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A dynamic population model for estimating all-cause mortality due to lifetime exposure history

Annette M. Bachand [a,b], Sandra I. Sulsky [a,*]

[a] Environ International Corporation, United States
[b] Colorado State University, United States

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ABSTRACT

We developed a comprehensive, flexible dynamic model that estimates all-cause mortality for a hypothetical cohort. All model input is user-specified. In the base case, members of the cohort may be exposed to a high risk product as they age. The counterfactual scenario includes exposure to both a high risk and a lower risk product. The model sorts the population into age and exposure categories, and applies the appropriate mortality rates to each category. The model tracks individual exposure histories, and estimates, at the end of each modeled age category, the number of survivors in the two exposure scenarios (base case and counterfactual), and the difference between them. Markov Chain Monte Carlo techniques are used to estimate the variability of the results. Model output was compared against US and Swedish life tables using population-specific tobacco exposure transition probabilities derived from the literature, and it produced similar survival estimates.

1. Introduction

Statistical models and simulation programs can be used to provide estimates of the health effects expected to result from changes in the distribution of a harmful exposure in a given population. Such changes can occur due to natural trends or to regulatory actions. If the projected changes are due to regulatory action, then modeled results allow direct assessment of the health impacts of alternative policies that might affect the distribution of the exposure in different ways, thus supporting the selection of one policy over another (Levy et al., 2006). Desirable features of such models are the clarity with which the underlying assumptions are stated, and the ability of the model to delineate the relationship between the estimates it produces and the assumptions underlying the model (Garrison 2003; Weinstein et al., 2003).

In this paper, we introduce a new tool, the Dynamic Population Model (DPM). The DPM builds on approaches described by others (Hoogenveen et al., 2008; Kulik et al., 2012; Levy and Friend, 2002; Tengs et al., 2004; Tengs et al., 2005; Tengs et al., 2001) but provides additional flexibility, with all parameters defined by the model user. It improves on the validity of previous models by accounting for age- and time-dependent changes in risks.

Starting with a hypothetical unexposed population and following the population as it ages, the DPM distributes subsets of the cohort into user-defined exposure categories, and applies the correct mortality rate to each category. In the base case, the population has access to only one type of product. In the counterfactual exposure scenario, proportions of the population may use an alternative product with a different risk profile. In this manner, the DPM estimates all-cause mortality in the hypothetical population under different exposure distributions, and compares the numbers of survivors expected under each exposure scenario. The example presented here, and the one upon which the model was built, uses cigarettes and a modified risk tobacco product (MRTP, e.g., smokeless tobacco) associated with lower health risks than cigarettes. It compares the number of survivors in a base case that includes never, current and former cigarette smokers, but no MRTP users, with the number of survivors in a counterfactual scenario that additionally includes never, current and former MRTP users.

2. Methods

2.1. The model

The DPM user defines the size of a hypothetical population. The DPM models a cohort, in which all members of this hypothetical population are the same age and none are exposed at the beginning of the simulation. The time variable is age (categorical). The DPM user specifies at which age to begin and end follow-up, and the age category width. All age categories must have the same width.

* Corresponding author. Address: 28 Amity Street, Suite 2A, Amherst, MA 01002, United States. Fax: +1 413 256 3503.
E-mail address: ssulsky@environcorp.com (S.I. Sulsky).

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2.2. Transitions between exposure states

The DPM distributes persons into age and exposure categories using age category-specific exposure transition probabilities entered by the DPM user. All cohort members begin as unexposed (to either product), shown in the top left-hand box of Fig. 1. As follow-up of the base case progresses (Fig. 1, top row), individuals either remain as unexposed (curved arrow) or transition to current use of the base case product (top row, second box), shown by the forward arrow. Current users may remain current users (curved arrow) or become former users in the next follow-up interval. Subsequently, former users may restart the base case product and quit again. Rows below the top in Fig. 1 are needed to describe the additional possibility of exposure to the alternative product in the counterfactual scenario. For example, unexposed cohort members (top left-hand box) may remain as unexposed (curved arrow) or transition to use of the alternative product (downward arrow). Current alternative product users may remain current users (curved arrow), switch to the base case product, become concurrent dual users of both products, or quit use of the alternative product in the next follow-up interval. Subsequently, persons can remain in their exposure category (curved arrow) or move into other exposure categories (forward arrow).

The DPM user can define the probability of transitioning from one exposure state to another from available data, or the transition probabilities can be specified to define a particular question of interest. For the example of smoking and MRTP use, assume that the smoking initiation rate among US males aged 13–17 years in a particular year of interest is 11%; then, the probability of transitioning from never tobacco user to smoker in age category 13–17 would be set by the DPM user to 11%. If the DPM user was interested in the effect on population mortality if, among US males aged 13–17, smoking initiation was 5% instead, the DPM user would set the probability of transitioning from never tobacco user to smoker in age category 13–17 to 5%.

The distribution of the cohort into exposure groups is simple enough to be applied in a spreadsheet. However, to obtain variability estimates of the output using Markov chain Monte Carlo techniques, we implemented the DPM in the WinBUGS computer program (version 1.4.3) (Lunn et al., 2000). Transition probabilities can be modeled as fixed (most appropriate for rates defining a specific question of interest) or normally distributed (most appropriate for rates based on estimates from the literature), but are bounded between 0% and 100%. Default means are equal to the respective estimated transition probabilities, and default standard deviation is equal to 1%. The standard deviation can be changed by the DPM user.

2.3. Mortality

A Poisson model embedded within the DPM estimates the number of deaths among persons with a particular exposure history involving only the base case product. The estimates are based on person-years and deaths by age, years of exposure and years since cessation of exposure entered by the user. Only survivors move on to the next age category. Specifically, *r.ne*, the mortality rate among persons who never used the base case (or the alternative) product and *r.bc* and *r.fbc*, the mortality rate among current and

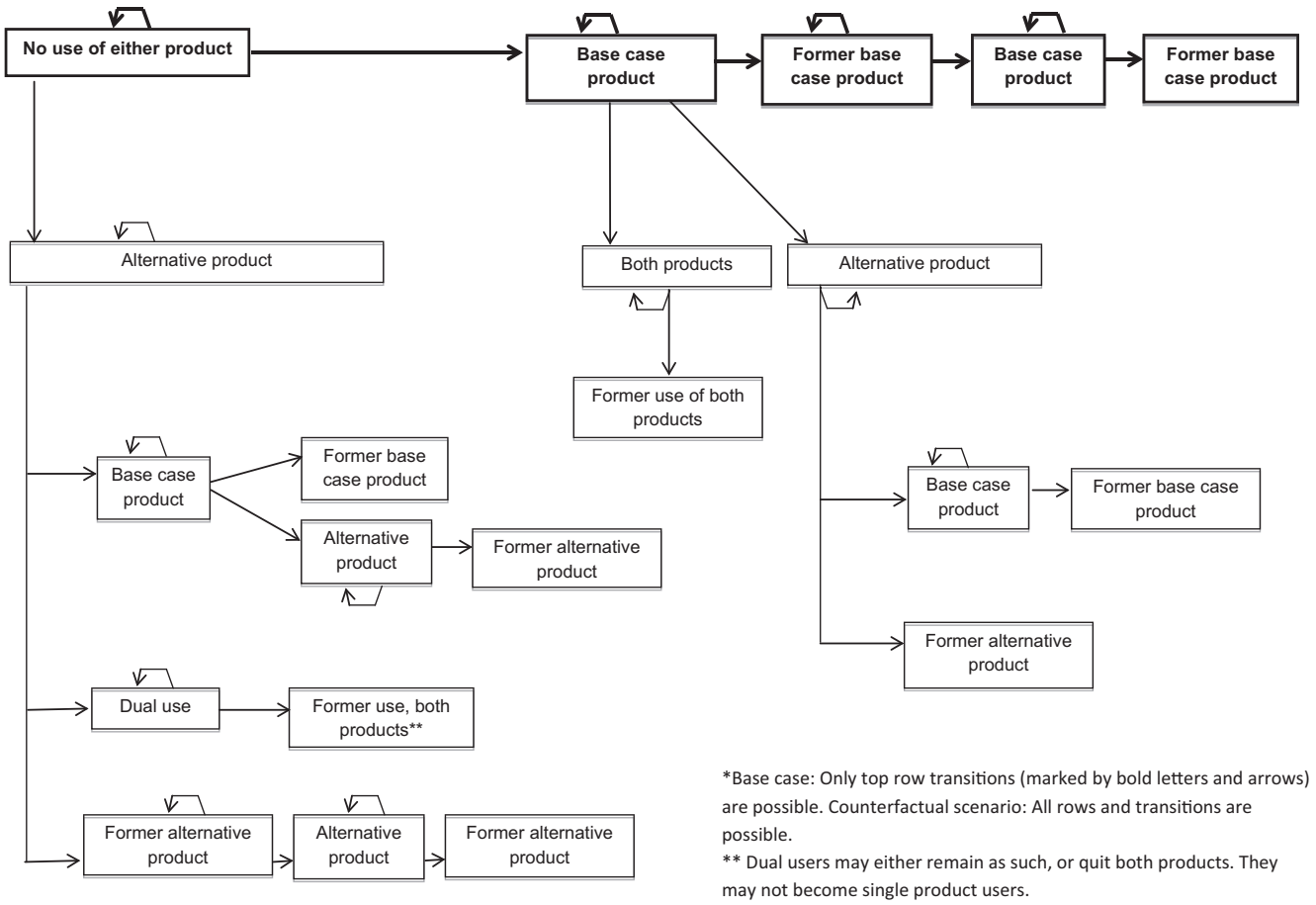

Fig. 1. Schematic representation of the distribution of persons into exposure categories by the Dynamic Population Model. Transitions for base case (top row, only) and counterfactual exposure scenarios (all rows).*

former users of the base case product, respectively, are estimated as

$$r.ne = e^{\beta_0+\beta_{age}+\beta_{agez}age^z}$$

$$r.bc = r.ne \times e^{\beta_0+\beta_{age}age+\beta_{agez}age^z}$$

$$r.fbc = r.bc \times e^{\beta_{yfbc}yfbc+\beta_{ayfbc}age\times yfbc}$$

where *bc* = base case product use, *fbc* = former base case product use, *ybc* = years of exposure to the base case product and *yfbc* = years since quitting the base case product.

To estimate mortality rates for the alternative product (*ap*), the DPM user enters the excess relative risk (ERR) for individuals with current exposure to the alternative versus the base case product, defined as the ratio of relative risks (RR) for the alternative and base case exposures:

$$\text{ERR} = \frac{\text{RR}.ap - 1}{\text{RR}.bc - 1}$$

The DPM then calculates age- and duration-specific mortality rates for the alternative product compared with the base case product, as follows: Because $\text{RR}.ap - 1 = \text{ERR}(\text{RR}.bc - 1)$ and, therefore, $\frac{r.ap}{r.ne} - \frac{r.ne}{r.ne} = \text{ERR}(\frac{r.bc}{r.ne} - \frac{r.ne}{r.ne})$ and $r.ap - r.ne = \text{ERR}(r.bc - r.ne)$,the mortality rate for current users of the alternative product is

$$r.ap = \text{ERR} \times r.bc + (1 - \text{ERR})r.ne.$$

Mortality rates for former users of the alternative product are calculated similarly, replacing *bc* with *fbc* and *ap* with *fap*.

For users of the base case product who switch to the alternative product, mortality rates are the product of four factors, representing risks from background, base case product use for the age range during which the base case product was used, alternative product use for the age range during which the alternative product was used, and former use of the base case product. Mortality rates for users of the alternative product who switch to the base case product are calculated similarly, but exclude risk for former use of the alternative product because the alternative product is assumed to have lower risks than the base case product. Mortality rates for persons switching to a different product and then quitting are calculated similarly, with former use replacing current use of the second product. Concurrent dual use is assumed to have the same mortality risk as use of the higher risk product. A detailed derivation of the mortality rates is shown in Appendix A.

The default prior distributions for the coefficients of the core Poisson model are non-informative normal distributions, with mean 0 and standard deviation 100. The log-transformed ERRs are assumed to be normally distributed, with mean equal to the log-transformed ERR and standard deviation 100. Default standard deviations can be changed by the DPM user.

2.4. Model output and applications

The DPM output includes the age-specific number of survivors under the base case and counterfactual scenario, and their difference. Output values are estimated after each iteration and summarized over all iterations using means and 95% posterior intervals (i.e., the 2.5th and 97.5th percentile of the distribution). The model input and output are summarized in Fig. 2.

The default output from the DPM is a comparison between survivors in the base case and counterfactual exposure scenarios. All possible exposure transitions can occur after conclusion of the fifth category of attained age, so age-specific numbers of survivors are displayed from that point forward. These results can be used to generate life tables with age category-specific remaining life expectancy and, if data are available, quality-of-life adjusted age

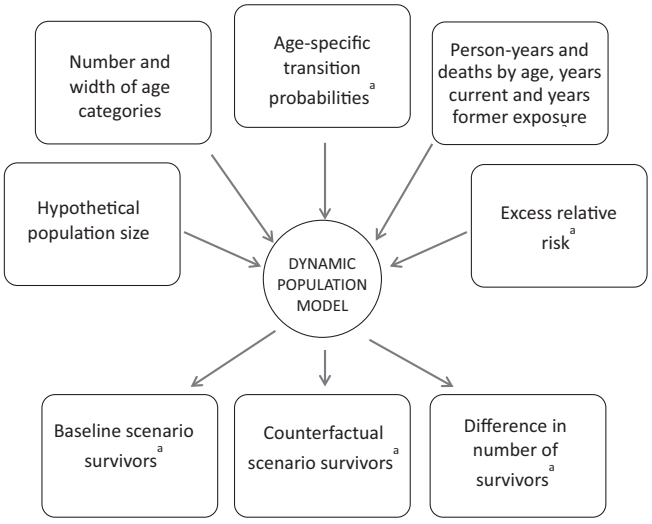

Fig. 2. Model input and output.

category-specific remaining life expectancy. Results can also be used to estimate tipping points, defined as the proportion of the population that must experience a reduction in harm to overcome the survival deficit arising from a proportion of the population experiencing an increase in harm, or vice versa. Tipping point analyses can be relatively simple, addressing only one harmful or beneficial exposure pattern and one exposure pattern expected to counteract the harm or benefit it produces. They can also be complex, addressing multiple interacting exposure patterns. Model input values can be systematically changed to allow for sensitivity analyses.

3. Validation of the model using cigarette and MRTP exposure data

The Kaiser Permanente (KP) cohort study provided age-, years of smoking- and years since quitting-specific mortality rates for men (Friedman et al., 1997), and, after some adjustments (Appendix B), these were used in the embedded Poisson model. There was no evidence of over- or under-dispersion, and including interaction terms for (age × duration of smoking) and (age × duration of quitting) provided a model with excellent fit, graphically and statistically (Pearson Chi-Square goodness of fit test p-value = 0.82), i.e., the mortality rates predicted by the model very closely matched the observed mortality rates. Fit was still good graphically and statistically (Pearson Chi-Square goodness of fit test p-value = 0.2) when we used the KP data for women. While the KP data were used to develop the structure of the Poisson model, mortality data by age, years of exposure (in this example, to smoking) and years since exposure cessation (i.e., quitting smoking) from any population can be used.

We compared modeled mortality estimates against mortality estimates using actual population life tables. To validate mortality estimates under the base case (no MRTP use), we predicted mortality in 2006 using age-specific 1980 US male smoking initiation (SAMHSA 1999) and cessation rates (Messer et al., 2007) to allow for adequate induction time (Table 1). The prevalence of smokeless tobacco use in US men has been fairly low and stable, around 5%

Table 1
Five-year cigarette smoking initiation and cessation rates per 100 person-years in 1980, US.

Age category	Smoking initiation rate[1]	Smoking cessation rate[2]
13–17	11.25	2.5
18–22	10.00	4.5
23–27	1.25	4.5
28–32	0.25	4.5
33–37	0.00	5.0
38–42	0.00	5.5
43–47	0.00	5.5
48–52	0.00	7.5
53–57	0.00	8.5
58–62	0.00	8.5
63–67	0.00	8.5
68–72	0.00	8.5

[1] Based on: Office of Applied Studies, National Household Survey on Drug Abuse (NHSDA), 1999, Appendix D, table 4.2 (http://www.samhsa.gov/data/NHSDA/tobacco/appendixd.htm).
[2] Based on: Messer et al. (2007).

(CDC 1994), and thus approximates a population without MRTP exposure. We compared the model results with the 2006 US life table for men (CDC 2009).

To validate the counterfactual scenario estimates, we used snus as an example MRTP. Snus use has been common among Swedish men, especially since the 1970s, and some ERR estimates were available that allowed estimation of all-cause mortality risk for users of snus compared to cigarette smokers. For current snus use versus current smoking, we used a conservative estimate of ERR = 0.11 (Levy et al., 2004). We assumed the same ERR for former snus users versus former smokers and that users of both products (dual users) had the same excess risk as smokers. We were able to define a counterfactual exposure scenario based on probabilities of transitioning between cigarettes, snus and dual use (Lundqvist et al., 2009) that, if the DPM worked correctly, should lead to an approximation of the 2006 Swedish life table for men (Sveriges officiella statistik 2012) (Appendix C). For validation of both the base case and the counterfactual exposure scenario, we used 10,000 iterations, after a burn-in of 2000 iterations, and considered a Markov chain to have converged if the Monte Carlo error was less than 5% of the sample standard deviation. Development of the DPM was not based on any specific input data. The input values specified above were only used to validate the predictions generated by the DPM.

Table 2 shows close correspondence between the US life table-based numbers of survivors and the model results for the base case. The number of survivors estimated by the DPM's base case was within 0.2% of the US life table-based number of survivors. Table 3 shows close correspondence between the model results and the Swedish life table-based numbers of survivors for the counterfactual exposure scenario. The number of survivors estimated by the DPM was within 0.3% of the Swedish life table-based number of survivors.

Table 2
Age-specific estimated survivors: 2006 US life table versus model-based estimates (starting with 1,000,000 12 year old male never tobacco users)[a].

Age category	Survivors based on US life table	Survivors based on base case (US)
38–42	957,654	957,100
43–47	940,866	939,200
48–52	915,745	914,300
53–57	880,470	879,800
58–62	832,268	832,000
63–67	764,922	765,600
68–72	674,217	674,300

[a] Age group 38–42 is the first age group where all possible transitions have occurred.

Table 3
Age-specific estimated survivors: 2006 Swedish life table versus model-based estimates (starting with 1,000,000 12 year old male never tobacco users).[a]

Age category	Survivors based on Swedish life table	Survivors based on exposure scenario (Sweden)
38–42	980,999	979,274
43–47	972,889	970,010
48–52	959,782	957,276
53–57	936,838	935,677
58–62	902,590	902,104
63–67	846,884	847,362
68–72	764,275	762,582

[a] Age group 38–42 is first age group where all possible transitions have occurred.

4. Discussion

The DPM was designed to estimate the change in survival expected when an alternative exposure is added to a population. It is structured to test the effect on mortality if some people substitute a new exposure for an existing exposure, or if some people who would not have been exposed at all in the base case are instead exposed to the new product in the counterfactual scenario. The DPM was specifically developed to estimate changes in survival, at the population level, when proportions of potential or actual cigarette smokers substitute use of a MRTP for all or some of their cigarettes, but it is not limited to this application.

Partial or complete substitution of a higher risk with a lower risk product should provide some health benefit. Evidence for the existence of such health benefits for cigarette smokers who switch to MRTP is provided by correlations between changing patterns of tobacco use and changing morbidity and mortality patterns observed in Sweden, where snus, a type of MRTP, has been commonly used by men for decades. Nevertheless, policy makers must consider potential unintended adverse consequences of policies promoting new MRTPs, including the possibility that current smokers who would have otherwise given up cigarettes instead substitute MRTPs for some or all of their cigarettes, and that non-tobacco users might initiate MRTP use and then become cigarette smokers instead of remaining as never tobacco users. The DPM supports the choice among alternative policies by allowing for comparison of the health consequences of various potential changes in the distribution of use of different products.

The model validation exercises showed that, given a sufficient induction period and reasonable input data, the DPM accurately predicts life tables in a population with no MRTP use (US) and a population with widespread MRTP use (Sweden). Depending on available data, other countries, time periods and types of exposure could have been used to validate the model. The results of the validation indicate that the DPM can provide meaningful data to compare the health effects of different hypothetical exposure distributions. If those distributions arise from alternative policies, then the DPM can be used to compare health consequences due to policy decisions.

The DPM has several limitations. Like all models, it is built on simplifying assumptions, specifically: (1) It allows testing the addition of a new exposure, but not removal of an exposure that exists in the base case. (2) The effects of using only two types of products are compared. (3) The DPM assumes that the rates of risk reduction associated with stopping use of the base case and the alternative products are proportional; this may not be true. (4) Mortality rates

depend on the overall duration of product use or quitting, but not on the amount of each product used nor the sequence of exposures. (5) Because the amount of exposure is not accounted for, the ERRs for current and former dual use vs. cigarette smoking are not modifiable by the user, and are set to one. (6) Although the DPM accommodates a large number of exposure patterns, it does not allow for concurrent dual exposure to revert to exposure to either single product, alone. (7) Only the direct effects of exposure to higher and lower risk products are considered. In the tobacco examples discussed here, the DPM does not account for changes to secondhand smoke exposures due to changes in the proportions of cigarette smokers in the population. (8) Finally, the DPM requires user-specified input data. The precision and validity of the outcome estimates depend on the certainty and validity of the model input selected.

The DPM estimates all-cause mortality as numbers of survivors. While the results also can be expressed as numbers of deaths, losses or gains in life expectancy, person-years, or disability-adjusted life-years due to the more widespread use of the alternative product, uncertainty estimates (i.e., posterior intervals) are not yet available for these alternative metrics. We have not attempted to use or to validate the DPM to model the effect of changing exposures other than to cigarettes and MRTP. Model input values can be systematically changed to allow for sensitivity analyses, and results can also be used to estimate tipping points.

Setting up the model to run properly in WinBUGS requires technical skills. Enhancements to the DPM currently under way include development of a user-friendly interface via a web portal; incorporation of morbidity (i.e., incident disease) as an outcome measure; and allowing user-specified ERRs for current and former dual exposure. A version of the model predicts cause-specific mortality, but the results have not yet been fully validated.

The main strengths of the model are its flexibility, its ability to account for uncertainty in the model input and output, its comprehensiveness, and its demonstrated validity. Specifically, all model input can be changed by the user, and the level of uncertainty in model input can be specified and is accounted for by the posterior intervals that estimate the variability of the results. There are no restrictions on age, time of initiation or time of cessation of exposure. The model estimates the number of survivors at the end of each age category, for each exposure history up to that point. Commonly observed exposure histories are accommodated but the user can restrict the model to a subset of transitions if not all exposure histories are of interest.

While other dynamic models focusing on risks associated with use of tobacco products have been described in the literature, most were developed to estimate changes in population-level risk due to changes in proportions of never, current and former smokers resulting from increasing smoking cessation rates and/or decreasing smoking initiation rates; they do not consider the effect of introducing a new product to a population (Kulik et al., 2012) (Levy and Friend, 2002) (Tengs et al., 2004; Tengs et al., 2005; Tengs et al., 2001) (Hoogenveen et al., 2008) (Kulik et al., 2012). Only two published models were designed to estimate the effects of introducing a MRTP to a population of never, current and former smokers, but the range of questions they can address is limited because they hold smoking initiation and cessation rates constant and do not allow transition probabilities to depend on age (Apelberg et al., 2010; Mejia et al., 2010). Specifically, the model proposed by Apelberg, Onicescu, et al. allows for very few transitions, assumes that transition probabilities do not depend on age and that mortality risk depends only on current tobacco exposure status and no other exposure metric. The Mejia, Ling et al. model also assumes that risk depends only on current tobacco exposure status (with no other exposure metric) and uses a limited number of exposure states and transitions (e.g., quitters of tobacco cannot revert to tobacco use); the model uses the same initiation, cessation and transition rates for the entire hypothetical population, regardless of age; and, quantifies the risk of tobacco related health by a health index that is assumed to be the same regardless of duration of tobacco use or cessation. The health index itself does not seem to be based on empirical data.

Although the DPM was developed with tobacco exposures in mind, it is not limited to this application. The key benefit of using models like the DPM to investigate the potential effects of public health policies that aim to shift populations from more harmful to less harmful exposures is their ability to hold constant all assumptions and factors other than the distribution of exposure or the comparative risk estimates. Because the model requires the user to specify the particular transition probabilities of interest and the risk associated with the new compared with the old exposure, the basis for evaluating policies is clarified. For example, the US Food and Drug Administration (FDA) has recently issued regulations for the identification of certain products as MRTP. Granting an MRTP designation might increase population-level harm if it encourages tobacco use (e.g., MRTP use instead of quitting or not starting to smoke). An MRTP designation might decrease population-level harm if it causes an adequate number of people to replace some or all of the cigarettes they currently smoke (a high risk exposure) with the MRTP (a lower risk exposure), or if more people quit using tobacco. The DPM can be used to test hypotheses such as these, and to evaluate the magnitude of the population shifts necessary to meaningfully increase or decrease harm.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.yrtph.2013.08.003.

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