May 24, 2017

SUPPLEMENT 1: DOCUMENTATION FOR THE E-CIGARETTE SUBSTITUTION MODEL

INTRODUCTION

The E-Cigarette Substitution Model was developed to examine the public health impact of an endgame strategy directed at replacing all or most cigarette use by e-cigarette use over a ten-year timeframe. The analysis begins with the Status Quo Scenario for smoking rates and health outcomes in the absence of e-cigarettes. An E-cigarette Substitution Scenario is then developed in which cigarette use is totally or partially replaced by e-cigarette use. Projected health outcomes under the Status Quo and E-cigarette Substitution Scenarios are compared to determine the public health impact. The model allows for a range of parameters, including scenarios at different levels of and time frames for e-cigarette substitution, e-cigarette and cigarette initiation and cessation, and e-cigarette harms.

The model is initialized in 2016 with the population classified as never, current and former cigarette smokers. To reflect the population of smokers alive today, the analysis is conducted for the population age 15 through age 99 in 2016. Projections are applied through the year 2100 to incorporate the potential health effects of those at younger ages. In developing the model, we assume a fixed population based on projections from the United Nations. This assumption simplifies the analysis, so that the focus is on prevalence rates.

We do not consider the use of other tobacco products, such as cigars or smokeless tobacco. A List of assumptions is found in Table 1.

Table 1. Assumptions in the E-cigarette Substitution Model

Assumptions	Reasons/Implications
General	
Analysis is confined to e-cigarette and cigarette use. No smokeless tobacco, cigars, etc.	Simplifies the analysis avoiding multiple pathways for substitution. These paths may hinder or reinforce the substitution of e-cigarettes for cigarettes.
Population is fixed	Simplifies the analysis. May understate total deaths due to a larger population in the E-cigarette Substitution Scenario due to the fewer deaths at early ages.
Status Quo Scenario	
Future initiation and cessation rates reflect levels and trends in past rates	Developed through 2012, before e-cigarette become more widely used.
No e-cigarette use	To contrast with the E-cigarette Substitution Scenario.
E-cigarette Substitution Scenario	
All transitions from cigarette to e-cigarette use occur within a specified number of years beginning in the year 2017	Made for simplicity**.** Impact depends on the 2016 prevalence rates, and years of transition can occur over long periods of time.
Same proportional transition rates from cigarette to e-cigarette across years subject to residual prevalence and cessation	Made for simplicity and tractability. Transition rates are determined by the initial and expected residual prevalence. Bias will depend on actual rates of transition by year.
Smokers continue to quit at the same rate as in the Status Quo	Assumes that those who continue to smoke are not substantially different from others. May bias the effects of the E-cigarette substitution scenario downward.
E-cigarette users quit at a rate δ × the Status Quo cessation rate	We initially assume the same rates for e-cigarette users (δ=1). The extent of cessation will depend on addiction liability, perceived risks, and other factors.
Those who quit cigarette before age 40 are treated as never smokers and similarly for e-cigarette users.	Risks are low for those who quit before age 40, especially at the ages when most tobacco –related deaths occur.
Former smokers who use e-cigarette users who quit after age 40 become former smokers with the risks of former smokers	Former smoker risks are assumed to be unaffected by e-cigarette use.
The excess risks of e-cigarette users are based on an excess risk relative to smokers	To provide a common metric for calculation.
For former smokers using e-cigarettes, excess risk is estimated as the former smoker risks plus a portion of the difference between the excess risk of current and former smokers	Assumes that the relative proportion of risks for former smokers is unaffected by the use of e-cigarettes. They may be higher if there is a negative synergistic effect of the two products or may be lower if the quantity smoked is substantially reduced while an e-cigarette users.
Excess risks of former e-cigarette users are relative to the excess risk of former smokers	Assumes that risk of former e-cigarette users fall at similar rates to those of former smokers.

DATA SOURCES

Smoking data

Data on current, former and never (cigarette) smoker prevalence rates by age and sex for 2016 were obtained from National Health Interview Surveys.[1] As described in Holford et al.,[1] estimates of initiation and cessation were developed by applying an age-period-cohort statistical model to data from the 1965-2012 National Health Interview Surveys while correcting for bias due to higher mortality among current and former smokers. The initiation and cessation rates were validated by comparing the projections over the period 1965 through 2010 against smoking prevalence rates.[34] Initiation was based on respondents stated age of initiation. Cessation was measured as the percent quit from smoking for at least two years to approximate cessation net of relapse, i.e., those who quit less than two years are assumed to be offset by those who will relapse after two years.

Death Rates

Death rates by were developed by age, sex and cigarette smoking status (never, former, and current). Holford et al.[1] applied a methodology by Rosenberg[2] to obtain all-cause cohort life tables for the 1864-1980 birth cohorts, which were then projected forward allowing for reduced death rates over time (e.g., corresponding to medical advances). The methodology uses (1) mortality relative risk estimates by sex and smoking status derived from the first two American Cancer Society Cancer Prevention Studies and (2) smoking prevalence described above to partition US all-cause mortality tables by smoking status.

Population

Population data were obtained from United Nations, Department of Economic and Social Affairs, Population Division (https://esa.un.org/unpd/wpp/DataQuery/), which provides yearly US population projections by 5-age groups (0-4,…,95- 99 and 100+) separately for males and females from 2016 through 2100. A five-year moving average process was applied to the population from age 15 through age 97 in 2018-2098 based on the population of the same cohort, and assumed that the age 98-99 declined by 35% each year by cohort based on data from previous ages.

We considered two other population sources, including population projections from the Census Bureau and (available from 2016 to 2060 for ages 0-100, and from Holford (available from 2016-2100 for ages 0-85). As shown in Table 1, the population for each age derived from UN generally differed by less than 5% from the Census Bureau and Holford data in 2016. However, it is systematically lower than the Census data for ages 25 to 80 by about 5% and lower than the Holford in age 0-70 by around 5% in 2060.

Table 1. Comparison of United Nations, Census Bureau and Holford Population data

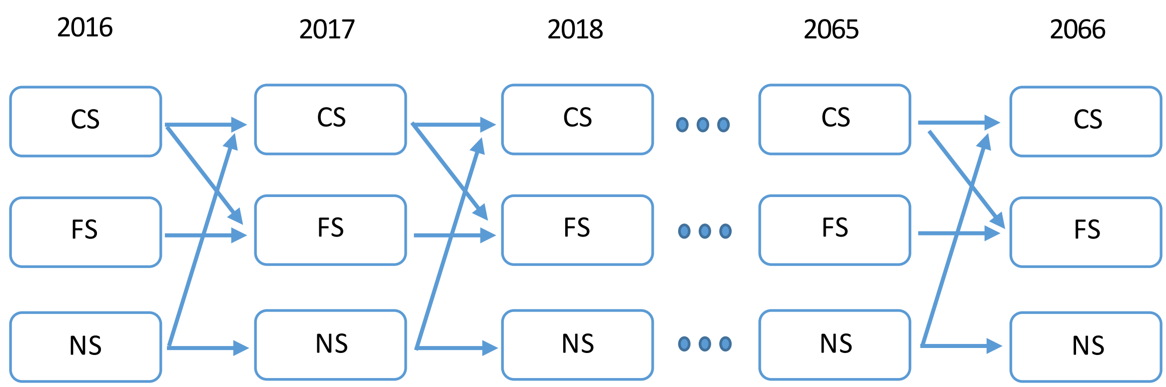
		2016			2060			2100	
		UN	Census vs UN (diff%)	Holford vs UN (diff%)	UN	Census vs UN (diff%)	Holford vs UN (diff%)	UN	Holford vs UN (diff%)
Male	**5**	**2,067,280**	-0.4%	0.1%	**2,387,824**	-2.0%	6.5%	**2,494,320**	11.2%
	15	**2,118,760**	1.1%	0.5%	**2,406,832**	-2.9%	5.2%	**2,539,800**	9.8%
	25	**2,329,200**	4.8%	3.9%	**2,460,032**	2.7%	7.9%	**2,580,880**	16.2%
	45	**2,061,080**	4.1%	3.6%	**2,406,464**	8.4%	11.7%	**2,632,973**	17.7%
	65	**1,694,720**	-2.0%	-2.3%	**2,274,128**	5.6%	-0.1%	**2,480,080**	7.3%
	84	**421,800**	-3.1%	-3.8%	**1,137,216**	-5.3%	-13.9%	**1,771,333**	-16.6%
	100+	**14,000**	3.3%		**177,000**	-3.8%		**556,000**	
Female	**5**	**1,980,440**	-0.6%	-0.1%	**2,281,992**	-2.0%	6.5%	**2,381,493**	11.4%
	15	**2,022,440**	1.5%	0.7%	**2,310,208**	-3.1%	4.4%	**2,430,267**	9.4%
	25	**2,202,040**	6.0%	5.2%	**2,383,048**	1.0%	4.9%	**2,481,427**	14.0%
	45	**2,044,000**	6.8%	6.4%	**2,368,560**	5.9%	8.9%	**2,554,907**	16.4%
	65	**1,841,320**	0.3%	-0.2%	**2,251,496**	7.2%	1.9%	**2,445,853**	9.4%
	84	**606,480**	-0.5%	-0.6%	**1,319,448**	3.1%	-3.5%	**1,895,320**	-5.6%
	100+	**61,000**	-3.8%		**453,000**	-4.3%		**1,183,000**	

Note: United Nations data has been extended and smoothed for all ages.

STATUS QUO (NO E-CIGARETTE) MODEL

Under the Status Quo Scenario, the population in 2016 is initially classified as never, current and former smokers. To project forward smoking rates in the absence of e-cigarette use, we apply age-specific and sex-specific initiation and cessation rates, and age- and sex-specific and smoking status-specific mortality rates. To gauge the complete effect of e-cigarette use, we assume no e-cigarette use in the Status Quo Scenario. As shown in Figure 1, never, current and former smokers evolve from never to current smoker and from current to former smoker from 2016 forward.

Figure 1 Transitions among different smoking statuses under the Status Quo



Notes: CS: Current smokers; FS: Former smokers; NS: Never smokers

While the data is distinguished by cohort, for ease of exposition, we describe the transitions by age- and time-specific transitions, but these rates will depend on the cohort chosen. For a given cohort, the prevalence of the never smokers at age a in year t is composed of the last year's survived never smokers who did not initiate smoking. With the initiation rate denoted as $Init_{a,t}$ at age a in year t, the prevalence of never smokers at age a in year t, $Prev\_never'_{a,t}$, is calculated as:

$$Prev\_never'_{a,t} = Prev\_never_{a-1,t-1} * (1 - DR\_never_{a-1,t-1}) * (1 - Init_{a-1,t-1}). \quad (1$$

For each cohort, the prevalence of smokers at age a in year t, $Prev\_smoker_{a,t}$, includes the prevalence of survived smokers at age a-1 in year t-1 who do not quit and the prevalence of survived never smokers at age a-1 in year t-1 who initiate smoking. With the cessation rate denoted as $Cess_{a,t,}$, smoker prevalence each year t, $Prev\_smoker'_{a,t}$, is calculated as:

$$Prev\_smoker'_{a,t} = Prev\_smoker_{a-1,t-1} * (1- DR\_smoker_{a-1,t-1}) * (1- Cess_{a-1,t-1})$$

$$+ Prev\_never_{a-1,t-1} * (1 - DR\_never_{a-1,t-1}) * Init_{a-1,t-1}. \qquad (2$$

The prevalence of former smokers at age a in year t, $Prev\_former'_{a,t}$, includes last year's survived former smokers at age a-1 and last year smokers at age a-1 who survived and quit, calculated as:

$$Prev\_former'_{a,t} = Prev\_former_{a-1,t-1} * (1 – DR\_former_{a-1,t-1}) +Prev\_smoker_{a-1,t-1}$$

$$* (1- Dr\_smoker_{a-1,t-1}) * Cess_{a-1,t-1}. \qquad (3$$

According to the formulas above, the total prevalence of current, former, and never smokers declines each year due to deaths, thereby summing to less than one. Since the population is exogenously provided, the prevalence of current, former, and never smokers is required to sum to 1. We inflate each prevalence by a correction factor developed as the reciprocal of a weighted average of survival rates (1- death rate) of smoking statuses where the weight is last year prevalence, i.e.,

$$Correction\ factor_{a,t} = 1/(Prev\_never_{a-1,t-1}*(1-DR\_never_{a-1,t-1}) + Prev\_smoker_{a-1,t-1}$$

$$*(1-DR\_smoker_{a-1,t-1}) + Prev\_former_{a-1,t-1}*(1-DR\_former_{a-1,t-1})). \qquad (4$$

The correction rate is applied to each prevalence to obtain the final prevalence rate, i.e.,

$$Prev\_never_{a,t} = Prev\_never'_{a,t} * correction\ factor_{a-1,t-1} \qquad (5a$$

$$Prev\_smoker_{a,t} = Prev\_smoker'_{a,t} * correction\ factor_{a-1,t-1} \qquad (5b$$

$$Prev\_former_{a,t} = Prev\_former'_{a,t} * correction\ factor_{a-1,t-1} \qquad (5c$$

Dividing equations (1, (2 and (3 by equation (4, equations 5a-5c then sum to one.

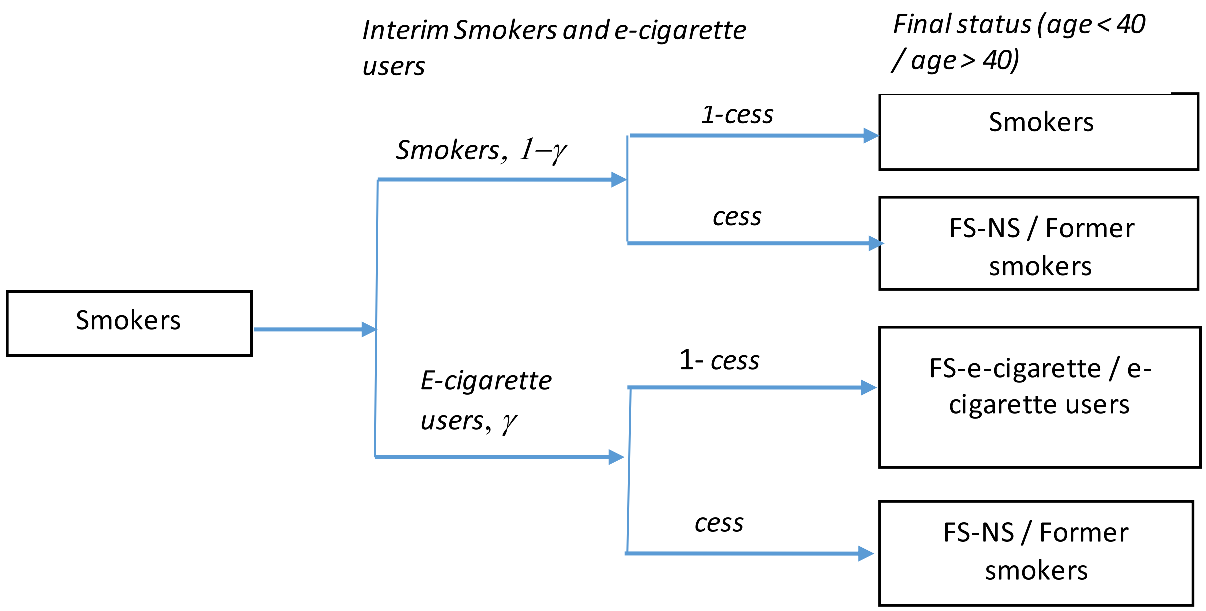
E-CIGARETTE SUBSTITUTION SCENARIOS

The E-Cigarette Substitution scenarios were constructed to show the effect of e-cigarette use, where e-cigarette use can lead to permanent replacement of cigarette smoking with e-cigarette use or temporary use of e-cigarettes that leads to no use of e-cigarettes or cigarettes ("no use"). The transitions are distinguished for 1) current smokers who transition out of smoking and 2) never smokers who would have initiated smoking.

CURRENT SMOKERS

We initially assume constant proportional transition rates (subject to residual smoking prevalence) from cigarette to e-cigarette across years, and the model is sufficiently flexible to allow for variations by age or cohort. As shown in Figure 2 for a given age and year, we distinguish the percent of smokers who temporarily transition into e-cigarette use each year by γ, with $1 - \gamma$ remaining as smokers.

Figure 2. Transitions from smoker of a particular age and year



As shown in Figure 2, those who were initially smokers may not only transition into e-cigarette uses, but may also quit as in the Status Quo Scenario. Since those who quit smoking before age 40 have minimal risks, it is assumed that current smokers below age 40 transition into e-cigarette users instead of former smokers using e-cigarette (as discussed below). Initial smokers still quit smoking into former smokers when age >= 40 (never smokers with smoking history when age < 40) at the original cessation rate as in Status Quo Scenario. In the next section, we consider variations from the Status Quo cessation rate. Like smokers, e-cigarette users also quit into former smokers when age >= 40 but never smokers with smoking history when age < 40.

Starting with the same prevalence of smokers, former smokers, and never smokers in 2016 as in the Status Quo Scenario, e-cigarette use is involved in the smoking/vaping transitions after 2016, where an n-year process of transition to e-cigarette use is modelled from the year 2017 leading to a residual smoking prevalence after n years The smoking prevalence of a specific cohort age a_0 in 2016 is denoted as $Prev\_smoker_{a0,2016}$. That group of smokers reduces to a target residual rate in n years, $Prev\_smoker_{a0+n,2016+n}$. The proportion of smokers transitioning out of smoking each year is modelled as occurring at a constant absolute change in prevalence over n years. In the absence of cessation as considered in Status Quo Scenario, the constant absolute change in prevalence each year relative to the prevalence in year 2016, γ_{a0}, is calculated as:

$$\gamma_{a0} = (Prev\_smoker_{a0,\,2016} - Prev\_smoker_{a0+n,2016+n})/Prev\_smoker_{a0,\,2016}/n \qquad \textit{(6a}$$

Taking into account the Status Quo cessation each year for that cohort, $Cess_t$, which may accelerate the e-cigarette transition process each year, the above formula is adjusted and generalized as:

$\gamma_{a0} = 1/n - Prev\_smoker_{a0+n,2016+n} / [n * Prev\_smoker_{a0,\,2016} * \Pi_{t\ from\ 2016\ to\ 2015+n}\ (1 - Cess_t)]$. (6b

From year 2016 to year 2016+n, the transition rate for those age a in year t, $\gamma_{a,t}$, has the general formula:

$\gamma_{a,t} = \gamma_{a0} / (1 - (t - 2016) * \gamma_{a0})$, $t= 2016, \ldots, 2015+n$ (7

The smoking prevalence in year t is calculated as:

$Prev\_smoker_{a,t}=Prev\_smoker_{a-1,t-1} * (1- \gamma_{a-1,t-1}) * (1-Cess_{a-1,t-1})$,

The transition rate $\gamma_{a,t}$ is assumed to be zero from the year 2016+n forward under the assumption of no additional transition from smoker to e-cigarette use after n years.

As an example, we consider a case where the smoking prevalence reach zeros ($Prev\_smoker_{a0+n,2016+n} = 0$) in ten years (n=10) for a specific cohort age a_0 in 2016. Table 2 begins with a starting smoking prevalence of 20% ($Prev\_smoker_{a0,2016}$ = 20%) and the Status Quo cessation rates of this cohort each year from 2016 to 2025. The initial transition rate $\gamma_{a0,2016} = \gamma_{a0}$ =10% can be obtained through formula (6b, and all following γs can be obtained through formula (7 and also listed as in Table 2. In this example, all smokers in 2016 transition out of smoking by the year 2026.

Table 2. Ten-year transition in smoking prevalence for a cohort with smoking prevalence of 20% in 2016 and residual prevalence of 0% in 2026.

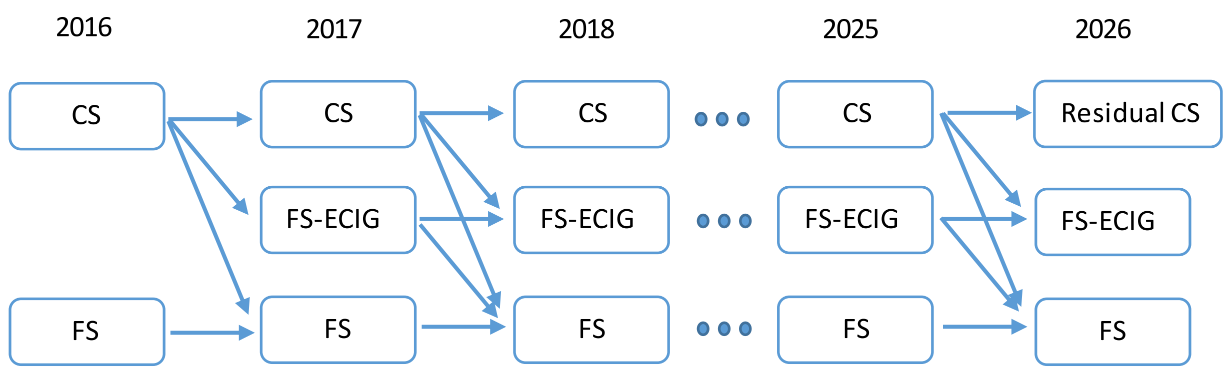
Year (t)	**2016**	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**
Status Quo Prev.	20.00%	19.6%	19.2%	18.7%	18.3%	17.9%	17.5%	17.1%	16.6%	16.2%	15.8%
Stay rate, 1-γ	90.0%	88.9%	87.5%	85.7%	83.3%	80.0%	75.0%	66.7%	50.0%	0.0%	
Transition rate, γ	10.0%	11.1%	12.5%	14.3%	16.7%	20.0%	25.0%	33.3%	50.0%	100.0%	
Cessation rate	2.1%	2.1%	2.2%	2.2%	2.3%	2.4%	2.4%	2.5%	2.5%	2.6%	
1-Cessation rate	97.9%	97.9%	97.8%	97.8%	97.7%	97.6%	97.6%	97.5%	97.5%	97.4%	
△Prevalence		2.4%	2.3%	2.2%	2.1%	2.0%	2.0%	1.9%	1.8%	1.7%	1.6%
Prevalence	20.0%	17.6%	15.3%	13.1%	11.0%	9.0%	7.0%	5.1%	3.3%	1.6%	0.0%

Notes: n = 10, $Prev\_smoker_{a0,\,2016}$ = 20%, $Prev\_smoker_{a0,\,2026}$ = 0%, $\Pi_{i=2016:2025}(1-Cess_i)$= 79.1%

Smokers Age 40 and Above in 2016

Smoker in 2016 transition into interim e-cigarette users (former smokers using e-cigarette) at a rate $\gamma_{a\text{-}1,t\text{-}1}$ and stay as interim smokers at a rate 1 - $\gamma_{a\text{-}1,t\text{-}1}$ in 2017, and those who remain smokers may quit to former smokers as illustrated in Figure 3. Both interim users quit at their own cessation rates in the same year.

Figure 3. Transitions from smokers to E-cigarette and former smoker status for cohorts age 40 and above in 2016 (2016 – 2026)



Notes: CS: Current smokers; FS: Former smokers; FS-ECIG: Former smokers using e-cigarettes. Although this diagram shows until 2026, the transitions after 2026 continue as no more smokers switch to e-cigarette users

The prevalence of smokers at age a in year t includes last year's survived smokers who do not transition to e-cigarette use and who do not quit smoking, and is calculated as:

$$Prev\_smoker'_{a,t} = Prev\_smoker_{a\text{-}1,t\text{-}1} * (1 - DR\_smoker_{a\text{-}1,t\text{-}1}) * (1 - \gamma_{a\text{-}1,t\text{-}1}) * (1 - cess_{a\text{-}1,t\text{-}1}) \quad (8$$

We note that after n years (as specified above), $\gamma_{a\text{-}1,t\text{-}1} = 0$.

Former smokers using e-cigarettes may quit, just as smokers may quit. We assume that this rate of quitting is proportional to the Status Quo cessation rate. That rate is adjusted by multiplying by δ, where δ would be less than one if it is harder to quit from e-cigarettes than cigarette use or e-cigarette users face lower risks, or may be greater than one if it is easier to quit from e-cigarettes than cigarette use or if e-cigarettes have higher health risks than expected. After allowing for this cessation, the prevalence of former smokers using e-cigarettes at age a in year t includes last year's survived former smokers using e-cigarettes and the interim e-cigarette users who do not quit e-cigarette use, calculated as:

$$Prev\_FS\text{-}ECIG'_{a,t} = Prev\_FS\text{-}ECIG_{a-1,t-1} * (1 - DR\_FS\text{-}ECIG_{a-1,t-1}) * (1 - \delta * cess_{a-1,t-1}) + Prev\_smoker_{a-1,t-1} * (1 - DR\_smoker_{a-1,t-1}) * \gamma_{a-1,t-1} * (1 - \delta * cess_{a-1,t-1}) \quad (9$$

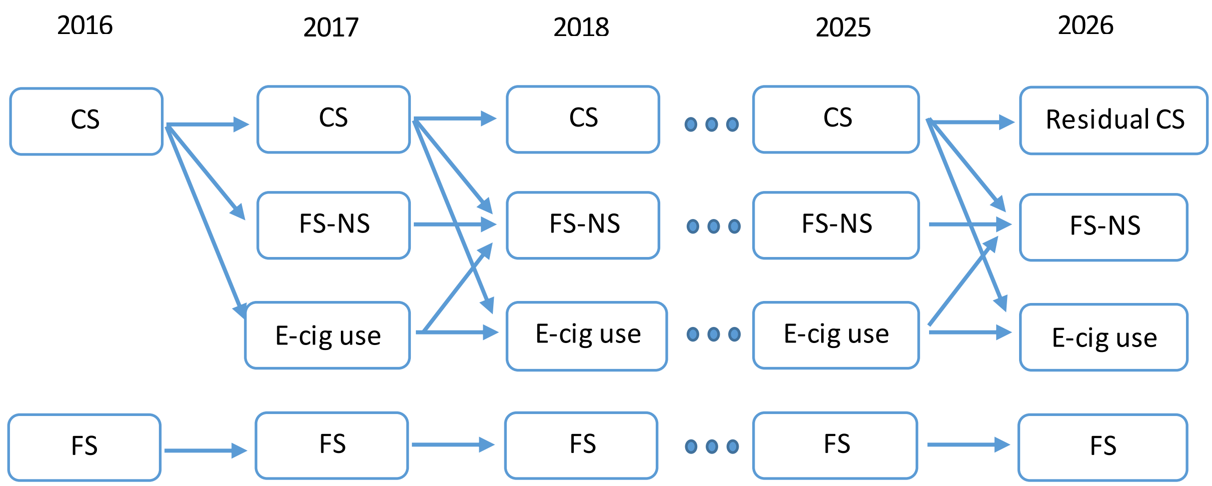
For smokers The prevalence of former smokers at age a in year t includes the prevalence of survived former smokers from last year, last year's survived smokers who quit including quitting from both interim smokers and interim e-cigarette users, and last year's survived former smokers using e-cigarette who quit, calculated as:

$$Prev\_former'_{a,t} = Prev\_formers_{a-1,t-1} * (1 - DR\_former_{a-1,t-1}) + Prev\_smoker_{a-1,t-1} * (1 - DR\_smoker_{a-1,t-1}) * [\gamma_{a-1,t-1} * \delta * cess_{a-1,t-1} + (1 - \gamma_{a-1,t-1}) * cess_{a-1,t-1}] + Prev\_FS\text{-}ECIG_{a-1,t-1} * (1 - DR\_FS\text{-}ECIG_{a-1,t-1}) * \delta * cess_{a-1,t-1} \quad (10$$

Smokers Less Than Age 40 In 2016

Similar to smokers age 40 and above, all smokers less than 40 years old in 2016 transition out of smoking after n years. Since those who quit smoking before age 40 have minimal risks, we assume that current smokers transition into interim e-cigarette users (e-cigarette users instead of former smokers using e-cigarette) at a rate $\gamma_{a-1,t-1}$ and stay as interim smokers at a rate $1 - \gamma_{a-1,t-1}$, then both temporary users quit at their own cessation rates in the same year as illustrated in Figure 4. Consequently, there are no former smokers using e-cigarette before age 40, i.e., $Prev\_FS\text{-}ECIG_{a<40,t}=0$. Never smokers with smoking history who quit from smoking are assumed to not initiate e-cigarette use, and for this reason we distinguish never smokers who quit from smoking (i.e., with a smoking history) by FS-NS from original never smokers.

Figure 4. Transitions from smoker to E-cigarette and never smoker status for cohorts less than 31 years old in 2016 (2016 – 2026)



Notes: CS: Current smokers; NS: Never smokers; E-cig: E-cigarette users; FS: Former smokers. Although this diagram shows until 2026, the transitions after 2026 continue as no more smokers switch to e-cigarette users.

In terms of the prevalence of smokers at age a in year t, $Prev\_smokers_{a,t}$, the formula is:

$$Prev\_smoker'_{a,t} = Prev\_smoker_{a-1,t-1} * (1 - DR\_smoker_{a-1,t-1}) * (1 - \gamma_{a-1,t-1}) * (1 - cess_{a-1,t-1}) \qquad (11$$

Instead of quitting into former smokers, those smokers who are less than 40 years old regardless of interim status will quit into never smokers with smoking history. Like former smokers using e-cigarette, the cessation rate of e-cigarette users less than age 40 is also adjusted by δ. Combined with last year's never smokers with smoking history, the prevalence of FS-NS at age a in year t, $Prev\_FS\text{-}NS_{a,t}$, is calculated as:

$$Prev\_FS\text{-}NS'_{a,t} = Prev\_FS\text{-}NS_{a-1,t-1} * (1 - DR\_FS\text{-}NS_{a-1,t-1}) + Prev\_smoker_{a-1,t-1}$$

$$* (1 - DR\_smoker_{a-1,t-1}) * [\gamma_{a-1,t-1} * \delta * cess_{a-1,t-1} + (1 - \gamma_{a-1,t-1}) * cess_{a-1,t-1}] + Prev\_ECIG_{a-1,t-1} *$$

$$(1 - DR\_ECIG_{a-1,t-1}) * \delta * cess_{a-1,t-1} \qquad (12$$

Since smokers and e-cigarette users quit cigarette use into former smokers after age 40 instead of never smokers with smoking history, never smokers with smoking history continue until death as those with never smoker risk and the formula is revised to:

$$Prev\_FS\text{-}NS'_{a,t} = Prev\_FS\text{-}NS_{a-1,t-1} * (1 - DR\_FS\text{-}NS_{a-1,t-1}) \qquad (13$$

Equation (10 above is used to calculate the prevalence of former smokers.

The prevalence of e-cigarette users at age a in year t, $Prev\_ECIG'_{a,t}$, includes the prevalence of survived e-cigarette users from last year, and those transitioned from last year's current smokers who survived, calculated as:

$$Prev\_ECIG'_{a,t} = Prev\_ECIG_{a-1,t-1} * (1- DR\_ECIG_{a-1,t-1}) * (1 - \delta * cess_{a-1,t-1}) +$$

$$Prev\_smoker_{a-1,t-1} * (1 - DR\_smoker_{a-1,t-1}) * \gamma_{a-1,t-1} * (1 - \delta * cess_{a-1,t-1}) \qquad (14$$

Since those below age 40 who quit e-cigarettes use and/or cigarettes use become never smokers with smoking history, there are no additional former smokers. The prevalence of former smokers at age a in year t only derives from last year's survived former smokers, as:

$$Prev\_former'_{a,t} = Prev\_formers_{a-1,t-1} * (1 - DR\_former_{a-1,t-1}) \qquad (15$$

For those who become e-cigarette users below age 40, they will quit into former e-cigarette users at $\delta * cess_{a-1,t-1}$ *after age 40, i.e.,* the remaining e-cigarette users start to quit into former e-cigarette instead of never smokers with smoking history. Therefore, the prevalence of former e-cigarette use is calculated as:

$$Prev\_F\text{-}ECIG'_{a,t} = Prev\_F\text{-}ECIG_{a-1,t-1} * (1- DR\_FS\text{-}NS_{a-1,t-1}) + Prev\_ECIG_{a-1,t-1}$$

$$* (1 - DR\_ECIG_{a-1,t-1}) * \delta * cess_{a-1,t-1} \qquad (16$$

Since those who quit smoking before age 40 have minimal risks, current smokers who substitute are considered e-cigarette users. However, when they become age 40, the cumulative harm of cigarette use becomes more significant and they start to transition into former smokers using e-cigarettes. Therefore, the prevalence of e-cigarettes includes those who survived and do not quit e-cigarette use, and the formula is updated as:

$$Prev\_ECIG'_{a,t} = Prev\_ECIG_{a-1,t-1} * (1- DR\_ECIG_{a-1,t-1}) * (1 - \delta * cess_{a-1,t-1}) + Prev\_never_{a-1}$$

$$* (1-DR\_never_{a-1,t-1}) * \beta * init_{a-1,t-1} \quad (17$$

Formula (9 above is used to calculate the prevalence of former smokers using e-cigarettes as cohorts 40 and above years old.

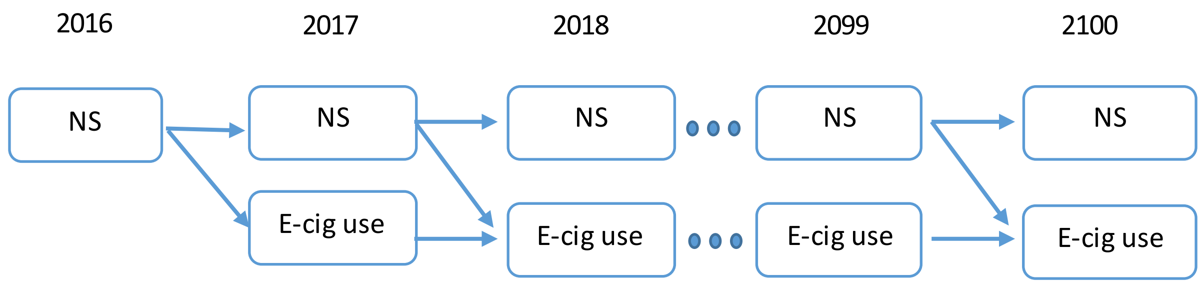
NEVER SMOKERS

Figure 3 shows transition from never smoker to e-cigarette users (after the residual smoking prevalence is reached). We assume that never smokers initiate e-cigarette use at the original smoking initiation rate multiplied by β, where $\beta > 0$. This parameter β may be greater than 1, allowing for more initiation into e-cigarette use than into smoking in Status Quo Scenario, e.g., if e-cigarettes has less perceived risk or has characteristics more desirable than cigarettes. The prevalence of never smokers at age a in year t, $Prev\_never_{a,t}$, is calculated as:

$$Prev\_never_{a,t} = Prev\_never_{a-1,t-1} * (1 - \beta * init_{a-1,t-1}) * (1 - DR\_never_{a-1,t-1}), \quad (18$$

where never smokers transition to e-cigarette status as shown in Figure 5.

Figure 5. Transitions from never smoker to e-cigarette users (2016 – 2100)



Notes: NS: Current smokers; E-cig use: E-cigarette users

The prevalence of e-cigarette users at age a in year t, $Prev\_ECIG_{a,t}$, is transitioned from the prevalence of survived e-cigarette users in the previous year and the new e-cigarette users who initiated from survived never smokers.

$$Prev\_ECIG_{a,t} = Prev\_ECIG_{a-1,t-1} * (1- DR\_ECIG_{a-1,t-1}) + Prev\_never_{a-1} * (1-DR\_never_{a-1,t-1}) * \beta * init_{a-1,t-1}. \quad (19$$

We note that a separate group of e-cigarette users has transitioned from smoking to e-cigarette use before age 40, as described in the previous section. Therefore the new initiated e-cigarette users should be added in formulas (14 and (17.

CORRECTION FACTORS

To incorporate death rates into the E-cigarette Substitution scenario and maintain the prevalence of all groups summing to one, a correction factor is applied as in the Status Quo Scenario. The correction factor is calculated as the reciprocal of the weighted average of survival rates depending on their prevalence. For all cohorts, the correction factor at age a-1 in year t-1 is:

$$Correction\ factor_{a-1,t-1} = 1/\Sigma[Prev\_i_{a-1,\ t-1} * (1 - DR\_i_{a-1,t-1})], \quad (20$$

where i = never smokers, smokers, former smokers, never smokers with smoking history, former smokers using e-cigarettes, e-cigarette users, and former e-cigarette users, so that the correction factor is:

$$Correction\ factor_{a-1,t-1} = 1/[Prev\_never_{a-1,t-1}*(1-DR\_never_{a-1,t-1})+Prev\_smoker_{a-1,t-1} * (1-DR\_smoker_{a-1,t-1})+ Prev\_former_{a-1,t-1}*(1-DR\_former_{a-1,t-1})+ Prev\_FS\text{-}NS_{a-1,t-1} * (1-DR\_FS\text{-}NS_{a-1,t-1})+ Prev\_FS\text{-}ECIG_{a-1,t-1}*(1-DR\_FS\text{-}ECIG_{a-1,t-1})+ Prev\_ECIG_{a-1,t-1} *(1-DR\_ECIG_{a-1,t-1})+ Prev\_F\text{-}ECIG_{a-1,t-1}*(1-DR\_F\text{-}ECIG_{a-1,t-1})]. \quad (21$$

Each of the above is multiplied by the correction factor as defined by equation (20.

HEALTH OUTCOMES

The death rate differs by age, sex, and smoking/vaping status in year t and at age *a*. The death rates regardless of cigarette or e-cigarette use are the same before age 40 for males (age 42 for females) and begin to diverge after age 40 (age 42) for current, former smokers using e-cigarettes, and e-cigarette users, and diverge after age 47 (age 55) for former smokers. At any given age, never smokers have the lowest death rate compared to current and former smoking statuses. Mortality rates are based on all-cause cohort life tables as described in the Data Sources section above.[3]

For the Status Quo Scenario, the number of premature deaths (PDs) is calculated for current and former smokers for each age as the product of excess risks and the corresponding population (projected US population[4] x prevalence rate). Excess risk for current (former) smokers is calculated as the difference between the mortality rate of current (former) smoker and the mortality rate of never smoker. Premature deaths (PDs) for current and former smokers are calculated as:

$$PD\_smoker_{a,t} = (DR\_smoker_{a,t} - DR\_never_{a,t}) * Prev\_smoker_{a,t} * Population_{a,t} \quad (22$$

$PD\_former_{a,t} = (DR\_former_{a,t} - DR\_never_{a,t}) * Prev\_former_{a,t} * Population_{a,t}$ (23

Life years lost (LYL) are estimated as the number of premature deaths multiplied by the expected years of life remaining of a never smoker at each age ($ExpLifeYear\_never_{a,t}$), and calculated as:

$LYL_{a,t} = (PD\_smoker_{a,t} + PD\_former_{a,t}) * ExpLifeYear\_never_{a,t.}$ (24

The life years lost for a given cohort is obtained as the sum of the life years lost over all remaining years, calculated as:

$Total\_LYL\_StatusQuo = \sum_{all\ age\ through\ 99} LYL_{a,t}$ (25

In the E-cigarette Substitution Scenario, PDs and LYL include those of e-cigarette users, former e-cigarette users and former smokers using e-cigarettes, as well as those of current and former smokers. Although the long-term implications of e-cigarette use are not yet known, they generally contain substantially lower levels of toxic substances.[5-8] A multi-criteria decision analysis estimated e-cigarette risks (denoted as Risk_ECIG) at 5% the cigarette risks,[6] similar to the risks of low-nitrosamine smokeless tobacco use.[9] We initially estimate the excess risk of exclusive e-cigarette users as 5% of the excess risk of current smokers, and excess risk of former e-cigarette users as 5% of the excess risk of former smokers. For former smokers using e-cigarettes, we assume the excess risk to be 5% of the difference between the excess risk of current and former smokers plus the excess risk of former smokers. Using death rates by age, sex, and smoking statuses (never smokers, smokers, and former smokers) provided by Holford, the death rate of e-cigarette and former smokers using e-cigarette are calculated as:

$DR\_ECIG_{a,t} = \text{Risk\_ECIG} * (DR\_smoker_{a,t} - DR\_never_{a,t}) + DR\_never_{a,t,}$ (26a

$DR\_F\text{-}ECIG_{a,t} = \text{Risk\_ECIG} * (DR\_former_{a,t} - DR\_never_{a,t}) + DR\_never_{a,t,}$ (26b

$DR\_FS\text{-}ECIG_{a,t}$ = Risk_ECIG * $(DR\_smoker_{a,t} - DR\_former_{a,t}) + DR\_former_{a,t}$ (26c

In the E-cigarette Substitution scenario, premature deaths may occur from those are currently smoke (before the transition to e-cigarette use), those who have quit smoking after age 40 and either use e-cigarettes (former smokers using e-cigarettes) or transition to no use (former smokers), and those who try e-cigarette use anytime and either keep using e-cigarettes or quit from e-cigarette use after age 40 (former e-cigarette users). Like in the Status Quo Scenario, excess risks are multiplied by the number of individuals in each of these categories to obtain the premature deaths for each category, i.e.,

$PD\_smoker_{a,t} = (DR\_smoker_{a,t} - DR\_never_{a,t}) * Prev\_smoker_{a,t} * Population_{a,t},$ (27a

$PD\_former_{a,t} = (DR\_former_{a,t} - DR\_never_{a,t}) * Prev\_former_{a,t} * Population_{a,t},$ (27b

$PD\_ECIG_{a,t} = (DR\_ECIG_{a,t} - DR\_never_{a,t}) * Prev\_ECIG_{a,t} * Population_{a,t},$ (27c

$PD\_F\text{-}ECIG_{a,t} = (DR\_F\text{-}ECIG_{a,t} - DR\_never_{a,t}) * Prev\_F\text{-}ECIG_{a,t} * Population_{a,t},$ (25d

and $PD\_FS\text{-}ECIG_{a,t} = (DR\_FS\text{-}ECIG_{a,t} - DR\_never_{a,t}) * Prev\_FS\text{-}ECIG_{a,t} * Population_{a,t.}$ (27e

Since the population is fixed, premature deaths are assumed to be independent of population change and the prevalence of cigarette or e-cigarette users. Life years lost (LYL) are estimated as the number of premature deaths multiplied by the expected years of life remaining of a never-smoker at each age ($ExpLifeYears\_never_{a,t}$) and is calculated as:

$$LYL_{a,t} = (PD\_smoker_{a,t} + PD\_former_{a,t} + PD\_ECIG_{a,t} + PD\_F\text{-}ECIG_{a,t} + PD\_FS\text{-}ECIG_{a,t}) * ExpLifeYears\_never_{a,t.} \quad (28$$

Life years lost for a given cohort is obtained as the sum of the life years lost over all remaining years, calculated as:

$$Total\_LYL\_ECIG = \sum_{all\ remaining\ age\ through\ 99} LYL_{a,t} \quad (29$$

PUBLIC HEALTH IMPACT

The public health impact measures the difference in health outcomes between the Status Quo and E-cigarette Substitution scenarios. The public health impact of e-cigarette use for a given cohort x (age x in 2016) is evaluated as the difference in LYL between the Status Quo and E-cigarette Substitution scenarios summed over all remaining ages (from current age through age 100, and the formula is:

$$LifeYearGain_x = TotalLYL\_StatusQuo - TotalLYL\_ECIG \quad (30$$

Dividing the life year gained for each cohort by its total population in 2016, we obtain the life year gain per capita for each cohort.

$$LifeYearGainPC_{x,} = LifeYearGain_x / Population_{x,2016} \quad (31$$

Analogously, the life year gain per smoker for each cohort is obtained as:

$$LifeYearGainPSmoker_x = LifeYearGain_x / Smoking\ Population_{x,2016}, \quad (32$$

where the Smoking Population is calculated as Population in 2016 multiplied by the smoking prevalence as in the Status Quo Scenario in 2016 for those above age 25 and at the age 25 smoking or prevalence of that cohort for those below age 25.

We obtain the population health impact by summing over all cohorts age 15 and above in 2016.

$$LifeYearGain\_ECIG = \Sigma_{all\ x} LifeYearGain_x \quad (33$$

$$LifeYearGainPC\_ECIG = \Sigma_{all\ x} LifeYearGainPC_x \quad (33$$

$$LifeYearGainPSmoker\_ECIG = \Sigma_{all\ x} LifeYearGainPSmoker_x \quad (34$$

USER GUIDE: HOW TO CHANGE MODEL PARAMETERS

The model is in Excel and can be easily modified to conduct different scenarios. The user can vary the parameters in the model by changing values in the Parameters worksheet. As structured above, parameters can be set for 1) the excess risks of e-cigarettes relative to smoking, 2) the transition rates from smoking to e-cigarettes, 3) the rate of initiating e-cigarette use and 4) the rate of cessation from e-cigarette and cigarette use.

The model is pre-specified to an excess e-cigarette risk at 5% that of smokers, but the model allows for variations in excess risk of e-cigarette relative to smoking. These risks can be changed by using the cell “C3” in the worksheet “Parameters” to consider scenarios with different e-cigarette risk. We note that the specified risk will also be used in determining the risk of former e-cigarette users and former smokers using e-cigarette.

The transitions from current smoking to e-cigarette use take place in the model over a pre-specified number of years, initially set equal to 10 years. The user can control the number of years (n) within which all current smokers in 2016 can be eliminated. The user can set the number of years in which the transition from current smokers through e-cigarette use takes place by changing “C17” in the “Parameters” worksheet. By setting “C17”, the user simultaneously sets the reduction rate of smokers as in the worksheet “Smoker reduction rate with e-cigarette”.

The model also allows for a residual smoking prevalence after an n-year transition period. The residual smoking prevalence can be adjusted by changing “C26” in the “Parameters” worksheet.

In the model, never smokers initiate e-cigarette use at the smoking initiation rate multiplied by β where $\beta > 0$. We allow initiation into e-cigarette use to vary by changing "C13" in the "Parameters" worksheet. Since e-cigarettes may have less perceived risk or has characteristics more desirable, a value of $\beta > 1$ can be specified that implies that there will be more initiation of e-cigarettes than smoking.

The model also allows e-cigarette users (e-cigarette users and former smoker using e-cigarettes) to quit at the cessation rate of smokers in the Status Quo case multiplied by δ. The parameter δ can be adjusted by changing "C21" for e-cigarette users and "C22" for former smokers using e-cigarette in the "Parameters" worksheet.

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