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A novel approach to assess the population health impact of introducing a Modified Risk Tobacco Product

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ABSTRACT

Based on the Food and Drug Administration's Modified Risk Tobacco Product (MRTP) Application draft guideline, Philip Morris International (PMI) has developed a Population Health Impact Model to estimate the reduction in the number of deaths over a period following the introduction of an MRTP. Such a model is necessary to assess the effect that its introduction would have on population health, given the lack of epidemiological data available prior to marketing authorization on any risks from MRTPs. The model is based on publicly available data on smoking prevalence and on the relationships between smoking-related disease-specific mortality and various aspects of the smoking of conventional cigarettes (CCs), together with an estimate of exposure from the MRTP relative to that from CCs, and allows the exploration of possible scenarios regarding the effect of MRTP introduction on the prevalence of CC and MRTP use, individually and in combination. By comparing mortality attributable in a scenario where the MRTP is introduced with one where it is not, the model can estimate the mortality attributable to CCs and the MRTP, as well as the reduction in the deaths attributable to the introduction of the MRTP.

1. Introduction

To obtain a risk modification order under the United States Food and Drug Administration's draft guidance (FDA, 2012), the applicant must demonstrate that the Modified Risk Tobacco Product (MRTP) benefits the health of the population as a whole, accounting for current, former and never smokers. Given the lack of population-level data available prior to marketing an MRTP on its risks or the level of uptake, Philip Morris International (PMI) is, in accordance with Section VI.B.4 of the draft guidance, developing a Population Health Impact Model to estimate the impact of the introduction of the product on mortality given assumptions concerning the exposure to the smoker from the MRTP relative to that from conventional cigarettes (CCs), and on the rate of uptake of the MRTP. The model estimates the impact on mortality in a population which survives until a specific time after the introduction of the MRTP on the market. Although the model was developed with focus on the US, it is also intended to be used for population health impact assessment in other countries, such as the UK, Germany, and Japan, for which the required data are available.

To predict the potential impact from the introduction of an MRTP, the model will allow the exploration of a wide range of scenarios assessing the possible effect of MRTP introduction on the prevalence of CC and MRTP use, individually and in combination. The input data are extracted from publicly available databases and the scientific literature, and are country-specific where available and applicable. The attributable deaths under the "MRTP Scenario" (with the introduction of the MRTP) will be compared with those under the "Null Scenario" (without the introduction of the MRTP) to estimate the reduction in attributable deaths. The purpose of this article is to describe, in detail, the data sources, modeling methodology, rationale and approach to the assessment of the potential impact from the introduction of an MRTP.

Abbreviations: CCs, conventional cigarettes; COPD, chronic obstructive pulmonary disease; E-component, epidemiological risk component; ER, excess risk; ETS, environmental tobacco smoke; IHD, ischemic heart disease; LC, lung cancer; MRTP, Modified Risk Tobacco Products; P-component, prevalence component; PMI, Philip Morris International; STPs, smoking transition probabilities; RR, relative risk.

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2. Methods

2.1. Prevalence (P)-component

The P-component is a Markov chain state-transition model to estimate changes in the distribution of CC and/or MRTP use occurring in a hypothetical population of a given size over a defined period, separately for the Null and MRTP Scenarios. Before the MRTP is introduced, the population has a country-specific distribution of CC smoking habits (current, former [by years since quitting] and never smoking). The population is followed over the simulation period by considering successive small time intervals, typically one year, during which only one change in smoking habits can occur. Smoking transition probabilities (STPs) are applied to each member of the population to determine whether they stay in the same group or change to a different one by the end of each interval. The STPs can vary based on the time since introduction of the MRTP and/or the time that the population member has spent in their current state. Thus, by the end of the simulation period, each member will have a complete smoking history, updated age, and (for former smokers) updated time since quitting.

Under the Null Scenario, the smoking histories relate only to use or non-use of CCs. Thus the possible STPs relate to never smokers starting to smoke CCs, current CC smokers quitting CCs, and former CC smokers reinitiating CCs. Under the MRTP Scenario, both CCs and the MRTP are available, increasing the complexity of the STPs. The possible STPs relate to never smokers starting to use the MRTP or CCs, former smokers re-initiating with the use of the MRTP or CCs, and current users of the MRTP or CCs quitting use of the product, or switching to the other product.

2.1.1. Data and data sources

The P-component will be populated with the distribution of CC smoking for twelve countries (Austria, Canada, France, Germany, Hungary, Italy, Japan, Poland, Sweden, Switzerland, the United Kingdom and the United States from 1986 onwards), but is expandable to allow the inclusion of additional data from future years and/or additional countries and regions.

2.1.1.1. Current and former smoking prevalence data. Prevalence data on current CC smoking will be extracted from International Smoking Statistics (ISS; Forey et al., 2002; Forey and Lee, 2002). Smoking prevalence data specific for sex-, age (in 5-year groups) and period (in 5-year groups) are available from all twelve countries up to at least 2005 (Forey et al., 2006–2013; Forey et al., 2007).

Age- and sex-specific prevalence data on former CC smokers, extracted from the same sources used for the ISS database, are readily available (Lee et al., 2009) for Austria, Canada, Germany, the United Kingdom and the United States. Data for Italy and Japan have been extracted, but are not yet published. Data extraction is planned for France, Hungary, Poland, Sweden and Switzerland, to ensure that there is prevalence data on former smokers from the same countries as the data on current CC smokers.

2.1.1.2. Distribution of former smokers by years quit. National age- and sex-specific data on the distribution of former smokers (by years since quitting) are also required. Preliminary investigations found data for all the countries, except Poland, but the publications vary in scope and quality, some using broad grouping of years since quitting, some presenting results only for limited age groups, and some being based on small samples. Further attempts will be made to obtain data by concentrating on data sources allowing customized analysis. Where relevant data cannot be found for a given country, the distribution may be estimated using the data for other countries that are similar with respect to economic and cultural aspects, including tobacco use history.

2.1.1.3. Estimating STPs for CCs from smoking distributions. Data on the prevalence of current and former CC smoking within the same birth cohort in successive periods do not allow direct estimation of STPs. This can be seen when examining the changes in the proportion of former CC smokers between periods. An increase from 36% in period 1 to 39% in period 2 could reflect 3% of the current CC smokers quitting smoking during the period, but cannot be distinguished from a scenario where 6% of former smokers re-initiated CC smoking, while 9% of CC smokers quit. Therefore, national data on the re-initiation rates of former smokers are required to estimate the STPs more precisely.

2.1.1.4. Estimating STPs for the MRTP. In the pre-market setting, STP estimates for the MRTP Scenario will be based on assumptions and product use patterns from controlled studies that cannot be validated with regard to post-market actual use. After the introduction of the MRTP, the preliminary STP estimates can be replaced by estimates derived using the data from a series of longitudinal cross-sectional surveys that are planned to initiate at the time of product launch. These cross-sectional surveys will also provide data on re-initiation rates for CCs.

2.1.2. Smoking histories

The smoking histories will be modeled starting with a large hypothetical population sample (e.g., 10,000). The start year is assumed to be before the introduction of the MRTP, so the population will be initially subdivided according to the sex-, age- and country-specific distribution of CC smoking status (current, former [by time since quitting], never) for that year. The population will then be followed up at successive small time intervals (typically one year) over a defined period. During any interval, the smoking status of each population member may change, assuming that smoking status can only change once per interval because the length of the time interval is sufficiently short to ignore multiple changes. The probabilities of these transitions are defined by the STPs. Although it is expected that the STPs will remain constant from year to year, the model will allow the STPs to vary over the period. At the end of the period, each population member will have a history of tobacco use. These histories will then be used to determine the distributions of CC and MRTP use at any time following the introduction of the MRTP and so allow the estimation of disease risks.

Where the end of the period is a recent year, the STP values for the Null Scenario can be selected based on time trends in smoking habits obtained from the data on current and former CC smoker prevalence. The smoking distribution predicted by the P-component at the end of the follow-up period should be closely aligned with its known distribution. The effects of alternative assumptions concerning the trends in smoking distributions and the choice of STPs will be considered in sensitivity analyses.

Fig. 1 shows the matrix of STPs required for the Null Scenario. Determining how smoking habits change in an interval requires knowledge of three STPs, P_{NC} = the probability that a never smoker (N) becomes a current smoker (C), P_{CF} = the probability that a current smoker (C) becomes a former smoker (F), and P_{FC} = the probability that a former smoker (F) becomes a current smoker (C).

The diagonal of the matrix running from the top left to bottom right reflects a situation without change in smoking habits. The cells marked with a zero are excluded because for two of these (a current or former smoker becoming a never smoker) the transition is impossible, while for the other (a never smoker becoming a former smoker) the transition requires multiple changes which

		Start of Interval		
		N	C	F
End of Interval	N	P_{NN} (= 1-P_{NC})	0	0
	C	P_{NC}	P_{CC} (= 1-P_{CF})	P_{FC}
	F	0	P_{CF}	P_{FF} (= 1-P_{Fc})

Fig. 1. STP matrix if the MRTP is not introduced (Null Scenario). N = never smoker; C = current smoker; F = former smoker; P_{NC} = probability a never smoker starts smoking; P_{FC} = probability a former smoker re-initiates smoking; P_{CF} = probability a current smoker quits smoking.

cannot occur within an interval. P_{NC} is likely to be zero for subjects older than 35 years.

Fig. 2 shows the matrix of STPs required for the MRTP Scenario. Here determining how smoking habits change within an interval requires knowledge of eight STPs. During each interval a population member can either remain in their current state or transition to the two other potential states. Again transitions to a never smoker or from a never to a former smoker are excluded.

It is important to account for interdependencies between the STPs. A transition to current MRTP use may be associated with quitting CC smoking, while reinitiating CC smoking by former smokers may be associated with quitting MRTP. Further, the set of STPs may vary by the time a population member has spent in each state and for the past states that they have been in (e.g., a smoker who has previously quit may be more likely to quit, and short-term quitters may be more likely than long-term quitters to re-initiate).

In the first place, it will be assumed that the probability of re-initiating smoking is independent of the product previously used. If post-marketing data reveals such a dependency, allowance can be made for this. The STP matrix also accounts for the probability that a never smoker initiates smoking. For older individuals

		Start of Interval			
		N	C_C	C_M	F
End of Interval	N	P_{NN}	0	0	0
	C_C	P_{NC}	P_{CC}	P_{MC}	P_{FC}
	C_M	P_{NM}	P_{CM}	P_{MM}	P_{FM}
	F	0	P_{CF}	P_{MF}	P_{FF}

Fig. 2. STP matrix if the MRTP is introduced (MRTP Scenario). N = never smoker; CC = current smoker of CCs; CM = current user of MRTP; F = former smoker; P_{NC} = probability a never smoker starts smoking CCs; P_{FC} = probability a former smoker re-initiates smoking CCs; P_{CF} = probability a current smoker of CCs quits smoking; P_{MC} = probability a current MRTP user switches to smoking CCs; P_{NM} = probability a never smoker starts using MRTP; P_{CM} = probability a current smoker of CCs switches to using MRTP; P_{FM} = probability a former smoker starts using MRTP; P_{MF} = probability a current user of MRTP quits using MRTP. The probabilities in each column add up to unity.

(above 35 years), this is likely to be zero. Although this is probably also the case for the MRTP, it may not necessarily be true.

Using the STP matrices presented in Figs. 1 and 2, the P-component generates distributions of smoking histories for each scenario at the end of the period being studied. These are then used in the E-component to estimate the reduction of smoking-attributable deaths in a population who survived since the introduction of the MRTP.

2.1.3. Considerations related to the P-component

2.1.3.1. Length of follow-up. The P-component will allow for follow-up of a population over up to 20 years. While the methodology could be extended to longer periods, such long-term projections may be unreliable.

2.1.3.2. Age range. As the epidemiologic risk (E)-component (see Section 2.2) requires data for the age range 30–79 years after up to 20 years follow-up, the initial age required in the population to be followed is 10 years. The E-component therefore starts with a population aged 10–79 years, and follow-up continues until they reach 79 years of age or the end of the follow-up period. This enables calculations of distributions of smoking habits for ages ranging from 30–79 years for the entire follow-up period.

2.1.3.3. Amount smoked. The P-component does not account for amount smoked and the STPs do not account for the possibility that a person continues to smoke the same product but changes the amount that they smoked.

2.1.3.4. Products other than CCs and MRTP. The P-component does not consider other tobacco products, such as cigars, pipes, or smokeless tobacco, which may bias the estimation of the reduction of deaths attributable to an MRTP if CC smokers switching to the MRTP tend to change their use of these other products. Unless evidence emerges that this occurs to any material extent, this possibility will not be accounted for because the estimation process would be overly complex.

2.2. Epidemiologic risk (E)-component

The E-component uses the smoking histories produced by the P-component to estimate the smoking-related attributable deaths from lung cancer (LC), ischemic heart disease (IHD), stroke, and chronic obstructive pulmonary disease (COPD). The difference between the number of deaths estimated under the Null Scenario and that estimated under the MRTP Scenario is an estimate of the change in the number of deaths from smoking-related diseases associated with the introduction of the MRTP. The model will only consider deaths between the ages of 30–79 years because there are extremely few smoking-related deaths before the age of 30 years, diagnoses at ages above 80 years are unreliable, and mortality and population data for some countries and years are unavailable for age groups above 75–79 years. As deaths will be estimated by age group, the model can also be used to estimate premature mortality (death before age 75).

For each sex and age group, the number of smoking-attributable deaths are estimated using relative risk (RR) estimates, for current and former smokers relative to never smokers. The RR estimates for current CC smokers are country-, disease-, sex- and age-specific and are based on meta-analyses of epidemiological data. For former CC smokers, the RR estimates by time since quitting are derived from the corresponding estimates for current smokers, assuming that the decrease in excess risk (ER = RR − 1) after quitting follows a negative exponential function. Disease-specific estimates of the half-life of the decrease are obtained by fitting the function to published data sets. As detailed elsewhere (P.N. Lee

et al., personal communication), various predictions using the negative exponential model (NEM) align closely with those of the multistage model, known to predict various observed features of the relationship between smoking and lung cancer (Lee, 1995).

If the "effective dose" is taken as 1 unit when smoking CCs, and as 0 units when not smoking, then the effective dose when using the MRTP is taken as F units (assumed to be <1). The smaller is F, the smaller the ER associated with use of the MRTP, and the closer the ER associated with switching from CCs to the MRTP becomes to zero, the ER associated with smoking cessation. Using the F value, the disease-specific RR estimates for current CC smokers, and the disease-specific half-life estimates associated with smoking cessation, the ERs associated with switching from CC to MRTP use can be derived.

Direct quantification of F would require long-term large-sample epidemiological health-outcome studies which cannot be conducted for a novel MRPT not yet marketed. Available indirect empirical CC vs. MRTP comparative evidence includes: (a) aerosol chemistry data on harmful and potentially harmful smoke constituents, (b) standard toxicology assessments (including cytotoxicity and mutagenicity assays) comprising in vitro and in vivo rodent inhalation study results, (c) pharmacokinetic and smoking topography data obtained from single and *ad libitum* product use clinical confinement and ambulatory studies, (d) analysis of blood and urinary biomarkers of exposure measured in clinical studies on smokers switching from CC to MRTP or smoking abstinence, and (e) measurements of functional and subjective health as well as clinical risk endpoints obtained from extended ambulatory cessation studies and long-term exposure response studies. Methods of aggregating these data are being developed to estimate the likely probability density of F considering the integrated available empirical evidence. Since there is inevitably uncertainty in the estimate, the population health impact will also be assessed using alternative plausible estimates of F.

2.2.1. Data and data sources

2.2.1.1. National population size and mortality data. Country-, sex- and age-specific data for recent years on the number of deaths from LC, IHD, stroke, and COPD for twelve countries of interest will be extracted from the latest World Health Organization estimates. Population size estimates, available for these countries from 1950 to 2010 (United Nations Population Division, 2010), will be used to convert numbers of deaths to death rates.

2.2.1.2. Relative risks. PMI has compiled databases containing the published epidemiological evidence of CC smoking-related risks of LC, IHD, stroke, and COPD. The lung cancer database includes 287 epidemiological studies published prior to 2000, each with over 100 cases of LC (Fry et al., 2013a; Lee et al., 2012a). The COPD database includes 133 studies published prior to 2007 (Forey et al., 2011). The database for IHD and stroke is more limited, including 43 studies published since 1990. These databases, recently expanded to include published studies related to smoking cessation, will be used to derive RR estimates of current and former smokers relative to never smokers by sex, period, and region. The evidence available from these databases suggests that the ER for current smoking varies linearly with amount smoked; thus, derivation of consumption-specific RRs is not needed.

2.2.2. Methodology

2.2.2.1. Half-life of excess risk. Recent research has shown that the decline of ER by time since quitting CC smoking is well described using a negative exponential model, with the fit of the model being shown to be adequate for IHD, stroke, and COPD (Lee et al., 2012b, 2014a,b), and for LC, provided that correction is made for reverse causation (Fry et al., 2013b). The decline in the ER is described by the half-life parameter (the time at which half the ER associated with continued CC smoking has disappeared), and varies significantly by disease, from about 5 years for IHD and stroke, to about 10 years for LC, and 13 years for COPD.

2.2.2.2. Negative exponential model. The negative exponential model used to describe the decline in disease-specific ER following smoking cessation is given in Eq. (1):

$$ER_Q(a,t) = ER_C(a)\exp\{-tL/H\} \quad (1)$$

where a is age, t is the time since quitting, $ER_Q(a)$ is the excess risk for quitters, $ER_C(a)$ is the ER for current CC smokers, L is $\log_e 2$, and H is the disease-specific half-life.

Eq. (1) describes the change in ER following a change in the effective dose from 1 to 0 units. The model can be adapted to describe the change in ER following a change in effective dose from 1 to F units, given in Eq. (2):

$$ER_{CH}(a,t) = ER_C(a)[F + (1-F)\exp\{-tL/H\}] \quad (2)$$

Here t is the time since the transition to the MRTP, and $ER_{CH}(a)$ is the ER following the change.

In practice, the patterns of CC and MRTP use may become more complex (e.g., current CC smokers may switch to MRTP and then restart smoking CCs, or former smokers may take up MRTP). A further adaptation of the negative exponential model is designed to cater for such situations. Defining $ER_1(a)$ as the ER relating to the habit being switched from, $ER_2(a)$ as that relating to the habit being switched to, the estimated ER relating to the switcher, $ER_{SW}(a,t)$, is then derived from

$$[ER_{SW}(a,t) - ER_2(a)]/[ER_1(a) - ER_2(a)] = \exp\{-tL/H\} \quad (3)$$

In Eq. (3), t is the time since the switch in habits. Note that Eq. (3) is consistent with Eqs. (1) and (2). Thus, with some rearrangement, substituting $ER_2(a) = 0$ and $ER_1(a) = ER_C(a)$ gives Eq. (1), while substituting $ER_2(a) = F{\cdot}ER_C(a)$ and $ER_1(a) = ER_C(a)$ gives Eq. (2). Eq. (3) can be used repeatedly for an individual following a sequence of changes, in order to estimate the ER at the end of the follow-up period, as described in more detail elsewhere (P.N. Lee et al., personal communication).

2.2.2.3. Number of deaths and increase in death rates associated with smoking. For each of the causes of death considered, death rates and numbers of smoking-attributable deaths will be estimated separately for the Null Scenario and the MRTP Scenario. For the Null Scenario, for a given country, year, sex, age group, and cause of death, data are assumed to be available for population size (N) and total number of deaths (D). The P-component outputs Null Scenario-specific estimates of use prevalence (P_i) by mutually exclusive CC smoking groups ($i = 0, 1, \ldots, s$), where $i = 0$ corresponds to never smoking, and s is the number of ever smoking groups in this scenario. The smoking groups not only include current smokers and quitters that have quit for various periods of time, but also those who have quit and re-initiated, possibly multiple times.

The corresponding estimates RR_i are derived with RR_0 defined as 1, as described above. If A_0 is the death rate of never smokers, then the number of deaths can be calculated as

$$D = NA_0\sum_{i=0}^{s} P_i RR_i \quad (4)$$

and the death rate in never smokers can be estimated by

$$A_0 = D/\left(N\sum_{i=0}^{s} P_i RR_i\right) \quad (5)$$

The death rate in smoking group i can then be estimated as

$$A_i = A_0 RR_i \quad (6)$$

The number of deaths in never smokers is given by

$$D_0 = NA_0P_0 \quad (7)$$

and the number of deaths that would have occurred if everyone had the same death rate as never smokers is given by

$$D^* = NA_0 \quad (8)$$

The number of smoking-attributable deaths, D_{ATTRIB}, is given by the following:

$$D_{ATTRIB} = D - D^* \quad (9)$$

The increase in the rate attributable to smoking, A_{ATTRIB}, is given by the following:

$$A_{ATTRIB} = D/N - A_0 \quad (10)$$

The MRTP Scenario uses the same estimates of population size (N) and total mortality (D) as before. However, the output from the P-component is from the distribution assuming that an MRTP was introduced, which provides estimates of prevalence (P'_j) by mutually exclusive groups of CC and/or MRTP usage ($j = 0, 1, \ldots, s'$), where $j = 0$ corresponds to never users of either product, and s' is the number of ever user groups in this scenario. The corresponding estimates RR'_j are again derived as described above. It is assumed that the death rate in the never user group, A'_0, is the same as that for never smokers, A_0, so that mortality rates in the other groups, A'_j, are given by

$$A'_j = A_0 RR'_j \quad (11)$$

Assuming that the population size N is unaltered, the total number of disease-specific deaths can then be calculated as

$$D' = N\sum_{j=0}^{s'}\left(P_j A'_j\right) \quad (12)$$

The reduction in the number of smoking-attributable deaths following the introduction of MRTP, D_{LESS}, is then given by

$$D_{LESS} = D - D' \quad (13)$$

The reduction in the death rate following the introduction of MRTP, A_{LESS}, is given by the following:

$$A_{LESS} = D_{LESS}/N \quad (14)$$

The summation of D_{LESS} over the sexes, ages, and causes of death is considered to estimate the overall effect of the introduction of the MRTP on the population that survives until the time point of interest.

The effect of the introduction of the MRTP can also be estimated for both sexes separately and for specific age groups. Estimates of the effect on premature mortality (deaths before 75 years of age) can be derived from the data by age.

These calculations are based on the assumption that the population size is the same under both scenarios. However, given that the introduction of the MRTP may decrease the death rate, the population size would be expected to be larger under the MRTP Scenario. Thus, if N^* is the increased population size for the MRTP Scenario, Eqs. (12) and (13) would be revised as follows:

$$D'' = D'N^*/N \quad (15)$$

$$D''_{LESS} = D - D'' \quad (16)$$

The increase in population size associated with the introduction of the MRTP can be estimated from the all-cause annual survival rates of the population for the year studied for both scenarios. Suppose that where the P-component concerns the possible introduction of the MRTP 20 years ago, the population size at the end of the 20 year period is N, the total number of deaths from LC, IHD, stroke, and COPD is $d1$ under the Null Scenario and $d2$ under the MRTP Scenario, and the total number of deaths from all other causes is $d3$. The relative survival rate for the MRTP Scenario compared with the Null Scenario, u, can then be estimated by

$$u = (N - d2 - d3)/(N - d1 - d3) \quad (17)$$

Given that, after 20 years, the relative annual survival rate associated with the introduction of the MRTP is u, and assuming that the logarithm of the relative annual survival rate increases linearly with years elapsed since the introduction of the MRTP (a plausible first approximation assuming that the STPs vary little over time), the relative annual survival rate after n years can be approximated by $u^{n/20}$. Thus, the survival rate over the entire 20-year period for the MRTP Scenario, relative to that for the Null Scenario, can be approximated by multiplying the 20 terms $u^{1/20}, u^{2/20}, \ldots, u^{20/20}$, resulting in $u^{10.5}$. This yields an estimate of the ratio required in Eq. (15), N^*/N. Even if the STPs change with time, this approach may yield a reasonable approximation to N^*/N. In theory, a more precise approach might be derived by dividing the follow-up period into intervals, with time invariant STPs, and estimating the effects on population size at the end of each interval.

2.2.2.4. Sensitivity analyses. Total and smoking-attributable deaths under the Null and MRTP Scenarios and their difference (reduction associated with introduction of MRTP) will be estimated in total, and separately by disease, sex, age, and smoking groups. Separating results for ever CC smokers who never used MRTP and MRTP users who never smoked CC should allow better understanding of the effects of the MRTP introduction on a specific population surviving since the MRTP launch. Not only can these results be obtained assuming that the population size is the same under both scenarios, based on Eqs. (4)–(14), but revised estimates can also be obtained accounting for the larger population assumed under the MRTP Scenario.

The method described above results in smoking history distributions that are based on single samples generated in the P-component under the Null and MRTP Scenarios based on the given STPs. This may result in uncertainty, and this can be assessed by comparing the results from multiple samples. Samples can also be generated using multiple sets of STPs to allow sensitivity analyses on how the estimates of smoking-attributable deaths depend on the choice of STPs. Similarly, as noted above, sensitivity analyses can also investigate the dependence of the estimates of smoking-attributable deaths on the F value chosen. Another source of error is the reliance on the RR and half-life estimates derived from meta-analyses. As these also provide variability estimates, based on random-effects models, sensitivity analyses can also be conducted (e.g., using alternative estimates ±1 standard error of the mean).

3. Discussion

We have described above the methods proposed for the estimation of the effect of MRTP introduction on LC, COPD, IHD, and stroke mortality. The methods account for many aspects of the smoking habit, including prevalence of current and former smoking, level of exposure, and time since quitting or switching. However, the duration of smoking at the start of the period is not considered in this analysis because the age-specific RRs used for CC smoking in the E-component reflect duration of smoking to a considerable extent, with minor variations in age of starting to smoke. Furthermore, it would be difficult to obtain valid sex-

and age-specific national data on the distribution of age of starting to smoke for the countries of interest. Failure to consider duration of smoking might lead to error in estimating the reduction in mortality associated with switching to an MRTP if, for example, those switching from CCs to the MRTP tended to be smokers with a below- or above-average duration of smoking. If this is the case, the P-component may have to be amended. Until this can be confirmed, we have omitted such an allowance to avoid added complexity.

If smokers switching from CCs to MRTP do not change their consumption per day, and if the risk of a disease is linearly related to the amount smoked, it seems reasonable to estimate the "effective dose", *F*, from data on exposure to cigarettes and relevant smoke constituents for MRTP smokers, relative to CC smokers. The *F* value can be adjusted to account for the failures of these assumptions. Thus, if there are changes in consumption on switching, *F* might be estimated based on relative daily exposure, rather than on relative exposure estimated on a per-cigarette basis. Similarly, non-linearity in the dose–response relationship may also be considered. This may be relevant if, for some diseases, the evidence suggests that the ER decreases less than proportionately to the amount smoked. Inevitably, there will be uncertainty in the estimation of *F*, given the lack of precise data on the response relationships with amount smoked owing to the incomplete knowledge of the association of relevant smoke constituents for each of the diseases considered, and because the risk from repeated exposure to small doses may not be estimated reliably from less frequent exposures to higher doses. In this model, this uncertainty will be addressed by sensitivity analyses with varying values of *F*.

Regarding the estimation of the mortality reduction associated with the introduction of an MRTP, environmental tobacco smoke exposure (ETS) is not considered. Recently updated meta-analyses of the epidemiological evidence on ETS and LC (Lee et al., 2013c,e), COPD (Lee et al., 2013a), IHD (Lee et al., 2013b,d), and stroke (Lee et al., 2013f) have shown that the RRs associated with ETS exposure in never smokers are much lower than the corresponding RRs for current smoking. Thus, for example, for LC, the RR for ETS exposure is currently estimated at 1.26, while that for current smoking is estimated at 8.43 (Lee et al., 2012a), the ER for ETS exposure being 0.26/7.43 = 3.5% of that for current smoking. This calculation suggests that whether or not the MRTP reduces the risk from ETS exposure would have little effect on the estimates of the reduction of mortality associated with MRTP introduction.

The proposed methods do not account for risk factors other than smoking that may affect the four diseases studied. This seems reasonable given that the introduction of an MRTP is not expected to affect their distribution. If evidence emerges that using or switching to MRTP substantially affects other factors unexpectedly (e.g., degree of alcohol consumption), then the methods proposed may require modification.

Although the P-component involves stochastic simulation to generate samples of smoking history distribution, the E-component does not involve simulation. The estimation of mortality rates involves age-, sex-, and country-specific data on cause-specific mortality and population size for the year of interest. Then, the smoking histories and RRs are applied to estimate the mortality rates attributable to smoking, without any allowance for variation in the number of subjects with a given tobacco history.

Although aging of the population and its effect on the STPs is accounted for by the P-component, it does not consider the mortality of the population during the period of interest; thus, the simulation is performed considering the survival of the entire population. For younger age groups, where the great majority survives the follow-up period, the differential mortality of never smokers, quitters, and current smokers is irrelevant. For older age groups, the STPs may result in some underestimation of never smokers and overestimation of ever smokers. Therefore, while in the absence of mortality, the proportion of never smokers in a cohort cannot increase with increasing age, because transition into a never smoker is not possible, the proportion can rise in a true population because of the better survival of never than ever smokers. The resulting bias should, however, effect similarly the smoking habit distributions derived for both the Null and MRTP Scenarios. In addition, the E-component is adjusted for differing survivals under the two scenarios.

The E-component may estimate MRTP-related reductions in deaths from some diseases even when rates actually rise. This is not indicative of an error; it is merely reflecting underlying adverse trends in risk factors other than cigarettes (e.g., obesity). In this situation, the estimate would suggest that had the MRTP not been introduced, the rise in rates from these diseases would have been greater.

The analysis is restricted to the most common smoking-related diseases as it would be difficult to obtain reliable estimates of the RR and half-life for all the less common diseases associated with smoking. Estimates for industrialized countries reported by Ezzati and Lopez (2003) in 2000 showed that there were a total of 2,427,000 smoking-attributable deaths (1,815,000 in men and 612,000 in women) and, of these, 1,853,000 (1,361,000 in men and 492,000 in women) were from LC, COPD, or cardiovascular diseases. Given that (Peto et al., 1994) IHD and stroke deaths correspond to 75% of the total 1,022,000 deaths from cardiovascular diseases (753,000 in men and 269,000 in women), and assuming that the relative risk from smoking is similar for all vascular diseases (Peto et al., 1994), the number of smoking-attributable deaths would reduce to 1,598,000 (1,173,000 in men and 425,000 in women). This corresponds to 66% (65% in men and 69% in women) of the total. Assuming that the proportional reduction of risk from introducing an MRTP is similar for all smoking-related diseases, this implies that overall estimates of deaths saved by a MRTP based on the four diseases studied would have to be multiplied by approximately 1.52 (1.55 in men, 1.44 in women) to yield an estimate for all smoking-related diseases.

4. Conclusion

The Population Health Impact Model estimates the reduction in the number of deaths attributable to smoking associated with the introduction of an MRTP by comparing, for a given year, the smoking-attributable mortality estimated to occur were the MRTP introduced a defined number of years before, with that estimated to occur were it not introduced. The difference should be indicative of the population-level effect of an MRTP introduction. The estimates may relate to a year in the future, where effects of current introduction of an MRTP are of interest, or to a recent year, where the hypothetical effects of a past MRTP introduction are being studied.

Conflict of Interest

R.W., G.B., Z.S.W., A.G.Z., and F.L. are employees of Philip Morris International. P.N.L. is an independent consultant in statistics and an advisor in the fields of epidemiology and toxicology to a number of tobacco, pharmaceutical, and chemical companies.

Transparency Document

The Transparency document associated with this article can be found in the online version.

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