Modeling the Population Health Effects of Camel Snus with Reduced Risk Information

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Attributions

The Dynamic Population Modeler (DPM(+1)) was developed by Ramboll Environ, with the support of RAI Services Company (RAIS), to address regulatory requirements for new tobacco products.

Drs. Bachand and Sulsky (Ramboll Environ) consulted on the Camel Snus MRTPA analysis plan, conducted the analyses using DPM(+1), and summarized the results.

Ramboll Environ's contribution to any regulatory submission on behalf of RAIS, including the Camel Snus MRTPAs, is strictly limited to the technical implementation of the DPM(+1), and does not include advocating the use of any specific tobacco (or nicotine) product.

Modeling of Population Health Effects

Camel Snus with Reduced Risk Information

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Introductory Remarks

Camel Snus MRTP Applications

Tobacco Exposure/Use Patterns
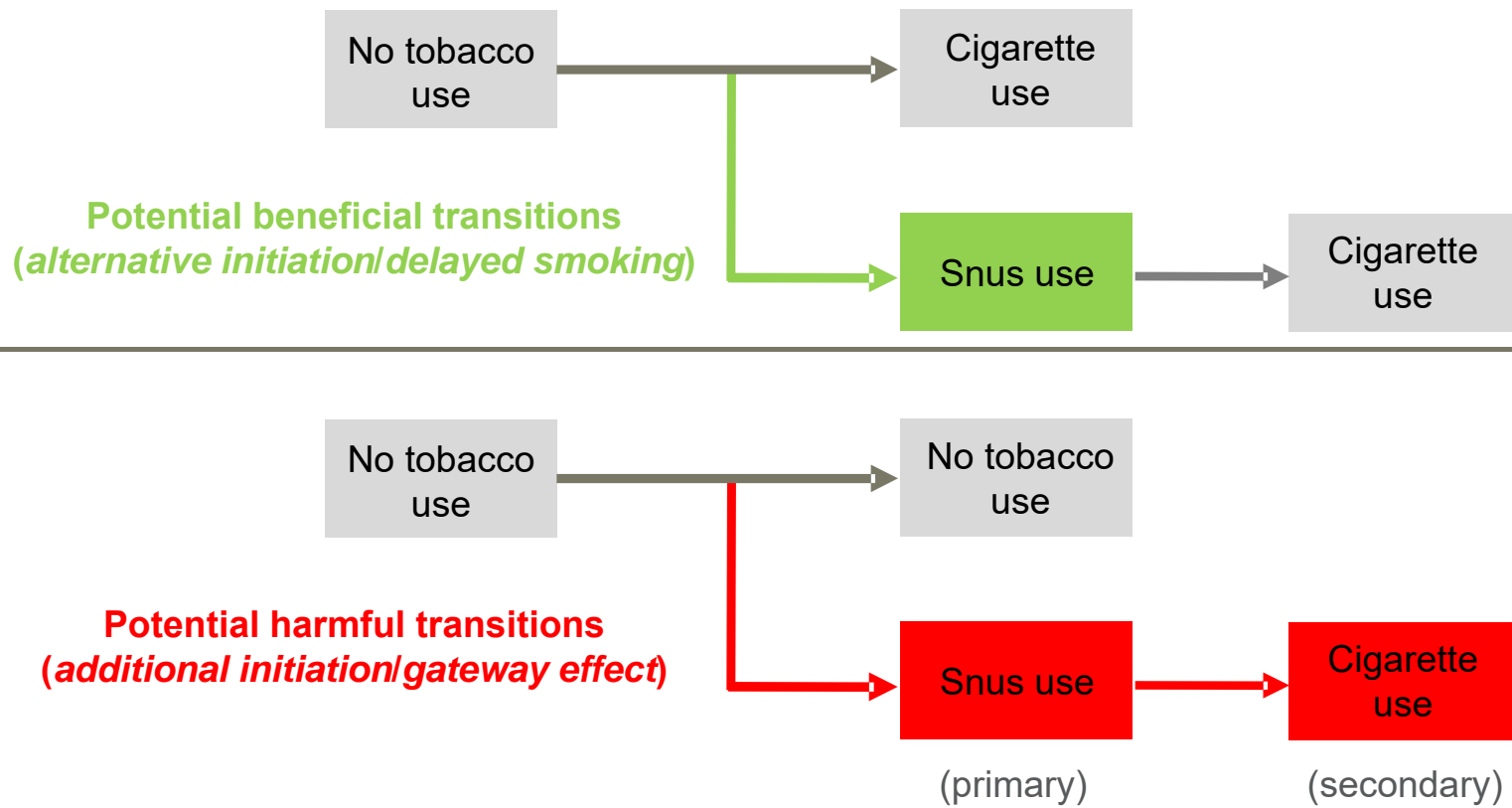
Camel Snus MRTP Applications - Overview

RJRT is seeking risk modification orders across 6 styles, under Section 911(g)(1) of the FSPTCA

Proposed advertising is intended for adult smokers, encouraging them to *switch completely* to Camel Snus to reduce their risk for smoking-attributable disease
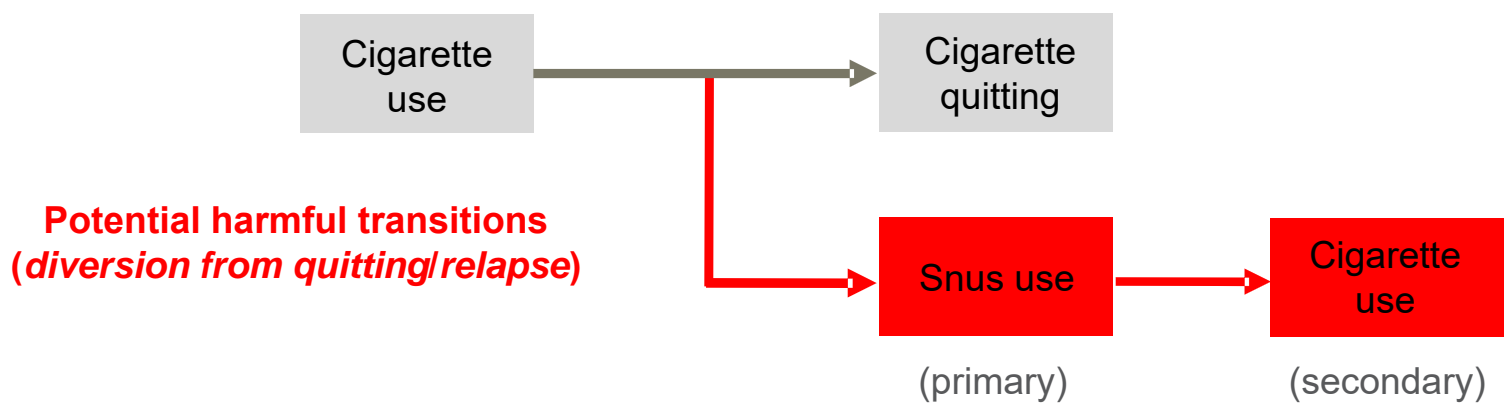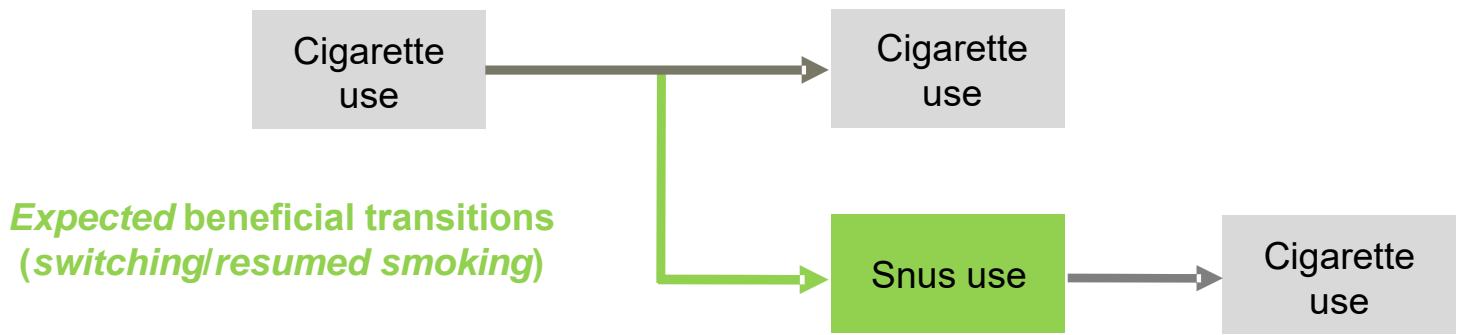
- includes cautionary statements to further educate smokers regarding serious health risks associated with smoking, addictive nature of tobacco products, and that quitting is best choice for smokers concerned about health risks
- retains four statutorily mandated rotating warning labels, without modification

Testing was conducted for all proposed advertising, consistent with FDA's required consideration of risks and benefits to the population as a whole

Increased Use of Camel Snus among Never Tobacco Users

Increased Use of Camel Snus among Current Cigarette Users

Expected beneficial transitions
(*switching*/*resumed smoking*)

| Cigarette use → Cigarette use |
| Cigarette use → Snus use → Cigarette use |

Potential harmful transitions
(*diversion from quitting*/*relapse*)

| Cigarette use → Cigarette quitting |
| Cigarette use → Snus use (primary) → Cigarette use (secondary) |

Research Strategy

Modeler Framework

Research Objectives

Dynamic Population Modeler (DPM(+1)) Framework[1,2]

Hypothetical population of one-million 12 year-old male never tobacco users followed in 5-year intervals (single cohort), with survival used as surrogate for population health

Smoking-attributable mortality calculated for each age interval - based on age, duration of use, and duration of use cessation; mortality rates for Camel Snus users based on excess relative risk (ERR) estimate (relative to smoking)

Primary beneficial/harmful transitions based on age-specific purchase probabilities from likelihoods of use testing (Camel Snus with reduced risk messaging); secondary *harmful* transitions based on hypothetical (in most cases, extreme) probabilities

[1] Bachand AM, Sulsky SI. A dynamic population model for estimating all-cause mortality due to lifetime exposure history. *Regul Toxicol Pharmacol.* 2013;67(2):246-51.

[2] Bachand AM, Sulsky SI, Curtin GM. Assessing the likelihood and magnitude of a population health benefit following the market introduction of a modified-risk tobacco product: Enhancements to the Dynamic Population Modeler, DPM(+1). *Risk Anal.* Apr 24 2017 [Epub ahead of print].

Research Objectives

Assess population health impact of changes in tobacco exposure patterns likely to result from Camel Snus with reduced risk messaging

Assess population health effects of particular changes in exposure patterns, individually and in limited combinations

Assess whether Camel Snus with reduced risk messaging is likely to have population health benefit even if harmful exposure transitions are extreme

Modeling Input Data

Base Case and Counterfactual Scenarios

Base Case (cigarette use only)

Age-specific mortality rates for never, current and former smokers calculated based on data from Kaiser-Permanente Cohort Study and 2000 U.S. Census

Transition probabilities calculated based on 2009 U.S. cigarette smoking initiation and 2005-2008 U.S. smoking cessation rates

Counterfactual Scenario (cigarette and/or snus use)

Mortality rates for Camel Snus users based on ERR estimates of 0.08 and 0.11 (consensus estimates for all-cause mortality risk associated with use of LNST)[3]

Primary beneficial/harmful transitions based on empirically derived estimates

Secondary harmful transitions of *delayed smoking*, *gateway effect*, *relapse* and *resumed smoking* based, in most instances, on extreme scenarios (50% of relevant users)

[3] Levy DT, Mumford EA, Cummings KM, et al. The relative risks of a low-nitrosamine smokeless tobacco product compared with smoking cigarettes: Estimates of a panel of experts. Cancer Epidemiol Biomarkers Prev. 2004;13(12): 2035-42.

Projected Purchase/Transition Probabilities

Age interval	Never tobacco users likely to initiate cigarette use[a]			Never tobacco users not likely to initiate cigarette use[b]		
		Purchase probability	Transition probability		Purchase probability	Transition probability
13-17	-	-	0.85	-	-	0.3
18-22	48	1.2	0.85	123	0.2	0.3
23-27	79	1.0	0.85	211	0.3	0.3
28-32	79	0.9	-	159	0.3	-
33-37	44	0.9	-	127	0.3	-
38-42	36	0.7	-	117	0.3	-
43-47	37	0.5	-	132	0.2	-
48-52	32	0.6	-	146	0.3	-
53-57	16	0.5	-	159	0.3	-
58-62	25	0.4	-	197	0.2	-
63-67	15	0.6	-	208	0.2	-
68+	10	1.2	-	225	0.2	-

[a] Relevant tobacco user group for estimating transition probability of *alternative initiation*

[b] Relevant tobacco user group for estimating transition probability of *additional initiation*

Projected Purchase/Transition Probabilities

Age interval	Smokers likely to quit cigarette use[c]			Smokers not likely to quit cigarette use[c]		
		Purchase probability	Transition probability		Purchase probability	Transition probability
13-17	-	-	-	-	-	-
18-22	8	15.4	15.4	33	13.4	13.4
23-27	15	22.1	22.1	75	12.9	12.9
28-32	36	13.6	13.6	102	16.0	16.0
33-37	33	11.3	11.3	130	9.1	9.1
38-42	30	11.3	11.3	112	7.3	7.3
43-47	19	5.4	5.4	144	6.5	6.5
48-52	18	7.1	7.1	135	5.9	5.9
53-57	21	5.6	5.6	123	3.3	3.3
58-62	20	2.6	2.6	113	2.6	2.6
63-67	16	1.8	1.8	84	2.8	2.8
68+	10	2.2	2.2	56	2.0	2.0

[c] Relevant tobacco user group for estimating transition probability of *diversion from quitting*

[d] Relevant tobacco user group for estimating transition probability of *switching*

Modeler Projections

Population Health Impact
Sensitivity Analyses

Population Health Impact

'Master model' (all primary transitions and secondary harmful transitions[*]) projected benefit of ~7,000 additional survivors

- scaling to full U.S. birth cohort yields >25,000 additional survivors

Reducing probabilities for primary transitions by 75%, while retaining probabilities for secondary transitions still resulted in survival benefit (~1,900 additional survivors)

Within context of 'master model', ERRs for Camel Snus as high as 0.45 still provide population health benefit

[*] Excludes secondary harmful transition of 50% *relapse* (projected, as post-hoc calculation)

Population Health Effect of Individual Transitions

Exposure transition	ERR	Difference in Survival	95% Posterior Interval	
Alternative initiation (0.85%)	0.08	155	132	178
Alternative initiation, followed by *delayed smoking* (50%)	0.08	87	70	105
Additional initiation (0.30%)	0.08	-145	-155	-134
Additional initiation, followed by *gateway effect* (50%)	0.08	-382	-400	-364
Switching (2.0%-16.0%, depending on age interval)	0.08	14,639	12,892	16,396
	0.11	13,925	12,261	15,611
Switching, followed by *resumed smoking* (50%)	0.08	8,093	7,127	9,063
Diversion from quitting (1.8%-22.1%, depending on age interval)	0.08	-390	-440	-341

Likelihood of Population Health Benefit

'Tipping point' analyses used to estimate proportion of *switching* necessary to fully offset extreme scenarios for harmful exposure transitions (ERR of 0.11)

- extreme *additional initiation* (equal to U.S. smoking initiation rates) requires 4.12% *switching* at each age interval for 'near zero' point estimate
- exaggerated *additional initiation* (10-fold higher than projected) and extreme *gateway effect* (50% of *additional initiators*) requires 2.8% *switching* (at each age interval)
- extreme *diversion from quitting* (50% of smokers likely to quit) requires 1.29% *switching* (at each age interval)

'Tipping point' analyses that included all primary/secondary harmful transitions indicated survival benefit if ~1.5% *switching* (at each age interval)

Impact of Increasing First Age Category of Product Use

ERR	First Age Category of Camel Snus Availability		Difference in Survival	95% PI	
	Alternative initiation and *additional initiation*	*Switching* and *diversion from quitting*			
0.08	13-17	18-22	7,374	6,416	8,346
	18-22	18-22	7,511	6,562	8,473
	23-27	23-27	6,248	5,466	7,048
	N/A	28-32	4,481	3,914	5,066
	N/A	33-37	2,345	2,046	2,655
	N/A	38-42	1,385	1,208	1,571
	N/A	43-47	779	678	885
	N/A	48-52	370	322	422

As first age category of Camel Snus use was systematically increased, survival benefit decreased and became negligible when product use began after age 55

Single cohort estimates provide insight into health impact to cross-sectional population (i.e., full U.S. population) if members of different ages are operationalized as members of different cohorts

Concluding Remarks

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DPM(+1) is validated model for estimating population mortality due to specified changes in tobacco use patterns, and was developed to address regulatory requirements

'Master model' results and sensitivity analyses consistently indicate that Camel Snus with reduced risk messaging is likely to benefit overall population health by decreasing tobacco-related mortality

Based on empirically derived probabilities, *switching* is only individual transition that provides sizable population health effect

'Tipping point' analyses indicate Camel Snus with reduced risk messaging is likely to have population health benefit

Disclosures

This research was supported by RAI Services Company (RAIS).

Dr. Curtin is employed by RAIS, a wholly owned subsidiary of Reynolds American Inc., whose operating companies market smokeless tobacco products.

Dr. Shiffman consults on tobacco harm minimization (including nicotine replacement therapy and vapor products) to Niconovum USA, RJ Reynolds Vapor Company and RAIS, all subsidiaries of Reynolds American Inc.

Dr. Shiffman also owns an interest in intellectual property for a novel nicotine medication.

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