A Clinical Model for Estimation of the Amount of Nicotine and NNK Absorbed from the Use of Moist Smokeless Tobacco Products

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Abstract

Assessment of exposure to nicotine and NNK between different moist smokeless tobacco (MST) products can be best conducted using a randomized crossover clinical trial design. However, the relatively long elimination half-life (e.g. ~52 days for NNK metabolites) would require an impractically long washout period, which makes it impossible to conduct crossover studies. We present here a unique clinical model to estimate the amount of nicotine and NNK absorbed (Amt_{abs}) from three MST products. In this model, we first measured the amount of nicotine and NNK in a fresh 2-g quid ($Amt_{original}$). Another 2-g quid of the same MST product was then used by subjects for 40 minutes. Following the use the amount of nicotine and NNK in the post-use quid (Amt_{post}) and expectorate (Amt_{exp}) were measured. The amount absorbed was estimated by $Amt_{abs} = Amt_{original} - (Amt_{post} + Amt_{exp})$. In this randomized crossover design study, adult male MST users (n=23) used the three MST products. Subjects used a 2-g MST quid for 40 minutes every 2 hours for a total of 6 uses (2 uses for each of the three products per randomization). All expectorates along with the used quid were collected for nicotine and NNK measurement. Overall, the LS Mean of estimated Amt_{abs} of the three products ranged from 2728.19 to 3454.74 μg for nicotine and from 215.94 to 263.74 ng for NNK. The results demonstrate a less invasive method to estimate the levels of nicotine and NNK absorbed by adult MST users.

Introduction & Objective

Introduction
Assessment of exposure to nicotine and NNK from moist smokeless tobacco (MST) products in clinical trials require relatively long period of time. This is mainly due to the long elimination half-life especially for NNK (e.g. ~52 days for NNK metabolites), which makes the crossover studies almost impossible. We estimate the amount of nicotine and NNK absorbed from MST products using a mass balance approach.

Objective
To estimate the amount of nicotine and NNK available for uptake during use of wintergreen flavored MST products in adult MST users

Table 1. Study Products

Moist Smokeless Tobacco Product	Nicotine (as-is) (mg/g)	NNK (as-is) (ng/g)
A. Commercial Product (Reference)	10.47	627
B. Prototype Product (Test)	12.33	715
C. Commercial Product (Reference)	10.92	765

Table 2. Study Population Characteristics

N = 23 (male)	Mean (SD)
Age (years)	40.2 (12.2)
BMI (kg/m²)	28.5 (4.3)
Tobacco Use History	
Number of dips per day	7.5 (3.7)
Number of cans per day	0.9 (0.7)

Methods

Study Population
- Healthy adult (21 years and above) male long cut wintergreen MST users
- Daily use at least ½ can MST in the past 6 months

Study Design
- Randomized, 3-way crossover
- Product use under controlled use condition:
  - A 2-g product (quid) use for 40 minutes per use
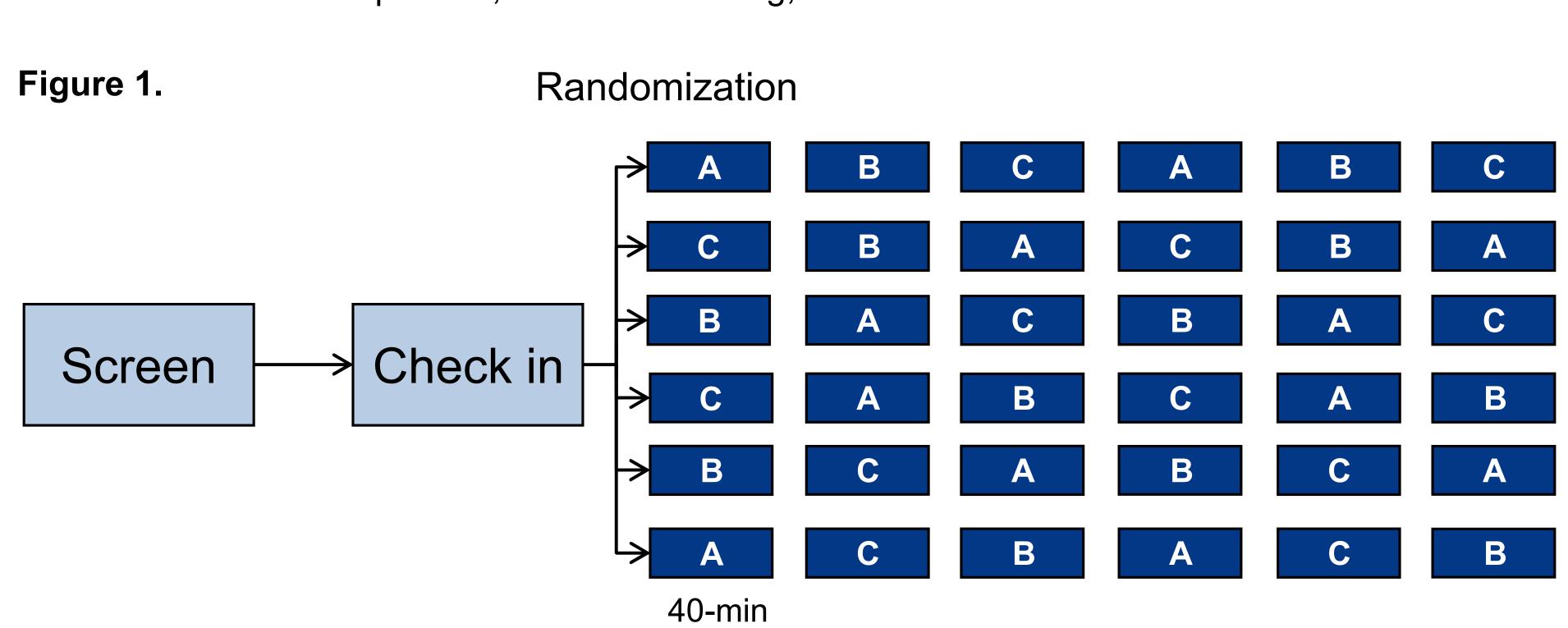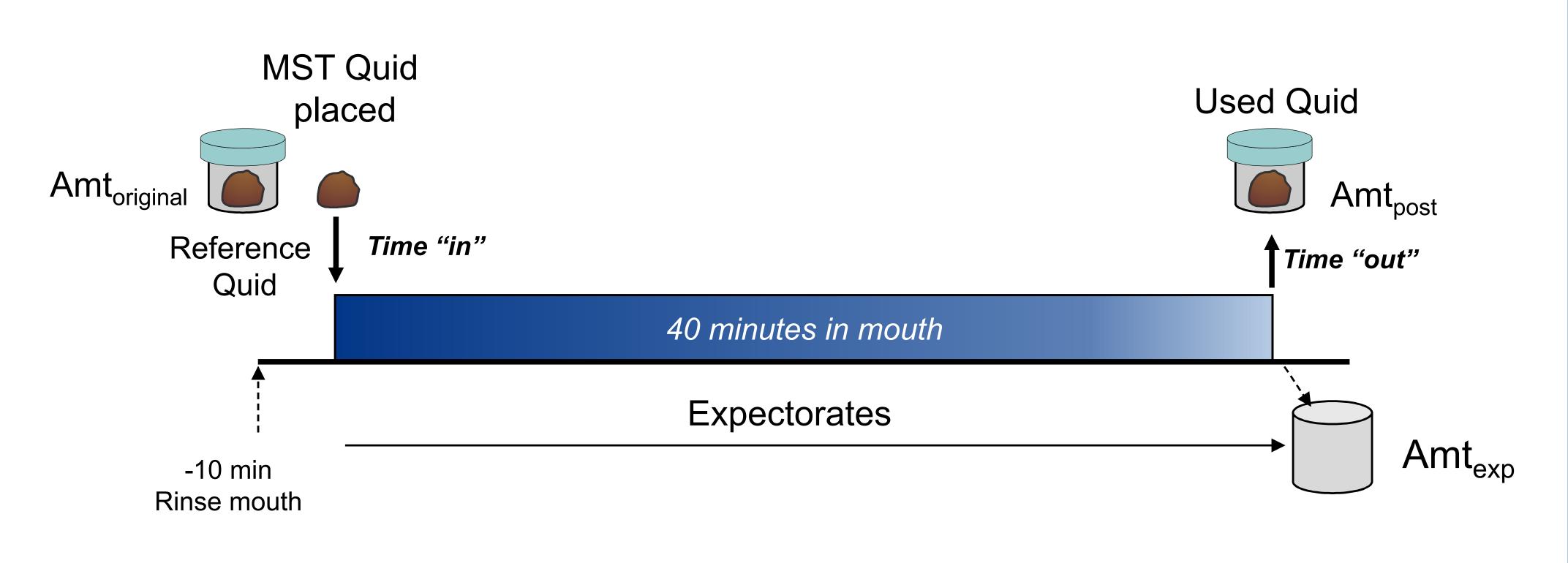 - Two uses for each product, one in the morning, one in the afternoon

Figure 1.

Figure 1. (Randomization diagram)

Figure 2. Product Use & Sample Collection

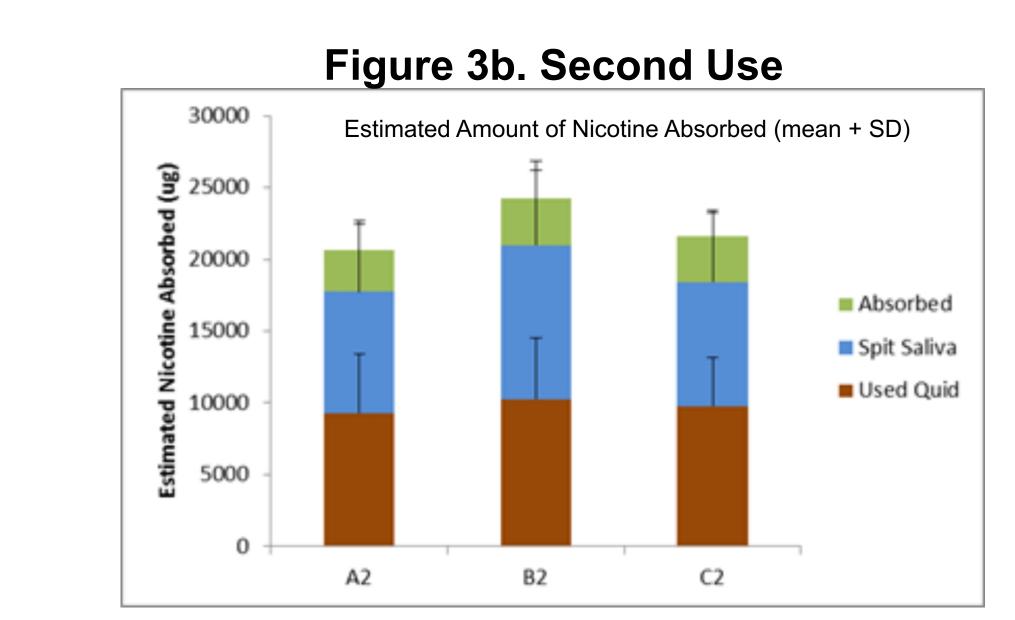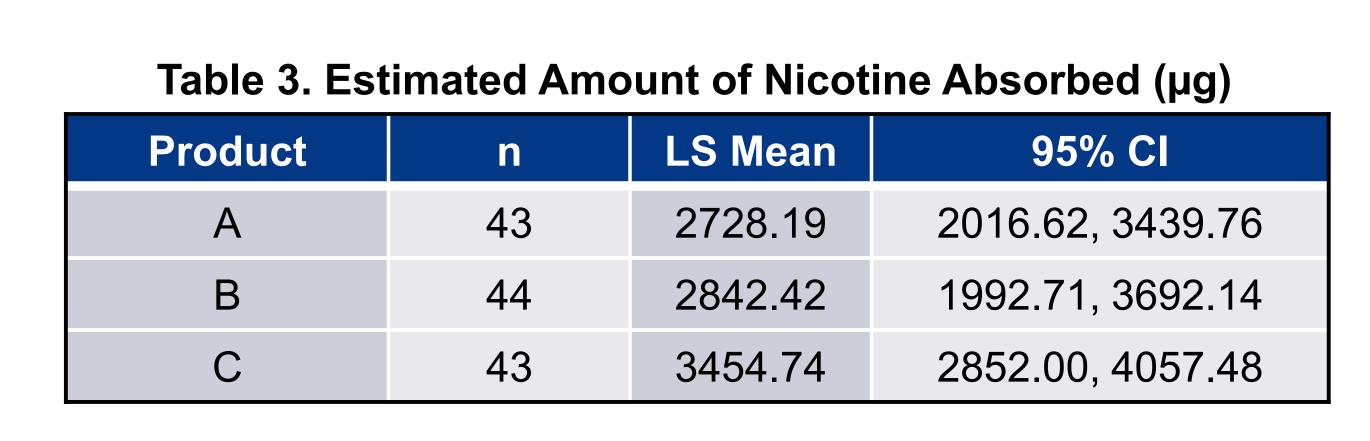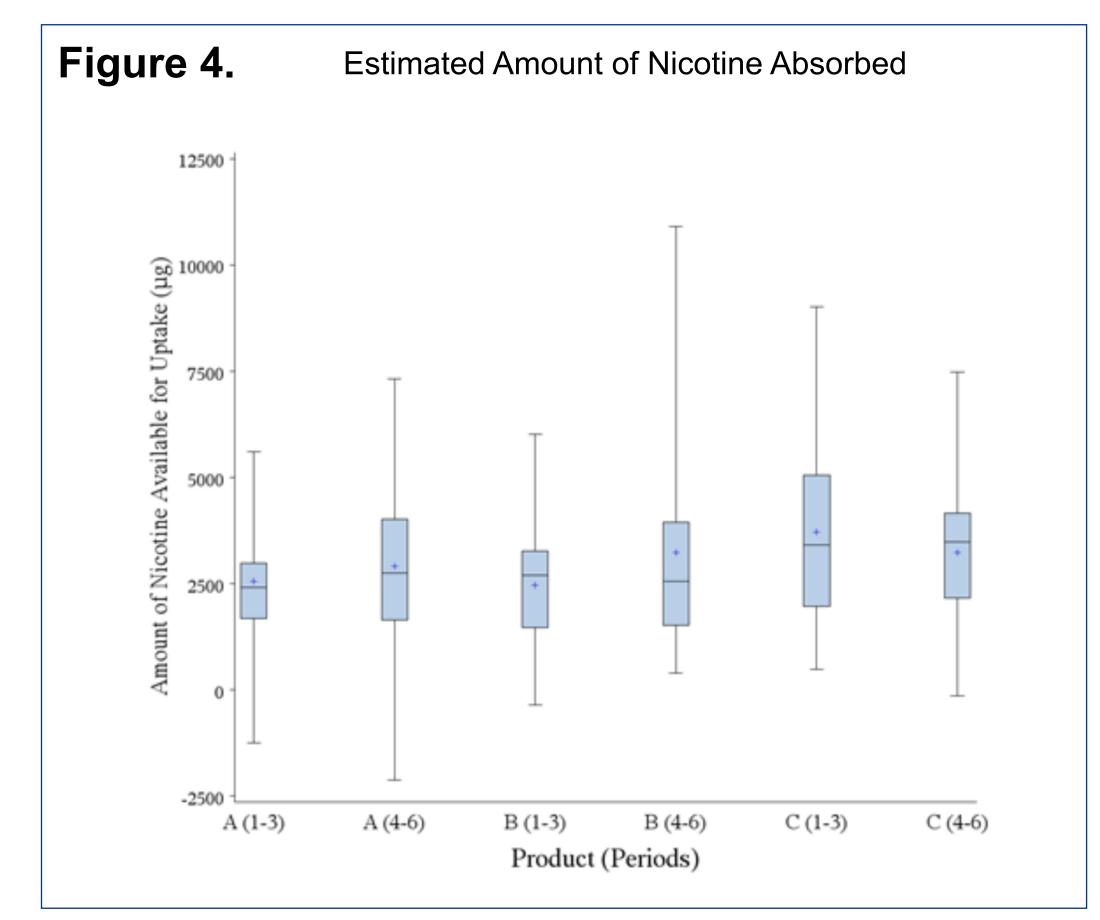Figure 2. Product Use & Sample Collection

Investigation
- Amount ($Amt_{original}$) of Nicotine and NNK were measured from the fresh quid (reference quid), used quid (Amt_{post}) and expectorates (Amt_{exp})
- Estimated amount absorbed $Amt_{abs} = Amt_{original} - (Amt_{post} + Amt_{exp})$

Results

Estimated Amount of Nicotine Absorbed

Figure 3a. First Use

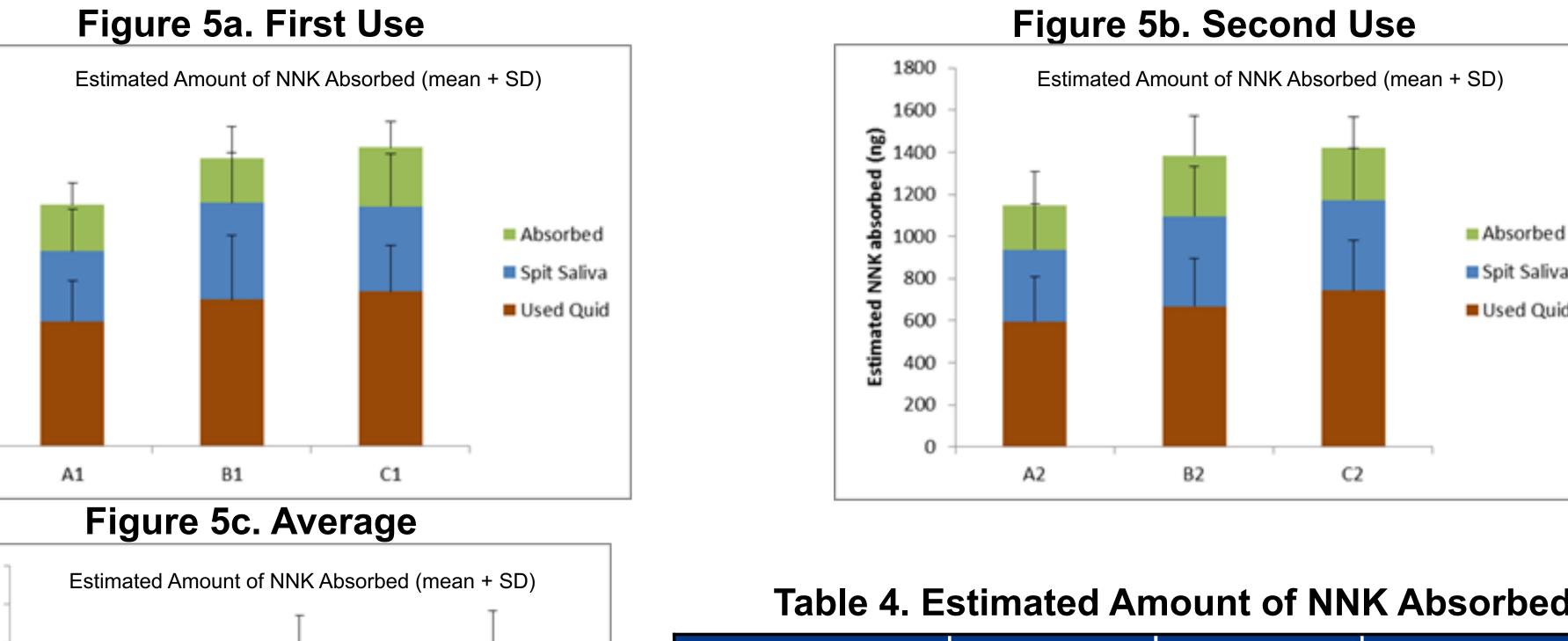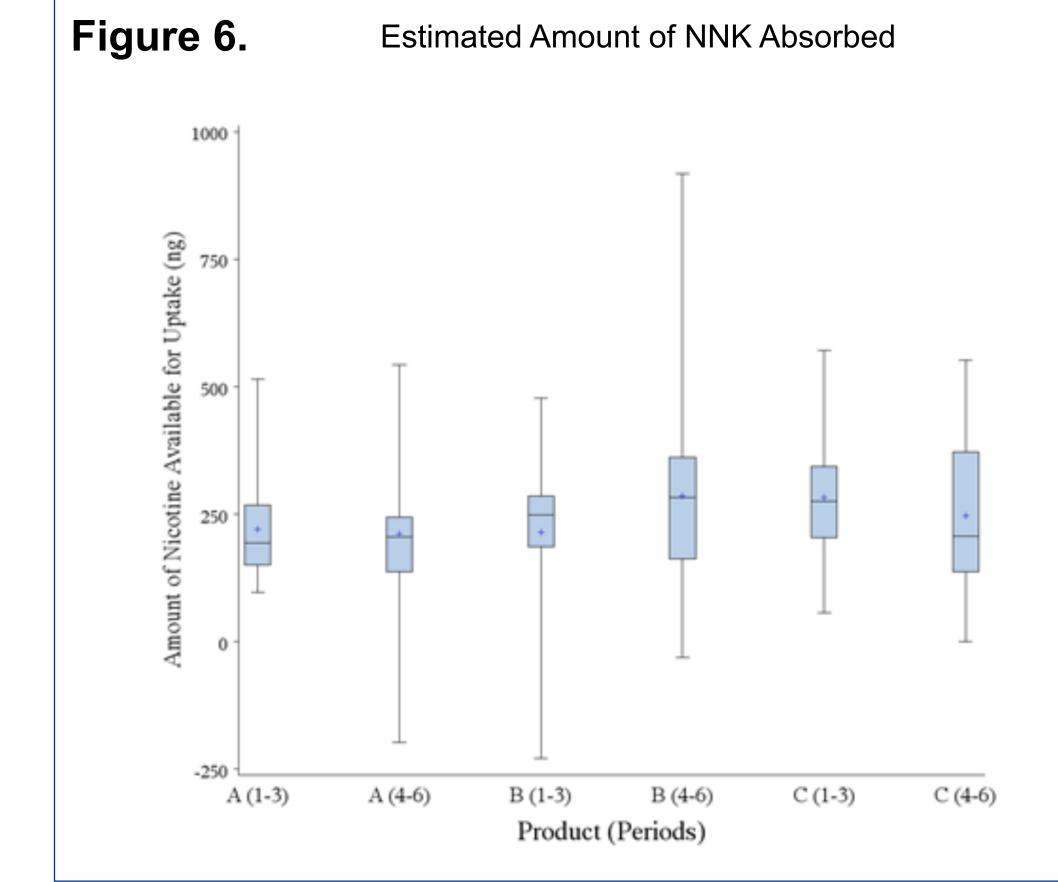Figure 3b. Second Use

Figure 3c. Average

Figure 4.

The whiskers represent the Maximum and Minimum values. The outer edges of the box represent the interquartile range, Q3 (75th percentile) and Q1 (25th percentile). The line inside the box represents the Median value, and the + represents the Mean value.

Table 3. Estimated Amount of Nicotine Absorbed (μg)

Product	n	LS Mean	95% CI
A	43	2728.19	2016.62, 3439.76
B	44	2842.42	1992.71, 3692.14
C	43	3454.74	2852.00, 4057.48

Estimated Amount of NNK Absorbed

Figure 5a. First Use

Figure 5b. Second Use

Figure 5c. Average

Figure 6.

The whiskers represent the Maximum and Minimum values. The outer edges of the box represent the interquartile range, Q3 (75th percentile) and Q1 (25th percentile). The line inside the box represents the Median value, and the + represents the Mean value.

Table 4. Estimated Amount of NNK Absorbed (ng)

Product	n	LS Mean	95% CI
A	44	215.94	164.08, 267.79
B	44	251.66	183.55, 319.77
C	44	263.74	204.96, 322.51

Summary & Conclusions

- On average, the estimated amount of nicotine absorbed during 40 min use of a 2-g quid for product A, B and C range from (LS Mean) 2728.19 to 3454.74 μg (approximately 12–17% of the nicotine measured in a 2-g unused quid).
- On average, the estimated amount of NNK absorbed during 40 min use of a 2-g quid for product A, B and C range from (LS Mean) 215.94 to 263.74 ng (approximately 18 - 19% of the NNK measured in a 2-g unused quid).
- Relatively large variability was observed in the estimated amount of nicotine and NNK absorbed.
- The results demonstrate a less invasive method to estimate the levels of nicotine and NNK absorbed by adult MST users.

No conflict of interest