Pharmacokinetics, Subjective Effects, and Abuse Liability of Nicotine Salt-Based Vaping Products With Tobacco or Unflavored E-liquids, SALTVAPE Study

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PROTOCOL TITLE:

Pharmacokinetics, Subjective Effects, and Abuse Liability of Nicotine Salt-Based Vaping Products with Tobacco or Unflavored e-liquids [**SALTVAPE** Study]

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PRINCIPAL INVESTIGATOR:

Amanda J Quisenberry PhD
Roswell Park Comprehensive Cancer Center
Elm and Carlton Street
Buffalo, New York 14263
716-845-4918
Amanda.Quisenberry@RoswellPark.org

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1 OBJECTIVES

- To determine the effect of nicotine salt (nicotine benzoate) and free-base nicotine in different flavored e-liquid solutions on puffing behaviors and systemic exposure to nicotine from ENDS by 1) Assessing short-term effects on nicotine cravings, withdrawal, and satisfaction from single use of ENDS refilled with flavored nicotine salt or flavored free-base nicotine solutions with two different flavors (tobacco or unflavored) in current daily ENDS users following an overnight fast; and 2) Comparing users' perceptions and preferences towards inhaling vapors containing nicotine salt (nicotine benzoate) or free-base nicotine with two different flavors (tobacco and unflavored) versus their regular brand.
- This project provides important information on whether the pharmacokinetics of nicotine delivery differ between salt and free-base forms of e-liquid of equivalent nominal concentration using the same device, and whether the previously observed effects of flavors on subjective effects differ between salt and free-base forms.

1.1 Primary Objective(s)

- Determine whether C_{max} or T_{max} differ between free-base and salt-based versions of the same liquid, controlling for flavoring and nominal nicotine concentration [main effect of salt]
- Determine whether the effect of flavoring on subjective effects (e.g., harshness, liking) differs between matched free-base and salt-based e-liquids [flavor X salt interaction]

1.2 Exploratory Objective(s)

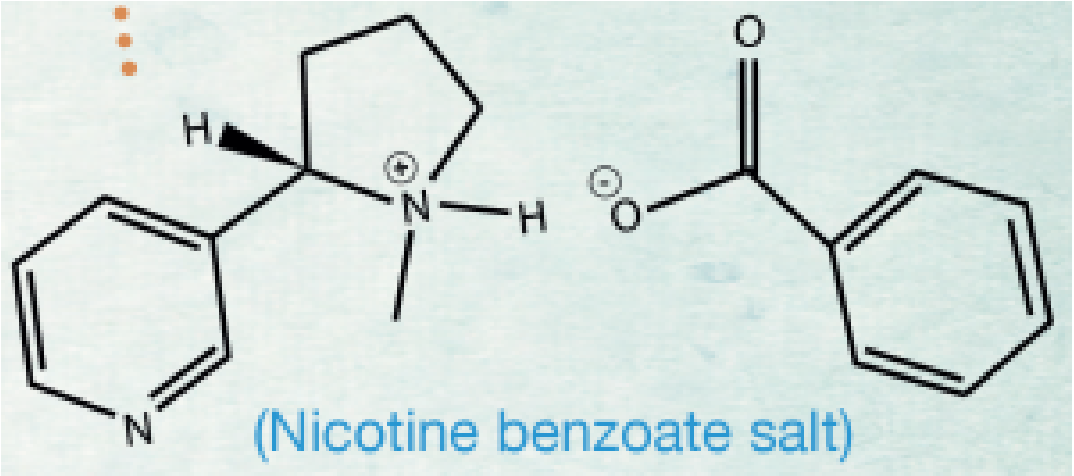
- Examine effects of salt and flavoring on abuse liability using the Experimental Tobacco Marketplace (ETM).

2 BACKGROUND

Over the last 10 years electronic cigarettes also known as electronic nicotine delivery systems (ENDS) have gained considerable popularity especially among youth. Although definitive data are lacking, nicotine from ENDS is likely absorbed through the upper aero-digestive tract through mucosal surfaces or lung parenchyma that are in direct contact with ENDS aerosol. ENDS design has evolved over the past few years, from the small vaporizers that resembled conventional tobacco cigarettes ("cig-a-likes") to larger tank systems ("mods"). "Pods," the newest generation of ENDS, have soared in popularity in the past year, most notably, one brand, Juul. As of first quarter 2018, (per Nielson data) Juul had more than 50% of the ENDS market share, surpassing all of big tobacco's e-cigarette products together. Use of Juul products ('juuling') among youth has raised significant concern. All pod devices have a simplistic compact design and features that make them lightweight, ultra-portable and easy to use inconspicuously, with many simply resembling a computer thumb drive.

Each pod holds **nicotine salt** solution. Although the exact physiological mechanisms of nicotine salts have not been studied in detail, these compounds are believed to increase the amount and rate of nicotine uptake in pod users, effectively increasing the dose of nicotine delivered to the circulation and central nervous system. Modification of physicochemical properties of tobacco products to increase its addictiveness and appeal to users is not a new approach: Tobacco

companies have been known to add ammonia to tobacco to enhance nicotine's bioavailability to smokers. In addition to their potentially increased bioavailability, nicotine salts appear to be easier to inhale, as users report less upper respiratory tract irritation when compared with other products containing high nicotine concentrations. While youth don't identify nicotine as a reason for choosing ENDS products (indeed, youth often don't know which products do and don't contain nicotine), nicotine likely plays a determining role in the continued teen use of ENDS. Pods contain solutions with highly concentrated nicotine salts, primary nicotine benzoate.



PILOT STUDIES: We measured total nicotine concentration in pod products, and found that all tested products contained high nicotine concentrations, varying from 22 to 59 mg/mL (1). These concentrations are much higher than reported in older ENDS products. We also measured total nicotine yields in aerosols generated from these products using a smoking machine and standardized laboratory puffing protocol. We estimated that users of prefilled pod systems (e.g. Juul) may inhale with 10 puffs from 0.77 to 0.85 mg of nicotine (1). This estimated nicotine dose is higher than previously reported in older generations of EC devices (0.02–0.51 mg/10 puffs) (2).

JUUL has emerged as the leading mass-marketed vaping product over the last year, and other manufacturers have commenced selling salt-based liquids. There is emerging evidence suggesting that this form of nicotine delivery allows for higher nominal concentrations to be combined with lower heating temperatures for aerosol generation to provide less perceived harshness and fewer volatile organic compounds on a per-unit-nicotine basis. However, the pharmacokinetics of nicotine delivery for salt-based liquids has not been fully elucidated, and it is unclear whether the salt *per se* affects absorption, subjective effects, or product choice under standardized conditions of use. Similarly, while anecdotal evidence from users suggests that JUUL-like products are perceived as less harsh, there is little evidence from controlled studies. There is also limited evidence from food research that sodium benzoate, the salt used in JUUL and other salt-based liquids, may enhance sweet tastes and suppress bitter tastes. So, salts may have additional effects on flavor perceptions. Understanding pharmacokinetics and subjective effects is crucial to understanding whether salt-based liquids differ from other e-liquids in terms of abuse liability. Behavioral economics provides additional insights into abuse liability, particularly with regard to appeal and substitution, which can be assessed with the Experimental Tobacco Marketplace (ETM) (3). The ETM, combined with PK and subjective effects data, can provide layers of insight into the abuse liability of salt-based flavored ENDS.

3 INCLUSION AND EXCLUSION CRITERIA

Screening: Upon calling, potential participants will be given a brief explanation of the study and their eligibility to participate will be determined (**Appendix D:** Telephone Screening Questionnaire). All participants who meet the inclusion and exclusion criteria summarized in **Section 3.1** and **Section 3.2** will be treated on an outpatient basis.
All four study visits will take place in the Department of Health Behavior - Human Exposure Lab at Roswell Park Comprehensive Cancer Center (Basic Science Bldg. Room 3920). The laboratory is 10'10.5" x 11'8" space equipped with a sink, multiple infusion chairs, and an Axis Communications video camera. In addition, the laboratory also has a specialized mechanical exhaust system designed to keep the room under negative air pressure at all times.

In order to minimize any carry-over effect, there will be a minimum 5-7-day wash-out period between each scheduled study visit and, the order of the e-liquid flavors will be randomly assigned.

3.1 Inclusion Criteria

- Age ≥ 21 years and ≤ 55 years
- Willingness to abstain from using ENDS product for 8-10 hours (overnight abstinence) prior to study visits
- Current daily ENDS user as determined by
    - Has used ENDS product every day for the past 6 months (by history)
    - Has used ENDS product or e-liquid containing nicotine (by history)
- Participant must understand the investigational nature of this study and sign and Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

Refer to **Appendix A** for the Investigator Study Eligibility Verification Form: Inclusion Criteria.

3.2 Exclusion Criteria

- Smoked cigarettes in the past 7 days.
- Currently smokes ≥ 5 cigarettes per month.
- Unstable medical conditions (such as unstable heart disease, uncontrolled hypertension, thyroid disease, diabetes, renal or liver impairment, or glaucoma) or psychiatric condition (such as current major depression, history of schizophrenia or bipolar disorder) or current regular use of psychiatric medications (such as major tranquilizers and antidepressants).
- History of serious side effects from nicotine or from any nicotine replacement therapies.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant or nursing females.
- Concurrent participation in another clinical trial

- Unwilling or unable to follow protocol requirements.
- Any condition which in the Investigator's opinion deems the participant an unsuitable candidate.

Refer to **Appendix B** for the Investigator Study Eligibility Verification Form: Inclusion Criteria.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

3.4 Special Populations

The following special populations are excluded from this study:

- Cognitively impaired adults/adults with impaired decision-making capacity
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

This is a single center study to be conducted at Roswell Park. The target accrual is 20 evaluable participants (participants who have completed all 4 study visits), with an equal number of males and females. Accrual is expected to take up to 4 years.

5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

Participants will be recruited from advertisements in local newspapers/magazines, posters, community centers, churches, and from several websites (Roswell websites, Craigslist.org, Facebook, and Instagram). An example of the participant recruitment material can be found in **Appendix C.** Applicants will be invited to call a local number. On calling, applicants will be given a brief explanation of the study and their eligibility to participate will be assessed **(Appendix D)**. Those who meet eligibility criteria will be included in the study and attend 4 weekly sessions. We anticipate that each session will take 120 minutes. After completion of each visit, participants will be asked to vape as usual over the next week, and the procedures will be repeated every week for the total of 4 visits.

Study participants will be compensated by cash for each study visit completed and will receive additional "bonus" cash if all study visits have been completed. Payments will be disbursed according to the following schedule (**Table 1):**

Table 1Study Payment Schedule

Study Visit	Payment Amount
1	$50.00
2	$60.00
3	$70.00
4	$80.00
All Visits Completed	$90.00 bonus
TOTAL	$350.00

6 MULTI-SITE RESEARCH

- Not Applicable – This is a single-site study.

7 STUDY TIMELINES

- The anticipated duration of intervention is 4 weeks. Each participant will be scheduled for 4 study visits. Study visits may occur at a minimum of 5-7 days apart, but no more than 4 weeks apart.
    - Each study session is expected to take approximately 2.0 to 2.5 hours.
    - The duration anticipated to enroll all study participants is 4 years.

8 STUDY ENDPOINTS

8.1 Primary Endpoint(s)

- Maximum concentration of nicotine in plasma (C_{max}), the area under the concentration – time curve from 0 to 120 min (AUC), and the time to maximum concentration (T_{max}).

8.2 Secondary Endpoint(s)

- Perceived harshness, satisfaction, liking, and relief of nicotine withdrawal symptoms.

8.3 Exploratory Endpoint(s)

- Demand indices including intensity and elasticity of demand for each device sampled and substitution levels of alternative tobacco products.

9 DESIGN

This is a single center, randomized, double blind clinical trial pilot. Using a 2 (free-base vs salt) x 2 (tobacco vs unflavored) factorial design, 20 current daily vapers will be asked to use one of four liquids across four 2.5-hour laboratory sessions. The order of the tested conditions will be randomized and study personnel as well as participants will be blinded to the four liquids throughout the study. Participants will be aged 21-55, use a vaping product daily, have a preferred flavor of tobacco, and not currently smoke cigarettes (no cigarette use in the past seven days and no more than 5 cigarettes in last 30 days). For each session, participants will arrive after overnight abstinence and be randomly assigned to one of the four liquids and puff according to a standardized protocol (10-minute bout, 20 puffs, 30 second inter-puff interval). Venous blood samples (4 mL) to measure nicotine will be drawn by a either certified phlebotomist through a butterfly needle or

through a catheter by a certified registered nurse before and at 2, 4, 5, 6, 8, 10, 13, 15, 20, 30, 45, 60, 90, and 120 min after onset of use. Samples will be processed within 2 hours and frozen at -80°C until analysis. Plasma samples will be analyzed for nicotine concentration using sensitive and validated UPLC-MS/MS method developed by TCORS analytical core located at Roswell Park. At the same time intervals, participants will complete standard subjective effects measures, including the Drug Effects scale, ENDS Nicotine Dependence Scale, Minnesota Nicotine Withdrawal Scale, Product Evaluation Scale, and the Duke Sensory questionnaire, Delay Discounting Task and the ETM with the product being tested available for the fixed price in the marketplace. Participants will be compensated by cash for each study visit completed and will receive an additional $90.00 bonus if all study visits have been completed **(Table 1).**

10 INTERVENTION

Active Substance and Source

During each visit, following an overnight abstinence, participants will be asked to take 20 puffs over 10 minutes (one puff every 30 seconds) from an Innokin EQs Ultra-Compact 2 mL Refillable Pod Vaporizer equipped with a 800mAh battery. All devices and solutions will be purchased from a local vape shop called the House of Vapor located in Kenmore, NY. Study personnel will set the device to 11.5W for every study session.

10.1 Dosing and Administration

The device will be filled with either (1) free-based nicotine e-liquid solution of unflavored (2) free-based nicotine e-liquid solution of tobacco flavor (3) salt-based nicotine e-liquid solution of unflavored or (4) salt-based nicotine e-liquid solution of tobacco flavor. Both the study personnel and study participants will be blinded to the solution flavor and nicotine concentration. All e-liquids will contain 0.148M nicotine (24 mg/mL free-base nicotine or 24 mg/mL nicotine benzoate). Participants are randomized to the order of the e-liquids by the study statistician using the Williams Design; a special case orthogonal latin squares design generated using SAS v9.3.

Intervention will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in **Section 13 and Section 17**.

Nicotine (3-(1-methylpyrrolidin-2-yl)-pyridine) the primary alkaloid in tobacco products binds stereo-selectively to nicotinic-cholinergic receptors on autonomic ganglia, the adrenal medulla, neuromuscular junctions and in the brain. Nicotine exerts two effects, a stimulant effect exerted at the locus ceruleus and a reward effect in the limbic system. Intravenous administration of nicotine causes release of acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, beta-endorphin and ACTH. Nicotine is a highly addictive substance. Nicotine also induces peripheral vasoconstriction, tachycardia and elevated blood pressure. Nicotine replacement therapies (like inhalers and patches) are used to treat smoking withdrawal syndrome. Nicotine is classified as a stimulant of autonomic ganglia.

Electronic nicotine delivery systems (ENDS) usually look similar to regular cigarettes, cigars, pipes, or pens, but do not contain tobacco. Instead, they are comprised of a battery-powered atomizer that produces vapor for inhalation from solutions that contain nicotine. Electronic cigarettes (e-cigarettes) are the most popular ENDS on the market. Different ENDS brands are engineered differently. The differences include the appearance, the nature of nicotine solution, the capacity of the cartridge containing the solution, the nature of the heating element, and size and

type of battery. Propylene glycol or glycerin, are primary used as solvents for nicotine. Solutions may contain just one or both solvents mixed with water. Various additives and flavorings are commonly added to nicotine solution, including fruit and candy flavors, ethyl alcohol, non-nicotine pharmacologically active compounds and stabilizers. ENDS devices of newer generation often contain nicotine salt solution. Although the exact physiological mechanisms of nicotine salts have not been studied in detail, these compounds are believed to increase the amount and rate of nicotine uptake in pod users, effectively increasing the dose of nicotine delivered to the circulation and central nervous system. The heating elements are usually thin (filament) wire made with various metals (nickel, chromium, copper coated with silver). These engineering features affect the chemical composition of the ENDS vapor. The type of ENDS and e-liquid solution that will be provided to study participants includes:

Table 2. ENDS and E-liquid Solutions

Innokin EQs Ultra-Compact Refillable Pod Vaporizer [1]	
Free-based nicotine solution Unflavored (24 mg/mL)	
Free-based nicotine solution Tobacco (24 mg/mL)	

Salt-based nicotine solution Unflavored (24 mg/mL nicotine benzoate)	
Salt-Based solution Tobacco (24 mg/mL nicotine benzoate)	

1 ENDS used at all 4 study visits

11 PROCEDURES INVOLVED

A total of 20 ENDS users will be recruited for this study with equal numbers of men and women. All participants will be seen after an overnight abstinence of approximately 8 hours at Roswell Park Comprehensive Cancer Center (The Department of Health Behavior Human Exposure Lab) on 4 separate occasions, at least 5-7 days apart (with a maximum of 4 weeks between visits allowed before the participant is taken off study). Each study visit is expected to last approximately 2.0 to 2.5 hours. The anticipated duration of intervention is 4 weeks.

After 8-10 hour overnight product abstinence (confirmed by self-report and expired CO less than 8 ppm), participants will be admitted to The Department of Health Behavior Human Exposure Lab. This will be done so that effect of various e-liquid solutions on nicotine withdrawal symptoms might be assessed. (For analysis purposes, once the study is closed and the blood samples are analyzed, anyone with a nicotine concentration ≤ 2 mL in their blood for the T0 sample will be deemed as adhering to the overnight abstinence. Anyone with a nicotine concentration > 2 mL in their blood for the T0 sample will be marked as not adhering to the abstinence. Adjustments will be made for the analysis of this finding and controls set in place when running statistics on order to account for this finding.

Participants will be asked to take 20 puffs over 10 minutes (one puff every 30 sec) from the assigned ENDS product (Innokin EQs Ultra-Compact 2mL Refillable Pod Vaporizer equipped with a 800mAh battery and wattage set to 11.5W), presumed equivalent in nicotine yield to a single cigarette (based on pilot studies 20 puffs generate aerosol with cumulative nicotine yields from 1.5 mg to 1.7 mg). Participants will be video-recorded to analyze puffing behaviors (product operation, number of puffs, and time of puffing and exhaling vapors). Participants will also be asked to provide a urine sample before the 10 min puffing session as well as after the 10 min puffing session. Urine samples will be tested for cotinine, NNAL and VOC metabolites.

Venous blood samples to measure nicotine will be taken either through butterfly needle by a certified phlebotomist or through a catheter by a certified registered nurse before and 2, 4, 5, 6, 8, 10, 13, 15, 20, 30, 45, 60, 90, and 120 min after onset of use of ENDS product with tanks of each e-liquid solution. A total of 60 mL of blood may be collected using a 4mL green top heparinized vacutainer blood collection tube during each visit (15 collection time points, 4 mL at each time

point, not all collection time points will be fulfilled at each visit). If the participant is experiencing excessive blood clotting, the butterfly needle will be removed and a new butterfly needle will be inserted to continue with blood collection (the number of new butterfly needle insertions will never exceed three per study session). The butterfly needle or catheter may be placed in upper extremity or the hand of the participant. Nicotine in plasma will be measured by a high sensitivity GC-MS/MS method (4). Vital signs will be taken and expired CO will be measured before and 3 minutes after the use of each e-liquid solution (CO monitor, Bedfont, UK). Females of child-bearing potential will be asked to test urine for pregnancy.

At visit one only, participants will be asked to complete several questionnaires including: Demographics **(Appendix E)**, Smoking History **(Appendix F)**, Time-line Follow Back to assess past 30 day tobacco product use (5) **(Appendix G)**, Penn State E-cigarette Dependence Index **(Appendix H)**, and Taste Preference **(Appendix I)**. During each visit participants will be asked to report on the Minnesota Nicotine Withdrawal Scale (MNWS) and the strength of nicotine withdrawal symptoms (craving, irritability, difficulty in concentration, and restlessness) before and after product use **(Appendix J)**. Participants will also rate their mood before and after product use (**Appendix K).** Satisfaction with and helpfulness of the product will be measured at the end of each session using an adapted questionnaire (**Appendix L**). Acute subjective responses to the effects of nicotine will also be measured using the Drug Effect Questionnaire (DEQ-5) after product use **(Appendix M)** as well as a questionnaire to assess a participant's craving to smoke **(Appendix N)**. Puffing topography will be assessed with an eTop monitor after all blood draws are complete. At this time, subjects will be asked to puff on the assigned ENDS product ad lib with the eTop monitor. Participants will also be asked to complete the product evaluation scale, which assesses subjective effects such as liking and satisfaction, at visit four after experiencing each e-liquid solution **(**Appendix O**)**. Additionally, participants will complete the Experimental Tobacco Marketplace product purchasing task **(Appendix P)**. During the ETM, participants will purchase hypothetical tobacco products in an online store analog with an account balance determined by past 30 day-tobacco product use at Session 1. The product being sampled during the session will be available for purchase under four different price conditions. Other tobacco products will be simultaneously available at a constant price. Average time to completion using four price conditions is 8 minutes. Participants will also be asked to answer a series of questions regarding involving Sensory Measures **(Appendix Q).**

Table 3. Schedule of Procedures and Observations

Visit	#1	#2	#3	#4
Week	**1**	**2**	**3**	**4**
Nicotine Solution	**E-liquid Solution #1**	**E-liquid Solution #2**	**E-liquid Solution #3**	**E-liquid Solution #4**
Informed Consent[1]	X			
Demographics and Smoking history (**Appendix E)** Timeline Follow-Back **(Appendix G)** Penn State E-Cigarette Dependence Index **(Appendix H)** Taste Preference **(Appendix I), ENDS Dependence Scale (Appendix R)**	X			
Vital signs	X	X	X	X
Blood Draw for Analytical Testing[2]	X	X	X	X
Pregnancy Test (Urine)	X	X	X	X
Urine Sample (before and after 10min puffing session)	X	X	X	X
Puffing Topography	X	X	X	X
CO *Pre and Post-Product Use*[3]	X	X	X	X
Minnesota Nicotine Withdrawal Scale (MNWS)(adapted) **(Appendix J)** *Pre and Post Product Use*	X	X	X	X
Positive Negative Affect Scale (PANAS) (**Appendix K)** *Pre and Post Product Use*	X	X	X	X
Satisfaction With and Helpfulness of the Products (**Appendix L)** *Post Product Use*	X	X	X	X
Drug Effect Questionnaire (DEQ-5) (**Appendix M)** *Post Product Use*	X	X	X	X
Modified Questionnaire of Smoking Urges (QSU-brief) (**Appendix N)** *Post Product Use*	X	X	X	X
Adverse Events	X	X	X	X
Concomitant Medications	X	X	X	X
Product Satisfaction Scale **(Appendix O)** *Post Product Use*				X
Experimental Tobacco Marketplace (ETM) **(Appendix P)**	X	X	X	X
Sensory Measures **(Appendix Q)** *Post Product Use &* Delay Discounting Task	X	X	X	X

1 Must be signed prior to any study related assessments or procedures.

2 See **Section 15** for Data and Specimen Banking

3 Expired CO will be measured before, and 3 minutes after the use of each product

12 WITHDRAWAL OF SUBJECTS

Participants will be given phone numbers for research associates and supervising physicians to call if there are adverse effects or other study-related problems. Participants will be advised that if they have any adverse effects and/ or wish to stop participating in the study for any reason, they are free to do so. Participants who are injured as a result of being in the study will have treatment available. The costs of such treatment may be covered by Roswell, depending on a number of factors.

Any participant who discontinues due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of AE will be reported in the participant's study records and to the study DSMB.

Reasons for intervention discontinuation/withdrawal from the study should be classified as follows:

- Death.
- Adverse side effects; related or unrelated to intervention.
- The Investigator may discontinue a participant if, in his/her judgement, it is in the best interest of the participant to do so.
- Noncompliance (defined as missing scheduled visit by more than 2 weeks without contact).
- Participant voluntary withdrawal. A participant may withdraw from the study at any time, for any reason.

13 RISKS TO SUBJECTS

The potential risks to participants in the clinical studies, and their likelihood and seriousness, are described below. Participants can choose, as an alternative, to not enroll in this study. Overall, there is minimal risk for serious adverse reactions as a consequence of enrolling in this study.

- *Nicotine overdose:* Some people who use ENDS may experience symptoms of nicotine overdose such as nausea, sleep disturbance, headache, and vomiting; however, these symptoms are usually mild and temporary. Before ENDS are used in human participants, they have undergone laboratory testing to assess the yields of nicotine present in the products; this will also provide quality control information to select the safest product.
    - The PK studies using ENDS in participants will be performed in a clinical setting accustomed to monitoring for adverse effects. The PI and Co-I's have considerable experience with conducting outpatient studies on novel nicotine delivery devices and their effects on participants, and will be able to provide appropriate safety monitoring.
    - Participants will also be instructed that the investigational products are not to be ingested. If a product is ingested by mistake, the participant will be instructed to call the study physician (Dr. Mahoney). If they are experiencing serious symptoms of nicotine overdose, the participant should contact Poison Control or Emergency Medical Services.
- *Nicotine withdrawal:* Many individuals who quit smoking exhibit a pattern of symptoms related to withdrawal from tobacco use. These symptoms include: sadness and anxiety, irritability, anger, difficulty concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Because participants in the studies will be asked to refrain from smoking and or using their ENDS for portions of the study, it is likely that they will experience some of these symptoms. Consent forms will include sections describing the possibility of this occurrence. Study personnel will be trained to recognize these symptoms and educate the participants about them.
- *Respiratory irritation*: Some people who use ENDS may experience irritation of the mucosal membranes of the upper respiratory tract, but as they are already regular ENDS

users we do not think that this is likely. We will exclude participants or postpone procedures if they demonstrate chronic or acute respiratory problems.

- *Inconvenience*: It is quite probable that participants will experience *inconvenience* due to the multiple study visits required.
- *Venipuncture* is required for study participation and this could lead to local pain, swelling, bruising or infection. Significant complications (beyond typical local pain and mild bruising) are expected to be uncommon. *The volume of blood to be withdrawn will never exceed 60 mL on any planned visit*. This amount of blood is safe for the participants and will not produce any injury to a healthy individual.
- *Emotional distress:* Participants may experience psychological discomfort during assessments when discussing feelings and attitudes about smoking and using ENDS, or from learning about the risks of smoking. However, all participants will be current ENDS users and we do not expect this type of reaction to be likely. Study personnel will be alerted to expect this from a small number of participants and will be trained to make referrals for mental health services as needed. Personnel will be trained to query for adverse emotional reactions during assessments and will be trained to deal with such reactions and to provide additional referrals if needed. In addition, if assessments indicate psychiatric concerns, referrals to appropriate psychological services will be provided.
- *Reproductive Risks*: Women will be advised to notify the study staff if they become or intend to become pregnant during the study period. Because nicotine and e-cigarette vapor safety for an unborn baby is unknown, participants will be told that they should not become pregnant while on this study nor should they nurse a baby. If a woman is pregnant or breast feeding, she may not participate in this study, and if she becomes pregnant during the study, she will be removed from the study.

As general measures to minimize the likelihood of participants experiencing these side effects staff will have the study physician's (Dr. Martin Mahoney) cell phone number and will contact Dr. Mahoney with all questions and concerns. We will also:

1. Employ a stringent list of exclusionary criteria to limit the chance of side effects listed above occurring. Potential participants will be screened for medical illnesses that would preclude the ENDS use and/or increase the risk of adverse events or side effects (e.g., respiratory diseases, cardiovascular conditions).
2. Administer the ENDS of the highest quality (based on the outcome of the pre-clinical studies).
3. Monitor self-reported side effects at each assessment time-point (i.e., each clinic visit). Participants will be informed about the potential for adverse events or side effects from ENDS use, including upper respiratory tract mucosa irritation, cough, phlegm, headache, nausea, and emotional distress from learning about the adverse health consequences of smoking. Participants will be told that they should proceed with caution until they are certain that ENDS do not affect their performance.
4. The study physician (Dr. Mahoney) will be alerted to any severe side effects or any reported adverse events. The study physician will review the information provided by the research staff and if applicable, will contact the study participant within 24 hours after being notified

to gather more information and determine the appropriate course of action for the participant. Ultimately, the study physician will decide if the adverse event is related to study treatment and whether the participant should discontinue its use.

Participants will be told that they should proceed with caution when using ENDS and to report any adverse symptoms or side effects to study personnel immediately.

14 POTENTIAL BENEFITS TO SUBJECTS

There is no direct benefit for those who decide to participate and enroll in this study.

15 DATA AND SPECIMEN BANKING

Pharmacokinetic Blood Sample Collection

Whole blood samples for analytical testing of nicotine and cotinine levels will be collected via venipuncture using a butterfly needle or a venous catheter using 4 mL green-top heparinized collection tubes. The blood will be drawn by either a certified study phlebotomist using a butterfly needle, or a venous catheter placed by a registered nurse. Blood sample collection will be obtained at each study visit prior to and 2, 4, 5, 6, 8, 10, 13, 15, 20, 30, 45, 60, 90, and 120 min after onset of use of each nicotine solution, approximately 4 mL will be taken at each time point (not all collection time points will be fulfilled at each study visit). If the participant is experiencing excessive blood clotting, the butterfly needle will be removed and a new butterfly needle will be inserted to continue with blood collection (the number of new butterfly needle insertions will never exceed three per study visit). The butterfly needle or venous catheter may be placed in the upper extremity or in the hand of the participant.

For all participants, the amounts drawn will not exceed 240 mL for the entire study and collection will not occur more frequently than 2 times per week.

Urine Sample Collection

Urine samples will be taken before and after ENDS product use. Female urine samples will be tested for pregnancy.

All blood and urine samples will be immediately transported to the Health Behavior Department Laboratory (Roswell Park Comprehensive Cancer Center); the blood samples will be centrifuged to separate the plasma from whole blood. The plasma will be aliquoted into cryovials that are labeled with the participant's initials, participant's study number, clinical study number, protocol time point, product, and protocol day. Urine samples will be transferred to 15 mL Flacon tubes. The samples will immediately be frozen at -70ºC or below in Dr. Goniewicz's Laboratory until analyzed. Plasma will be analyzed for cotinine and nicotine using UPLC-MS/MS method (6). Urine samples will be tested for cotinine, NNAL and VOC metabolites. Female urine samples will be tested for pregnancy. All blood and urine sample results are recorded in logs and kept in:

Dr. Goniewicz's Laboratory
Gratwick Basic Science Building (GBSB)
Health Behavior Department Laboratory
Laboratory location: 4th Floor, Room 4942
Laboratory phone: 716-845-8603
Dr. Goniewicz's office number: 716-845-8541

If there are remaining blood or urine samples after all analysis has been done and the participant checks yes on the consent document to having any extra samples stored for future studies, then the samples will be kept in a -70°C or below freezer in Dr. Maciej Goniewicz's Laboratory listed above. If there are remaining samples and the participant checks no on the consent document to having any extra samples stored, then the extra samples of that participant will be immediately destroyed once they are taken off study or completed.

Any future research on the remaining samples will only be done under IRB-approved protocols.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

16 MEASUREMENT OF EFFECT

Not Applicable

17 SAFETY EVALUATION

17.1 Safety Monitoring

ENDS have been used before by us or by other researchers that we are aware of, and the risks appear to be minimal. Monitoring for safety will be carried out by review of all clinical complications and all of the data by the PI and Co-Investigators including Physicians. Reporting of adverse events will follow requirements mandated by the both IRBs (Committees on Human Research, CHRs). This will be followed by a detailed written report within ten (10) working days. In addition, any incidents or problems involving the conduct of the study or patient participation, including problems with the recruitment and/or consent processes will be reported within ten (10) working days. The Principal Investigator will provide a discussion of any problems noticed during each year in the course of the study to the both IRBs (CHRs) on an annual basis. The standard adverse event grading scale will be used to report any potential adverse events from phlebotomy, study device or other study procedures: 1) Mild AE – did not require treatment; 2) Moderate AE – resolved with treatment; 3) Severe AE – resulted in inability to carry on normal activities and required professional medical attention; 4) Life-threatening or disabling AE; and 5) Fatal AE. The supervising study physician will be notified of all grades 2 through 5 AEs. Additionally, Dr. Quisenberry will be notified of all grades 4 and 5 AEs. Grade 3 through 5 AEs will be reported to the IRBs (Grades 4 and 5 - within 24 hours; Grade 3 - within 10 days). Grade 2 will be included in the yearly progress report. Grade 1 will not be reported. Frequency of Safety Reviews: Subject safety data reporting is a formal part of weekly research group meetings at both collaboration centers and during teleconferences between PI and Co-I; safety reviews will be conducted through review of all clinical complications and data when it returns, including laboratory data. Safety data are collected on a daily basis. Safety reviews will be conducted annually in conjunction with the protocol renewal to IRBs.

17.2 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
  - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per Section 17.7.

17.2.1 Reporting Unanticipated Problems

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

18 DATA MANAGEMENT AND CONFIDENTIALITY

To ensure data security and confidentiality, all assessments will be administered by trained research study staff, and blood draws will be performed by certified phlebotomists or registered nurses.

Data management activities will be performed using REDCap (Research Electronic Data Capture). REDCap is a secure web-based application that supports data capture and management for research studies. In the event of REDCap being inaccessible for a study visit, paper copies of the questionnaires will be administered to the participant at that point in time and data entry will be performed by the assigned Senior Research Associate after the study session is completed. Data can be entered and changed only by those with the rights to do so.

All participant records and data will be held in the Health Behavior Department at Roswell Park Comprehensive Cancer Center. All personnel involved in the conduct of this study are Roswell Park staff.

- Access to the data by all necessary research personnel will be through a password-protected network computer. At no time will data be downloaded on a thumb drive or other portable media or laptop. Participant identity will not be disclosed in the event of publication or sharing of data.

- Participant identity will not be disclosed in the event of publication or sharing of data.
- Any paper files containing identifiers (if applicable to the research) will not be taken off Roswell Park premises; they will be kept in a locked filing cabinet in a secure building on the Roswell Park's campus.
- PHI will be not re-used or disclosed for purposes other than research use.
- There are no outside entities to which PHI will be disclosed.
- Essential documents will be retained per Roswell Park's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with Roswell Park.

19 STATISTICAL PLAN

19.1 Sample Size Determination

The sample size calculations are based on the primary analysis of the area under plasma nicotine concentration-time curve (AUC nicotine), which is compared between salt and free-base forms of e-liquid. A simplified calculation is based on the two-sided two-sample t-test, where a sample size of n=18 provides 80% power (at a significance level of 0.05) to detect a true difference of at least 700 ng/mL × min. This is based on the assumption that the within-patient standard deviation of the response variable is 500 ng/mL × min.

The reduction in AUC of 700 ng/mL x min corresponds to 4-fold reduction in nicotine content in tobacco cigarettes. This effect was observed among smokers who switched from cigarettes with high nicotine content (12 mg) to low nicotine content cigarettes (4 mg)

To account for potential drop-out, a maximum of 20 participants will be enrolled. Accrual for this study is expected to take 4 years.

19.2 Randomization

This study is a randomized within-subject cross-over study, where the order of *four types of nicotine solutions* that the participant receives will be randomized. Participants will be provided with cartridges of maximum available amounts of nicotine (labeled as high: approx. 24 mg). All participants and study personnel will be blinded to the flavor names and nicotine content in cartridges. Participants will be provided with cartridges of different nicotine solutions at each visit, instructed on how to use the product, and partake in the controlled 10-minute puffing session (1 puff every 30 seconds, 20 puffs total).

Note: In order to minimize any carry-over effect, there will be a minimum 5-7-day wash-out period between each scheduled study visit and, the order of the nicotine solutions will be randomly assigned (with a different randomization order for each participant). In addition, we will consider linear mixed models that will incorporate a carry-over effect. This will provide a more conclusive analysis, but also potentially validate the effectiveness of the wash-out period, which could help in the design of future studies.

19.3 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

19.4 Primary Analysis

The primary objective is to evaluate whether AUC nicotine, C_{max} or T_{max} differ between free-base and salt-based versions of the same liquid, controlling for flavoring and nominal nicotine concentration.

Each outcome will be modeled as a function of base (free-base versus salt-based), flavor (tobacco versus unflavored), their interaction, prior combination indicator (for carry-over effect), and a random subject effect using a linear mixed model. All model assumptions will be verified graphically and transformations will be applied as appropriate. The effect of "base" on the AUC nicotine, C_{max} and T_{max} measures will be evaluated using tests about the least square means of "base". Additionally, 95% confidence intervals about the mean differences will be obtained.

19.5 Secondary Analysis

The secondary objective is to evaluate the effect of flavoring on subjective effects (i.e. perceived harshness, satisfaction, liking, and relief of nicotine withdrawal symptoms) differences between matched free-base and salt-based e-liquids.

Each outcome will be modeled as a function of base, flavor, their interaction, prior combination, and a random subject effect using a linear mixed model. All model assumptions will be verified graphically and transformations will be applied as appropriate. An F-test about the interaction-term of base and flavor will be used to determine whether the impact of flavor on these subject measures differs between bases.

19.6 Exploratory Analysis

Exploratory analysis/analysis of exploratory aim: First, to quantify the relationship between purchasing and the price of e-cigarettes, the data will be fit to a modification of a model proposed by Hursh and Silberberg (2008):

$$Q = Q_0 + 10^{k(e^{-\alpha Q_0 C} - 1),}$$

where Q is amount of the commodity purchased, C is the price, Q_0 is the derived initial consumption without cost constraints (i.e., demand intensity and a secondary measure of abuse liability), k is the logarithmic range of the function, and α is the demand elasticity (i.e., sensitivity to price and the primary measure of abuse liability). Q and C are determined by the data and k is a set constant, leaving only Q_0 and α as free parameters to be fit. Second, the fit parameters, Q_0 and α will be compared with a 2 (nicotine type: salt- or free-based) X 2 (flavor: tobacco or unflavored) ANOVA to determine the abuse liability level of nicotine type, flavor, and the interaction between the two. Then, to analyze the level of substitution of alternative tobacco products, we will fit linear regressions for each product type. Slopes that differ from zero will be considered substitutes within each product availability condition. To compare the level of substitutability in the different product availability conditions, slopes will be compared using a 2 X 2 ANOVA.

20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

Subjects will be given phone numbers for research associates and supervising physicians to call if there are adverse effects or other study-related problems. Subjects will be advised that if they have any adverse effects and/ or wish to stop participating in the study for any reason, they are free to do so. The data collected from this study will be organized by a unique identification number assigned to the participant so that their identity will be available only to project staff and will remain completely confidential. The clinical study coordinator and staff and PI of the study will have access to the data records. All study records will be kept electronically in Roswell Park Comprehensive Cancer Center maintained and secured equipment. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

21 VULNERABLE POPULATIONS

Not Applicable.

22 COMMUNITY-BASED PARTICIPATORY RESEARCH

Not Applicable.

23 SHARING OF RESULTS WITH SUBJECTS

No results will be shared with study participants or with parties outside of the research team.

24 SETTING

All study sessions will take place in The Health Behavior Human Exposure Lab located at Roswell Park Comprehensive Cancer Center. The research team will identify and recruit potential participants from the Western New York region.

25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Participants will be given phone numbers for research associates and supervising physicians to call if there are adverse effects or other study-related problems. Participants will be advised that if they have any adverse effects and/ or wish to stop participating in the study for any reason, they are free to do so.

The data collected from this study will be organized by a unique identification number assigned to the participant so that their identity will be available only to project staff and will remain completely confidential. The clinical study coordinator and staff and PI of the study will have access to the data records. All study records will be kept electronically in Roswell Park Comprehensive Cancer Center maintained and secured equipment.

Any data, specimens, forms, reports, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking

programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26 RESOURCES AVAILABLE

All data and specimen collection will be done by trained registered nurses, clinical research coordinators, research associates, or certified phlebotomists working on this study.

All study procedures will be performed in the:

Health Behavior Human Exposure Lab
Gratwick Basic Science Building (GBSB)
Laboratory location: 3rd Floor, Room 3920
Laboratory phone: 716-845-3312

The laboratory is 10'10.5" x 11'8" space equipped with a sink, multiple infusion chairs, and an Axis Communications video camera. In addition, the laboratory also has specialized mechanical exhausts and ducts designed to keep the room under negative air pressure at all times.

In addition, our University at Buffalo collaborator, Nicholas Felicione, will be involved in design, data analysis, and manuscript preparation.

27 PRIOR APPROVALS

No prior approvals.

28 COMPENSATION FOR RESEARCH-RELATED INJURY

If the participant believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-3597.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor (716-845-3161) will be able to provide an explanation of coverage and to answer questions the participant may have regarding study related billing.

The participant is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

29 ECONOMIC BURDEN TO SUBJECTS

Participants will be responsible for transportation to and from the research site and any costs that might entail. The remainder of the study will be conducted at no financial cost or obligation to the participant.

30 CONSENT PROCESS

The Investigator (or IRB approved designee) is responsible for obtaining written consent from each participant in accordance with ICH-GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant

according to ICH-GCP, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be given to the CRS Regulatory Research Associate for the Regulatory Binder. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

The consenting process will take place at the first visit for every participant. The consent MUST be signed by every participant before any study procedure is performed.

The Roswell Park SOP: Informed Consent Process for Research (HRP-090) will be followed.

31 PROCESS TO DOCUMENT CONSENT IN WRITING

The Roswell Park "SOP: Written Documentation of Consent (HRP-091)" will be followed.

32 DRUGS OR DEVICES

During each visit, participants will be asked to take 20 puffs over 10 minutes (one puff every 30 seconds) from an Innokin EQs Ultra-Compact 2 mL Refillable Pod Vaporizer equipped with a 800mAh battery **(Table 2)**. Study personnel will set the device to 11.5W at every study session. The device will be filled with either (1) free-based nicotine e-liquid solution of unflavored (2) free-based nicotine e-liquid solution of tobacco flavor (3) salt-based nicotine e-liquid solution of unflavored or (4) salt-based nicotine e-liquid solution of tobacco flavor. Both the study personnel and study participants will be blinded to the solution flavor and nicotine concentration.

All e-liquids will contain 0.148M nicotine (24 mg/mL free-base nicotine or 42 mg/mL nicotine benzoate).

33 REFERENCES

1. Goniewicz ML, Boykan R, Messina CR, Eliscu A, Tolentino J. High exposure to nicotine among adolescents who use Juul and other vape pod systems ('pods') Tobacco Control. 2018 September 7; doi: 10.1136/tobaccocontrol-2018-054565. PMID: PMC6453732
2. Goniewicz ML, Hajek P, McRobbie H. Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications. Addiction. 2014 Mar; 109(3):500-7. PMID: 24345184
3. Bickel WK, Moody LN, Snider SS, Mellis AM, Stein JS, Quisenberry AJ. 2017. The behavioral economics of tobacco products: Innovations in laboratory methods to inform regulatory science, in: Hanoch Y, Barnes A, Rice T, (Eds.), Behavioral economics and healthy behaviors: Key concepts and current research. Routledge, London.
4. Xu AS, Peng LL, Havel JA, Petersen ME, Fiene JA, Hulse JD. Determination of nicotine and cotinine in human plasma by liquid chromatography-tandem mass spectrometry with atmospheric-pressure chemical ionization interface. J Chromatogr B Biomed Appl. 1996 Jul 12;682(2):249-57. PMID: 8844417
5. Sobell LC, Sobell MB. 1992. Timeline Follow-back: A technique for assessing self-consumption., in: Allen J, Litten RZ, (Eds.), Measuring Alcohol Consumption: Psychosocial and Biological Methods. Humana Press, Totowa, NJ, pp. 41-72.
6. Jacob P 3rd, Yu L, Duan M, Ramos L, Yturralde O, Benowitz NL. Determination of the nicotine metabolites cotinine and trans-3'-hydroxycotinine in biologic fluids of smokers and non-smokers using liquid chromatography-tandem mass spectrometry: biomarkers for tobacco smoke exposure and for phenotyping cytochrome P450 2A6 activity. J Chromatogr B Analyt Technol Biomed Life Sci. 2011 Feb 1;879(3-4):267-76. PMID: 21208832
7. Hursh SR, Silberberg A. Economic demand and essential value. Psychol Rev. 2008 Jan; 115(1): 186-98. PMID: 18211190

34 APPENDICES/ SUPPLEMENTS

Appendix A INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM INCLUSION CRITERIA

Participant Name: _____

Participant ID: _____

Title: Pharmacokinetics, Subjective Effects, and Abuse Liability of Nicotine Salt-Based Vaping Products with Tobacco or Unflavored e-liquids [**SALTVAPE** Study]

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 21 years and ≤ 55 years	
☐	☐	☐	2. Current daily ENDS user as determined by: a) Has used ENDS product everyday regularly for the past 6 months (by history); and b) has used ENDS product or e-liquid containing nicotine (by history).	
☐	☐	☐	3. Willingness to abstain from using ENDS and any other nicotine-containing products (incl. tobacco cigarettes) for 8-10 hours (overnight abstinence) prior to study visits.	
☐	☐	☐	4. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix B INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM EXCLUSION CRITERIA

Participant Name: _____

Participant ID: _____

Title: Pharmacokinetics, Subjective Effects, and Abuse Liability of Nicotine Salt-Based Vaping Products with Tobacco or Unflavored e-liquids [**SALTVAPE** Study]

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
			1. Smoked cigarettes in the past 7 days	
			2. Currently smokes ≥ 5 cigarettes per month.	
☐	☐	☐	3. Unstable medical conditions (such as unstable heart disease, uncontrolled hypertension, thyroid disease, diabetes, renal or liver impairment,, or glaucoma) or psychiatric condition (such as current major depression, history of schizophrenia or bipolar disorder) or current regular use of psychiatric medications (such as major tranquilizers and antidepressants).	
☐	☐	☐	4. History of serious side effects from nicotine or from any nicotine replacement therapies.	
☐	☐	☐	5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	6. Pregnant or nursing female participants.	
☐	☐	☐	7. Concurrent participation in another clinical trial	
☐	☐	☐	8. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	9. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**

If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

Appendix C Recruitment Flyer

Appendix D Telephone Screening Questionnaire

Date		
Participant number		
What is your date of birth? *(age ≥ 21 years ≤ 55 years)*	_____/_____/_____	
Do you currently use ENDS (Electronic Nicotine Delivery System or E-Cigarette)? *(must be yes)*	Yes ☐	No ☐
Have you used ENDS for at least 6 months? *(must be yes)*	Yes ☐	No ☐
Does your ENDS contain nicotine? *(must be yes)*	Yes ☐	No ☐
What flavour do you prefer?	☐	
"Are you currently…." Or "Have you…."	**YES**	**NO**
Smoked cigarettes in the past 7 days?	☐	☐
Smoke more than 5 cigarettes in a month?	☐	☐
Pregnant/breastfeeding *(females only)*	☐	☐
Being treated for any medical conditions (such as unstable heart disease, uncontrolled hypertension, thyroid disease, diabetes, renal or liver impairment, or glaucoma)	☐	☐
Being treated for any psychiatric conditions (such as current major depression, history of schizophrenia or bipolar disorder) or current regular use of psychiatric medications (such as major tranquilizers and antidepressants).	☐	☐
Being treated for any illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	☐	☐
Ever had any history of serious side effects from nicotine or from any nicotine replacement therapies.	☐	☐
NEED TO ANSWER 'NO' TO ALL CRITERIA. IF ANSWERED 'YES' TO ANY OF ABOVE: INELIGIBLE How did you hear about our study? _____		

If Eligible:

Great— it looks like you're eligible to participate in the study. Can I have your name and number in case we get disconnected?

Participant Name	Phone Number

Thank you. Now I'd like to give you some more information before asking whether you'd like to make an appointment to come in for your first study session. The purpose of this study is to determine the levels of nicotine effectively delivered by various types of e-liquid solutions to the bloodstream and to compare users' preferences and perceptions of the various e-liquid solutions. If eligible this study requires 4 visits where we ask that you test out different e-liquid solutions, complete surveys and give blood samples. Is this something you think you are interested in doing?

If Answer No:

Thank you for your time. If you have any friends or family that may be interested in this study, feel free to pass along our number. Again, thank you for your time. Goodbye.

If Answer Yes:

Great! We would like to set up an appointment to have you come here to Roswell for your first study session? I would also like to mention that this research has received ethics clearance from the Roswell Park Institute Institutional Review Board and all the information you provide will be kept strictly confidential. Only the investigators directly associated with the study will have access to this information and it will be destroyed once the study is completed. This study is funded by the National Institute of Health (NIH) and the investigators have no affiliations with any tobacco company or maker of nicotine products.

I realize I've given you a lot of information- do you have any questions about the study?

Would you like to make an appointment to come in for your fist session?

If no:

Thank you and goodbye.

If yes:

Great.

We need to book you for an appointment here at Roswell. These are scheduled for [*time to be determined*] on [*day of week to be determined*]

DATE: _____

Time: _____

Directions

You may park in the ramp which is located on the corner of Carlton and Michigan Streets; we will reimburse your parking. After parking, walk across the street and enter through the main entrance of Roswell. Once you walk in someone will be waiting for you by the gift shop and ATM which will be right on your left. We would like to give you a confirmation phone call the day before your visit. Is this a good number to reach you at on that day?

If not: What would be a good number to reach you at? _____

If Ineligible:

Unfortunately, we won't be able to conduct the study with you. However, we have studies running all the time so would you mind leaving us your name and number to contact you about other studies?

Name	Phone Number

We thank you for your interest and if you have any friends or family that may be interested in the study, feel free to pass along our number. Again, we are sorry that it is not going to work. Goodbye.

Appendix E

Demographics

1. What is your birthdate?

   MM/DD/YYYY _____
   [] Don't know
   [] Refused

2. [Follow-up question if participant selects "don't know"] – ONLY IF THEY SELECT DON'T KNOW TO QUESTION #1
   About how old are you?
   AGE_____
   [] Don't know
   [] Refused

3. On your original birth certificate, was your sex assigned as male or female?
   [] Male
   [] Female
   [] Don't know
   [] Refused

4. To which gender identity do you most identify?
   [] Male
   [] Female
   [] Transgender female
   [] Transgender male
   [] Gender variant/ Non-Conforming
   [] Other __if selected let them write in response_____

5. What race or races do you consider yourself to be? Please select one or more.
   CHECK ALL THAT APPLY
   [] American Indian or Alaska Native
   [] Asian
   [] Black or African American
   [] Native Hawaiian or Pacific Islander
   [] White
   [] Other
   [] Don't know
   [] Refused

6. Do you consider yourself to be Hispanic, Latino, or of Spanish origin?

[] Yes
[] No
[] Refused
[] Don't know

7. Where do your ancestors come from? ONLY IF THEY SELECT YES TO QUESTION #6
   [] Puerto Rican
   [] Cuban/Cuban America
   [] Dominican Republic
   [] Mexican/Mexican American
   [] Central/South American
   [] Other Latin American
   [] Other Hispanic or Latino

8. What is your best estimate of the total income of all family members from all sources, before taxes, in the last calendar year?
   [] Less than $10,000
   [] $10,000 to $14,999
   [] $15,000 to $19,999
   [] $20,000 to $24,999
   [] $25,000 to $29,999
   [] $30,000 to $34,999
   [] $35,000 to $39,999
   [] $40,000 to $49,999
   [] $50,000 to $74,999
   [] $75,000 to $99,999
   [] $100,000 to $149,999
   [] $150,000 to $199,999
   [] $200,000 or more
   [] Prefer not to say

9. What is the highest grade or level of school you have completed or the highest degree you have received?
   [] 8th grade
   [] 12th grade, no diploma
   [] High school graduate
   [] GED or equivalent
   [] Some college, no degree
   [] Associate degree
   [] Bachelor's degree (ex.: BA, AB, BS, BBA)
   [] Master's degree or higher
   [] Refused
   [] Don't know

10. We would like to know about what you do—are you working now, looking for work, retired, keeping house, a student, or what?
    [] Working now
    [] Only temporarily laid off, sick leave or maternity
    [] Looking for work
    [] Retired
    [] Disabled, permanently or temporarily
    [] Keeping house
    [] Student
    [] Other (Specify) __if selected let them write in response_____

11. Are you pregnant now?
    [] Yes
    [] No
    [] NA

Appendix F

Smoking History

1.) Have you ever smoked a cigarette, even one or two puffs?

☐ Yes
☐ No *(Skip to question #6)*

2.) For about how long did you smoke?

☐ I still use them *(skip to question #5)*
☐ Just tried one or two cigarettes
☐ A few days
☐ A couple of weeks
☐ A few months
☐ About 1 year
☐ More than 2 years

3.) Why did you stop smoking

_____

_____

_____

_____

_____

4.) When you did smoke, how many cigarettes, on average, did you smoke per day?

_____ per day

5.) When was the last time you smoked a cigarette?

☐ Today
☐ This past week
☐ About a month ago
☐ A few months ago
☐ More than a year ago

6.) What type(s) of e-cigarettes have you used before? (even once, check all that apply)

☐ Disposable
☐ Rechargeable with replacement cartridges
☐ eGO model with refillable tank
☐ Vaporizer with refillable tank
☐ Pods devices like Juul or similar
☐ e-Cigar
☐ e-Pipe
☐ Other (please describe)_____

7.) Have you ever used an e-cigarette similar to any of the devices pictured below?

	YES ☐	NO ☐
	YES ☐	NO ☐
	YES ☐	NO ☐
	YES ☐	NO ☐
	YES ☐	NO ☐

	YES ☐	NO ☐
	YES ☐	NO ☐

8.) Do you currently vape e-liquid containing nicotine?

☐ Yes
☐ No

9.) Do you currently vape e-liquid containing nicotine salt?

☐ Yes
☐ No
☐ Don't know

10.) What level of nicotine do you most commonly use?

☐ 0-2 mg
☐ 3-5 mg
☐ 6-11 mg
☐ 12-17mg
☐ 18-23 mg
☐ 24-36 mg
☐ 37-42 mg
☐ 43-50 mg
☐ 51 or more mg
☐ Other
*Please Specify:*_____if checked participant prompted to write in details

11.) **What flavor(s) of e-cigarettes have you tried before? (list all)**

_____

_____

_____

_____

_____

Appendix G

Time-Line Follow-Back

30 Days	ETM ID:	RA:	Date:	Notes

		Date	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
		Weekday																														
In the last 30 days, have you used		Cigarettes: TOTAL (#)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Usual Brand of Cigarette	y	**Cigarettes: Usual (#)**																														
Non-usual Brand of Cigarette	n	Cigarettes: Non-usual (#)																														
Cigars	n	Cigars (#)																														
Cigarillos	n	Cigarillos (#)																														
Little Cigars	n	Little Cigars (#)																														
Chew/Dip	n	Chew/Dip (# of pinches)																														
Snus	n	Snus (# of pinches or pouches)																														
Hookah	n	Hookah (# of episodes)																														
Bidis	n	Bidis (#)																														
E-cigarette	n	E-cigarette (# of episodes)																														
		E-cigarette (mL of e-cig fluid)																														
Other tobacco product	n	Other tobacco products																														
Nicotine Patch	n	Nicotine Patch (#) ≥21 mg																														
		Nicotine Patch (#) 14 mg																														
		Nicotine Patch (#) 7 mg																														
		Nicotine Patch (#) Unknown																														
Nicotine Gum	n	Nicotine Gum (#) 2 mg																														
		Nicotine Gum (#) 4 mg																														
		Nicotine Gum (#) Unknown																														
Nicotine Lozenge	n	Nicotine lozenge (#) 2 mg																														
		Nicotine lozenge (#) 4 mg																														
		Nicotine lozenge (#) Unknown																														
Nicotine Nasal Spray	n	Nicotine Nasal Spray (# of sprays)																														
Nicotine Inhaler	n	Nicotine Inhaler (# of cartridges)																														
Other nicotine product	n	Other nicotine replacement product																														
		Date																														
		Weekday																														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30

Appendix H

Penn State E-cigarette Dependence Index

1. How many times per day do you usually use your electronic cigarette (assume that one "time" consists of around 15 puffs or lasts around 10 minutes)?
   - ☐ 0-4 times/day
   - ☐ 5-9 times/day
   - ☐ 10-14 times/day
   - ☐ 15-19 times/day
   - ☐ 20-29 times/day
   - ☐ 30+ times/day

2. On the days that you can use you electronic cigarette freely, how soon after you wake up do you use your electronic cigarette?
   - ☐ 0-5 min
   - ☐ 6-15 min
   - ☐ 16-30 min
   - ☐ 31-60 min
   - ☐ 61-120 min
   - ☐ 121+ min

3. Do you sometimes awaken at night to use your electronic cigarette?
   - ☐ Yes
   - ☐ No

4. If yes, how many nights per week do you typically awaken to use your electronic cigarette?
   - ☐ 0–1 nights
   - ☐ 2–3 nights
   - ☐ 4+ nights

5. Do you use an electronic cigarette now because it is really hard to quit?
   - ☐ Yes
   - ☐ No

6. Do you ever have strong cravings to use an electronic cigarette?
   - ☐ Yes
   - ☐ No

7. Over the past week, how strong have the urges to use an electronic cigarette been?
   - ☐ None/Slight
   - ☐ Moderate/Strong
   - ☐ Very Strong/Extremely Strong

8. Is it hard to keep using an electronic cigarette in places where you are not supposed to?
   - ☐ Yes
   - ☐ No

9. Did you feel more irritable because you couldn't use an electronic cigarette?
   - ☐ Yes
   - ☐ No

10. Did you feel nervous, restless, or anxious because you couldn't use an electronic cigarette?
    - ☐ Yes
    - ☐ No

Appendix I

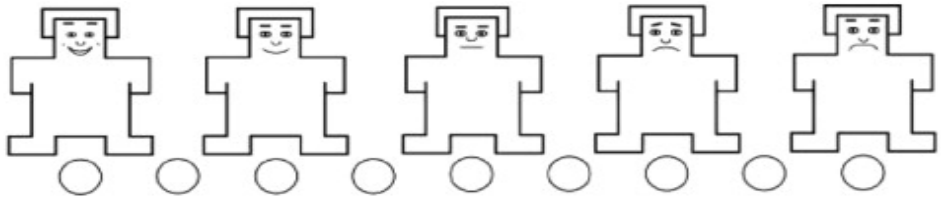
Taste Preference

(Meier et al JPSP 2012)

For each of the foods shown below, please check the box that corresponds to how much you like or dislike that food. If you never tried a food, please check that box.

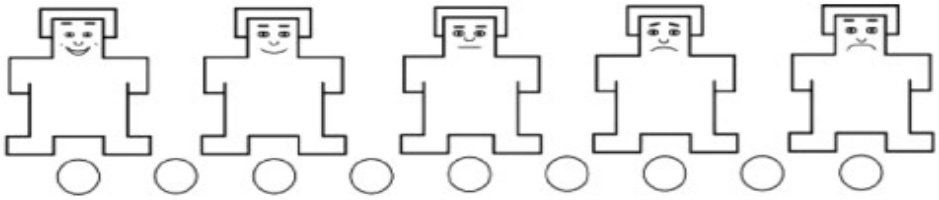
1.) Sweet items:

1a.) Candy



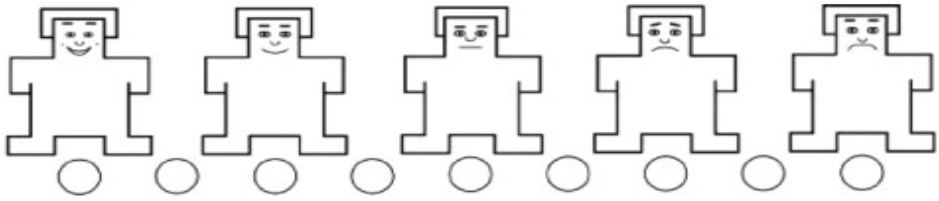
○ Never tried

1b.) Caramel



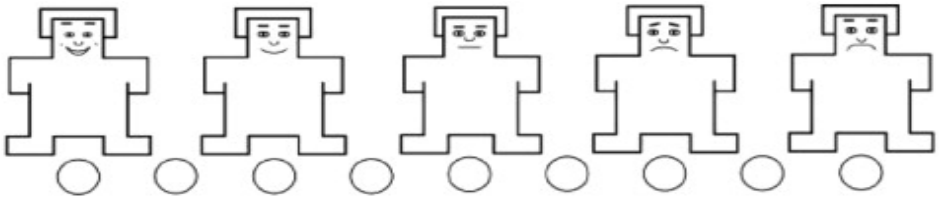
○ Never tried

1c.) Chocolate cake



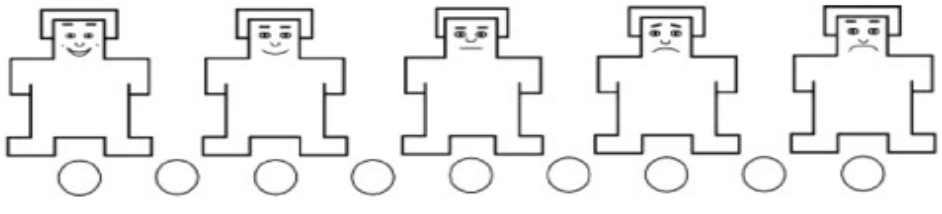
○ Never tried

1d.) Honey



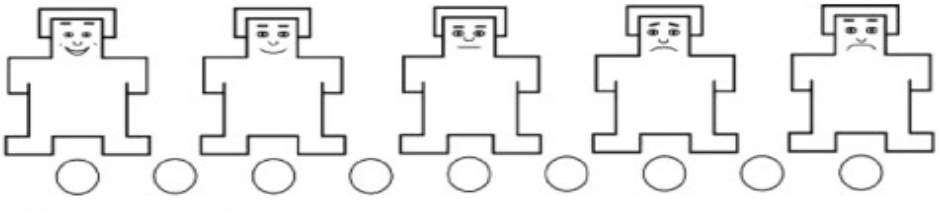
○ Never tried

1e.) Ice cream



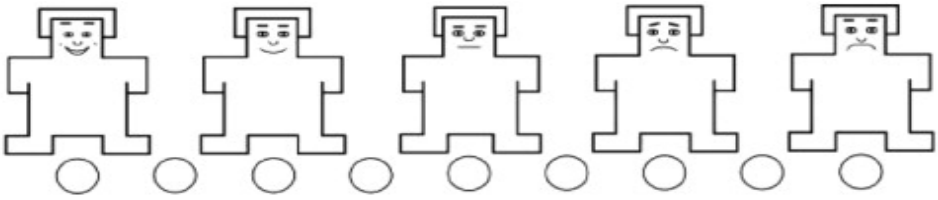
○ Never tried

1f.) Maple syrup



○ Never tried

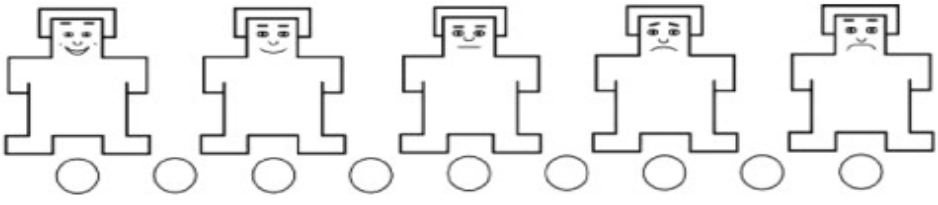
1g.) Pears



○

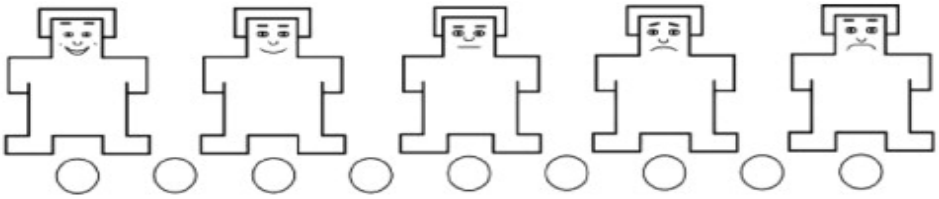
Never tried

1h.) Raisins



○ Never tried

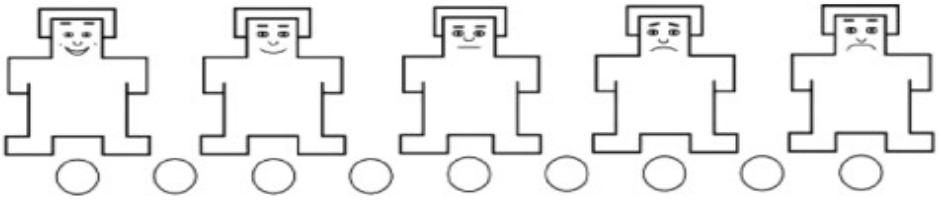
1i.) Strawberries



○

Never tried

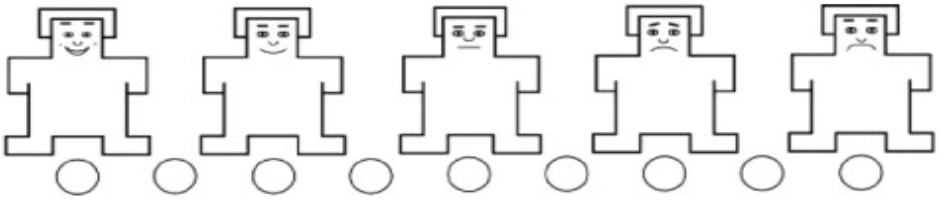
1j.) Sugar



○ Never tried

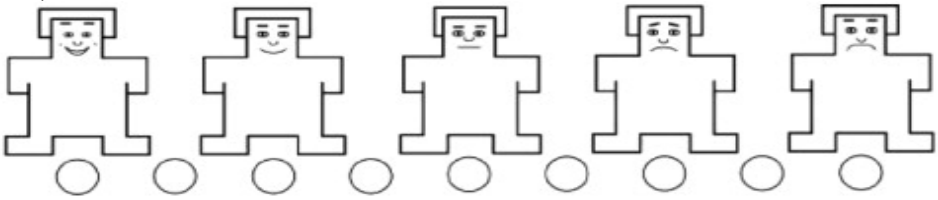
2.) Sour items:

2a.) Granny Smith apples



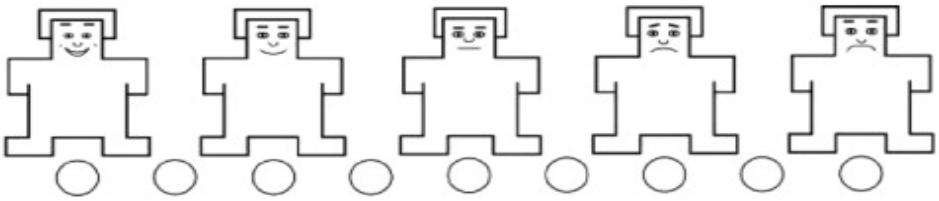
○ Never tried

2b.) Lemons



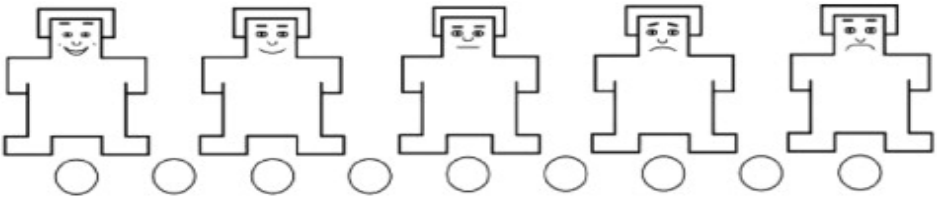
○ Never tried

2c.) Lemon drops



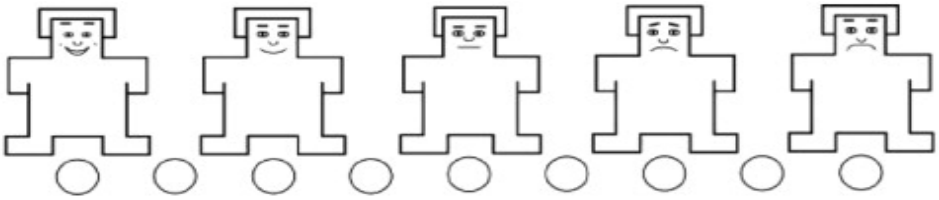
○ Never tried

2d.) Limes



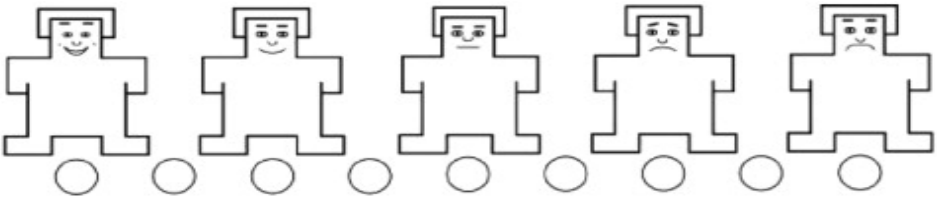
○ Never tried

2e.) Lime sherbet



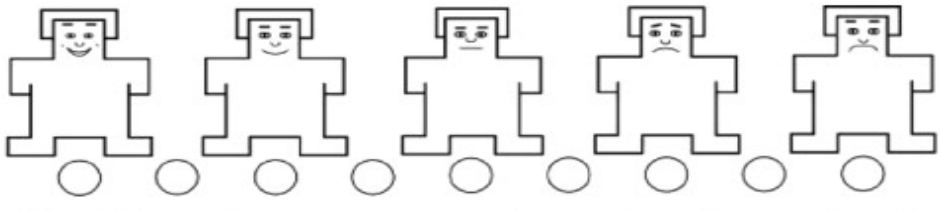
○ Never tried

2f.) Plain yogurt



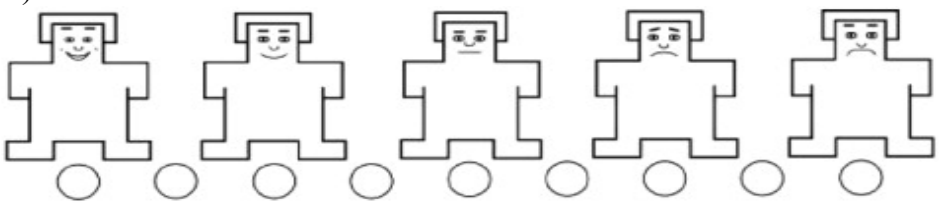
○ Never tried

2g.) Sauerkraut



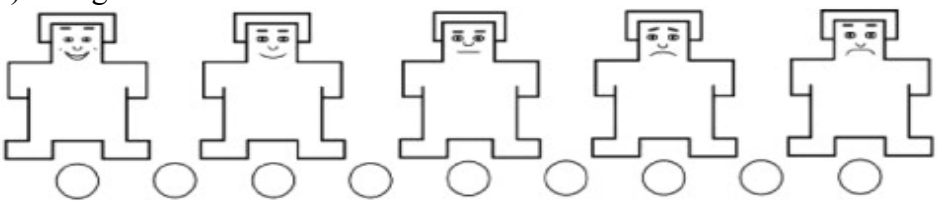
○ Never tried

2h.) Sour cream



○ Never tried

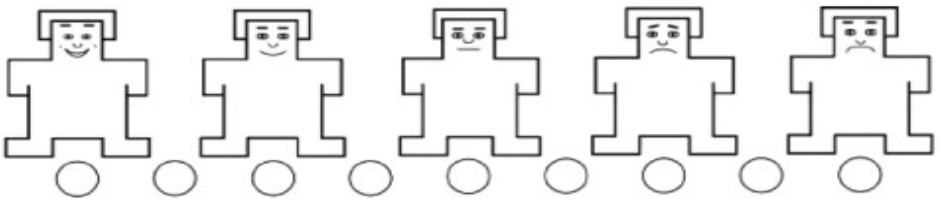
2i.) Vinegar



○ Never tried

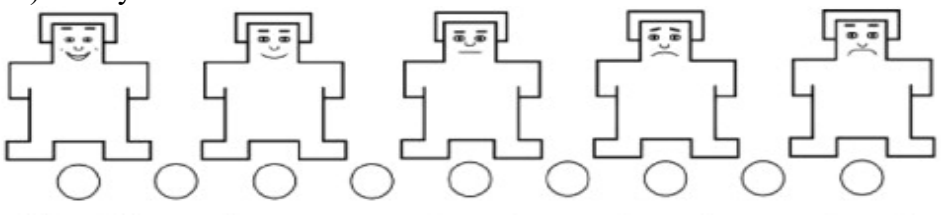
3.) Bitter items:

3a.) Beer



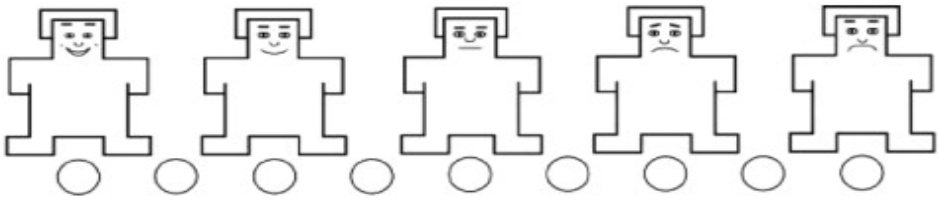
○ Never tried

3b.) Celery



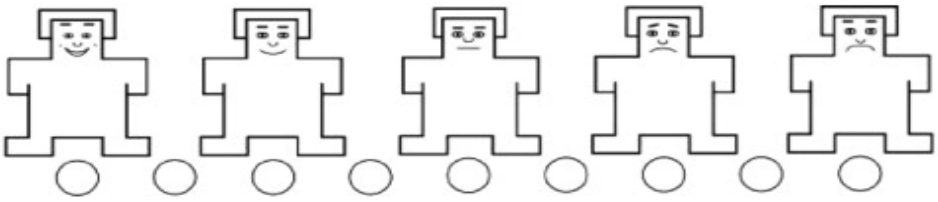
○ Never tried

3c.) Coffee



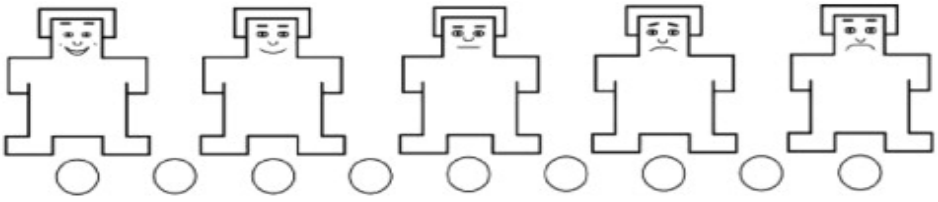
○ Never tried

3d.) Cottage cheese



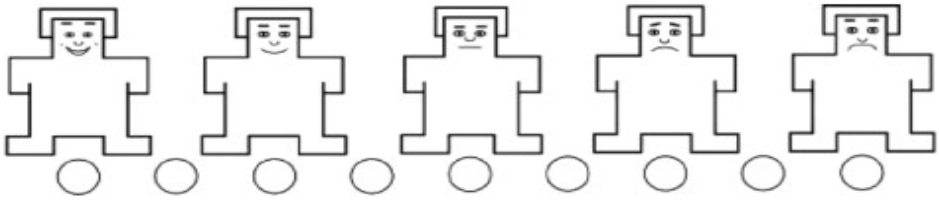
○ Never tried

3e.) Ginger ale



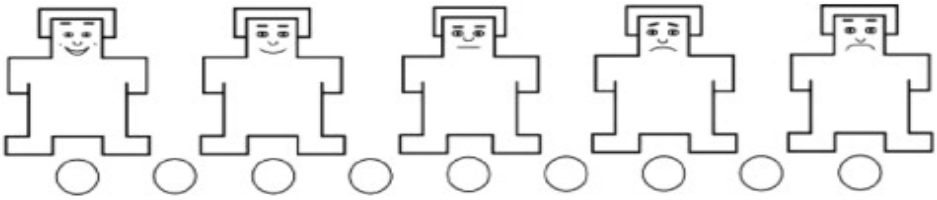
○ Never tried

3f.) Grapefruit



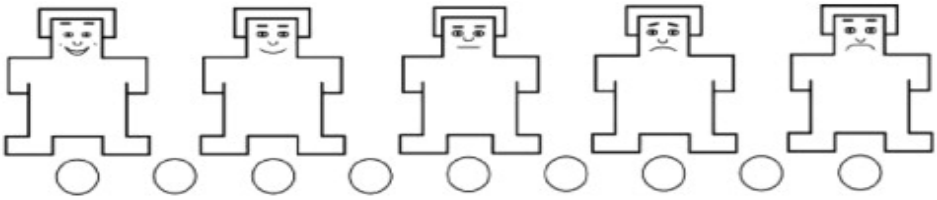
○ Never tried

3g.) Radishes



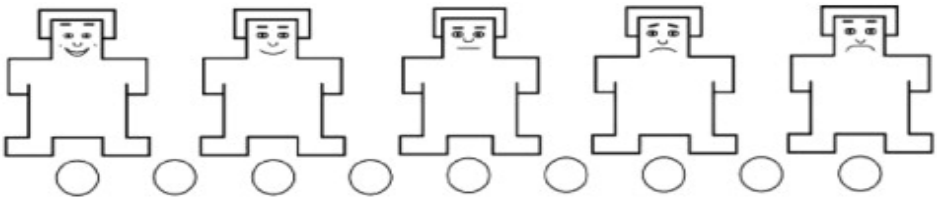
○ Never tried

3h.) Rye bread



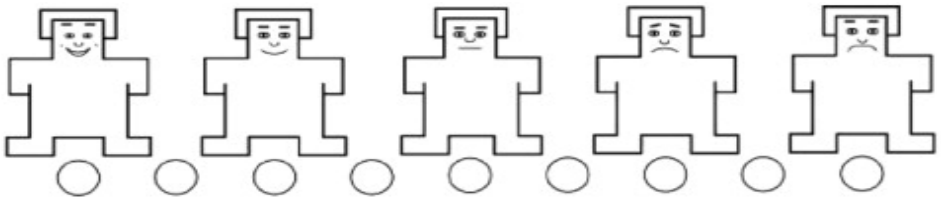
○ Never tried

3i.) Tea



○ Never tried

3j.) Tonic water

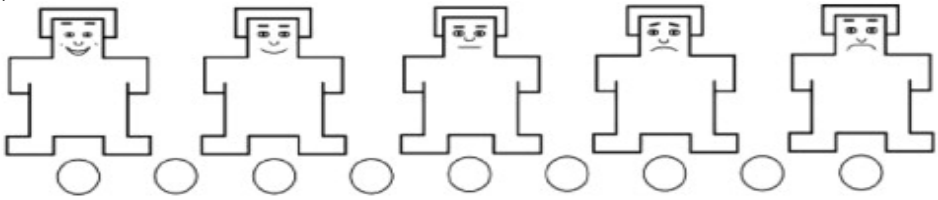


○

Never tried

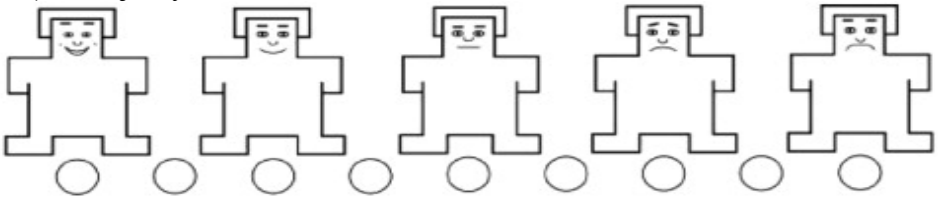
4.) Salty items:

4a.) Bacon



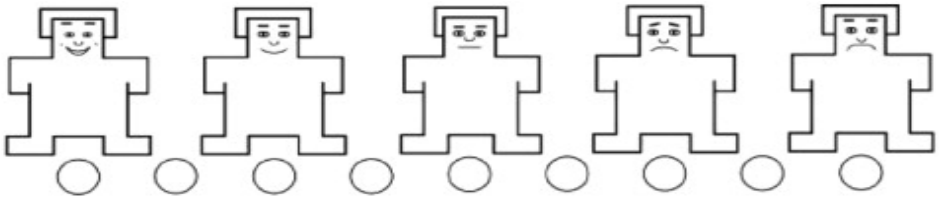
○ Never tried

4b.) Beef jerky



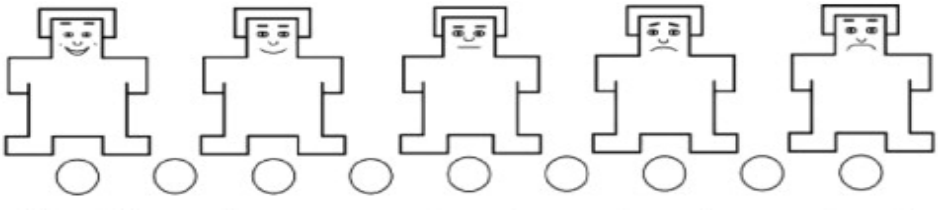
○ Never tried

4c.) Caviar



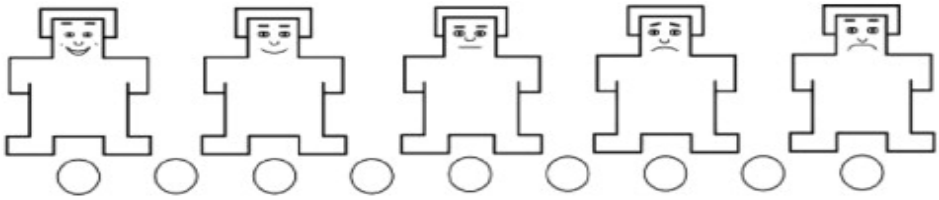
○ Never tried

4d.) Dill pickles



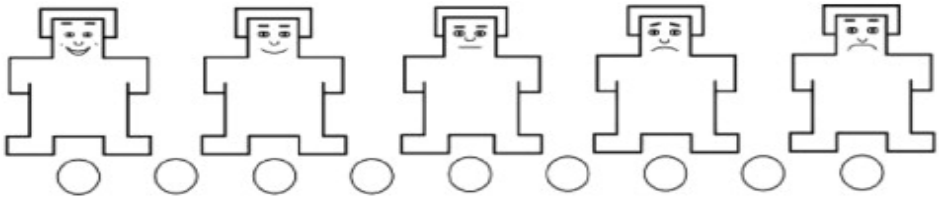
○ Never tried

4e.) Green olives



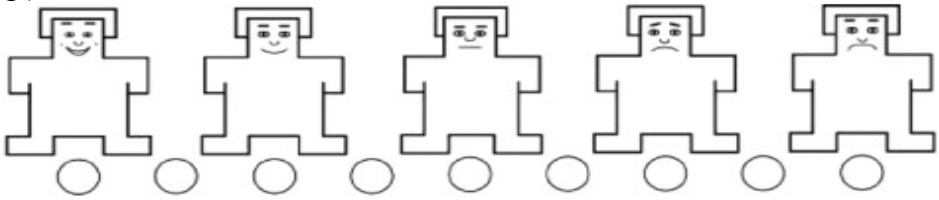
○ Never tried

4f.) Pretzels



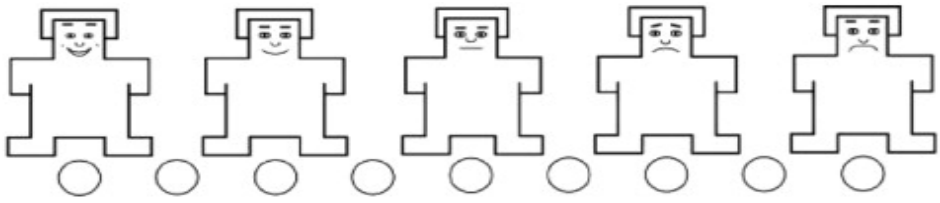
○ Never tried

4g.) Salt



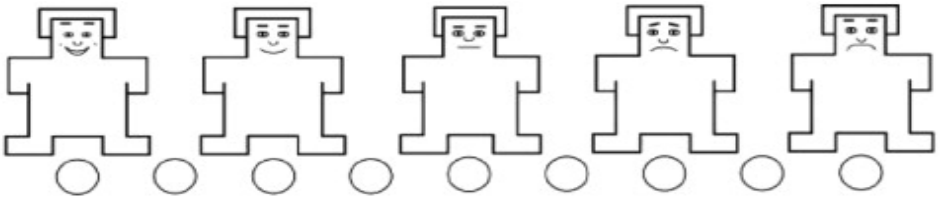
○ Never tried

4h.) Saltine crackers



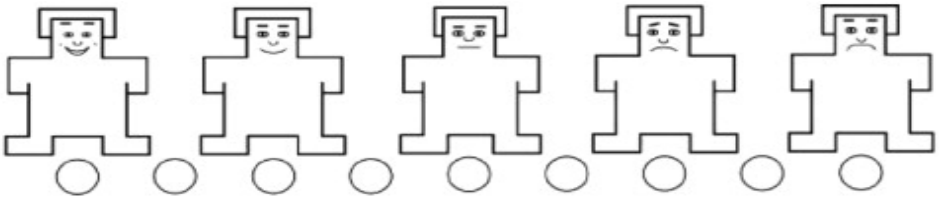
○ Never tried

4i.) Salty peanuts



○ Never tried

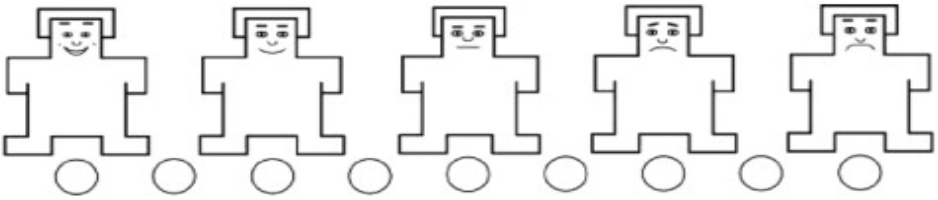
4j.) Soy sauce



○ Never tried

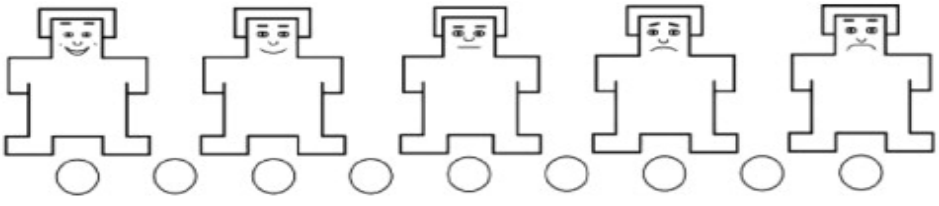
5.) Spicy items:

5a.) Cajun foods



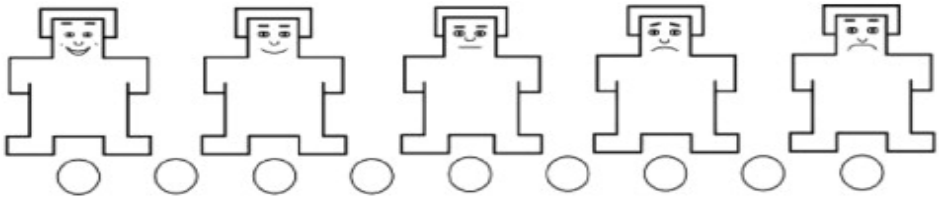
○ Never tried

5b.) Cayenne pepper



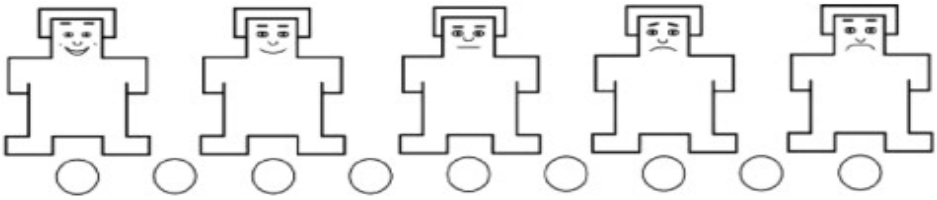
○ Never tried

5c.) Chilies



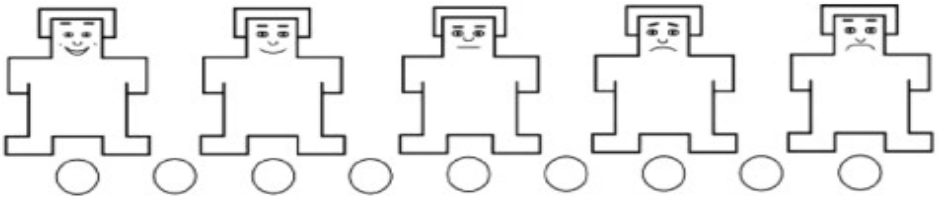
○
Never tried

5d.) Curry



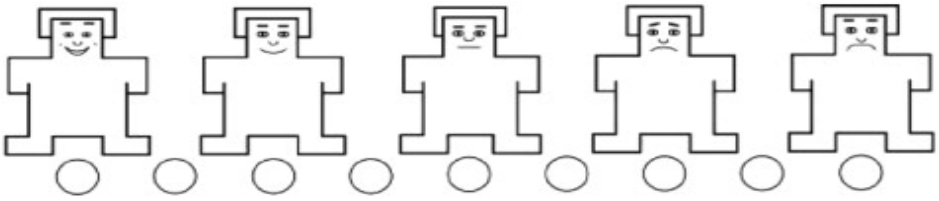
○ Never tried

5e.) Horseradish



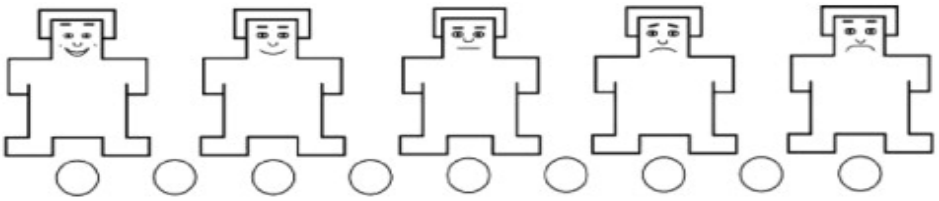
○ Never tried

5f.) Hot salsa



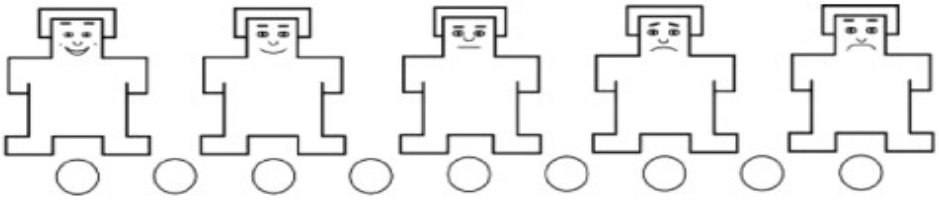
○ Never tried

5g.) Jalapeno peppers



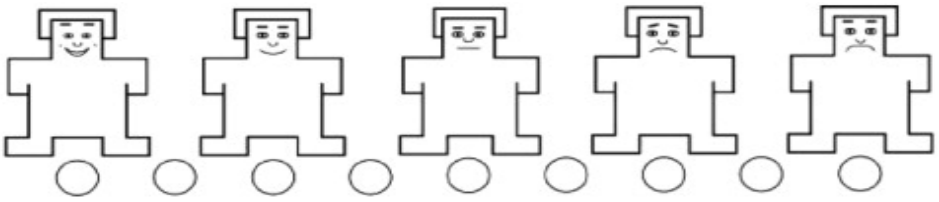
○ Never tried

5h.) Spicy sausage



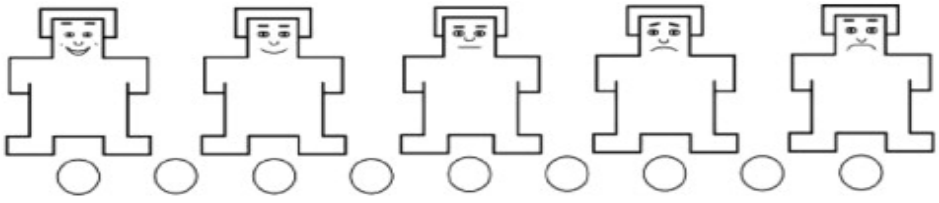
○ Never tried

5i.) Peppers



○ Never tried

5j.) Tabasco sauce



○ Never tried

Appendix J

Minnesota Tobacco Withdrawal Scale

How are you feeling at this very moment? **Please mark an (X) in ONE box for each condition**					
	Not at all	**Slightly**	**Somewhat**	**Very**	**Extremely**
Depressed	☐	☐	☐	☐	☐
Irritable	☐	☐	☐	☐	☐
Anxious, nervous	☐	☐	☐	☐	☐
Restless	☐	☐	☐	☐	☐
Dizziness	☐	☐	☐	☐	☐
Hungry	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐
Poor concentration	☐	☐	☐	☐	☐

Appendix K

The Positive Negative Affect Scale (PANAS)

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you feel this way right now, that is, at the present moment. Remember, there is no right or wrong answer so please give us your honest opinion.

1	2	3	4	5
very slightly or not at all	a little	moderately	quite a bit	extremely

_____	interested	_____	Irritable
_____	Distressed	_____	Alert
_____	Excited	_____	Ashamed
_____	Upset	_____	Inspired
_____	Strong	_____	Nervous
_____	Guilty	_____	Determined
_____	Scared	_____	Attentive
_____	Hostile	_____	Jittery
_____	Enthusiastic	_____	Active
_____	Proud	_____	Afraid

Appendix L

Product Evaluation Form: Satisfaction With and Helpfulness of the Product

Please answer the following questions about the Nicotine Solution you just used. ***Please mark an (X) in ONE box for each question***					
	Much less than my regular device & e-liquid	**A little less than my regular device & e-liquid**	**The same as my regular device & e-liquid**	**A little more than my regular device & e-liquid**	**Much more than my regular device & e-liquid**
1. How good did it taste?	☐	☐	☐	☐	☐
2. How pleasant was it?	☐	☐	☐	☐	☐
3. How much did it relieve your urge to vape	☐	☐	☐	☐	☐
4. How was the effect of the e-Cig vapor on your:					
Tongue?	☐	☐	☐	☐	☐
Nose?	☐	☐	☐	☐	☐
Back of mouth and throat?	☐	☐	☐	☐	☐
Windpipe?	☐	☐	☐	☐	☐
Chest?	☐	☐	☐	☐	☐
5. How harsh was it?	☐	☐	☐	☐	☐
6. How much e-cigarette taste	☐	☐	☐	☐	☐

versus 'just air' did you get?					
	Much less than my regular device & e-liquid	**A little less than my regular device & e-liquid**	**The same as my regular device & e-liquid**	**A little more than my regular device & e-liquid**	**Much more than my regular device & e-liquid**
7. Was it embarrassing to use in front of others?	☐	☐	☐	☐	☐
8. How hard was it to draw vapor from?	☐	☐	☐	☐	☐
9. How fast did it relieve your urge to vape?	**It did not relieve my urge to smoke** ☐	**Within a few puffs** ☐	**Within 5 minutes** ☐	**Within 10 minutes** ☐	**Within 15 minutes** ☐

10.) How satisfying did you find the ENDS product and solution compared to your normal

11.) How enjoyable did you find the ENDS product and solution compared to your regular device and solution? (please mark an (X) on ONE of the boxes)

1	2	3	4	5	6	7	8	9	10
							→		

cigarettes

Not enjoyable at all	***As enjoyable as normal cigarettes***

12.) How dangerous to your health did you find the ENDS product and solution compared to your regular device and solution? (please mark an (X) on ONE of the boxes)

1	2	3	4	5	6	7	8	9	10

Less dangerous than normal cigarettes	***More dangerous than normal cigarettes***

Appendix M –Drug Effect Questionnaire

This questionnaire asks about how you are feeling after using the provided nicotine product. Please draw a mark on the line to show how strongly you are feeling each of the following effects **right now**. You can mark anywhere on the line, but please draw a vertical line (one that goes straight up and down).

1. **Do you FEEL a nicotine effect right now?**

NOT AT ALL — EXTREMELY

2. **Are you HIGH right now?**

NOT AT ALL — EXTREMELY

3. **Do you DISLIKE any of the effects you are feeling right now?**

NOT AT ALL — EXTREMELY

4. **Do you LIKE any of the effects you are feeling right now?**

NOT AT ALL — EXTREMELY

5. **Would you like MORE nicotine right now?**

NOT AT ALL — EXTREMELY

Appendix N

Modified Questionnaire of Smoking Urges (QSU-breif)

Please answer each statement below on a scale from 0 (Strongly Disagree) to 100 (Strongly Agree)

1. I have a desire for my regular device and e-liquid right now. _____
2. Nothing would be better than using my regular device and e-liquid right now. _____
3. If it were possible, I would probably use my regular device and e-liquid right now. _____
4. I could control things better right now if I could use my regular device and e-liquid right now. _____
5. All I want right now is my regular device and e-liquid right now. _____
6. I have an urge for my regular device and e-liquid right now. _____
7. My regular device and e-liquid would taste good right now. _____
8. I would do almost anything for my regular device and e-liquid right now. _____
9. Using my regular device and e-liquid would make me less depressed. _____
10. I am going to use my regular device and e-liquid as soon as possible. _____

Appendix O

Nicotine Solution Rating Scale

1.) Please order the following nicotine solutions you tested from 1- 4 based on how satisfied you were with the solutions.

(4= Most satisfying and 1= Least satisfying)

Product	Rating
Solution A	_____
Solution B	_____
Solution C	_____
Solution D	_____

Appendix P

Experimental Tobacco Marketplace

Account Balance $50.00 | Cart Total $0.00

$16.79
JUUL E-Cigarette Classic Tobacco
160 mg nicotine/91 cigarettes
0 Add to Cart
Product Description

$16.79
JUUL E-Cigarette Crème Brulee
160 mg nicotine/91 cigarettes
0 Add to Cart
Product Description

$16.79
JUUL E-Cigarette Fruit Medley
160 mg nicotine/91 cigarettes
0 Add to Cart
Product Description

$16.79
JUUL E-Cigarette Mango
160 mg nicotine/91 cigarettes
0 Add to Cart
Product Description

$16.79
JUUL E-Cigarette Menthol
160 mg nicotine/91 cigarettes
0 Add to Cart
Product Description

$16.79
JUUL E-Cigarette Virginia Tobacco
160 mg nicotine/91 cigarettes
0 Add to Cart
Product Description

$31.24
NicoDerm CQ Patch Clear
147 mg nicotine/84 cigarettes
0 Add to Cart
Product Description

$13.65
Nicorette Gum Cinnamon Surge
80 mg nicotine/46 cigarettes
0 Add to Cart
Product Description

$13.65
Nicorette Gum White Ice Mint
80 mg nicotine/46 cigarettes
0 Add to Cart
Product Description

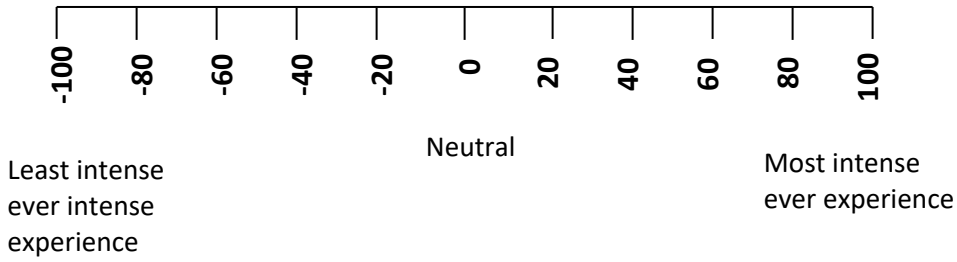
$18.99
Nicorette Lozenge Mint
80 mg nicotine/46 cigarettes
0 Add to Cart
Product Description

Appendix Q

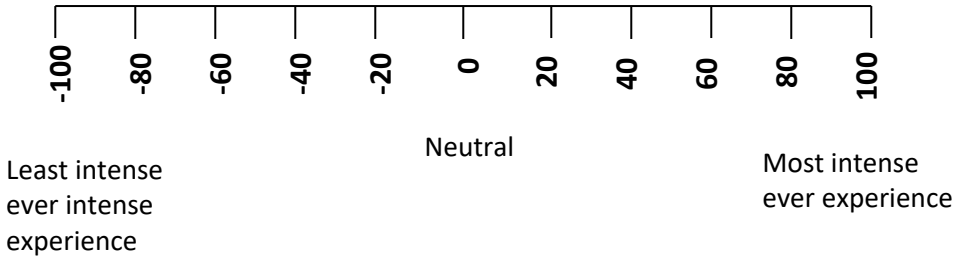
Sensory Measures

Based on the e-liquid you just tried, please rate the taste on the following characteristics:

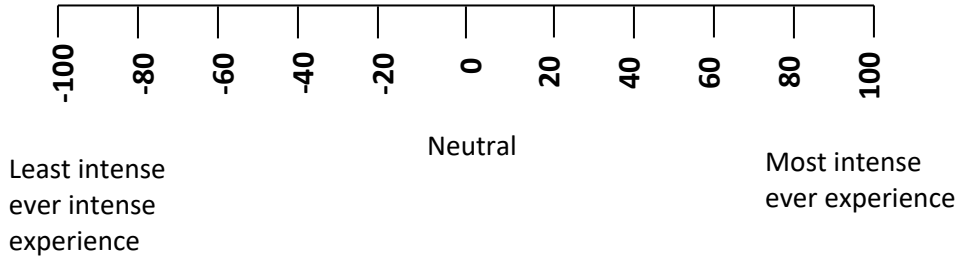
1.) Pleasantness



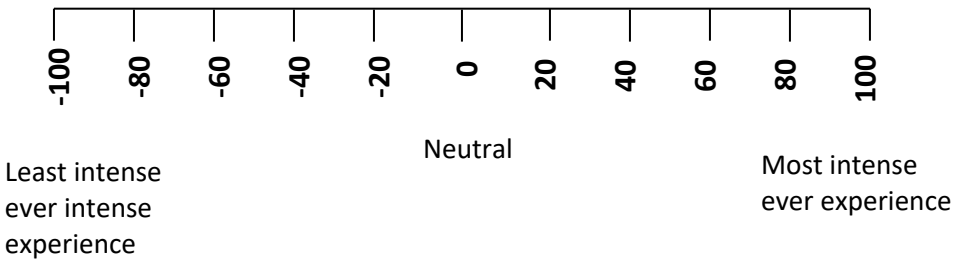
2.) Irritation



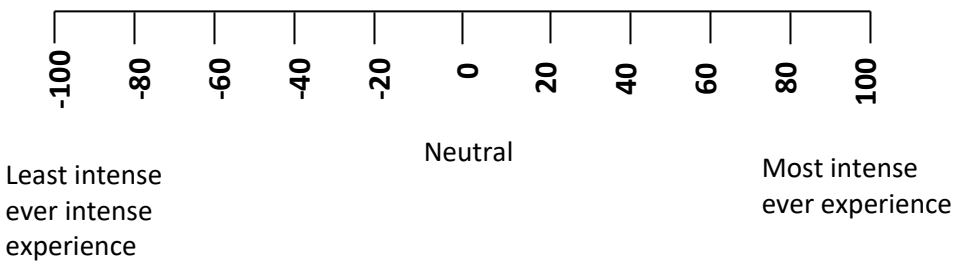
3.) Relaxing



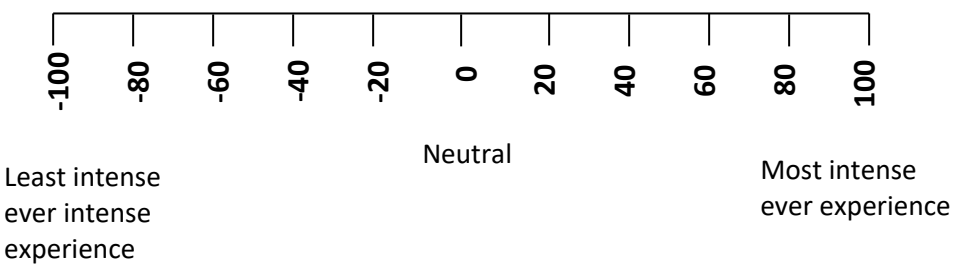
4.) Satisfying



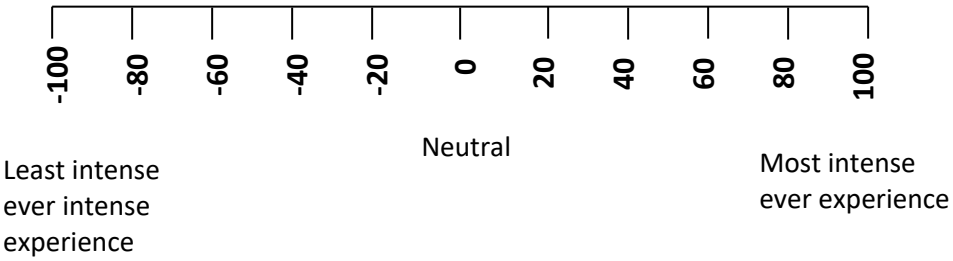
5.) Sweet



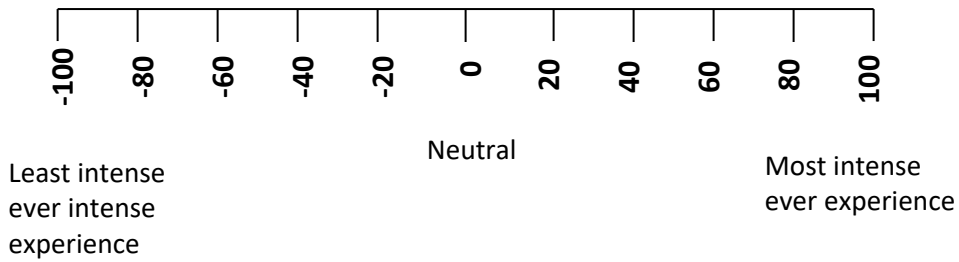
6.) Sour



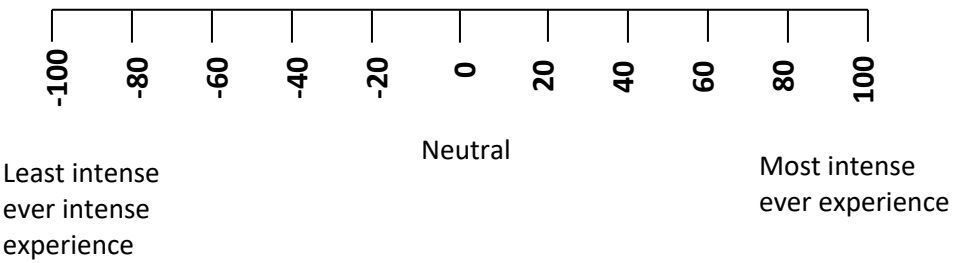
7.) Bitter



8.) Cool/cooling



9.) Sharp/biting/astringent/pungent



Sensory

	1 Strongly Agree	2	3	4	5	6	7 Strongly Disagree
1. I like the smell of the vapor.							
2. I like the taste of vaping.							
3. I like the feeling of creating vapor clouds.							
4. I like how creating vapor clouds looks visually appealing / cool.							
5. I like the flavor of vapor.							
6. I like how vaping makes me feel good physically.							
7. I like the feeling of satisfaction that I get from vaping.							
8. I like the feeling of pleasure that I get from vaping.							
9. I like doing vape tricks (eg. Blowing vapor clouds or shapes like rings).							

E-cigarette Experience Scale

PROMIS-E

	0 Never	1	2	3	4 Almost Always
1. I find myself reaching for my e-cigarette without thinking about it.					
2. I drop everything to go out and buy e-cigarettes or e-juice.					
3. I vape more before going into a situation where vaping is not allowed.					
4. When I haven't been able to vape for a few hours, the craving gets intolerable.					

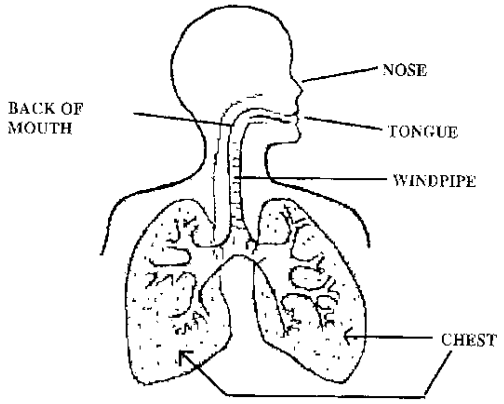
SHERI-E

Vaping/using an e-cigarette/JUULing is something…….

	1 Agree	**2**	**3**	**4**	**5**	**6**	**7 Disagree**
1. I do automatically.							
2. I do without having to consciously remember.							
3. I do without thinking.							
4. I start doing before I realize I'm doing it.							
5. I would find hard not to do.							
6. That is typically "me".							

Duke Sensory Evaluation

Please rate the puffs you just took.

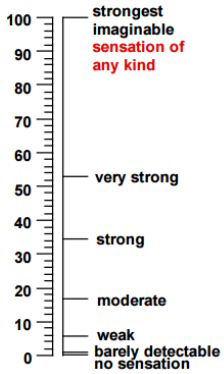
	1 Not at all	2 Very little	3 A little	4 Moderately	5 A lot	6 Quite a lot	7 Extremely
1. How much did you like the puffs you just took?							
2. How satisfying were the puffs you just took?							
3. How high in nicotine do you think the puffs were?							
4. How similar to your own brand were the puffs?							
Rate how strong the puffs were in the following places.  							
5. Strength of puffs on tongue?							
6. Strength of puffs in nose?							

7. Strength of puffs in back of mouth and throat?							
8. Strength of puffs in windpipe?							
9. Strength of puffs in chest?							

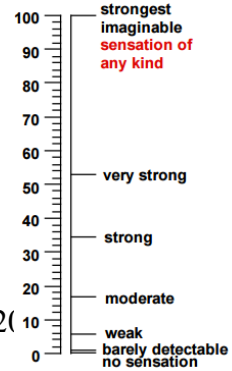
HEDONIC ATTRIBUTE PROFILE

For each item, please indicate how you would describe the ECIG you just used by placing a mark on the vertical numbered line.

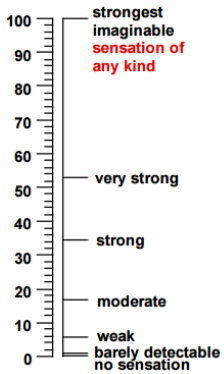
1.) Draw



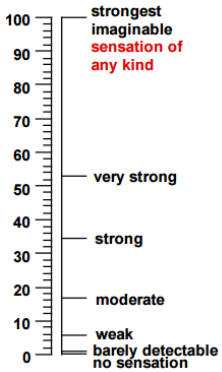
2.) Mouthful of vapor



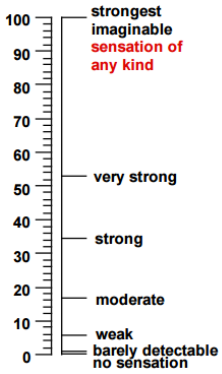
3.) Visible vapor



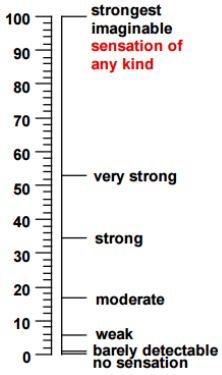
4.) Smell



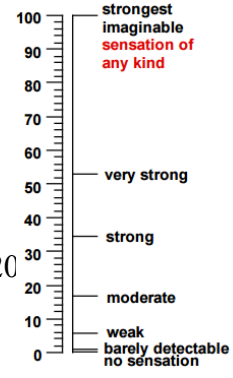
5.) Impact



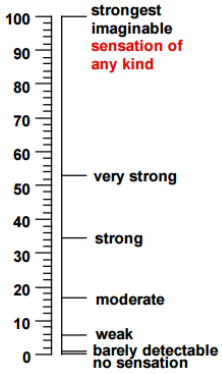
6.) Irritation



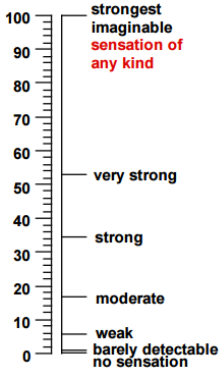
7.) Strength



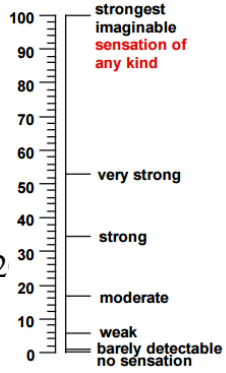
8.) Smoothness



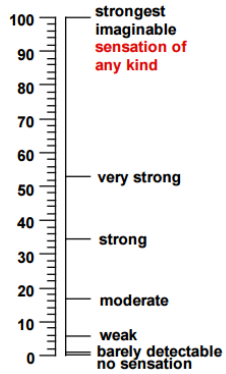
9.) Taste



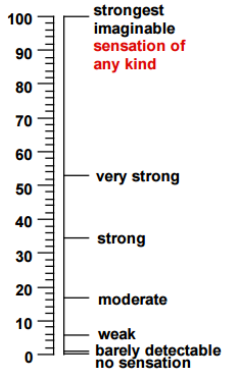
10.) Aftertaste



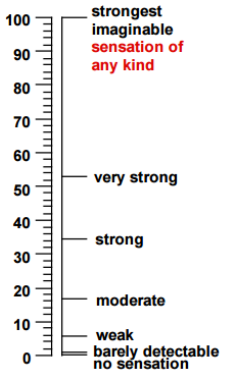
11.) Throat hit



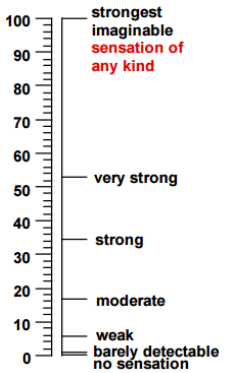
12.) Dryness



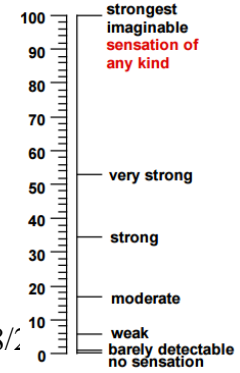
13.) Tingling



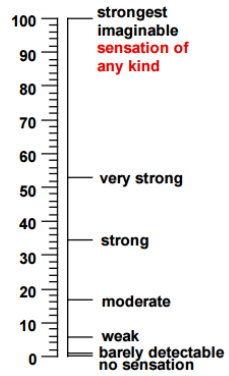
14.) Burning



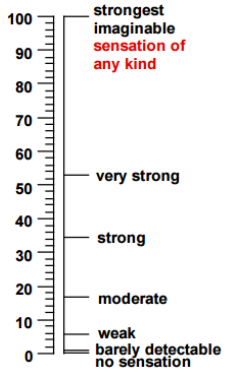
15.) Similarity to usual brand



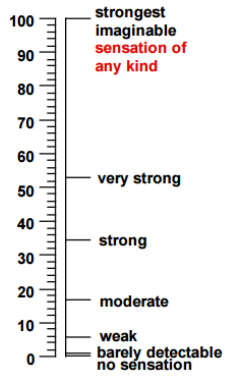
16.) How would you describe the overall <u>flavor sensation</u> of the ECIG you just used?



17.) How would you describe the overall harshness/irritancy of the ECIG you just used?



18.) How would you describe the throat hit of the ECIG you just used?


100
90
80
70
60
50
40
30
20
10
0
strongest imaginable sensation of any kind
very strong
strong
moderate
weak
barely detectable
no sensation

Appendix R

ENDS Nicotine Dependence Scale

1. If you currently or did you previously smoke cigarettes regularly, how many cigarettes a day do/did you smoke?
   - o I never smoked cigarettes regularly <0>
   - o 1 – 10 < 1 >
   - o 11 – 20 < 2 >
   - o 21 – 30 < 3 >
   - o 31+ < 4 >

2. Do you use other forms of tobacco such as cigars, cigarillos, hookah, or smokeless tobacco?
   - o No < 0 >
   - o Yes < 1 >

3. Do you vape more frequently during the first few hours after awakening than during the rest of the day?
   - o Yes < 1 >
   - o No < 0 >

4. How soon after you wake up do you vape?
   - o 0 – 5 m < 3 >
   - o 6 – 30 m < 2 >
   - o 31 – 60 m < 1 >
   - o 61+ m < 0 >

5. Of all the times that you vape, which time would you hate most to give up?
   - o 1st of Day < 1 >
   - o All Others < 0 >

6. Do you find it difficult to refrain from vaping in places where it is forbidden?
   - o Yes < 1 >
   - o No < 0 >

7. How many pods, cartridges, or refills do you typically use each week?
   - Less than 1 per week < 0 >
   - 1 – 4 per week < 1 >
   - 5 or more per week < 2 >

8. How often do you vape?
   - 1 day or less each week < 0 >
   - 2 – 3 days each week < 1 >
   - 4 – 6 days each week < 2 >
   - 7 days each week < 3 >