm2 and treatment duration of 24 h are appropriate for acute toxicity testing.

109. INFLUENCES OF GENETICS AND NITROGEN APPLICATION RATE TO FLUE-CURED TOBACCO AGRONOMIC CHARACTERISTICS AND CHEMICAL CONSTITUENTS. Matthew VANN; NC State University, Raleigh, NC, USA

Proposed federal regulations put forth that the nicotine concentration in tobacco should be lowered to non-addictive levels (0.3 to 0.5 mg g^{-1}). The proposed standards are 90 to 95% lower than the nicotine concentration typically documented in commercially available flue-cured tobacco cultivars. Research was conducted in six environments to evaluate two cultivars with normal nicotine levels (K326 and NC95) and four genotypes with low nicotine levels (DH16A, DH22A, DH32, and LAFC53). Each cultivar and genotype was paired with three nitrogen application rates: 70, 85, and 100% of the recommended rate specific to each growing environment. As N application declined, so too did cured leaf yield and concentration in K326 and NC95. These factors were generally not affected by N application in the low alkaloid genotypes. Moreover, LAFC53 consistently produced the lowest cured leaf visual quality, economic value, and reducing sugar concentration among the cultivars evaluated. This observation demonstrates that DH16A, DH22A, and DH32 are agronomically superior to LAFC53. Despite reductions in nicotine, the lowest documented concentration, which was measured in LAFC53, was 10-fold greater than the proposed minimum. Overall, nitrogen did not influence the measured parameters as much as genetics; therefore, additional research that involves other agronomic practices is warranted. In addition, further genetic manipulation will be required to meet the standards proposed by regulatory groups.

110. POTENTIAL ULTRA-LOW NICOTINE LIMIT IN TOBACCO – CAN WE MEET IT? Anne FISHER[1], Colin Fisher[1], Barunava Patra[1], Huihua Ji[1], Jeffrey Kinney[1], Shengming Yang[2] and Stacey Slone[1]; [1]University of Kentucky, Lexington, KY, USA, [2]US Department of Agriculture, Fargo, ND, USA

The FDA has sought comments on a possible nicotine limit of 0.3-0.5 mg/g in the filler of cigarettes. Over the years, we have tested the conventional low

alkaloid (LA) *nic1nic2* mutants, agronomic practices known to lower alkaloids, and a combination of LA lines and agronomic practices; none of which consistently met this limit. We are now testing two gene-edited ultra-low alkaloid lines and two F_4 lines combining a novel low alkaloid gene and the *nic1nic2* mutants. We used the Burley 21 (Bu21) alkaloid series as checks. The nicotine+nornicotine range across stalk positions for Bu21 was 33.2-46.3 mg/g and for LA Bu21 was 2.60-3.42 mg/g. For the two F_4 lines, the range was 2.19-2.80 and 1.80-2.71: significantly lower than LA Bu21 only in the primings, but consistently lower in the other stalk positions. For the two gene-edited lines, the range was 0.513-0.679 and 0.546-0.703, significantly lower than LA Bu21 in all stalk positions. Only the two gene-edited lines had significantly lower yields (2,774 and 2,794 kg/ha) than the Bu21 check (3,602 kg/ha). The poorest quality was in the two F_4 lines (grade indices of 35 and 36), which were consistently, but not significantly, lower than LA Bu21 (53), itself significantly lower than the check, Bu21 (82). The two gene-edited lines had grade indices consistently, but not significantly, higher than the F_4 lines and lower than LA Bu21. We conclude that we cannot consistently meet a 0.5 mg/g nicotine limit, not at this time, not with our current knowledge; although nicotine can be reduced to a level lower than the LA lines, albeit with yield and quality penalties.

111. Withdrawn

112. Withdrawn

113. Withdrawn

114. Withdrawn

115. SWITCHING AWAY FROM CIGARETTES ACROSS 24 MONTHS AMONG US ADULT SMOKERS WHO PURCHASED THE JUUL SYSTEM. Nicholas GOLDENSON[1], Saul Shiffman[2], Gem M. Le[1] and Ryan A. Black[1]; [1]Juul Labs, Inc, Washington, DC, USA, [2]PinneyAssociates, Pittsburgh, PA, USA

Evidence strongly suggests that electronic nicotine delivery systems (ENDS), while not without risk, are less harmful than combustible cigarettes. Accordingly, adult cigarette smokers who switch to ENDS likely benefit their individual health, and widespread complete switching can positively benefit

population health. Rates of switching away from combustible cigarettes (i.e., past 30-day abstinence from cigarette smoking) among US adult smokers who purchased the JUUL System were previously reported up to 12 months between 2018-2020. The present analysis extends this to examine switch rates out to 24 months in groups of adult established smokers with a range of smoking characteristics and histories. Adult (≥21 years) current established smokers (smoked within the past 30 days at baseline, smoked ≥100 cigarettes in their lifetime and currently smoking 'some days' or 'every day') were recruited into the Adult JUUL Switching and Smoking Trajectories (ADJUSST) Study following their first purchase of a JUUL Starter Kit. Past 30-day switching (yes/no) was assessed via online surveys at 6 follow-ups up to 12 months, with additional follow-ups at months 15, 18, 21, and 24. Past 30-day switching across the second year after purchase (months 12 to 24) was calculated in the total sample (N=17,986 at baseline) and in six subgroups of smokers defined by baseline smoking frequency and duration: (1) Infrequent Short-Term Smokers; (2) Infrequent Long-Term Smokers; (3) Frequent Short-Term Smokers; (4) Frequent Long-Term Smokers; (5) Daily Short-Term Smokers; and (6) Daily Long-Term Smokers. In the total sample of established smokers, rates of past 30-day switching away from cigarettes increased across the second year after JUUL purchase: 12-month (51.2%), 15-month (52.6%), 18-month (55.8%), 21-month (57.7%) and 24-month (58.6%). Rates of switching varied by smoking subgroup: at the 24-month assessment switch rates ranged from 68.8% among infrequent short-term smokers to 49.7% among daily long-term smokers. Switch rates among adult smokers were maintained and, indeed, continued to increase across the second year after a JUUL purchase. Higher switch rates were observed among less frequent and shorter-term smokers, but even daily long-term smokers reported switch rates approximating 50% two years after first purchasing JUUL. A substantial proportion of adult smokers, including long-term daily smokers, who purchase JUUL subsequently switch away from combustible cigarettes. Smokers with more extensive histories of smoking may require more time to achieve complete switching.

116. COMPARING ADULT SMOKERS WHO SWITCHED TO JUUL VS CONTINUING SMOKERS: BIOMARKERS OF EXPOSURE AND OF POTENTIAL HARM AND RESPIRATORY SYMPTOMS. Saul SHIFFMAN[1], Douglas R. Oliveri[2], Nicholas I. Goldenson[2], Qiwei Liang[2], Ryan A. Black[2] and Snigdha Mishra[2]; [1]PinneyAssociates, Bethesda, MD, USA, [2]Juul Labs, Inc, Washington, DC, USA

More research on the effects of long-term switching in real-world contexts is needed to complement existing evidence from short-term randomized studies that switching from cigarette smoking to ENDS reduces toxicant exposures, and also extends to reduction in clinical symptoms.

This cross-sectional, observational study assessed adults who had smoked ≥10 cigarettes/day for ≥10 years. Analyses compared two groups: (1) 124 continuing cigarette smokers (Smokers); and (2) 140 former smokers who switched to JUUL-brand ENDS exclusively for at least 6 months, with the average being 3 years (Switchers).

Analyses examined geometric means for biomarkers and arithmetic means for other endpoints adjusted for demographics, smoking history, and lifestyle factors.

Nicotine levels were significantly higher in Switchers, who were unusually-heavy users of JUUL (>2.5 times more likely to consume at least 20 pods/month than a more general JUUL-user sample). All other biomarkers of exposure [NNAL (BOE for NNK); HPMA3 (acrolein); COHB (CO); MHBMA (1,3-butadiene); SPMA (Benzene); HMPMA (Crotonaldehyde); CEMA (Acrylonitrile)] were significantly lower among Switchers. Even after adjustment for demographic and lifestyle factors, multiple biomarkers of potential harm (sICAM-1 [primary], and e.g., white blood cell count, MCP1, HbA1c, 8-epi-PGF2α) were significantly lower in Switchers than Smokers; HDL was significantly higher. Dependence on JUUL among Switchers was significantly lower than Smokers' dependence on cigarettes. Switchers' respiratory symptom scores were significantly lower than Smokers'.

Compared to continuing smokers, smokers who switched to JUUL and were using JUUL heavily had substantially lower exposures to multiple toxicants; favorable differences in markers of inflammation, endothelial function, oxidative stress, and cardiovascular risk; and less respiratory symptoms. These findings suggest that switching from cigarettes to JUUL likely reduces smokers' health risks.

117. UTILIZING REAL-WORLD TOPOGRAPHY DATA TO DEFINE SMOKE MACHINE PUFFING REGIMEN FOR ENDS. Robert UNDERLY and Randy Weirdman; RAI Services Company, Winston-Salem, NC, USA

The standards set by the International Organization of Standardization (ISO) for puff regimen serve the important role of unifying testing parameters under which products can be compared against one another and provide a baseline for establishing standard outputs or thresholds for determining product limits. These standards shaped the early landscape of tobacco product evaluation and created a harmonized pathway toward building methods to evaluate product constituents. Early in the development of tobacco product standards the Federal Trade Commission (FTC) stated that the standards they used were not intended to determine the amount of exposure individual consumers had to products (combustible cigarettes at the time), but instead, to determine the product output given a prescribed machine puffing regimen. This same distinction is made when considering and adopting ISO standards. Although the purposes of these standards are clear, the utilization of data generated under these conditions by regulatory bodies has been called into question by academic institutions and public health officials as they may not accurately reflect real world use of new products (ENDS in particular). In order to understand the perceived differences between standardized testing regimen and the ways in which consumers use ENDS products, nearly 1.5 million puffs, collected in an ambulatory real-world setting, were evaluated to determine the use characteristics of consumers. With this data it is possible to determine the various percentiles of use, defining upper and lower bounds of testing parameters for machine puffing regimen to accurately reflect device outputs relative to consumer use.

118. DESIGN OF A RANDOMIZED MULTI-SITE, OPEN-LABEL, 8-WEEK, ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS) ACTUAL USE STUDY. Mandara SHETTY; British American Tobacco, Southampton, Hampshire, UK

The FDA Center for Tobacco Products recommends assessment of the public health impact of new tobacco products, either in a simulated use setting or a real-world environment, to understand how U.S. adult consumers actually use the products. We designed a randomized, multi-site, open-label, 8-week, prospective observational study, at sites geographically dispersed within the U.S among adult tobacco consumers between 21 and 60 years of age. Participants are regular smokers of at least 5 cigarettes per day and are provided the Study IP, an Electronic Nicotine Delivery System, for *ad libitum* use over a 6-week Actual Use Period (AUP) in their real-life environments. The

study consists of a pre-screening period, a screening/enrollment visit, a 1-week baseline assessment period (BAP), a 6-week AUP, and a 1-week close-out period. Subjects will choose freely among the Study IP available in one of the three study arms to which they are randomly assigned. The three study arms are organized by Study IP flavor categories: tobacco, menthol, and non-tobacco-non-menthol, available in two flavored variants and in two nicotine concentrations (i.e., 1.5% and 5%). Enrollment is determined based on subjects indicating an interest to use all three variants. This design has been chosen to assess the relative impact of availability and use of different e-liquid flavors on changes in cigarette consumption. Participants complete interviewer-led surveys and are resupplied Study IP at the site visits. Participants self-report their daily use of all combustible cigarettes and any other tobacco and nicotine product (TNP) use during BAP and AUP (including Study IP) on an eDiary. Adverse health experiences are collected through passive surveillance via a hotline throughout the study.

119. SWITCHING EXCLUSIVELY FROM SMOKING TO USING GLO RESULTS IN SIGNIFICANT, SUBSTANTIAL REDUCTIONS IN EXPOSURE TO CIGARETTE SMOKE TOXICANTS. Nathan GALE, David Azzopardi, Mike McEwan, Filimon Meichanetzidis and Senthil Vel; B.A.T. (Investments) Ltd, Southampton, UK

A proposed tobacco harm reduction approach for those who would not otherwise quit smoking relies on the proposition that the health burden of smoking can be reduced by encouraging switching exclusively to products that while not being risk free have the potential to reduce or eliminate toxicant exposure and reduce smoking-related harms. Heated Tobacco Products (HTP) deliver a nicotine-containing aerosol with lower or immeasurable levels of toxic constituents associated with combusting tobacco.

This randomized, ambulatory study assessed whether selected biomarkers of exposure (BoE) to cigarette smoke toxicants are reduced in smokers switched exclusively to a glo HTP for three months, compared to those who continue to smoke cigarettes.

Participants were healthy smokers assigned to continue smoking or to switch exclusively to one of five variants of the glo HTP, smokers who abstained from cigarette smoking, and never-smokers. BoE to a range of carcinogens and

respiratory, cardiovascular, and reproductive toxicants included in FDA's established list of HPHCs were assessed at baseline and three months. Daily SMS questionnaires and haemoglobin levels of N-(2-cyanoethyl)valine were used to assess compliance with cigarette smoking restrictions.

Compared to the continued smoking group, the groups switched to the glo HTP exhibited significant and substantial reductions from baseline in levels of BoE to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, 1,3-butadiene, acrolein, benzene, and carbon monoxide, along with several secondary endpoint BoE.

Alongside chemical and toxicological studies undertaken on the glo HTP used in this study, these findings add to the weight of evidence that support our belief that smokers who switch exclusively to use of the glo HTP reduce their exposure to tobacco smoke toxicants linked with smoking-related diseases compared to those continuing to smoke.

120. APPLYING FACTOR ANALYSIS TO UNDERSTAND PRODUCT DIFFERENCES OBSERVED IN CLINICAL STUDIES. Yisha HE, Jingzhu Wang, Lai Wei, Raheema Muhammad-Kah, Jeffery Edmiston and Edward Largo; Altria Client Services, Richmond, VA, USA

Objectives: The objective of this study was to identify factors that underly nicotine pharmacokinetics and subjective effects assessments and to examine how test products are differentiated along the identified factors.

Methods: We conducted Principal Component Analysis (PCA) using data from three randomized crossover pharmacokinetic clinical studies: 1) nicotine pouch (NP) strength study (n=30) tested seven products: five different nicotine strength (ranging from 1.5mg to 8mg) mint NPs, participants' own-brand cigarettes (OBC) and moist smokeless tobacco (MST). 2) NP flavor study (n=42) tested seven products: six different flavored NPs (4mg nicotine) and participants' OBC. 3) e-Vapor study (n=30) tested five products: four different flavored e-vapor products and participants' OBC.

Results: Based on PCA results, top factors identified were conceptualized as product satisfaction, adverse feelings, and tobacco nicotine withdrawal effect. In NP strength study, these factors together explained 57.5% of data variation. We observed that product types (e.g., cigarettes versus oral products) can be

differentiated by the product satisfaction factor, where the factor score is highest for OBC, followed by own-brand MST and new products (NP/e-vapor). Product nicotine levels can be differentiated by adverse feelings factor for NPs, where the factor score is highest in NPs containing 8mg nicotine compared to lower nicotine NPs. Product flavor variation was not differentiated by any of the identified factors for NPs and e-vapor products.

Implications: While PK and subjective responses can be used to assess product platform and nicotine strength differences effectively, product flavor varieties may not be strongly associated with differences in PK and subjective responses.

SYMPOSIUM PANEL: ASSESSMENT OF ENDS INGREDIENTS. Michael OLDHAM; Juul Labs, Inc, Washington, DC, USA

The workshop will combine six presentations illustrating different approaches and aspects o the assessment of ENDS ingredients with a 30-minute panel discussion where presenters will answer questions/discuss topics from the workshop participants. The six presentations not only describe traditional toxicological approaches to ENDS ingredient evaluation (e.g., toxicological literature review, ingredient thermal degradation analysis, in vitro, in vivo testing) including advanced read across techniques, but several also encompass toxicology relevant new assessment methods. These new assessment methods include in vitro assays for assessment of respiratory sensitization, use of more realistic 3D tissue constructs and aerosol delivery systems.

121. EVALUATING ORAL HEALTH AFTER SWITCHING FROM CIGARETTES TO NICOTINE POUCHES. Jianmin LIU[1], Jingzhu Wang[1], Jeffery S. Edmiston[1], Mohamadi A. Sarkar[1], Maria Gogova[1], Kimberly R. Milleman[2], Jeffery L. Milleman[2] and Abigail L. Yoder[2]; [1]Altria Client Services, Richmond, VA, USA, [2]Salus Research, Fort Wayne, IN, USA

Completely switching from cigarette smoking to oral tobacco-derived nicotine products, like nicotine pouches, presents a harm reduction opportunity for adult smokers who are unable or unwilling to quit using tobacco. The objective of this study was to characterize the changes in gingival inflammation, dental plaque, and extrinsic dental stain in adult smokers who switched to on!® nicotine

pouches (NPs) compared to those that continued to smoke (CS) combustible cigarettes for 24 weeks. Adult smokers with Modified Gingival Index (MGI) ≥ 1.75 and Bleeding Index (BI) ≥10 bleeding sites were randomized into the following groups: NP: subjects (n=88) were asked to stop smoking and switch to use of NPs; CS: subjects (n=61) continued smoking their own brand cigarettes. Assessments of MGI, BI, Plaque Index (PI), extrinsic dental stain (Lobene Stain Index, LSI), Periodontal Probing Depth (PPD) and bleeding on probing (BOP) were performed at baseline, then at 12-, and 24-weeks. All subjects received a complete dental scaling and polishing following the baseline assessments. Forty subjects from the NP and 45 from the CS groups completed the study. The mean MGI, BI, and LSI (stain area and intensity) in the NP group at weeks 12 and 24 were significantly lowered ($p<.05$) compared to baseline as well as to the CS group. No changes were observed for the remaining dental endpoints at subsequent follow-up visits for both NP and CS groups. In a population of adult smokers with moderate gingivitis, switching to nicotine pouches reduced levels of gingival inflammation and extrinsic dental stain.

122. A TIERED APPROACH TO ENDS INGREDIENT ASSESSMENT.
Irene ABRAHAM; JT International, Geneva, Switzerland

The human health risk assessment of electronic nicotine delivery system (ENDS) ingredients is complex, even for an experienced toxicologist. First, the risk assessor must consider the individual implications of each ingredient, whether mono- or multi-constituent based, along with the mixture of these ingredients in the formulation. Then consideration must be given to the behavior of the ingredients within the device, including reactions before and during product use, such as thermal degradation. It is not unusual for these considerations to result in a single risk assessment covering dozens of discrete substances. The information is coupled with the exposure considerations to allow the risk assessment to progress, taking into account both systemic and local endpoints. Throughout this process, the assessor must also determine the quality of the available data, the impact of the absence of data, how to manage uncertainty and whether additional data is required to conclude the assessment. A tiered approach is useful when evaluating the information gathered and data generated in the course of conducting these types of assessments. During this talk, we will cover several tiers including: 1) Use of literature reviews and screening criteria for hazard identification, including options for managing the potentially very large datasets; 2) Read across using in silico tools and other methods of data gap

filling to balance unknowns and uncertainty during risk characterization; and 3) Considerations of the whole formulation and exposure under intended conditions of use.

123. ESTABLISHING AN ENDS IN VITRO AND IN VIVO INGREDIENT ASSESSMENT STRATEGY USING A TOOLBOX APPROACH. Florence VONMOOS and Karsta Luettich; Philip Morris Products, Neuchatel, Switzerland

Electronic Nicotine Delivery Systems (ENDS) comprise a wide variety of electronically powered devices used to heat an e-liquid that is typically composed of various flavors, with or without nicotine, diluted in propylene glycol- and vegetable glycerol-based solutions. While many flavor ingredients used in e-vapor products are “Generally Recognized as Safe” (GRAS) for oral consumption according to the Flavor and Extract Manufacturers Association (FEMA), many have insufficient safety data on inhalation exposures. Establishing a safety assessment strategy to separately analyze flavoring compounds in a comprehensive hazard characterization battery and in vitro and in vivo safety tests would be very challenging. More pragmatic approaches are needed for the combined evaluation of their potential toxicity when inhaled.

We conducted several non-clinical studies evaluating flavoring ingredients (>200), e-liquid formulations, and ENDS aerosols. The ingredients were initially screened for quality, purity, and FEMA GRAS status, followed by a comprehensive review of the available toxicological data. The flavor ingredients were assigned to 38 groups based on their chemical structure. Each group’s representative chemical was selected based on the specific toxicological properties of these compounds. The selected representatives were combined into a mixture that was used in traditional regulatory toxicology tests, alternative in vitro assays (e.g., high-content screening and ToxTracker), and chronic inhalation toxicology studies in A/J mice.

This flavor “toolbox” will help identify potential hazards associated with the tested flavorings and their respective chemical groups, thus expanding the relevance of a single animal study to more than 200 compounds, in line with 3R principles.

124. A PRODUCT STEWARDSHIP ASSESSMENT STRATEGY FOR E-

LIQUIDS. Liam SIMMS; Imperial Brands, Bristol, UK

This presentation will provide an overview of the assessment strategy employed by Imperial Brands plc for novel e-liquids from a European perspective only. All manufacturers have a duty to understand how products interact and behave in terms of consumer health and any potential risks that may arise.

The initial desk-based assessment reviews all the ingredients used in e-liquid specification. Initial checks include screening for CMRS (Carcinogens, Mutagens, Reproductive Toxins and Respiratory Sensitizers) using a combination of QSAR techniques and published literature. All ingredients used are checked to be of a suitable quality and purity, ensuring that the ingredients used are below internal limits based on toxicology and anticipated exposure. Following the successful completion of this desk-based evaluation, candidate e-liquids and their aerosols are assessed using the CORESTA Biological battery (Ames, IVM, NRU) and compared to a reference cigarette. Whole aerosol exposures are employed to assess the biological impact of the aerosol mixture. Any atypical results are investigated further with mechanistic *in vitro* studies (e.g., high content screening & mechanistic reporter assays) and dosimetry. Based on all this information, a decision for the e-liquid suitability is made by the Product Stewardship Toxicologists, and, if deemed acceptable, the e-liquid can proceed through the broader assessment process.

The described process is in keeping with assessment processes published by other manufacturers of e-liquids and the UK Committee of Toxicology's proposed assessment process, ensuring that high quality, suitable e-liquids are developed in a timely manner.

125. NEW ASSESSMENT METHODS FOR ENDS INGREDIENTS. Arno GUTLEB; Invitrolize, Belvaux, Luxembourg

Relevant models mimicking different areas of the lung *in vitro* are commercially available and represent the whole respiratory system from the nasal cavity to the alveolar barrier. These commercial models can be based on primary cells or cell lines with the inherent advantages and limitations of the two different approaches.

In the past most *in vitro* models including those representing the pulmonary

system were usually based on a single cell-type and in case for the pulmonary system even cultured under submerged conditions, which is not the physiological situation for lung cells. In recent years complex models using more than one cell type in a 3D orientation were developed and have become widely applied.

Endpoints studied in these various models can range from carcinogenesis, irritation to inflammation, and more recently also respiratory sensitization. The models can be incubated in static, pressurized or cyclic systems. Overall, models should be as complex as necessary to mimic the physiological responses studied and as simple as possible to reach that goal while allowing dosimetry and measurement of relevant endpoints.

Existing *in vitro* models will be presented, and a special focus will be on the state-of-the-art to identify the hazard of respiratory sensitization.

126. EVALUATION OF SYNTHETIC COOLING AGENTS WS-3 AND WS-23 IN 90-DAY INHALATION TOXICITY STUDIES IN SPRAGUE DAWLEY RATS. Richard SAVORY; B.A.T. (Investments) Ltd, Southampton, UK

Synthetic cooling agents such as WS-3 (N-ethyl-5-methyl-2-propan-2-ylcyclohexane-1-carboxamide) and WS-23 (2-isopropyl-N,2,3-trimethylbutanamide) are increasingly used in tobacco/nicotine products to add sensorial attributes. Scientific consensus is that these agents, widely used in food and cosmetics, are odourless and flavourless. Here, we discuss the toxicological effects via inhalation of WS-3 and WS-23 in separate 90-day nose-only inhalation toxicity studies in rats, conducted in accordance with OECD 413 and scientific necessity to establish safety. Rats were exposed for 6 hours per day, for either 5- or 7-days a week to WS-3 or WS-23 solubilised in propylene glycol, respectively, to aerosol concentrations that represent a range of potential human exposures from the use of commercial e-cigarettes or other inhaled tobacco/nicotine products.

WS-3 and WS-23 showed no adverse clinical signs at the levels studied. Dose-related pulmonary and systemic exposures were demonstrated from an aerosol achieving a consistent particle size of <3µm. Treatment related findings were found in the liver, respiratory tract/lungs and adrenals. Male specific alpha 2µ-globulin nephropathy was noted in rats treated with WS-23. All changes were considered non-adverse. Adaptive hepatic changes were restricted to increased liver weights resulting from hepatocellular hypertrophy, with vacuolation

occurring only after WS-23 treatment. The changes in nasal epithelium and macrophage incidence in the lung were consistent with inhalation of aerosols and particles. Changes in adrenal glands were minimal and not considered biologically relevant. Both compounds were non-genotoxic following repeated dosing, determined by the *in vivo* micronucleus (OCED 474) and the Comet assay (OECD 489). No Observed Adverse Effect Concentrations (NOAEC) could be derived that were sufficient to support the concentrations of WS-3 and WS-23 in commercial e-liquids and inhaled tobacco/nicotine products.

127. TOXICOLOGICAL ASSESSMENT OF ELECTRONIC NICOTINE DELIVERY SYSTEMS USING SEVERAL 2D AND 3D IN VITRO CYTOTOXICITY AND GENOTOXICITY ASSAYS. Robert LEVERETTE; RAI Services Company, Winston-Salem, NC, USA

In vitro toxicological assessment of next generation tobacco products, including Electronic Nicotine Delivery Systems (ENDS), is essential to the premarket tobacco product application (PMTA) process. The use of a series of *in vitro* assays, looking at several biological endpoints, adds to the weight of scientific evidence necessary for regulators to determine if marketing a tobacco product is appropriate for the protection of public health.

This presentation will highlight progression of the *in vitro* ENDS testing strategy implemented by RAI Services Company (RAISC). In the first RAISC ENDS PMTA, products were assessed using standard regulatory *in vitro* assays, including the Ames, *in vitro* micronucleus, and Neutral Red Uptake assays. These tests were implemented to assess the cytotoxicity and genotoxicity of the e-liquids as well as aerosol collected matter (ACM) and gas vapor phase (GVP) fractions in liquid test sample form. Although initially, aerosol fractions were tested separately, subsequent rounds of ENDS PMTA testing combined these fractionated aerosol samples (ACM, GVP) to better represent aerosol exposure in humans. Ultimately, freshly generated, unfractionated whole aerosol (WA) delivered directly to cell cultures at the Air-Liquid Interface is the preferred method of exposure. Thus, current, and evolving WA methods are being developed and incorporated into RAISC's ENDS *in vitro* testing repertoire. As new biologically relevant and/or physiologically representative approach methods (NAMs) become important tools for *in vitro* testing, RAI has implemented 3D human airway tissue constructs for the WA cytotoxicity and oxidative stress testing of ENDS aerosols. With increased interest in NAMs and

evolving criteria for *in vitro* testing data, companies must remain diligent in method development and utilization of modern *in vitro* testing for future ENDS toxicological assessments.

128. PERCEPTIONS OF NICOTINE AND TOBACCO PRODUCTS IN THE US ADULT POPULATION – A LATENT CLASS ANALYSIS. Hui CHENG, Sade Jones and Joshua Karelitz; Altria Client Services, Richmond, VA, USA

Misperceptions about nicotine and the relative harm of smoke-free tobacco products are common among US adults. It is not clear whether heterogeneous subgroups exist. In this study, we aimed to identify population subgroups regarding perceptions of nicotine and harms of tobacco products (including smoke-free products) and examine subgroup characteristics.

We conducted a latent class analysis based on 11 indicators of perceptions about nicotine and health-related harms of tobacco products, using data from wave 4 of the PATH study. Logistic regressions were used to assess variables correlated to class membership (i.e., demographic variables and tobacco use history).

The latent class analysis identified six classes: (1) High-Harm Perception Class (39%), (2) Pro-E-Cigarette Class (21%), (3) Low Harm Perception of Some-Day Use Class (18%), (4) Low-Harm Perception Class (10%), (5) Correct Perception Class (7%), and (6) Mid-Harm Perception Class (4%). The Correct Perception Class was the only class with low probability (7%) of perceiving nicotine as the chemical that caused cancer; all other classes had >40% probability of this misperception. Individuals in all classes had moderately low probabilities (≤25%) of correctly perceiving smokeless tobacco as less harmful than cigarettes. Compared to the other classes, individuals in the Correct Perception Class were more likely to be males, younger, individuals of non-white race/ethnicity, or individuals with higher levels of education or income; they were also more likely to currently use e-cigarettes. Individuals who were currently smoking cigarettes or using smokeless tobacco were more likely to be in the Low-Harm Perception classes.

Misperceptions about nicotine and the harms of tobacco products are common, tended to occur among certain demographic groups, and varied by tobacco use status among US adults.

129. AN EXPLORATION ON RELATIVE HARM PERCEPTIONS OF PORTIONED ORAL NICOTINE PRODUCTS AMONG POTENTIALLY VULNERABLE POPULATIONS. Christie POWELL[1], Red Thaddeus D. Miguel[2] and Isabella Steffensen[2]; [1]RAI Services Company, Winston-Salem, NC, USA, [2]Thera-Business Consulting, Ottawa, ON, Canada

Understanding the relative harm perceptions (RHPs) between portioned oral nicotine products (PONPs) and cigarettes is critical to tobacco regulatory strategies. Leveraging the National Tobacco Use and Transitions Survey (NTTS) dataset (N=370,007), analyses addressed three questions among 14,368 ever PONP users, focusing on potentially vulnerable populations (PVPs): (1) do RHPs differ when assessed by a direct single-item question on comparative harm versus a two-item indirect measure of harm (perceived level of harm for PONPs and cigarettes independently)?; (2) do PVPs' RHPs differ compared to a non-PVP group (respondents not meeting any PVP threshold)?; and (3) what is the association between RHP and cigarette cessation/reduction? Four PVP samples were defined as: 21-24 years old; some high-school or less; Hispanic/non-White; and <$40,000 annual income. Results showed weak agreement for the overall sample (κ=0.30) and for PVP groups (κ=0.17 to κ=0.32), when comparing the direct with indirect measures. Additionally, each PVP group had a statistically significantly (all p-values <0.0001) lower proportion of less harmful RHPs of PONPs (31.6% to 42.2%) compared to the non-PVP group (49.5%). Among established cigarette smokers, there was a higher percentage of former smokers who identified PONPs as being less harmful than cigarettes across all PVP groups (all p-values <0.05). Further, respondents also smoking a year prior reported higher 1-year smoking reduction rates among those who identified PONPs as being less harmful than cigarettes across all PVP groups; age (p-value=0.0006) and income (p-value=0.0051) being statistically significant. These findings suggest an opportunity for industry, public health, and regulators to better inform the public on the lower relative risks of PONPs, particularly PVPs who potentially have the most to gain from transitioning to these products.

130. THE EFFECTS OF A MODIFIED-RISK CLAIM FOR AN ENDS PRODUCT TO INCREASE SMOKERS' BEHAVIORAL INTENTIONS TO USE THE PRODUCT ARE COMPLETELY MEDIATED BY THE CLAIM'S EFFECTS ON RISK PERCEPTIONS. Saul SHIFFMAN[1], Stacey McCaffrey[2] and Ryan Black[2]; [1]PinneyAssociates (consultant to Juul Labs, Inc),

Bethesda, MD, USA and University of Pittsburgh, Pittsburg, PA, USA, [2] Juul Labs, Inc, Washington, DC, USA

131. Abstract omited

132. NICOTINE EXTRACTION FROM POLYPROPYLENE MODERN ORAL PACKAGING. Owen BUSSEY, Cody Perry and Serban Moldoveanu; Reynolds American, Winston-Salem, NC, USA

Many nicotine pouch products are sold in polypropylene packaging and over time nicotine can be absorbed into the packaging. This packaging can be recycled but there may be regulatory limits on the level of absorbed nicotine in some countries. This research describes two methods for nicotine extraction and quantitation from polypropylene modern oral packaging in support of recycling claims in the United Kingdom. The first extraction method included a 48-hour Soxhlet methanol extraction with an extraction efficiency of 89%. The second method included a 2-hour microwave methanol extraction demonstrating an equivalent efficiency. The extraction efficiency of each method was determined using pyrolysis GCMS of a reference piece of plastic from each sample before and after extraction. The quantitation method for the extract used liquid chromatography with ultraviolet detection. Experimental formulations were used for a comparison study between the Soxhlet and microwave extraction techniques. Samples tested included some with nicotine formulations ranging from 4 mg to 10.9 mg per pouch and 3 to 12 months in age. Data showed levels not exceeding 0.095% nicotine by mass of the plastic which was well below the threshold of 0.25% nicotine in the recyclability claims.

133. DETECTION OF THE PRESENCE OF TOBACCO IN TEA BASED HEAT-NOT-BURN SMOKING DEVICES. Serban MOLDOVEANU; Reynolds American, Winston-Salem, NC, USA

Herbal sticks typically based on tea and containing added nicotine are used in some commercial heat-not-burn smoking devices. Such herbal sticks are usually indicated as “tobacco free”. The material from such sticks may have the aspect of reconstituted tobacco or that of granules of reconstituted plant material. To verify that the herbal sticks do not contain tobacco either added intentionally or due to a contamination during the stick production, a method for detecting the potential presence of tobacco in such materials is described in this study. Since

nicotine is added to the plant material, this can be associated with low levels of minor alkaloids that can be present even in synthetic nicotine. For this reason, the analysis of potential presence of tobacco was focused on the analysis of the presence of solanesol. Solanesol is a compound typical for *Solanaceae* plants and it is absent in tea. Two procedures were developed for solanesol detection. One procedure is based on a GC-MS method and it is used for positive qualitative detection of tobacco. The other procedure is based on a HPLC-UV method and it is capable to detect 1 μg/mL solanesol in a hexane extract of the plant material. A number of commercially available herbal sticks were analyzed for traces of tobacco.

134. PUFF-BY-PUFF CHEMICAL CHARACTERIZATION OF HEATED TOBACCO AEROSOL. Kaitlyn SUSKI, Brad Ingebrethsen, Raj Rao, Josh Kurzman and Emily Dong; Juul, Labs, Inc, Washington, DC, USA

The chemical composition of aerosol particles impacts how people perceive them sensorially. Bulk chemical measurements are not sufficient to fully characterize aerosols generated from heated tobacco products (HTP) because the chemical composition can change puff to puff throughout a session. To better understand the puff-resolved evolution of HTP aerosol, puff-by-puff collection and analysis methods were developed.

A testbed was used to investigate aerosol formation from heated tobacco and humectant mixtures. The Pax 3 device outfitted with a metal capsule hand-filled with shredded tobacco and humectant mixtures was used as our initial testbed. The device was puffed 10-15 times per session with each puff collected either on a different filter pad or single-stage impactor substrate. For analysis of particle water content, the pads were analyzed using Karl Fischer titration. For nicotine and glycerin (VG), pads extracted with ethanol were analyzed by GC-FID.

These studies showed that nicotine, VG and water all have different release profiles over the session. In general, the particle mass per puff starts low (< 1 mg) and then increases to a peak (3.8-4.3 mg) before either flattening out or decreasing at the end of the session. Water vapor mass per puff peaks at puff 2 or 3, followed by nicotine. Nicotine peaks at a puff number that changes from puff 5 to 10 based on the water content in the tobacco + humectant mixture, which was varied by relative humidity conditioning. These results demonstrate that the chemical composition of HTP aerosol can vary significantly throughout the session and thus, highlight the importance of puff-by-puff chemical

characterization for HTP aerosol.

135. HOW FLUFFY IS YOUR PACK? JOHN LAUTERBACH; Lauterbach and Associates, Deland, FL, USA

Cigarette packing density affects the properties of cigarette smoke. Are the same principles applicable to the packing of waterpipe tobacco (WPT) in the bowl of the waterpipe (WP)? According to websites designed for users of WPT, packing does matter, depending on type of WPT and type of bowl used, but no data was provided to support the assertion. We use phunnel bowls where the heated air passes over, rather than through, the WPT. We haven't focused on packing density as there is little room in the small phunnel bowls (Tangiers) for fluffing a 10-g sample of WPT as the usable volume of bowl is about 12 mL (ceramic bowls, handmade). Thus, we compacted the WPT down so that the surface of the WPT was at least 4 mm from the top of the bowl. For runs made at reduced power with two layers of prepunched foil, we found that a popular of flue-cured (FC) WPT had more weight loss at lower temperatures than a popular brand of dark air-cured (DAC) WPT. We now report our research with a phunnel bowl (Vapor Hookah Messiah bowl) that has approximately 30 mL usable volume, but we maintained the WPT load at the same load as the small phunnel bowls. We used two popular brands of blueberry flavor WPT, one DAC, the other FC. The maximum loads were 18 g and 19 g, for DAC and FC, respectively. Based on "A technical analysis of pack density" (https://masonshishaware.com/blogs/hookah-blog/the-ultimate-density-guide), we should have used 14 g, and 13 g, respectively, instead of 10 g. Hence, we were using "semi-fluff" packings. HPLC data on products, residues after heating, and emissions will be presented, along with data from runs using the recommended sample loads.

136. DEVELOPMENT OF CERTIFIED REFERENCE CIGARS REPRESENTING THREE PRODUCT CATEGORIES. Ruth MCNEES, Huihua Ji, Stacey Slone, Brent Shelton, Matt Craft, JT Hall, Orlando Chambers and Ling Yuan; University of Kentucky, Lexington, KY, USA

The Center for Tobacco Reference Products (CTRP) has provided tobacco reference products for research since 1968. In 2016, CTRP was awarded the first of three cooperative agreements with the U.S. Food and Drug Administration (FDA) to produce certified reference tobacco products to expand the scientific knowledge within the tobacco research community. Certified reference tobacco products manufactured under the first two cooperative agreements include the 1R6F certified reference cigarette and the four certified reference smokeless

tobacco products - 1S4 Swedish Style Snus, 1S5 Snus, 3S1 Loose Leaf Smoking Tobacco, and 3S3 Moist Snuff. All current certified reference tobacco products have been used in the proficiency testing program for tobacco products under the A2LA accreditation of CTRP. The current FDA cooperative agreement is for the development of certified reference cigar products that represent the three largest product categories – large cigars, cigarillos, and filtered cigars. Multiple commercially available products within each product category were tested to define the design parameters for manufacturing reference products representative of each product category. All three reference products have been produced, and characterization of each product is currently underway at ISO 17025 accredited laboratories. The results of the characterization will be published in the Certificate of Analysis for each product, and the fully characterized products will be made available to tobacco researchers and incorporated into the proficiency testing program coordinated by CTRP. The design parameters, results of characterization, and future uses for the newly produced certified reference cigars will be presented.

CONFERENCE HISTORY

Technical Conference on Analytical Methods for Tobacco	1947 – 1948
Research Conference on Tobacco	1949
Research Conference on the Chemistry of Tobacco	1950
Tobacco Chemists' Research Conference	1951 – 1997
Tobacco Science Research Conference	1998 – present

1	1947	Oct 22-23	Philadelphia, PA	Eastern Regional Res. Lab
2	1948	Nov 22-23	Philadelphia, PA	Eastern Regional Res. Lab
3	1949	Oct 17-18	Richmond, VA	Medical College of VA
4	1950	Sept 11-12	State College, PA	Pennsylvania State College
5	1951	Oct 25-26	Durham, NC	Duke University
6	1952	Dec 4-5	Louisville, KY	University of Louisville
7	1953	Oct 1-2	Winston-Salem, NC	Bowman Grey
8	1954	Nov 11-12	Richmond, VA	Medical College of Virginia
9	1955	Oct 6-7	Raleigh, NC	NC State College
10	1956	Nov 8-9	Washington, DC	USDA
11	1957	Oct 10-11	New Haven, CT	Connecticut Agriculture Research Station
12	1958	Oct 23-24	Durham, NC	Duke University
13	1959	Oct 29-30	Lexington, KY	University of Kentucky
14	1960	Oct 13-14	Winston-Salem, NC	Wake Forest University
15	1961	Oct 4-6	Philadelphia, PA	USDA
16	1962	Sept 26-28	Richmond, VA	Virginia Institute Scientific Research
17	1963	Sept 22-25	Montréal, Quebec	Canada Department Agriculture
18	1964	Oct 20-22	Raleigh, NC	NC State University
19	1965	Oct 26-28	Lexington, KY	University of Kentucky
20	1966	Nov 1-3	Winston-Salem, NC	Wake Forest University
21	1967	Oct 18-19	Durham, NC	Duke University
22	1968	Oct 17-18	Richmond, VA	Virginia Institute Scientific Research
23	1969	Oct 22-24	Philadelphia, PA	USDA
24	1970	Oct 28-30	Montréal, Quebec	Canada Department Agriculture
25	1971	Oct 6-8	Louisville, KY	University of Kentucky
26	1972	Oct 22-28	Williamsburg, VA	VPI & SU
27	1973	Oct 3-5	Winston-Salem, NC	Wake Forest University

28	1974	Oct 28-30	Raleigh, NC	NC State University
29	1975	Oct 8-10	College Park, MD	USDA
30	1976	Oct 18-20	Nashville, TN	University of Tennessee
31	1977	Oct 5-7	Greensboro, NC	UNC-G & NC AT&T Univ.
32	1978	Oct 30-Nov	Montréal, Canada	Canadian Tobacco Manufacturing Council
33	1979	Oct 29-31	Lexington, KY	University of Kentucky
34	1980	Oct 27-29	Richmond, VA	VPI & SU
35	1981	Oct 6-9	Winston-Salem, NC	Wake Forest University
36	1982	Oct 24-27	Raleigh, NC	NC State University
37	1983	Oct 10-13	Washington, DC	USDA & University of Maryland
38	1984	Nov 5-8	Atlanta, GA	USDA & University of Georgia
39	1985	Oct 2-5	Montréal, Canada	Canadian Tobacco Manufacturing Council
40	1986	Oct 13-16	Knoxville, TN	University of Tennessee
41	1987	Oct 4-7	Greensboro, NC	UNC-G & NC AT&T University
42	1988	Oct 2-5	Lexington, KY	University of Kentucky
43	1989	Oct 2-5	Richmond, VA	VPI & SU
44	1990	Sept 30 - Oct 3	Winston-Salem, NC	Wake Forest University
45	1991	Oct 20-23	Asheville, NC	NC State University
46	1992	Sept 27-30	Montréal, Quebec	Canadian Tobacco Manufacturing Council
47	1993	Oct 18-21	Gatlinburg, TN	University of Tennessee
48	1994	Sept 25-28	Greensboro, NC	UNC-G & NC AT&T University
49	1995	Sept 24-27	Lexington, KY	University of Kentucky
50	1996	Oct 20-23	Richmond, VA	VPI & SU
51	1997	Sept 14-17	Winston-Salem, NC	Wake Forest University & R. J. Reynolds Tobacco Co.
52	1998	Sept 13-16	Atlanta, GA	University of Georgia & Schweitzer-Mauduit
53	1999	Sept 12-15	Montréal, Quebec	Canadian Tobacco Manufacturing Council
54	2000	Sept 24-27	Nashville, TN	United States Tobacco Manufacturing
55	2001	Sept 9-12	Greensboro, NC	Lorillard Tobacco Company
56	2002	Sept 29-Oct 2	Lexington, KY	University of Kentucky
57	2003	Sept 21-24	Norfolk, VA	Virginia Tech University
58	2004	Sept 19-22	Winston-Salem, NC	R. J. Reynolds Tobacco Co.
59	2005	Sept 25-28	Atlanta, GA	Schweitzer-Mauduit Intl.

60	2006	Sept 17-20	Montréal, Quebec	Rothmans, Benson & Hedges
61	2007	Sept 23-26	Charlotte, NC	Wattenspapier
62	2008	Sept 21-24	Nashville, TN	U.S. Smokeless Tobacco Manufacturing Company
63	2009	Sept 27-30	Amelia Island, FL	Lorillard Tobacco Company
64	2010	Oct 3-6	Hilton Head, SC	Cerulean & Global Laboratory Services
65	2011	Sept 18-21	Lexington, KY	The University of Kentucky
66	2012	Sept 9-12	Concord, NC	R. J. Reynolds Tobacco Co.
67	2013	Sept 15-18	Williamsburg, VA	Borgwaldt
68	2014	Sept 28-Oct 1	Charlottesville, VA	delfort Group
69	2015	Sept 20-23	Naples, FL	ITG Brands
70	2016	Sept 18-21	Palm Beach Gardens, FL	Cerulean
71	2017	Nov 28-Dec 1	Bonita Springs, FL	Tobacco Technology Inc & eLiquidTech
72	2018	Sept 16-19	Memphis, TN	American Snuff Company & RAI Services Company
73	2019	Sept 15-18	Leesburg, VA	Altria Client Services
74	2021	Aug 29-31	Boston, MA	Imperial Brands
75	2022	Sept 11-14	New Orleans, LA	RAI Services Company
76	2023	Sept 24-27	Norfolk, VA	Juul Labs, Inc

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137. CORESTA STRATEGY, COOPERATION AND ACHIEVEMENTS.
Johan Lindholm[1], Helena Digard[2], Rob Stevens[3] and Stéphane Colard[4]; [1]Swedish Match, Stockholm, Sweden, [2]BAT Investments Limited, Southampton, UK, [3]RAI Services Company, Winston Salem, NC, USA, [4]CORESTA, Paris, France

The mission of CORESTA is to promote and facilitate international cooperation and best practices in scientific research relative to tobacco and its derived products. Solidly based governance rules are defined and published to optimally fulfil this mission, and responsibilities are delegated by a General Assembly to a Board and a Scientific Commission. In 2023, hundreds of scientists from 168 organisations and 43 countries are cooperating in working groups to develop consensual methods, tools and guidelines, and to conduct collaborative studies.

A Strategy House composed of four strategic areas, eight strategic subjects and 16 workstreams has been elaborated with the objective to efficiently drive activities. A circular process of cooperation has also been implemented to prioritize, monitor and report progress on projects, to debate and align contributors' views, and to inform stakeholders. Such a framework leads to the production and publication of an impressive number of quality materials on a wide range of topics.

The vision of CORESTA being to be recognised as an authoritative source of publicly available, credible science and best practices, this poster will describe and illustrate the Strategy House, the collaborative framework, the 5-year plan and 2-year expected deliverables, and the main achievements over the last three years.