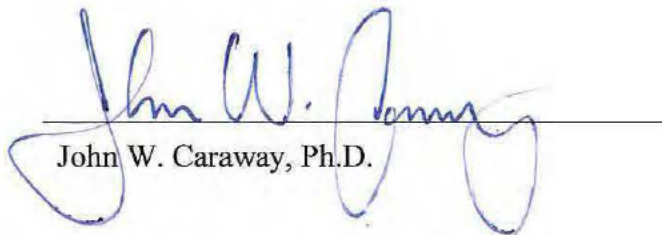



SNUS AFTER USE – MARKET ADOPTER PILOT STUDY

R&D Human Studies Research Protocol CSD-0804

Principal Investigator, Human Studies:



John W. Caraway, Ph.D.

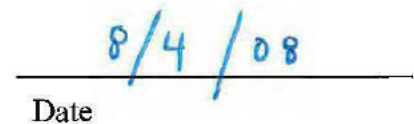


Date

Sr. Director, Clinical Studies:



Michael F. Borgerding, Ph.D.



Date

SNUS AFTER USE – MARKET ADOPTER PILOT STUDY

FACILITIES & ADMINISTRATION

Sponsor and Test Facility

*R. J. Reynolds Tobacco Company
Research and Development
950 Reynolds Blvd.
Winston-Salem, NC 27105*

Labstat International ULC

*262 Manitou Drive
Kitchener, Ontario
Canada N2C 1L3
Contact: Catherine Ambrose
(519) 748-5409 x125*

Bellomy Research

*2150 Country Club Rd.
Winston-Salem, NC 27104
Contact: Jeff Goldman
(336) 721-1140*

Study Administration

Study Director, Clinical Studies / Human Studies: John W. Caraway, Ph.D.

OBJECTIVE

The purpose of this pilot study is to characterize the maximum potential exposure to selected tobacco constituents typically experienced by persons that choose and regularly use CAMEL Snus products. The maximum potential exposure will be determined by measuring and comparing the amounts of selected tobacco constituents in unused product versus product after use.

EXPERIMENTAL DESIGN

This study was designed to address the objective defined above and will consist of the following principal steps:

1. The study will be conducted in states where CAMEL Snus is sold at retail.

2. A recruitment in Austin, TX, Dallas, TX and Raleigh, NC will be undertaken by Bellomy Research of Winston-Salem to identify 15 usual brand (UB) users for each CAMEL Snus variety to be tested. The varieties to be tested are CAMEL Snus – Original, CAMEL Snus – Spice and CAMEL Snus – Frost.
3. For the initial visit (Day 0), recruits will come to the central location test (CLT) site. At the site, the test will be described to the recruits and they will be given an opportunity to enroll in the test and provide informed consent. After signing the informed consent form, participants will complete a short demographic survey.
4. Participants will be given a collection packet with three (3) labeled jars for their used snus pouches. Participants will be instructed to collect all snus pouches used on Day 1, Day 2 and Day 3 in the jar appropriately labeled for that specific day. Participants will also be instructed to save all packaging tins of snus used during each collection day. Participants will be instructed to store the collected snus in a freezer at the end of each day until they return to their designated CLT site. The participants will return to their designated CLT site on Day 4 and turn in their collection containers of used snus pouches and complete a group of surveys. They will also be instructed to provide the testing facility with each Camel Snus tin from which the pouches were collected.
5. The collected used pouches will be frozen until they are shipped to a designated contract laboratory (Labstat International in Kitchener, Ontario, Canada) where the number of used snus pouches collected for each participant by day will be counted. The used pouches will also be analyzed for one or more of the following constituents: nicotine; N-nitrosonornicotine (NNN); 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK); N'-nitrosoanatabine (NAT); N'-nitrosoanabasine (NAB); arsenic; cadmium; chromium; lead; nickel; benzo[a]pyrene (B[a]P) based on the number of available used snus pouches collected. The designated laboratory will also be responsible for recording the product lot number on each snus tin collected by the snus user.

Methods and Materials

Test Products

All test materials for this study are brands that are in the marketplace. The brands include CAMEL Snus – Original, CAMEL Snus – Spice and CAMEL Snus – Frost. All subjects will be required to provide their own snus during testing. They will also provide the snus product packaging (tins) used during the collection of pouches so that product lot numbers may be identified. The identification will take place at the designated contract analytical laboratory after subject testing and will not interfere with the ability of the subjects to participate in the test or their compensation.

Subjects

The snus users will be recruited in Austin, TX, Dallas, TX and Raleigh, NC by Bellomy Research. Twenty one (21) Camel snus users will be recruited in each city to complete 15 participants per city for a total of 45 completed subjects. The 45 subjects will be evenly distributed across the three Camel Snus varieties: Frost, Original and Spice. Male or female snus users age 21-55 whose usual brand (≥ 3 months) is one of the selected study brands will be accepted. To be eligible, subjects must report using at least 8 snus

pouches per day. Each participant will be required to make two visits to a designated test site.

Study Procedure

A screening session will be held before study enrollment to explain the protocol to potential subjects. At the conclusion of the screening, potential subjects who agree to the conditions of the study will be enrolled in the study. Following the screening, the study is planned to run five days for each snus user. Informed consent ([Attachment 1](#)) will be obtained from all subjects before any experimental procedures begin. Unique identification numbers will be generated for each subject; the numbers will be used throughout the study to protect subject confidentiality. After signing the informed consent, subjects will complete a short demographic questionnaire ([Attachment 2](#)).

Subjects will be provided with glass jars for collecting used snus pouches at their initial visit (Day 0). Subjects will collect used snus on three consecutive days. Subjects will be instructed to only use their UB of Snus, and not to use any other varieties during the three day test. They will be instructed to collect used pouches from all snus used on the following day (Day 1). They will be instructed to collect all pouches, from the first snus pouch used in the morning to the last pouch used before going to bed. The subjects will be instructed to save the pouches in the glass jar designated for their first collection. They will be instructed to store the jar in a freezer until their return to their testing site. Subjects will also be instructed to save each snus tin from which pouches are collected during the entire study. On Day 2, they will also collect all pouches, from the first snus pouch used in the morning to the last pouch used before going to bed. The subjects will be instructed to save the pouches in the glass jar designated for their second collection and again to store the jar in a freezer until their return to their testing site. On Day 3, the subjects will again collect all used pouches, from the first snus pouch used in the morning to the last pouch used before going to bed. The subjects will be instructed to save the pouches in the glass jar designated for their third collection and to store the jar in a freezer until their return to their testing site. On Day 4, subjects will return to the testing site at their appointed time and turn in their collection containers and complete a group of questionnaires ([Attachments 3 to 5](#)). They will turn in all snus tins from which the pouches were collected. They will also empty any partial tins used during the collection periods and surrender the packaging materials at the site.

Subjects who successfully complete each phase of the study will receive compensation of \$150 for time and travel. In the event that a subject does not complete all of the requirements of the study, a subject could receive partial compensation according to the following schedule:

Initial site visit/informed consent/initial visit surveys - \$10
Snus Collection 1 - \$40
Snus Collection 2 - \$40
Snus Collection 3 - \$40
Final site visit/final visit surveys - \$20

Subjects must turn in all snus tins from which the pouches were collected in order to receive the Snus collection compensations.

The used snus pouches will be frozen at the test site and shipped at the conclusion of the study (via overnight courier) to Labstat International for measurement of nicotine, TSNAs (NNN, NNK, NAT, NAB), B[a]P and/or trace metals (As, Cd, Cr, Ni, Pb). Sample can be shipped only on Monday or Tuesday.

Sample questionnaires are attached. At a minimum, the following screening and Snus usage information will be collected for each study subject:

- Usual brand (Camel Snus)
- UB variety (Quotas for Frost, Original and Spice)
- Length of time using UB
- Number of pouches used daily (minimum of 8)
- History of certain medical conditions (if yes, exclude from study)
- Standard demographics (age, gender, race, education and income)

Analysis of Used Snus Pouches

Analysis of unused and used snus pouches will be applied in this study to determine the potential exposure of CAMEL Snus market adopters to nicotine, TSNAs, B[a]P and metals when using their usual brand of CAMEL Snus.

End determinations for nicotine, TSNAs, B[a]P and trace metals will be performed by Labstat International in Kitchener, ON, Canada using their standard test methods.

The amount of an analyte extracted from a used pouch will be calculated from the difference between the average level of that analyte in unused pouches from at least three (3) determinations and the amount of that analyte determined in a used pouch.

References

- (1) None included.

Keywords

after use, arsenic, benzo[a]pyrene, cadmium, chromium, lead, market adopter, metals, nickel, nicotine, snus, TSNAs, CAMEL Snus

ATTACHMENT 1.

INFORMED CONSENT CHECKLIST

For a Constituent Exposure Study Among Users of Camel Snus

Sponsored by R. J. Reynolds Tobacco Company

- ____ YOU STATE THAT YOU ARE AT LEAST 21 YEARS OF AGE.
- ____ YOU HAVE VOLUNTARILY AGREED TO BE PART OF THIS RESEARCH STUDY. NOBODY HAS PRESSURED YOU TO TAKE PART IN IT.
- ____ You are not postponing a decision to quit using snus just to take part in this study.
- ____ You understand that you can ask the study administrator questions at any time if there is something in this form or about the study that you do not understand. [include name and contact number]
- ____ You are aware of the Surgeon General's warnings concerning snus:
- This product is not a safe alternative to cigarettes.
 - This product may cause mouth cancer.
 - This product may cause gum disease and tooth loss.
- ____ All samples collected from you and all data pertaining to you will be identified only by a code number. The link between the code and your identity will be maintained *in strictest confidentiality*.

WHY THIS STUDY IS BEING DONE

- ____ This study is designed to assess the maximum potential exposure to selected tobacco constituents typically experienced by CAMEL Snus users.

YOU UNDERSTAND THE FOLLOWING:

- ____ You state that you use at least 8 pouches of Camel Snus each day.
- ____ This study will last 4 days, not including today, and you will return to your testing facility on Day 4 for a final visit that will last about 15 minutes.
- ____ You will be required to collect every Camel Snus pouch that you use on Days 1-3 in the containers provided and return the containers to the study administrator on Day 4.

_____ You will be required on Day 4 to give the study administrator each Camel Snus tin from which the pouches were collected during testing. If a tin is unfinished, you will be given a container to put the remaining pouches in to take with you.

_____ You will be paid \$150 at the end of the study.

Do you have any questions? YES _____ NO _____

YOU UNDERSTAND THAT YOUR INVOLVEMENT IN THIS STUDY INCLUDES THE FOLLOWING:

_____ You are **not** required to indicate if you have any of the following conditions, but you should **not** participate in the study if you have any of the following:

- **Heart disease, including angina (chest pain)**
- **Kidney disease**
- **Liver disease such as hepatitis**
- **Any other serious diseases such as cancer**
- **Any other medical condition that might be affected by tobacco use**

_____ In signing this consent form and participating in this study, you are stating that to your knowledge you do not have any of these conditions and are in generally good health

_____ (WOMEN ONLY) You must not participate in the study if you are pregnant, breast feeding or are planning to become pregnant during the course of the study.

_____ In signing this consent form, you confirm that you have answered all questions and you know of no reason why you should not participate in this study.

_____ You are free to withdraw from the study at any time.

Do you have any questions? YES _____ NO _____

This the _____ day of _____, 2008.

Subject (PRINT NAME)

Person Administering Consent

Signature

INTERVIEWER: PLEASE ATTACH A COPY OF A STATE OR FEDERALLY ISSUED PHOTO ID TO THE BACK OF THIS CONSENT FORM.

ATTACHMENT 2

Austin.....	-01
Dallas	-02
Raleigh	-03

Initial Visit Sample Questionnaire

1. Besides Snus, which of the following other tobacco products, if any, do you regularly use? (PROGRAMMER: ALLOW MULTIPLE RESPONSES)

Moist snuff or dip in a round can.....-1
Chewing tobacco.....-2
Cigarettes - 3
Pipe tobacco.....-4
Cigars.....-5
Little cigars - 6
Tobacco tablets.....-7
Other (Specify) - 8
None - 9
- 1a. In a typical day, how many times do you use moist snuff or dip? (RECORD EXACT NUMBER)
 - 1b. In a typical day, how many cigarettes do you smoke in a typical day? (RECORD EXACT NUMBER)
2. Which of the following nicotine replacement products, if any, do you regularly use? (PROGRAMMER: ALLOW MULTIPLE RESPONSES)

Nicotine patch.....-1
Nicotine gum - 2
Nicotine lozenges.....-3
Nicotine nasal spray.....-4
Nicotine inhaler - 5
Other (Specify) - 6
None - 7

The next few questions are for classification purposes only.

3. Was the last grade of school you completed...?

Grade school (grades 1-8)..... -1
High school (grades 9-11) -2
High school graduate (grade 12) -3
Technical school..... -4
1 year of college -5
2 years of college..... -6
3 years of college..... -7
4 years of college..... -8
Graduate school..... -9

4. Is your approximate yearly household income group...?

Less than \$20,000	-1
\$20,000 to \$40,000	-2
Over \$40,000 to \$60,000	-3
Over \$60,000 to \$80,000	-4
Over \$80,000 to \$100,000	-5
Over \$100,000 to \$120,000	-6
Over \$120,000	-7

5. How old were you at your last birthday?

[] (ACCEPT WHOLE # 0-100; DO NOT ACCEPT A RANGE)

6. To ensure proper representation of race, are you...?

White (Caucasian)	-1
African American (Black)	-2
Asian	-3
Hispanic	-4
Another race (SPECIFY)	-5
[]	

[PROGRAMMER: COUNT RESPONDENTS AS COMPLETES AT Q6. UPON BEING COUNTED AS A COMPLETE, THE PACKET ID# IN THE PORTAL WILL POPULATE BASED ON THE PREASSIGNED FACILITY ID#S]

Thank you for your help and including your opinion as part of our research.

ATTACHMENT 3

Austin.....	-01
Dallas	-02
Raleigh.....	-03

Final Visit Sample Questionnaire

1. Did you forget to place any used pouches into the collection containers over the past 3 days?

Yes.....-1 (CONTINUE)

No-2 (SKIP TO Q.3)

2. Approximately how many pouches did you forget to place into the collection container?

Collection 1 [] (ACCEPT WHOLE # 1-99; DO NOT ACCEPT A RANGE)

Collection 2 [] (ACCEPT WHOLE # 1-99; DO NOT ACCEPT A RANGE)

Collection 3 [] (ACCEPT WHOLE # 1-99; DO NOT ACCEPT A RANGE)

3. Thinking about the number of CAMEL Snus pouches you used over the past 3 days, was it more, less, or about the same compared to the number of CAMEL Snus pouches you usually use?

More pouches than usual-1

About the same number of pouches as usual-2

Less pouches than usual.....-3

4. Which of the following other tobacco products, if any, did you use over the past 3 days? (PROGRAMMER: ALLOW MULTIPLE RESPONSES)

Moist snuff or dip in a round can.....-1

Chewing tobacco.....-2

Cigarettes.....-3

Pipe tobacco.....-4

Cigars.....-5

Little cigars-6

Tobacco tablets.....-7

Other (Specify)-8

None-9

5. Which of the following nicotine replacement products, if any, did you use over the past 3 days? (PROGRAMMER: ALLOW MULTIPLE RESPONSES)

Nicotine patch.....-1

Nicotine gum-2

Nicotine lozenges.....-3

Nicotine nasal spray.....-4

Nicotine inhaler-5

Other (Specify)-6

None-7

6. When using the Camel Snus product, where in the mouth do you typically place the pouch?

- In the front between upper lip and gum-1
- In the front between lower lip and gum-2
- On the upper side between teeth and cheek-3
- On the lower side between teeth and cheek-4
- Under your tongue-5
- Different locations-6
- Do not have a set pattern.....-7

7. Do you typically move the Camel Snus pouch around or reposition it while you are using it?

- Yes.....-1
- No-2

8. How long do you typically keep the Camel Snus pouch in your mouth?

- Less than 5 minutes.....-1
- 5 to 9 minutes.....-2
- 10 to 30 minutes.....-3
- Longer than 30 minutes-4

9. Do you use multiple pouches of Camel Snus at the same time?

- Yes.....-1
- No-2 [SKIP TO Q12]

10. When you use multiple pouches of Camel Snus, how many do you use at one time?

- 2 pouches-1
- 3 pouches-2
- More than 3 pouches.....-3

11. What percent of the time would you say you use multiple pouches of Camel Snus at the same time?

- Less than 25% of the time.....-1
- 25% to 50% of the time-2
- More than 50% of the time-3

12. Do you ever drink beverages while using Camel Snus?

- Yes.....-1
- No-2

13. Were you able to freeze the samples after each day of collection?

- Yes.....-1
- No-2

14. Thinking about the **Overall Study**: (PROGRAMMER: EACH STATEMENT SHOULD APPEAR ONE AT A TIME)

[RANDOMIZE STATEMENTS]	Yes	No
The gratuity that I will be paid for my time is a fair amount.....	-1	-2
The facility gave me clear instructions on how to complete the study....	-1	-2
The location of the facility was convenient.....	-1	-2
The field site was able to answer my questions	-1	-2
The field site provided a good variety of days for me to visit their office...	-1	-2
I would be willing to participate in a similar study in the future.....	-1	-2

15. Would you consider participating in a similar study in the future?

Yes.....-1

No-2

16. Do we have your permission to contact you in the future to ask some questions about your tobacco use at that time?

Yes.....-1

No-2

17. A similar study may be conducted again in the future. We value your feedback. Please provide any questions or comments about this study. (PROGRAMMER: ALLOW FOR OPEN-ENDED ANSWER)

Thank you for your help and including your opinion as part of our research.

ATTACHMENT 4

The Fagerström Test for Nicotine Dependence (FTND)

1. How soon after you wake up do you smoke your first cigarette?

Within 5 minutes..... ☐₃

6 – 30 minutes..... ☐₂

31– 60 minutes..... ☐₁

After 60 minutes..... ☐₀

2. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. in church, at the library, in cinema, etc.?

Yes..... ☐₁

No..... ☐₀

3. Which cigarette would you hate most to give up?

The first one in the morning..... ☐₁

Any other..... ☐₀

4. How many cigarettes per day do you smoke?

≤ 10..... ☐₀

11 – 20..... ☐₁

21– 30 ☐₂

≥ 31..... ☐₃

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?

Yes..... ☐₁

No..... ☐₀

6. Do you smoke if you are so ill that you are in bed most of the day?

Yes..... ☐₁

No..... ☐₀

Reproduced with permission.

Source: Heatherton, T. F., L. T. Kozlowski, et al. (1991). "The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire." Br J Addict 86(9): 1119-27.

ATTACHMENT 5

The Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco

[Ebbert JO et al. (2006) Addictive Behaviors 31:1716-1721]

(modified for use with snus users)

1. How soon after you wake up do you place your first Snus pouch?
Within 5 minutes.....☐₃
6 – 30 minutes.....☐₂
31 – 60 minutes.....☐₁
After 60 minutes.....☐₀
2. How often do you intentionally swallow tobacco juice?
Always.....☐₂
Sometimes.....☐₁
Never.....☐₀
3. Which snus would you hate to give up most?
The first one in the morning.....☐₁
Any other.....☐₀
4. How many tins per week do you use?
More than 3.....☐₂
2 – 3.....☐₁
1.....☐₀
5. Do you snus more frequently during the first hours after awakening than during the rest of the day?
Yes.....☐₁
No.....☐₀
6. Do you snus if you are so ill that you are in bed most of the day?
Yes.....☐₁
No.....☐₀