Population Modeling of Modified Risk Tobacco Products Accounting for Effects of Cigarettes per Day

Bill Poland, Ph.D.[1], Florian Teischinger, Ph.D.[2]

[1]Certara Strategic Consulting, 845 Oak Grove Ave. Suite 115, Menlo Park, CA 94025, USA, Bill.Poland@certara.com ; [2]SRA, JT International SA, 8, rue Kazem Radjavi, CH-1202 Geneva, Switzerland, Florian.Teischinger@jti.com

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ABSTRACT

The FDA's draft guidance on Modified Risk Tobacco Product (MRTP) applications recommends simulation models to evaluate net public health impacts of MRTP candidates such as electronic cigarettes (e-cigs) and snus. These products might reduce mortality risk among smokers who switch to them, but risks being debated include extended dual use, increased total initiation to tobacco products, relapse of former smokers, role as a gateway to smoking, and long-term health risks of the new product. We developed a two-product simulation model to explore possible population impacts of an MRTP. The conventional cigarette (CC) sub-model incorporates effects of age, gender, cigarette per day (CPD), and time since quitting. The MRTP sub-model allows transitions to and from dual use and MRTP alone, and effects of dual use on CC quit rates. A product use history generator simulates individuals, who are then aggregated over a large random sample. This approach provides greater flexibility than Markov state models, allowing detailed CPD modeling for example. In order to reflect the high uncertainty in long-term prediction, we model a broad range of probability-weighted scenarios.

Smokers who add an MRTP without fully switching tend to smoke fewer CPD, reducing mortality risk based on studies of large cohorts of smokers. The relationship of relative mortality risk to CPD appears steepest at very low CPD (e.g., <5-10 CPD), indicating that quitting even from a low CPD level remains better than CPD reduction. We simulated effects of different levels of CPD reduction, starting with distributions of CPD by age and sex from National Survey on Drug Use and Health (NSDUH). Varying the CPD reduction from 0% to >50% had a greater effect on cumulative deaths than varying other assumptions, such as transition rates to and from dual use and relative harm from the MRTP vs. CC. Therefore, simulation models to assess population effects of MRTPs should include benefits from CPD reduction by dual users, in conjunction with added risks from the MRTP. In addition, following up dual-user CPD histories and quit rates over time should be an essential part of post-market studies.

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OBJECTIVES

- Extend a simulation model of present and future use of CC and MRTP [Poland et al. 2015, 2014], to account for effects of CPD changes over time on mortality

- Illustrate evaluation of net impacts of the MRTP on population mortality, addressing FDA expectations for quantifying net public health impact [FDA 2012].

METHODS

- An annual individual simulation model with two tobacco products (**Fig. 1**), previously developed in Excel/Visual Basic, was extended to incorporate gradual exponential transitions of relative risk when an individual changes tobacco product use, including CPD.

  o Excess Risk (ER) is defined in terms of Relative Risk (RR, relative to a never-user):
    ER = RR - 1.

  o When a change in tobacco product use changes equilibrium (long-run target) ER, ER(t) moves exponentially toward the new equilibrium:
    $ER(t) = ER_{eq} + [ER(0) - ER_{eq}] \exp(-k\,t)$.

METHODS (continued)

  o The slope of change k depends on age and sex and was fitted to a prior model of the decay of RR over time since quitting [Mendez et al. 2001].

  o The same slopes were used to make ER(t) change gradually after *any* tobacco product initiation, addition, change in use level, or cessation.

- CPD was related to equilibrium mortality risk using data from large cohort studies (**Fig. 2**).

- A hypothetical MRTP (such as an e-cig) was assumed to become available in the first simulation year, with reference-case transition rates and risk relative to CCs as shown in **Table 1**. Dual users were assumed to reduce CPD.

- *Low and high* MRTP inputs reflect uncertainty over the time horizon (**Fig. 3**).

- A population of 50,000 was simulated over 2012-2060, and smoking prevalence and mortality rates were aggregated from individual smoking and MRTP use histories (**Fig. 4**).

Table 1. Hypothetical MRTP inputs (reference case)

Initiation: **25%** of would-be CC initiators instead initiate the MRTP; an additional **5%** (also in units of CC initiators without the MRTP) who would have been non-users instead initiate the MRTP; former smokers relapse to the MRTP at **0.5%/year**.

Dual use: smokers add the MRTP at **5%/year**; MRTP users add CC at **0.5%/year**.

Cigarettes/Day & Mortality Impact: dual users smoke **42%** fewer CC, reducing excess relative risk of mortality by amounts depending on initial CPD, typically by 25%.

Quitting: MRTP users quit the MRTP at the same rate as smokers (age and sex dependent); dual users quit the MRTP at **0.5%/year** and quit cigarettes at **125%** of the smoker quit rate.

Health risk: the excess risk of mortality from MRTP use relative to no tobacco use is **4%** of that of CC smoking.

Figure 1. Two-product (CC and MRTP) model

Each node represents a subpopulation, and each arrow represents a flow proportional to the current subpopulation (except for incoming new population). Numbers correspond to numbered MRTP inputs in **Fig. 3**.

Dashed arrows indicate transitions not currently used: only one transition occurs at a time (e.g., C-B-M but not C-M, and B-C-F but not B-F). The red arrow (F-M) is the only form of relapse allowed; otherwise, cessation is permanent. The CC-only model has zero transition into B and M.

Additional data are tracked by individual in each node, including age, sex, CPD, and years since quitting cigarettes.
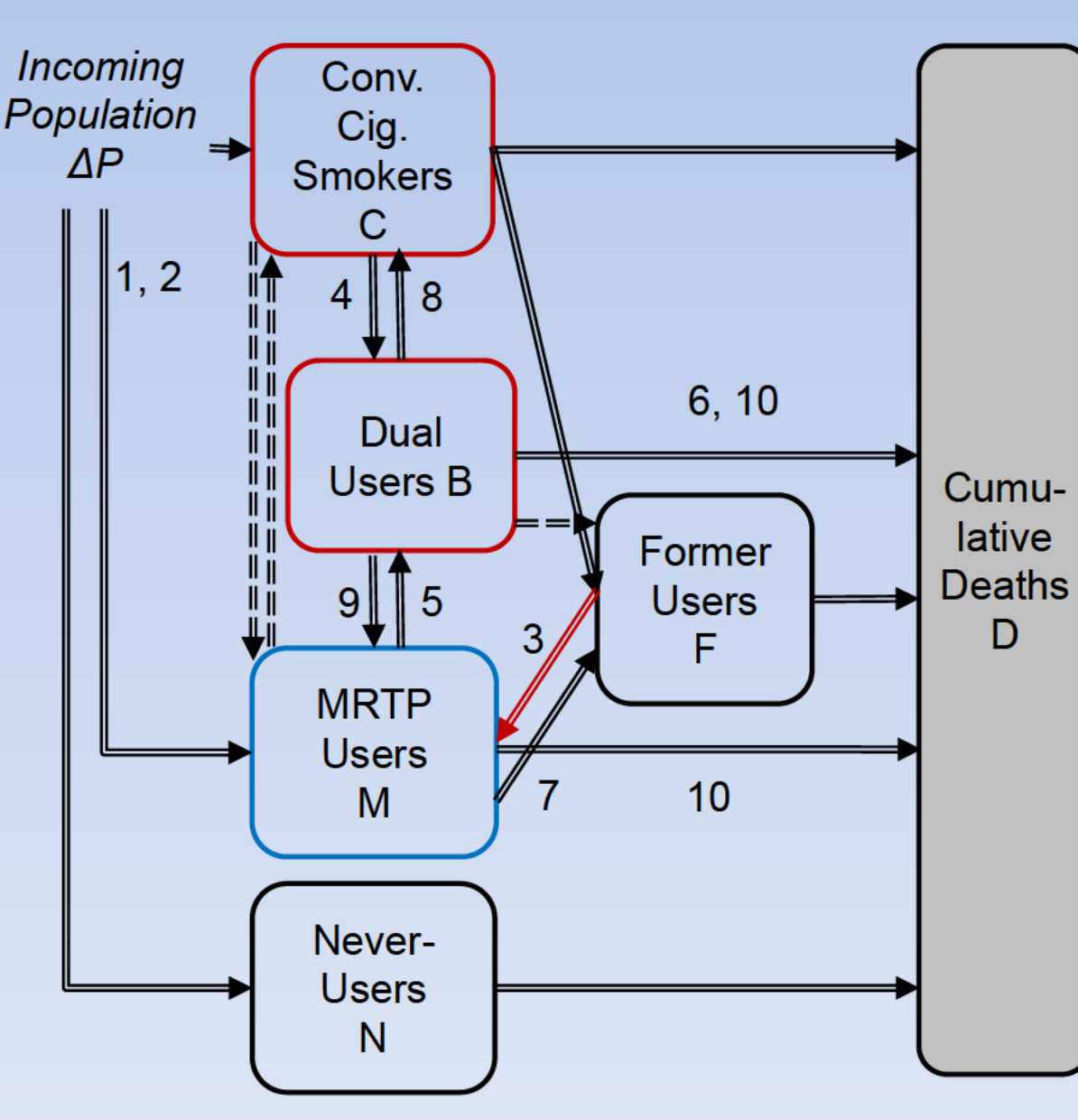
RESULTS

ER was estimated to decay more slowly at older ages: 9.5% per year at ages 40 and 50, 6.5% per year at age 60, 4.5% per year at age 70, and 2.5% per year at age 80. The same exponential slopes were used for men and women due to negligible differences.

Fig. 2: RR was found to increase sharply with CPD at low CPD levels, i.e., light or intermittent smoking carries a much higher risk than never smoking, then more slowly at higher CPD levels. Differences in sex were small and therefore omitted. A logarithmic curve served to fit the data.

Fig. 3: Varying CPD reduction by dual users between 0 and 84% had the greatest impact on mortality through 2060 among 10 input sensitivities.

Fig. 4: Effects of the key inputs accumulate over time. If the MRTP does not induce dual users to reduce CPD, its net effects (due to lower RR and higher quit rate offset by dual use and some former smoker uptake) cancel out in this hypothetical example, leaving results similar to the CC-only case.

Figure 2. Relative risk of death vs. CPD, and fitted curve. Relative risk increases with CPD, though RRs vary by study and may also increase with years smoking.

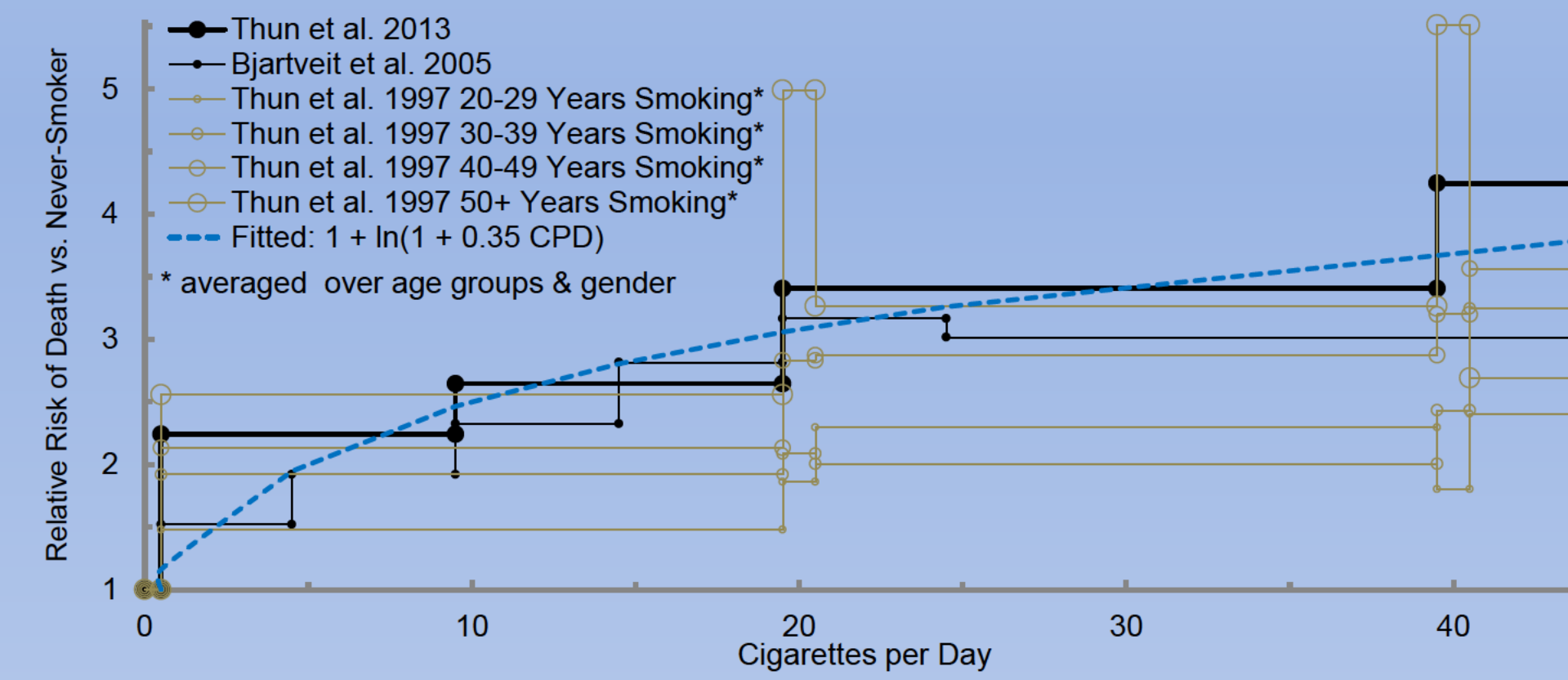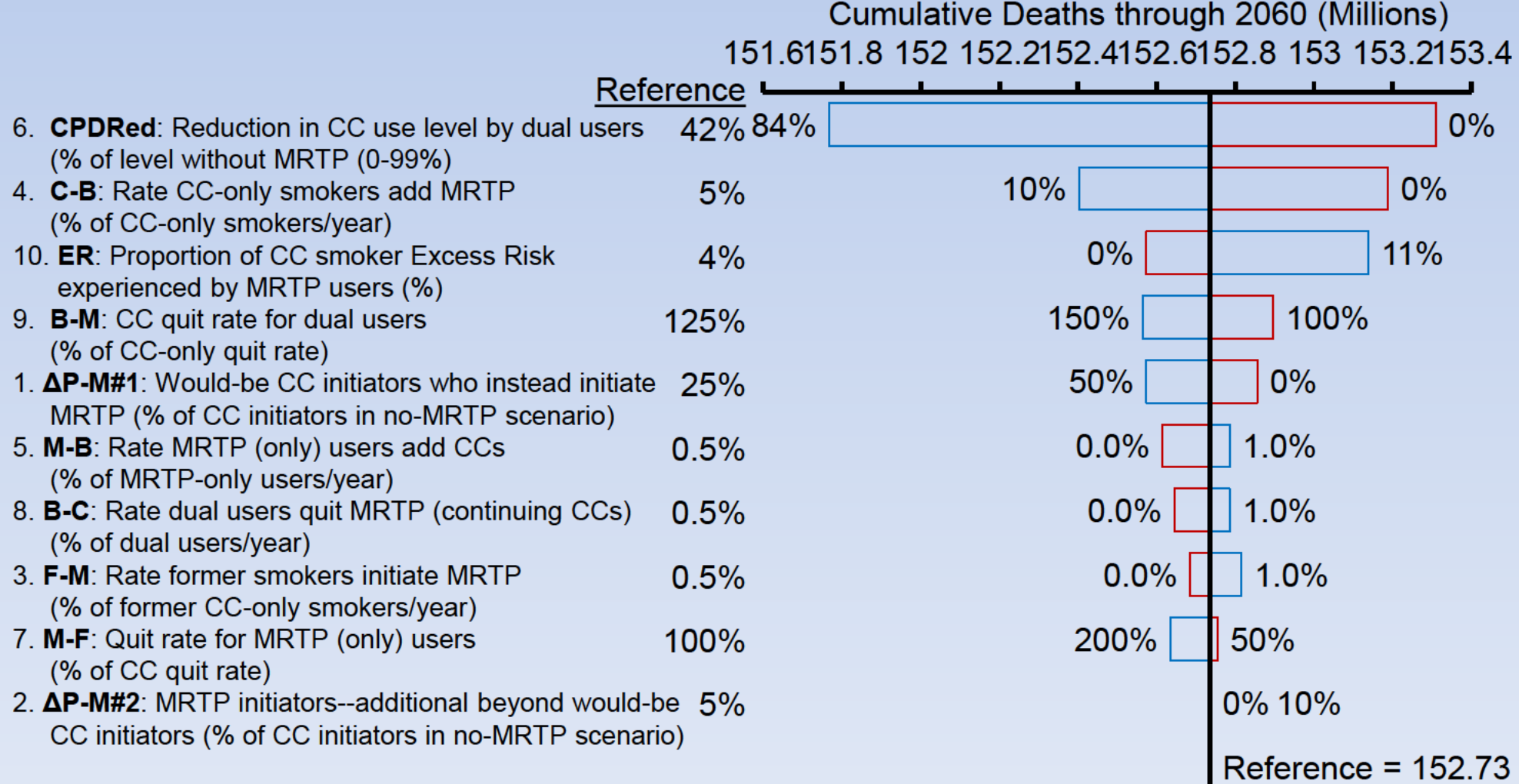* averaged over age groups & gender

Figure 3. Sensitivity of MRTP effects on mortality through 2060

Each of 10 MRTP inputs is varied one-at-a-time through its indicated range. The reference line is the output with all inputs at their reference values. Red bars result from low input values and blue bars from high input values. Bars on the left side of the reference line indicate positive impact (lower mortality), whereas bars on the right indicate negative impact. *Caution: comparison of bar lengths is meaningful only if input ranges are consistent (e.g., 10th to 90th percentiles).*

		Reference		
6. **CPDRed**: Reduction in CC use level by dual users (% of level without MRTP (0-99%))	42%	84%		0%
4. **C-B**: Rate CC-only smokers add MRTP (% of CC-only smokers/year)	5%		10%	0%
10. **ER**: Proportion of CC smoker Excess Risk experienced by MRTP users (%)	4%		0%	11%
8. **B-M**: CC quit rate for dual users (% of CC-only quit rate)	125%		150%	100%
1. **ΔP-M#1**: Would-be CC initiators who instead initiate MRTP (% of CC initiators in no-MRTP scenario)	25%		50%	0%
5. **M-B**: Rate MRTP (only) users add CCs (% of MRTP-only users/year)	0.5%		0.0%	1.0%
8. **B-C**: Rate dual users quit MRTP (continuing CCs) (% of dual users/year)	0.5%		0.0%	1.0%
3. **F-M**: Rate former smokers initiate MRTP (% of former CC-only smokers/year)	0.5%		0.0%	1.0%
7. **M-F**: Quit rate for MRTP (only) users (% of CC quit rate)	100%		200%	50%
2. **ΔP-M#2**: MRTP initiators--additional beyond would-be CC initiators (% of CC initiators in no-MRTP scenario)	5%		0%	10%

Cumulative Deaths through 2060 (Millions)
151.6 151.8 152 152.2 152.4 152.6 152.8 153 153.2 153.4

Reference = 152.73

RESULTS (continued)

Figure 4. Change in illustrative simulated cumulative US deaths relative to two-product reference case. Case 0 includes CC only. The 0 line is the two-product reference case. The other cases show effects over time of low and high input values of the top five bars in **Fig. 4**.
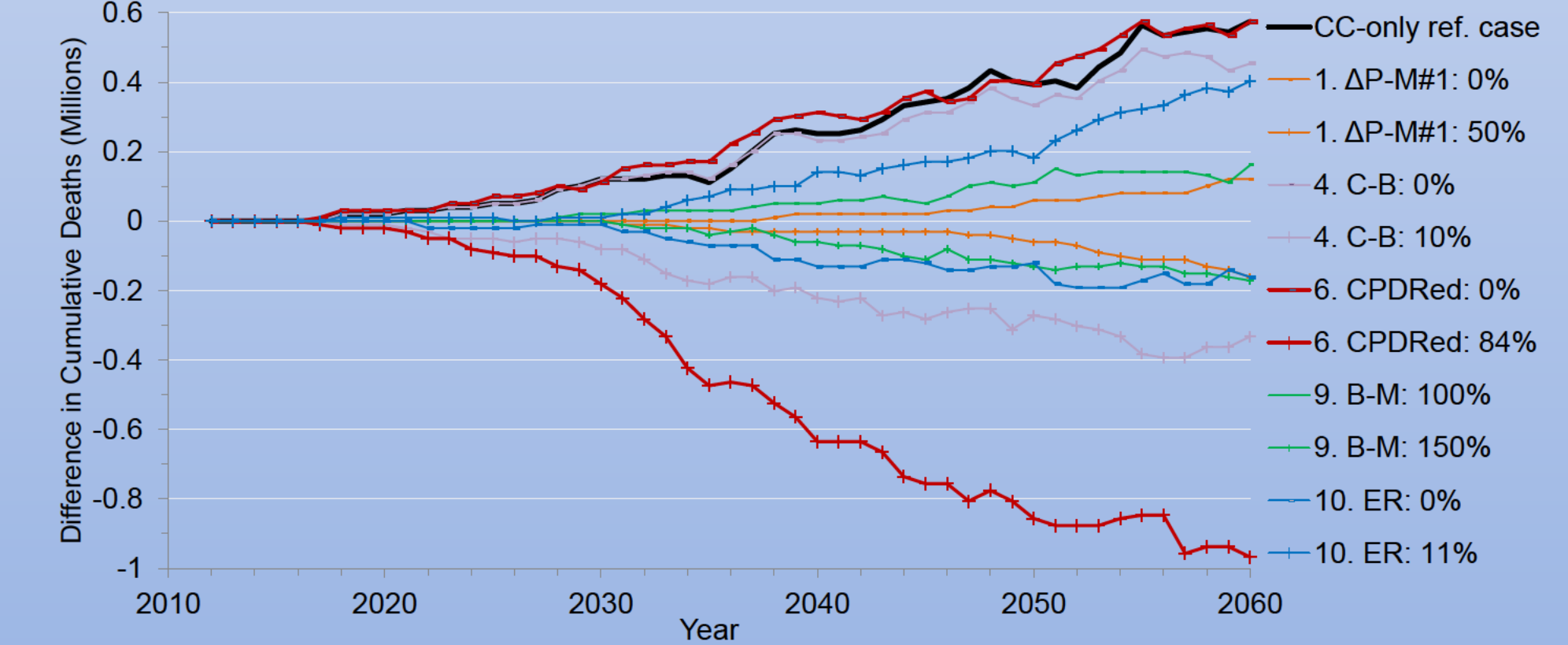
DISCUSSION

- The model combines strengths of other smoking prevalence and mortality prediction models: two tobacco products, full age and sex demographics, and *time-varying effects of CPD* and years since quitting on mortality.

- Individual Monte Carlo simulation provides the flexibility to model *gradual* relative risk changes over time, after changes in tobacco product use.

- Hypothetical MRTP inputs show that *CPD reduction is important* to model because it could make the difference between no net mortality reduction and substantial reduction.

- A *long time horizon* is necessary to properly assess public health impacts.

- Future research may include: 1) refining *input distributions* with new data, 2) refining *sub-models* such as CPD-mortality accounting for full CPD history, 3) varying *transition rates* (currently fixed in %/year) over time, e.g., to reflect possible time-courses of market penetration, and 4) increasing *sample size and time horizon* for better accuracy.

REFERENCES

Bjartveit & Tverdal 2005. Health consequences of smoking 1-4 cigarettes per day. *Tob Control* 14:315-320. PMID:16183982.

FDA 2012. Modified Risk Tobacco Product Applications, Draft Guidance. March 2012.

Mendez & Warner 2001. The Relative Risk of Death for Former Smokers: The Influence of Age and Years Quit. Unpublished monograph at www.umich.edu/~dmendez/tobacco/RRiskmonograph.doc.

Poland et al. 2015. Population Modeling of Modified Risk Tobacco Products. *The Toxicologist* 144(1), Abstract #573.

Poland et al. 2014. A Simulation Environment for Population Dynamics Models of Tobacco Products. *The Toxicologist* 138(1), Abstract #646.

Thun et al. 2013. 50-year trends in smoking-related mortality in the United States. *N Engl J Med* 368:351-64.

Thun et al. 1997. Age and the exposure-response relationships between cigarette smoking and premature death in Cancer Prevention Study II. Chapter 5 in: Smoking and Tobacco Control Monograph No. 8. NIH Pub. No. 97-4213.