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Quantifying the risk-reduction potential of new Modified Risk Tobacco Products

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ABSTRACT

Quantitative risk assessment of novel Modified Risk Tobacco Products (MRTP) must rest on indirect measurements that are indicative of disease development prior to epidemiological data becoming available. For this purpose, a Population Health Impact Model (PHIM) has been developed to estimate the reduction in the number of deaths from smoking-related diseases following the introduction of an MRTP. One key parameter of the model, the F-factor, describes the effective dose upon switching from cigarette smoking to using an MRTP.

Biomarker data, collected in clinical studies, can be analyzed to estimate the effects of switching to an MRTP as compared to quitting smoking. Based on transparent assumptions, a link function is formulated that translates these effects into the F-factor. The concepts of 'lack of sufficiency' and 'necessity' are introduced, allowing for a parametrization of a family of link functions. These can be uniformly sampled, thus providing different 'scenarios' on how biomarker-based evidence can be translated into the F-factor to inform the PHIM.

1. Introduction

Modified Risk Tobacco Products (MRTPs) aim at avoiding to impose on their users increased risks of chronic disease morbidity and mortality at levels caused by smoking cigarettes. We have developed a computational population health impact model (PHIM) to compare smoking-attributable deaths with and without the introduction of an MRTP (Lee et al., 2017; Weitkunat et al., 2015). The model requirements include estimates of the probabilities of switching between various tobacco product use behaviors (never, current smoking, current MRTP use, current dual use, former) and of excess risks of smoking versus never smoking of the major smoking-related diseases, by time quit (Forey et al., 2011; Fry et al., 2013; Lee et al., 2012a, 2012b, 2014a, 2014b). When the exposure to harmful and potentially harmful constituents (HPHCs) is reduced in an MRTP's aerosol compared to the smoke of a cigarette, it can be assumed that the effective dose of the MRTP is below that of a cigarette, albeit higher than what results from smokers quitting the use of tobacco products altogether. The PHIM thus also requires an excess risk-moderating effective dose factor F, located somewhere between continued cigarette smoking (F = 1) and cessation (F = 0). Given the lack of epidemiological data for a novel product, the focus of the present contribution is on deriving an appropriate estimate based on data obtained in clinical studies. The estimation problem is to quantify the degree of effective dose reduction that is achieved by cigarette smokers switching to an MRTP, based on effects (biomarkers of exposure and clinical risk endpoints obtained in clinical studies) which are indicative of, but are not directly measuring, risk reduction.

The evidentiary gap is rooted in the type of evidence available on any particular MRTP prior to market launch. For the Tobacco Heating System THS developed by Philip Morris International, a comprehensive body of nonclinical data is available substantiating profound reductions in HPHC concentrations compared to cigarettes. Furthermore, clinical studies in which smokers either continued smoking, switched to THS or quit all tobacco use have demonstrated substantial favorable changes in biomarker levels in participants switching to THS compared to continuing smokers, approaching those observed in the abstinence group (Roethig et al., 2005, 2007; Haziza et al., 2016a; Haziza et al., 2016b; Lüdicke et al., 2017, 2017a, 2017b; Tricker et al., 2012a, 2012b, 2012c, 2012d). Most of the effects occurred only a few days after the switch and were found to be largely sustained or even pronounced after three months. The observed reductions in biomarker levels mostly exceeded 50 percent, compared to subjects continuing to smoke cigarettes, and

Abbreviations: CC, cigarette consumption; ER, excess risk; HPHC, harmful and potentially harmful constituents; LOS, lack of sufficiency; MRTP, Modified Risk Tobacco Products; NEC, necessity; PHIM, Population Health Impact Model; PMI, Philip Morris International; RCs, relative changes; THS, Tobacco Heating System

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for some biomarkers were in the 70 to 90 percent range. While such findings clearly point towards reductions in disease risks incurred by smokers switching from cigarettes to the new product, they do not translate in a simple way to levels of disease risk reduction. To know whether a biomarker level reduction by 70 percent translates into a 70 percent reduction of risk, or rather to less or more, would require to know the dose-response relationships between the marker reductions and their impact on health outcome probabilities. These relationships are, however, unknown to date. The problem is sharpened as multiple biomarkers are involved, with effect sizes differing across markers. While the predictive value of the observed biomarker changes with regard to changes in disease risks can eventually be determined once health outcomes become available for smokers having switched to the novel product for years, such epidemiological evidence is currently lacking. Attempting to estimate the impact of biomarker changes on disease risks directly would require making assumptions on the shape and on the parameters of the marker-change vs. risk-change dose-response relationships, neither of which appears to be easily justifiable. To avoid these necessities, the approach presented here reformulates the estimation problem in terms of assumptions and parameters which are not directly referring to the unknown dose-response relationship but to parameters that reflect simpler concepts that have the potential to be easier substantiated with available evidence and which lend themselves to a fruitful and transparent scientific discourse. The proposed approach for making the transition from biomarker to risk reduction requires assumptions, which are described in detail below, as well as a modeling based on Monte Carlo simulations.

2. Methods

2.1. Clinical data

Data from four clinical studies conducted in Poland (study A), Japan (studies B and C) and in the US (study D) were analyzed, all studies being of randomized, controlled, open-label, 3-arm parallel group design (Haziza et al., 2016a, 2016b; Lüdicke et al., 2017a; Lüdicke et al., 2017b). For each study, 160 smokers were enrolled and randomized in a 2:1:1 ratio to the Switch (from cigarettes to the MRTP), ongoing cigarette consumption (CC) and Cessation groups. The Switch group involved the Tobacco Heating System 2.2 (THS) in its regular (studies A and B) and menthol variants (studies C and D). THS 2.2 is composed of the THS holder (the tobacco heating device), the THS tobacco stick, and the charger unit (Smith et al., 2016).

In studies C and D, the 5-day confinement period was followed by a subsequent 85-day ambulatory period. Biomarkers of exposure to selected harmful and potentially harmful constituents and clinical risk markers were assessed at baseline and at the end of both periods (Table 1). While it is not possible to date to quantify all biological effects of all harmful and potentially harmful cigarette smoke constituents (HPHCs) in humans, due to a lack of accurate methods of determination or the absence of constituent-specific biomarkers, the US Food and Drug Administration and the World Health Organization have established a list of HPHCs recommended to be measured for tobacco products (FDA (Food and Drug Administration), 2012; WHO Study Group et al., 2008). These have served as the main reference for selecting the biomarkers assessed in the analyzed clinical studies and prespecified in the study protocols. In addition to biomarkers of exposure, a set of clinical risk markers was measured and included in the present analysis, the selection based on these markers (a) being representative of several mechanistic pathways associated with smoking-related diseases, (b) being affected by smoking, and (c) the smoking-induced effects being reversible in the short to mid-term (i.e. within one week to one year) upon cessation.

Table 1
Biomarkers of exposure and clinical risk markers assessed in four randomized clinical studies.

Biomarkers of Exposure	Harmful and Potentially Harmful Smoke Constituents	Matrix	Study			
			A	B	C	D
Tobacco Specific						
Total NNAL	NNK	Urine	x	x	x	x
Total NNN	NNN	Urine	x	x	x	x
Tobacco Related						
MHBMA	1,3-butadiene	Urine	x	x	x	x
3-HPMA	Acrolein	Urine	x	x	x	x
S-PMA	Benzene	Urine	x	x	x	x
COHb	CO	Blood	x	x	x	x
Exhaled CO	CO	–	x	x	x	x
1-OHP	Pyrene	Urine	x	x	x	x
4-ABP	4-ABP	Urine	x	x	x	x
1-NA	1-NA	Urine	x	x	x	x
2-NA	2-NA	Urine	x	x	x	x
o-tol	o-tol	Urine	x	x	x	x
CEMA	Acrylonitrile	Urine	x	x	x	x
HEMA	Ethylene oxide	Urine	x	x	x	x
3-HMPMA	Crotonaldehyde	Urine	x	x	x	x
3-OH-B[a]P	B[a]P	Urine	x	x	x	x
Clinical Risk Markers	**Domain**					
WBC	Inflammation	Blood	x	x	x	x
HDL	Lipid metabolism	Serum	–	–	x	x
LDL	Lipid metabolism	Serum	–	–	x	x
Triglycerides	Lipid metabolism	Serum	x	x	x	x
Total cholesterol	Lipid metabolism	Serum	x	x	x	x
sICAM-1	Endothelial dysfunction	Serum	–	–	x	x
8-epi-PGF2α	Oxidative stress	Urine	x	x	x	x
11-DTX-B2	Platelet activation	Urine	x	x	x	x
HbA1C	Metabolic syndrome	Serum	–	–	x	x
Fibrinogen	Cardiovascular risk factor	Plasma	–	–	x	x
hs-CRP	Cardiovascular risk factor	Serum	–	–	x	x
Systolic and diastolic blood pressure	Cardiovascular risk factor	–	x	x	x	x
FVC %pred	Lung function	–	x	x	x	x
FEV_1 %pred	Lung function	–	x	x	x	x
FEV_1/FVC	Lung function	–	x	x	x	x

Abbreviations: 11-DTX-B2: 11-dehydro-thromboxane B2; 1-NA: 1-aminonaphthalene; 1-OHP: total 1-hydroxypyrene; 2-NA: 2-aminonaphthalene; 3-;HMPMA: 3-hydroxy-1-methylpropylmercapturic acid; 3-HPMA: 3-hydroxypropylmercapturic acid; 3-OH-B[a]P: 3-hydroxybenzo(a)pyrene; 4-ABP: 4-aminobiphenyl; 8-epi-PGF2α: 8-epi-prostaglandine F2α; B[a]P: benzo(a)pyrene; BoExp: biomarker of exposure; CEMA: 2-cyanoethylmercapturic acid; CO: carbon monoxide; COHb: carboxyhemoglobin; CRM: clinical risk marker; FEV_1 %pred: percentage of predicted forced expiratory volume in 1 s; FVC: percentage of predicted forced vital capacity; HbA1C: hemoglobin A1C; HDL: high density lipoprotein cholesterol; HEMA: 2-hydroxyethyl mercapturic acid; HPHC: harmful and potentially harmful constituent; hs-CRP: high-sensitive C-reactive protein; LDL: low density lipoprotein cholesterol; MHBMA: monohydroxybutenyl mercapturic acid; NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN: N-nitrosonornicotine; o-tol: o-toluidine; sICAM-1: soluble inter-cellular adhesion molecule; S-PMA: S-phenylmercapturic acid; total NNAL: total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; WBC: white blood cells count.

2.2. Statistical methods

In the Population Health Impact Model (Weitkunat et al., 2015) the F-factor was introduced as an unknown parameter ranging from 0 to 1, describing a change in effective dose from 1 to F units due to switching from cigarette consumption (CC) to using THS:

$$ER_{Switch}(a, t) = ER_{CC}(a)(F + (1 - F)e^{-t \cdot ln(2)/H}) \quad (1)$$

In Eq. (1), a is the age, t is the time since switching to THS, ER_{CC} is the excess risk due to sustained cigarette consumption, and H is the disease-specific time required after smoking cessation for the excess risk