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

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 pre-specified 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
FEV1 %pred	Lung function	–	x	x	x	x
FEV1/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; FEV1 %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:

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

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

to be halved. Upon smoking cessation, F is zero and the equation simplifies to $ER_{Cessation}(a, t) = ER_{CC}(a)e^{-t \cdot ln(2)/H}$.

Based on this, F can be expressed as the proportion of the excess risk reduction achieved by smoking cessation that is retained by switching to THS:

$$F = \frac{ER_{Switch}(a, t) - ER_{Cessation}(a, t)}{ER_{CC}(a) - ER_{Cessation}(a, t)} \tag{2}$$

Currently, no epidemiological health outcomes data is available regarding ER_{Switch} for THS and thus F cannot be directly estimated.

In contrast, clinical biomarker data (including biomarkers of exposure and clinical risk markers) can be analyzed at baseline and after a period of some days or weeks. For a given set of biomarkers i = 1, …, p, the baseline-corrected values for each subject, j, can be calculated by $\Delta_{ij} = X_{ijf} - X_{ij0}$, where X_{ijf} is the log-transformed follow-up value and X_{ij0} is the log-transformed baseline value (the log transformation aims at ensuring a normal distribution for the Δ_{ij}). With $\mu_i(G)$ denoting the mean values of Δ_{ij} for a given tobacco use behavior group G, the relative change RC_i for a biomarker i represents the "relative position" of Switch between Cessation and CC (similarly to F in the excess risk equation, Eq. (1)) for biomarker i:

$$RC_i = \frac{\mu_i(Switch) - \mu_i(Cessation)}{\mu_i(CC) - \mu_i(Cessation)} \tag{3}$$

If a clinical study only includes the groups Switch and Cessation and if the study time frame is relatively short, it might be reasonable to assume that $\mu_i(CC) = 0$. In such a case, Eq. (3) simplifies to Eq. (4), making the CC group unnecessary for estimating F:

$$RC_i = 1 - \frac{\mu_i(Switch)}{\mu_i(Cessation)} \tag{4}$$

Deriving F from biomarkers involves the following three critical steps: Step 1: Computing relative changes (and their uncertainty) for a set of biomarkers; Step 2: Linking these relative changes to the final F-factor value, based on a set of reasonable assumptions, and incorporating some level of uncertainty regarding the link between relative changes and F through Monte Carlo simulations; Step 3: Performing sensitivity analysis on the assumptions.

Step 1: Computing relative changes and their uncertainty

To compute the relative change of a given biomarker and its uncertainty, two assumptions are made for each biomarker:

1. Baseline-corrected values, Δ_{ij}, are normally distributed within group G with mean $\mu_i(G)$ and standard deviation $\sigma_i(G)$; the original data values were log-transformed before calculating baseline-corrected values to meet the assumption of normality more closely.
2. (a) The group means $\mu_i(G)$ are ordered: $\mu_i(CC) \geq \mu_i(Switch) \geq \mu_i(Cessation)$ and $\mu_i(CC) > \mu_i(Cessation)$ or, alternatively, (b) $\mu_i(CC) \leq \mu_i(Switch) \leq \mu_i(Cessation)$ and $\mu_i(CC) < \mu_i(Cessation)$, implying that a biomarker is relevant only if it differentiates the CC group from the Cessation group. Without loss of generality, it is assumed that all biomarkers fulfill assumption 2(a); otherwise, if a biomarker fulfills assumption 2(b), it can be simply used with its sign inverted. Using Eq. (4), assumption 2 simplifies to: $0 \geq \mu_i(Switch) \geq \mu_i(Cessation)$ and $0 > \mu_i(Cessation)$ or, alternatively, $0 \leq \mu_i(Switch) \leq \mu_i(Cessation)$ and $0 < \mu_i(Cessation)$.

The probability distribution of $\mu_i(G)$ is considered following a Student distribution described as

$$\mathbb{P}\left(\frac{\mu_i(G) - \overline{\Delta_i(G)}}{S_{\Delta_i(G)}/\sqrt{n}}\right) \sim t_{n-1} \tag{5}$$

where $\overline{\Delta_i(G)}$, $S_{\Delta_i(G)}$, and n denote the mean, standard deviation, and size of group G, respectively, and t_{n-1} refers to the t-distribution with n-1 degrees of freedom (cf. section 1 of the Supplementary Material for a
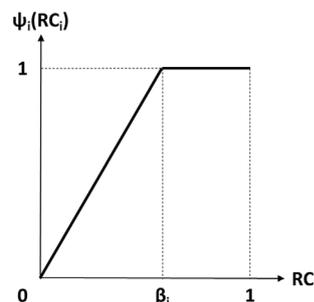
Fig. 1. Shape of the sigmoid type ψ response function. RC_i, β_i, and $\Psi_i(RC_i)$ denote the relative change, the threshold, and the relative contribution to the F-factor of biomarker i, respectively. The plateau at 1 for any $RC_i > \beta_i$ implies that a relative change maximally contributes to the F-value if it exceeds the β_i threshold.

formal justification).

Given the theoretical distribution of $\mu_i(G)$, relative changes can be obtained by using Eq. (3) or Eq. (4) with values sampled from it. By repeating this multiple times, a posterior distribution of relative changes for biomarker i is derived, quantifying not only its average value but also its entire probability distribution.

To only select biomarkers responding to smoking cessation (assumption 2a), only those with a positive 5%-quantile of the empirical $\mu_i(CC) - \mu_i(Cessation)$ posterior distribution are included in the analysis. If the Switch group shows a more favorable effect than the Cessation group for a given biomarker, i.e., $\mu_i(CC) > \mu_i(Cessation) > \mu_i(Switch)$, the biomarker is not excluded from the analysis but rather the support of the distribution for the Switch group is restricted by imposing the assumption $\mu_i(CC) \geq \mu_i(Switch) \geq \mu_i(Cessation)$ during the Monte Carlo procedure. In case of equivalence of the Switch and Cessation distributions this results in a distribution with a mode close to zero.

Step 2: Identification of link functions between relative changes and the F-factor

The key assumption made is the existence, in principle, of a set of biomarkers being fully predictive of the disease risk and an unknown increasing function that links the relative changes of those biomarkers to the F-factor (typically thought of as a multidimensional sigmoid-type relationship). As the measured biomarkers and clinical risk endpoints may not be fully predictive of disease risk, this lack of predictive ability ("lack of sufficiency", LOS) must be accounted for. To make this problem tractable, it is assumed that the link function can be written as a weighted sum of increasing functions of single RC_i's (one for each measured biomarker) plus a function that represents this 'missing information'. Consequently, F can be written in the form:

$$F = \underbrace{\sum_{i=1}^{p} \alpha_i \psi_i}_{'Measured\ biomarkers'} + \underbrace{\alpha_0 \psi_0}_{'Missing\ information'} = \sum_{i=0}^{p} \alpha_i \psi_i \tag{6}$$

where the α_i's are positive numbers that sum up to 1, the ψ_i's range from 0 to 1, ensuring that F ranges from 0 to 1, and each ψ_i (i > 0) being an increasing function of RC_i. To study this functional relationship between the F-value and the relative changes, a Monte Carlo approach is used, consisting of sampling the α_i weights and the ψ_i's.

Sampling the α_i weights: The parameter α_0 represents the lack of sufficiency and is the weight of missing information due to unmeasured (or unknown) biomarkers that, combined with the measured biomarkers, would be fully predictive of disease risk. The parameters α_i, i = 1, …, p, represent the weight of each (measured) biomarker for predicting disease risk. The α_i's (i = 1, …, p) can all be equal or they can be informed by expert judgments based on their relative importance (with the constraint that they sum up to 1). Given the difficulty of defining values for α_i (including LOS), scenarios are drawn to incorporate uncertainty around these parameters by sampling a

Table 2
Biomarker changes (mean ± standard deviation) 5 or 90 days after baseline. The results are based on log-transformed data and are pooled across studies.

Biomarker	Assessment Day	Cigarettes		Smoking Abstinence		THS	
		N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Biomarkers of Exposure							
MHBMA	Day 5	156	−0.09 ± 0.43	138	−2.11 ± 1.13	306	−2.1 ± 0.99
(pg/mg creat)	Day 90	73	0.07 ± 0.5	46	−1.38 ± 1.04	117	−1.61 ± 0.99
3-HPMA	Day 5	157	−0.06 ± 0.33	138	−1.29 ± 0.51	308	−0.8 ± 0.4
(ng/mg creat)	Day 90	73	−0.02 ± 0.47	46	−0.92 ± 0.69	117	−0.68 ± 0.47
S-PMA	Day 5	156	−0.03 ± 0.48	138	−2.36 ± 0.7	306	−2.28 ± 0.75
(pg/mg creat)	Day 90	73	−0.04 ± 0.54	46	−1.9 ± 1.1	117	−1.86 ± 0.99
COHb	Day 5	157	−0.01 ± 0.19	139	−1.04 ± 0.48	309	−1.01 ± 0.45
(%)	Day 90	73	0.01 ± 0.27	46	−0.54 ± 0.43	117	−0.69 ± 0.4
Exhaled CO	Day 5	158	−0.03 ± 0.43	140	−1.9 ± 0.75	310	−1.85 ± 0.68
(ppm)	Day 90	73	−0.14 ± 0.79	46	−1.62 ± 0.98	117	−1.63 ± 0.82
Total NNAL	Day 5	157	−0.02 ± 0.35	138	−1.01 ± 0.38	308	−0.83 ± 0.32
(pg/mg creat)	Day 90	73	0.12 ± 0.45	46	−1.55 ± 1.34	117	−1.31 ± 0.76
Total NNN	Day 5	157	0.1 ± 0.51	138	−3.41 ± 1	307	−1.37 ± 0.87
(pg/mg creat)	Day 90	73	−0.04 ± 0.64	46	−2.76 ± 1.31	117	−1.54 ± 0.94
Total 1-OHP	Day 5	156	−0.19 ± 0.24	138	−1.03 ± 0.39	306	−1 ± 0.39
(pg/mg creat)	Day 90	73	0.09 ± 0.34	46	−0.45 ± 0.47	117	−0.48 ± 0.56
1-NA	Day 5	157	0.03 ± 0.35	138	−3.15 ± 0.63	308	−3.05 ± 0.66
(pg/mg creat)	Day 90	73	0 ± 0.44	46	−2.43 ± 1.13	117	−2.52 ± 1.02
2-NA	Day 5	157	−0.03 ± 0.34	138	−2 ± 0.63	308	−1.99 ± 0.69
(pg/mg creat)	Day 90	73	0 ± 0.38	46	−1.58 ± 0.79	117	−1.88 ± 0.74
4-ABP	Day 5	157	−0.02 ± 0.37	138	−1.73 ± 0.69	308	−1.73 ± 0.7
(pg/mg creat)	Day 90	73	0.1 ± 0.47	46	−1.17 ± 0.96	117	−1.39 ± 0.82
o-tol	Day 5	155	−0.12 ± 0.46	138	−0.94 ± 0.64	308	−0.88 ± 0.68
(pg/mg creat)	Day 90	72	−0.06 ± 0.56	46	−0.52 ± 0.83	117	−0.67 ± 0.96
CEMA	Day 5	157	−0.09 ± 0.31	138	−1.94 ± 0.43	308	−1.84 ± 0.41
(ng/mg creat)	Day 90	73	0.04 ± 0.42	46	−2.09 ± 1.13	117	−2.16 ± 0.88
HEMA	Day 5	157	−0.17 ± 0.41	138	−1.09 ± 0.53	308	−1.04 ± 0.56
(pg/mg creat)	Day 90	73	0.12 ± 0.44	46	−0.63 ± 0.76	117	−0.77 ± 0.67
3-OH-B[a]P	Day 5	157	−0.11 ± 0.35	138	−1.53 ± 0.68	308	−1.41 ± 0.71
(fg/mg creat)	Day 90	73	0.04 ± 0.54	46	−0.87 ± 0.74	117	−1.04 ± 0.81
HMPMA	Day 5	157	−0.16 ± 0.35	138	−1.4 ± 0.67	307	−1.24 ± 0.64
(ng/mg creat)	Day 90	73	−0.11 ± 0.48	46	−0.68 ± 0.77	117	−0.83 ± 0.73
Clinical Risk Markers							
WBC (GI/L)	Day 90	73	−0.04 ± 0.21	46	−0.1 ± 0.29	117	−0.09 ± 0.21
Total cholesterol (mg/dL)	Day 90	73	−0.02 ± 0.12	46	0.02 ± 0.1	117	−0.03 ± 0.12
HDL (mg/dL)	Day 90	73	−0.01 ± 0.14	46	0.07 ± 0.14	117	0.06 ± 0.14
LDL (mg/dL)	Day 90	73	−0.06 ± 0.16	46	−0.01 ± 0.17	117	−0.07 ± 0.18
Triglycerides (mg/dL)	Day 90	73	0.04 ± 0.24	46	0.08 ± 0.27	117	−0.01 ± 0.26
sICAM-1 (ng/mL)	Day 90	73	−0.01 ± 0.16	46	−0.15 ± 0.23	117	−0.13 ± 0.19
8-epi-PGF2α (pg/mg creat)	Day 90	73	0.11 ± 0.26	46	0.04 ± 0.42	117	−0.01 ± 0.26
11-DTX-B2 (pg/mg creat)	Day 90	73	−0.14 ± 0.4	46	−0.3 ± 0.33	117	−0.23 ± 0.49
HbA1C (%)	Day 90	73	0 ± 0.04	46	−0.01 ± 0.04	117	0 ± 0.04
Fibrinogen (mg/dL)	Day 90	73	0 ± 0.22	46	−0.03 ± 0.18	117	−0.04 ± 0.19
hs-CRP (mg/L)	Day 90	73	0.3 ± 1.12	46	0.05 ± 1.13	117	0.14 ± 1.05
Systolic BP (mmHg)	Day 90	73	−0.04 ± 0.1	46	−0.02 ± 0.08	117	−0.04 ± 0.08
Diastolic BP (mmHg)	Day 90	73	−0.05 ± 0.12	46	−0.03 ± 0.1	117	−0.05 ± 0.12
FEV$_1$ (%pred)	Day 90	41	−0.01 ± 0.07	37	0.01 ± 0.06	70	0.02 ± 0.05
FVC (%pred)	Day 90	41	0 ± 0.06	37	0.01 ± 0.06	70	0.01 ± 0.05
FEV$_1$/FVC (Derived)	Day 90	72	−0.01 ± 0.04	46	0 ± 0.06	117	0 ± 0.03

Abbreviations: 11-DTX-B2: 11-dehydro-thromboxane B2; 1-NA: 1-aminonaphthalene; 1-OHP: 1-hydroxypyrene; 2-NA: 2-aminonaphthalene; 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; BP: blood pressure; CEMA: 2-cyanoethylmercapturic acid; CO: carbon monoxide; COHb: carboxyhemoglobin; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; HbA1C: hemoglobin A1c; HDL: high density lipoprotein cholesterol; HEMA: 2-hydroxyethyl mercapturic acid; HMPMA: 3-hydroxy-1-methylpropylmercapturic acid; hs-CRP: high sensitive C-reactive protein; LDL: low density lipoprotein cholesterol; MHBMA: monohydroxybutenyl mercapturic acid; N: number of subjects analyzed; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNN: N-nitrosonornicotine; o-tol: o-toluidine; SD: standard deviation; sICAM-1: soluble inter-cellular adhesion molecule; S-PMA: S-phenylmercapturic acid; WBC: white blood cells.
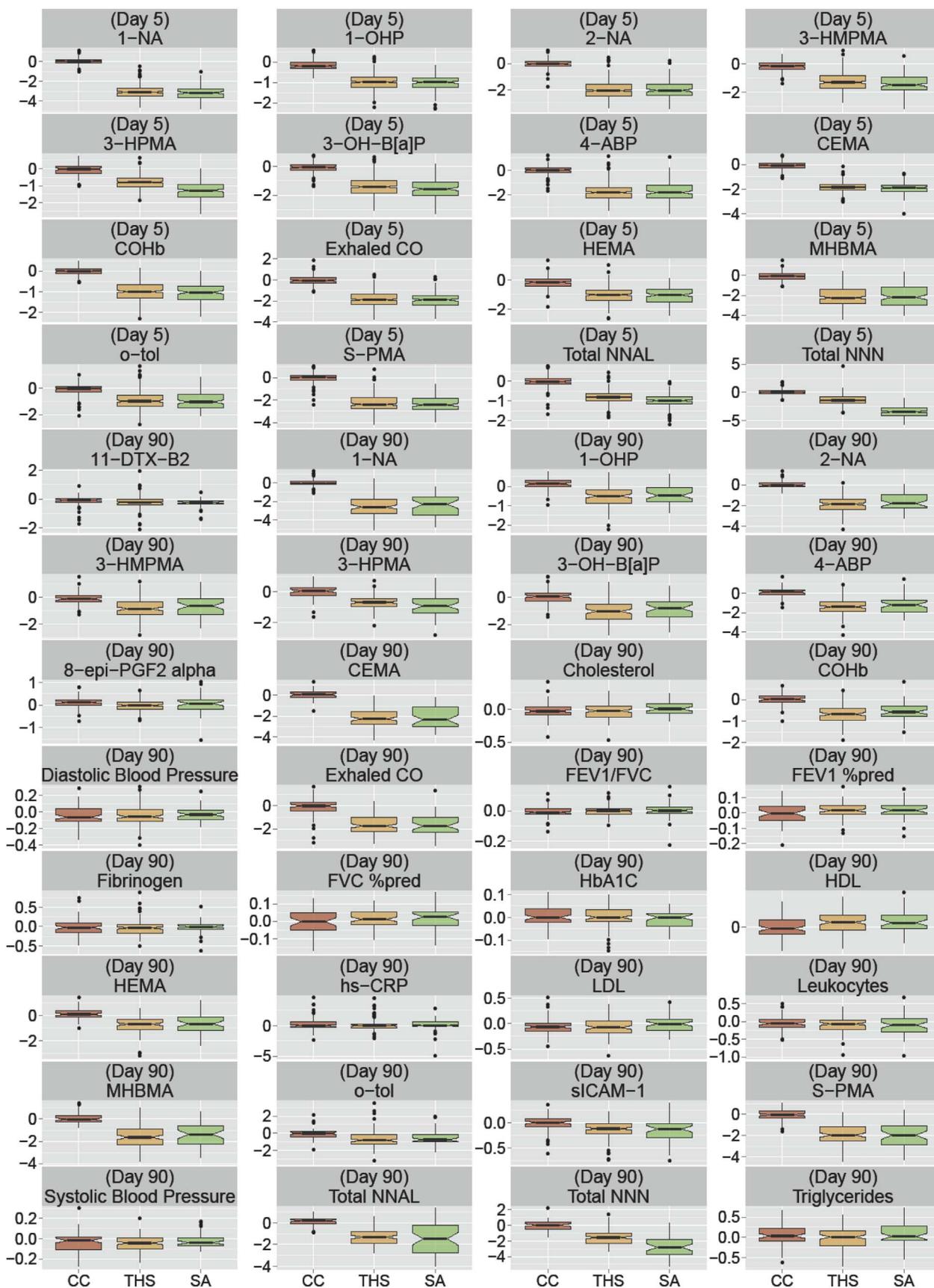
Fig. 2. Boxplots of biomarker changes 5 or 90 days after baseline (log-transformation was applied to biomarker measurements before computing the change between day 5/90 and baseline) for each group (left: continued cigarette consumption, CC; middle: switching to THS; right: smoking abstinence, SA). The boxes represent quartiles of the distribution and the line its median.

Table 3

Relative change posterior distributions (original units of biomarkers retained, although relative changes are unitless; abbreviations specified in footnote of Table 2).

Biomarker	Assessment Day	Mean ± SD	Quantiles			
			Q1	Median	Q3	[5%,95%]
Biomarkers of Exposure						
MHBMA	Day 5	0.04 ± 0.03	0.02	0.04	0.06	[0,0.1]
(pg/mg creat)	Day 90	0.05 ± 0.04	0.02	0.04	0.08	[0,0.14]
3-HPMA	Day 5	0.38 ± 0.03	0.36	0.38	0.39	[0.33,0.42]
(ng/mg creat)	Day 90	0.26 ± 0.09	0.21	0.27	0.33	[0.1,0.41]
S-PMA	Day 5	0.04 ± 0.02	0.02	0.04	0.06	[0.01,0.09]
(pg/mg creat)	Day 90	0.08 ± 0.06	0.04	0.07	0.11	[0.01,0.19]
COHb	Day 5	0.05 ± 0.03	0.02	0.05	0.07	[0.01,0.11]
(%)	Day 90	0.04 ± 0.04	0.01	0.03	0.06	[0,0.12]
Exhaled CO	Day 5	0.04 ± 0.03	0.02	0.04	0.06	[0.01,0.1]
(ppm)	Day 90	0.07 ± 0.05	0.03	0.07	0.11	[0.01,0.18]
Total NNAL	Day 5	0.18 ± 0.03	0.16	0.18	0.2	[0.12,0.23]
(pg/mg creat)	Day 90	0.18 ± 0.09	0.11	0.18	0.24	[0.03,0.33]
Total NNN	Day 5	0.6 ± 0.02	0.59	0.6	0.61	[0.57,0.63]
(pg/mg creat)	Day 90	0.44 ± 0.05	0.41	0.44	0.48	[0.35,0.52]
1-OHP	Day 5	0.04 ± 0.03	0.02	0.04	0.06	[0,0.09]
(pg/mg creat)	Day 90	0.12 ± 0.08	0.05	0.1	0.17	[0.01,0.28]
1-NA	Day 5	0.03 ± 0.02	0.02	0.03	0.05	[0.01,0.07]
(pg/mg creat)	Day 90	0.05 ± 0.04	0.02	0.04	0.07	[0,0.12]
2-NA	Day 5	0.03 ± 0.02	0.01	0.02	0.04	[0,0.07]
(pg/mg creat)	Day 90	0.03 ± 0.03	0.01	0.02	0.04	[0,0.08]
4-ABP	Day 5	0.03 ± 0.02	0.02	0.03	0.05	[0,0.08]
(pg/mg creat)	Day 90	0.05 ± 0.04	0.02	0.04	0.08	[0,0.14]
o-tol	Day 5	0.09 ± 0.05	0.04	0.08	0.12	[0.01,0.18]
(pg/mg creat)	Day 90	0.12 ± 0.09	0.05	0.1	0.17	[0.01,0.28]
CEMA	Day 5	0.05 ± 0.02	0.04	0.05	0.06	[0.01,0.09]
(ng/mg creat)	Day 90	0.06 ± 0.04	0.02	0.05	0.08	[0,0.14]
HEMA	Day 5	0.06 ± 0.04	0.03	0.06	0.08	[0.01,0.13]
(pg/mg creat)	Day 90	0.08 ± 0.06	0.03	0.07	0.12	[0.01,0.21]
3-OH-B[a]P	Day 5	0.08 ± 0.04	0.05	0.08	0.11	[0.02,0.15]
(fg/mg creat)	Day 90	0.06 ± 0.05	0.02	0.05	0.09	[0,0.16]
HMPMA	Day 5	0.12 ± 0.04	0.09	0.12	0.15	[0.04,0.19]
(ng/mg creat)	Day 90	0.08 ± 0.06	0.03	0.07	0.12	[0.01,0.2]
Clinical Risk Markers						
WBC (GI/L)	Day 90	0.29 ± 0.17	0.16	0.28	0.41	[0.04,0.58]
HDL (mg/dL)	Day 90	0.29 ± 0.17	0.16	0.29	0.41	[0.04,0.58]
Triglycerides (mg/dL)	Day 90	0.79 ± 0.19	0.71	0.85	0.93	[0.4,0.98]
sICAM-1 (ng/mL)	Day 90	0.22 ± 0.13	0.12	0.21	0.31	[0.03,0.45]
11-DTX-B2 (pg/mg creat)	Day 90	0.28 ± 0.15	0.18	0.28	0.39	[0.05,0.54]
HbA1C (%)	Day 90	0.77 ± 0.2	0.68	0.83	0.92	[0.35,0.98]
Systolic BP (mmHg)	Day 90	0.15 ± 0.11	0.05	0.12	0.21	[0.01,0.35]
Diastolic BP (mmHg)	Day 90	0.19 ± 0.15	0.07	0.16	0.27	[0.02,0.46]

'uniform' Dirichlet distribution with parameters (LOS, $\alpha_1, ..., \alpha_p$), where $\sum_{i=1}^{p} \alpha_i = 1 - LOS$. This ensures that the average set of weights over all scenarios is close to (LOS, $\alpha_1, ..., \alpha_p$), the Dirichlet distribution being the most uniform distribution for parameters constrained to sum up to 1.

Sampling the ψ_i's: The ψ_i's translate the relative change of biomarker i to their impact on the unknown effective dose change $F \in [0,1]$. ψ_0 is being dealt with by sampling the uniform distribution for every set of α_i's. Assuming that LOS ($= \alpha_0$) is equal to 1, i.e., the measured biomarkers conveying no information on disease risk, the sampled scenarios are thus leading, on average, to a set of weights $\{\alpha_0 = 1, \alpha_1 = 0, ..., \alpha_p = 0\}$ and to a distribution of ψ_0 close to uniform over [0,1], and thus to a distribution of F also close to uniform over [0,1], implying that no information was obtained by measuring non-informative biomarkers. This is consistent with the assumption that F-values between 0 and 1 are equally likely (uniform distribution) when no prior information is considered or available.

For ψ_i (i = 1, ..., p) a single parameter piecewise linear approximation of a sigmoid is used:

$$\psi_i(RC_i) = \begin{cases} \frac{RC_i}{\beta_i} & \text{if } RC_i < \beta_i \\ 1 & \text{otherwise} \end{cases} \quad (7)$$

where $\beta_i \in (0,1)$. The sigmoid type response function has a plateau at 1

for any $RC_i > \beta_i$, implying that a relative change contributes to the F-factor if it is below the β_i threshold. Rather than defining individual β_i's, the necessity parameter $NEC \in (0,1]$ is introduced. It specifies the lower bound for the sampled β_i's, defining the minimal biomarker change required for a disease risk reduction. If a relative change for any biomarker is less than NEC the F-factor is reduced to below 1. To incorporate the uncertainty about the β_i's they are uniformly sampled over the interval (NEC, 1].

As shown in Fig. 1, if $\beta_i = 1$ the ψ_i function is linear with slope 1, any relative change then contributing to a reduction of the F-factor, which would be a non-conservative approach. The contribution to F is maximal when the effect of Switch is similar to continued cigarette consumption (CC) for a given biomarker i, as then both the corresponding relative change and, due to Eq. (7), $\psi_i(RC_i)$ are 1. If, on the other hand, the effect of Switch is similar to Cessation the corresponding relative change, and consequently $\psi_i(RC_i)$, are both close to 0, thus decreasing the F-factor.

Each sampling of a set of α_i's and a set of β_i's leads to the creation of one link function between the relative changes and F. By sampling the posterior distributions of the relative changes many times, a distribution of F is obtained, accounting for all sources of uncertainties.

The described approach is summarized by the following algorithm:
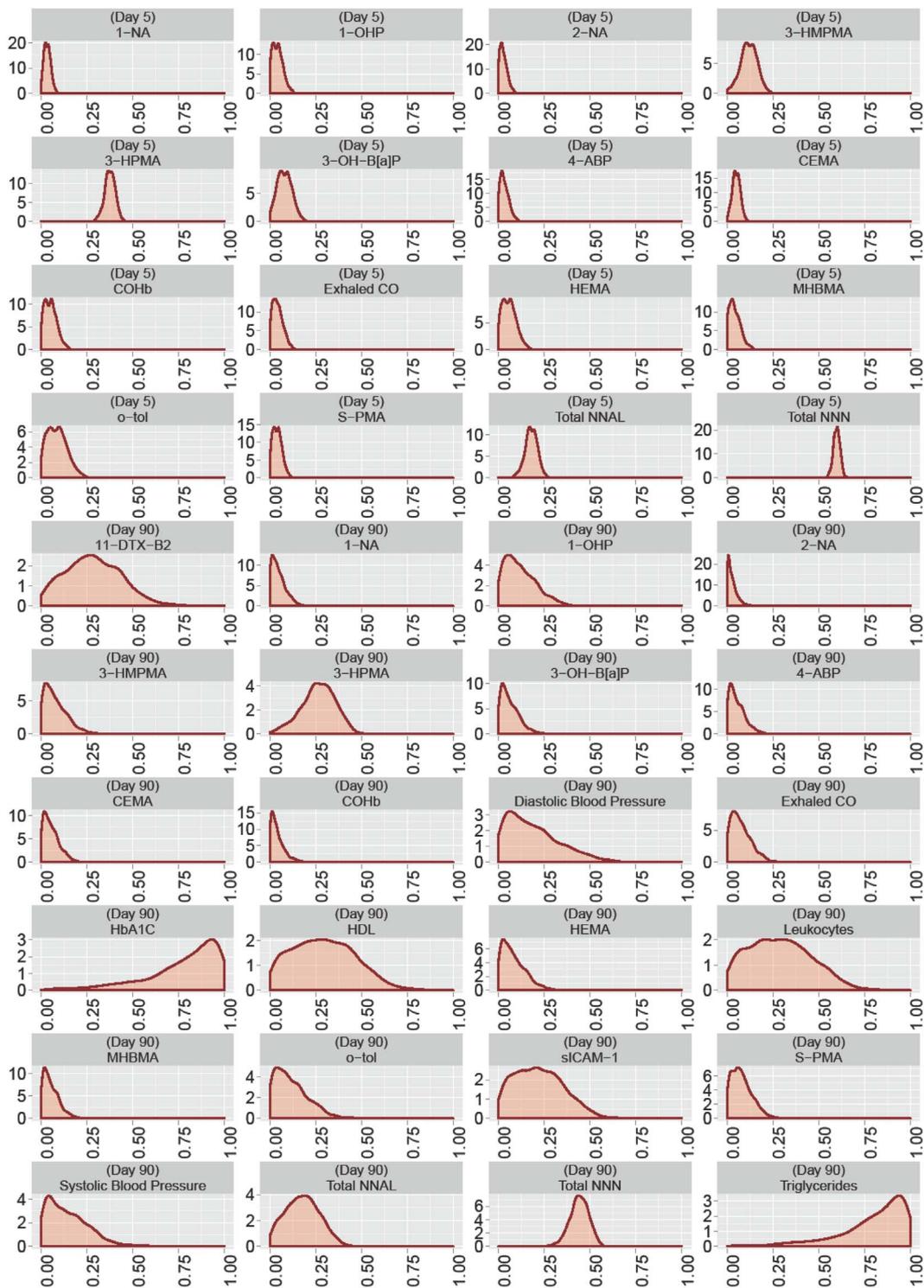
Fig. 3. Posterior probability distributions of the biomarker-specific relative changes.

- Using the means, standard deviations, and samples sizes of the various groups G (CC, Switch, and Cessation) and Eq. (5) and Eq. (3) (or Eq. (4)), samples of relative changes are obtained for each biomarker i.
- If the distribution of the relative changes for a given biomarker does not exhibit a positive 5%-quantile for the posterior $\mu_i(CC) - \mu_i(Cessation)$ distribution, the biomarker is excluded from further analysis.
- LOS and NEC values are adopted, based on available knowledge and expert judgement.

- The following is repeated many times:
  o Sample a set of α_i's from a Dirichlet distribution with parameters $(LOS, \alpha_1, ..., \alpha_p)$
  o For each $(p + 1)$-tuple obtained in the previous step, sample a set of β_i's from a uniform distribution over (NEC, 1]
  o Combine the sampled relative changes with every sample of β_i's using Eq. (7) and with the sampled set of α_i's using Eq. (6)
- Generate the F-values obtained under all plausible link functions and relative changes sampled in the first step.
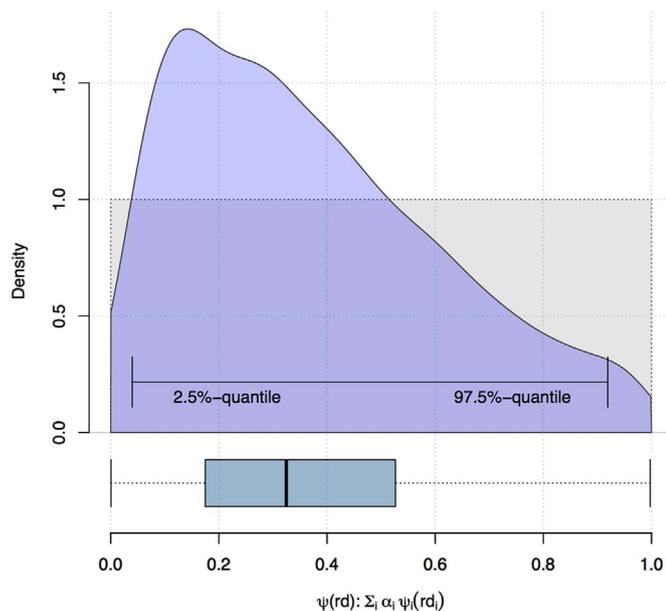
Fig. 4. Posterior F-value distribution from the sampled link functions with parameters LOS and NEC equal to 0.5 on top of the uniform distribution (grey). The interval bounds are the 2.5% and 97.5% quantiles, an alternative representation of the distribution is given by the boxplot under the distribution plot (the box represent the quartiles of the distribution and the line its median).

For the present analysis, with LOS = 0.5 and NEC = 0.5, 1000 samples were drawn to estimate the posterior RC_i distributions, for each of which 10,000 scenarios were generated by sampling the α_i's and β_i's.

Step 3: Sensitivity analysis

To assess the impact of the assumptions required for transforming biomarker data to the F-factor, sensitivity analyses were conducted by (i) varying the lack of sufficiency and necessity; (ii) omitting one biomarker at a time.

3. Results

The data collected in the four clinical studies were pooled for the present analyses. To account for the different pathogenetically relevant levels of evidence between biomarkers of exposure on the one hand, and clinical risk markers (e.g., COHb and HDL) on the other, the sum of the hyper-parameters α_i for the latter was weighted 1.5-fold relative to the sum of the hyper-parameters of the former. The sum of all hyper-parameters was constrained to 1-LOS.

Table 2 provides descriptive statistics of the changes in the log-transformed values of the analyzed biomarkers between day 5 (day 90) and baseline. The observed patterns of change from baseline were generally similar across biomarkers, those in the CC group being close to 0 and clear reductions visible for the Switch and Cessation groups (Fig. 2). For some biomarkers (e.g., 1-NA at day 5, 1-OHP at day 5, S-PMA at day 90), the changes seen in the Switch group were similar to those in the Cessation group. For other biomarkers (e.g., 3-HPMA at day 5, Total NNN at day 5, Total NNN at day 90), the changes observed in the Switch group were between those in the CC and Cessation groups. As can be seen there are biomarkers for which the Switch effect appears to be more favorable than the Cessation effect. Based on the above assumptions, these effects were 'truncated' not to exceed the Cessation effects.

Assumption 2 of an effect of Cessation was not met at day 90 for total cholesterol, high sensitive C-reactive protein, fibrinogen, LDL cholesterol, percent of predicted FEV_1 value, percent of predicted FVC value, prostaglandin F2α and the derived FEV_1/FVC ratio.

The posterior distributions of the relative changes of all biomarkers included in the analysis are summarized in Table 3 and shown in Fig. 3.

While the mode of the posterior probability (i.e., the point at which the distribution curve is maximal) of the relative changes was close to 0 for some biomarkers, it was above 0.5 for others and for some even close to 1 (e.g., triglycerides). As expected, modes close to 0 were found for biomarkers for which the reductions found in the Switch group were similar to those in the Cessation group (e.g., 1-NA at day 5, 1-OHP at day 5, S-PMA at day 90). Modes close to 0.5 were found for biomarkers for which the changes in the Switch group were between those in the CC and Cessation groups (e.g., 3-HPMA at day 5, Total NNN at day 5, Total NNN at day 90). The uncertainty of the posterior distribution of the relative changes was found to vary considerably across biomarkers. Clinical risk markers tended towards larger modes compared to biomarker of exposure, as well as towards higher uncertainty. This is related to the difference between the CC and Cessation groups being smaller for clinical risk markers than for biomarkers of exposure, and clinical risk markers tending to require more time for cessation effects to manifest.

Fig. 4 depicts the distribution of 10,000,000 F-factor values obtained through 10,000 scenarios sampling the α_i's and β_i's for each of the 1000 relative changes calculated per biomarker. The median is located at about 0.33 and 50% of the values are between 0.17 and 0.53. The mode of the F-factor distribution is at about 0.15, deviating from the median due to the positive skew of the distribution. The uncertainty around the F-factor is relatively large and values as small as 0.1 or as large as 0.9 still have some probability mass, and thus cannot be fully excluded. Nevertheless, the probability mass of the F-factor distribution is clearly shifted to the left compared to the uniform prior distribution before any biomarker data had been analyzed. While Eq. (4) was used to obtain the above results, using Eq. (3) resulted in a very similar F-factor distribution (cf. Supplementary Material).

Sensitivity analysis results regarding lack of sufficiency and necessity are shown in Fig. 5. While small modifications of the parameters resulted only in limited changes of the F-factor distribution, including extreme parameter values in the population health impact modeling can inform about the effects of the choice of these parameters on the model predictions.

To assess the impact of individual biomarkers on the F-factor distribution, analyses were conducted with each individual biomarker left out from one run (Fig. 6). As can be seen, removing one biomarker at a time did not substantially modify the posterior distribution of plausible F-factor values.

Additionally, the F-factor distribution was estimated by analyzing each study individually. For the short-term effects studies (5 days in confinement) a LOS of 2/3 was chosen, as the assessment period is shorter and only biomarkers of exposure were measured. This resulted in F-factor distributions consistent with that of the main analysis, confirming the robustness of the approach with respect to inter-study variability. Consistency with the F-factor distribution described above was also found after analyzing separately the two studies with a 85-day ambulatory period (LOS = 0.5). The corresponding results are contained in the Supplementary Material.

4. Discussion

Smoking-related disease risks are well understood, due to cigarette smoking being prevalent for many decades and epidemiological data being available. This is different for novel nicotine and tobacco products, including products with the potential to reduce health risks compared to smoking cigarettes. The reason is that novel products either have not yet been marketed or have not been used by a sufficient number of users for a long enough period of time; typically ten or more years for chronic disease risk to become measureable in epidemiological studies (although the effects of quitting can be demonstrated in a much shorter period for heart disease and stroke). Unfortunately, other than with for example exposure to specific infectious agents, the mechanistic understanding of the pathogenesis of chronic smoking-related
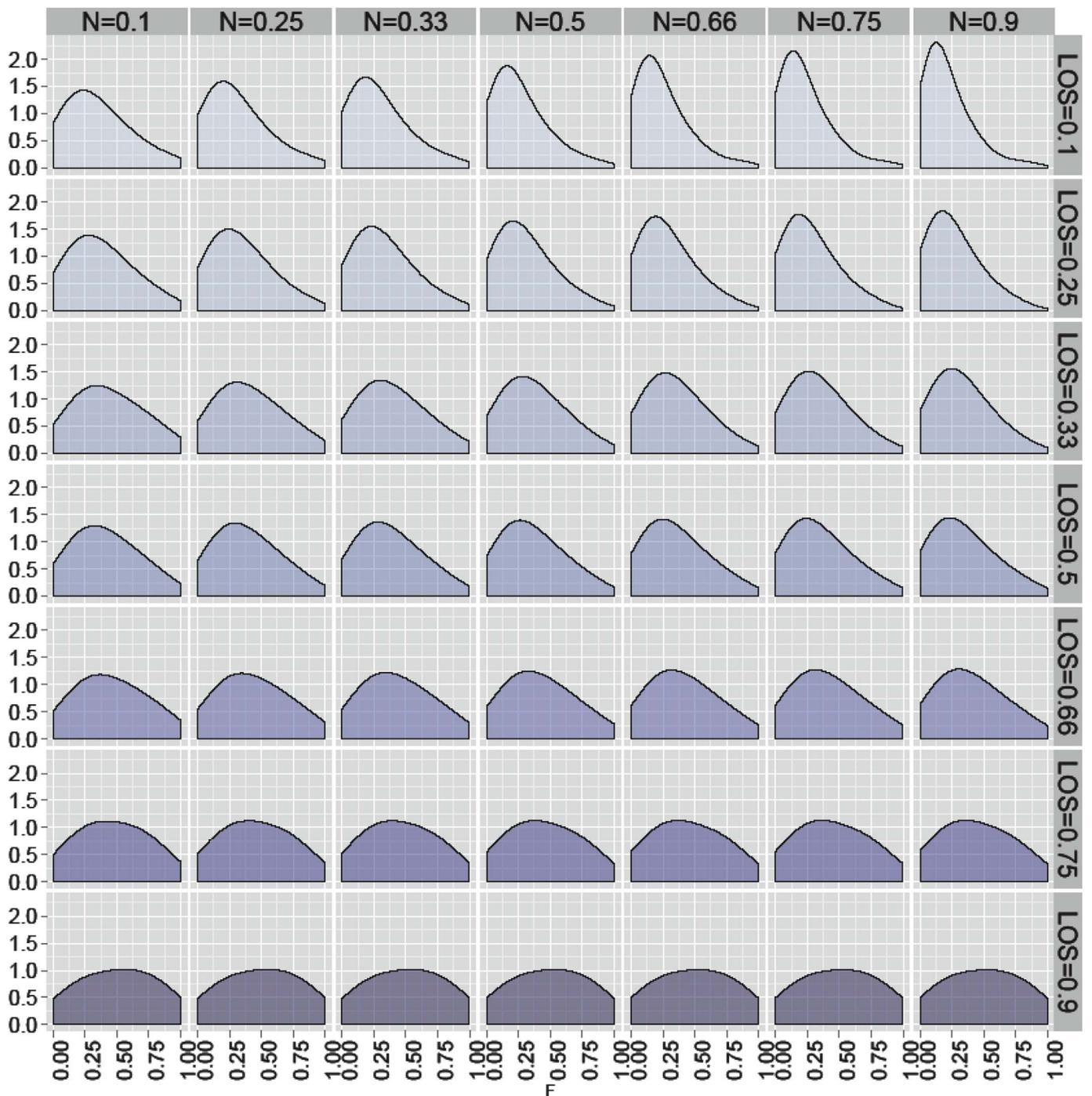
Fig. 5. Sensitivity analysis for combinations of necessity (N) and lack of sufficiency (LOS), showing the posterior distribution densities (ordinate) and F-factor values (abscissa).

diseases does not so far allow firm conclusions on health risks from exposure characteristics. In spite of this uncertainty, not making potentially reduced risk products available to smokers that would otherwise continue smoking would imply restricting these smokers to continue using cigarettes and so imposing health risks and doing harm. Thus, attempting to estimate risks and potentials of risk reduction is mandatory in order to provide the best possible evidence for health policies.

The required risk assessment has to reach beyond individual risks and needs to comprise the risks of the population as a whole. This is due to the fact that even with a truly reduced risk product and thus risk reduction in individual smokers who switch to this product, adverse population health impacts cannot be excluded. The reason is that

subgroups outside the target group, including former and never smokers or smokers who would otherwise have quit, might be attracted to using the product and some eventually transitioning to (or continuing to use) cigarettes, thus potentially offsetting, at the level of the population as a whole, the beneficial effects obtained in the target group. The population health impact model that has been developed to address these questions (Weitkunat et al., 2015) does, however, require estimation of the reduction of the effective dose (F-factor) that is achieved by switching from cigarette smoking to an MRTP. Short of measured health outcomes, exposure effects and clinically relevant biological changes can be quantified in clinical studies by means of biomarkers of exposure and clinical risk markers. The challenge of estimating the effective dose based on such data has been addressed in the present
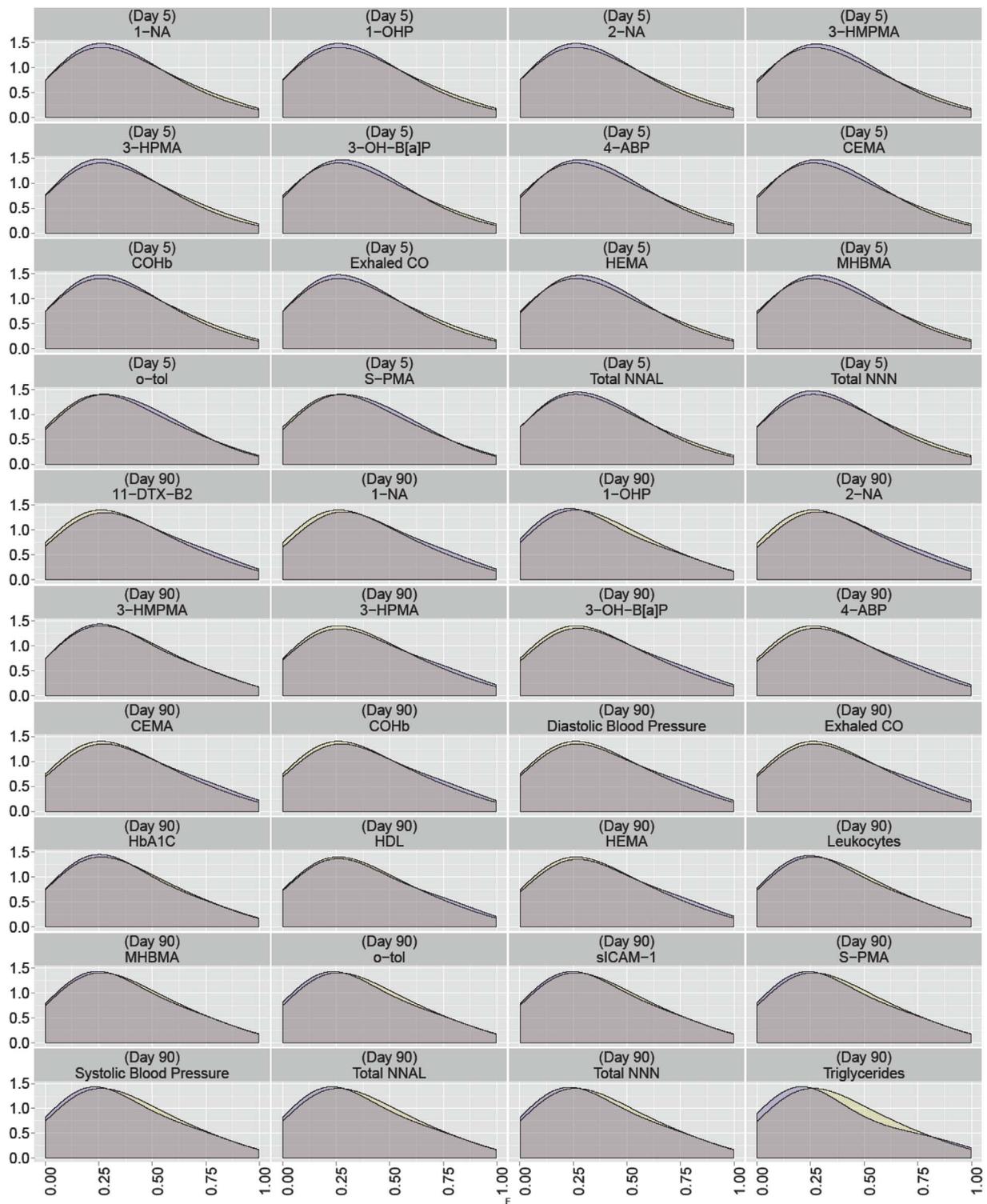
Fig. 6. Posterior density (ordinates) of the F-values for all, and all minus one, biomarkers. The yellow area indicates the posterior distribution when all biomarkers are analyzed, the purple area the posterior distribution when the indicated marker is omitted from the analysis.

methodological development.

The empirical basis for estimating F is related to the quantitative change observed in a set of biomarkers upon switching from cigarette smoking to the new product. The posterior distributions of the relative changes are estimated using a non-informative prior distribution, minimizing the amount of subjective information entering the estimation.

Rather than attempting to directly estimate F from available data, a

re-parametrization of the estimation problem was undertaken so that instead assumptions on two more objectively justifiable parameters are required. The first, lack of sufficiency, quantifies the informativeness of the set of biomarkers and clinical risk markers analyzed to characterize exposure-specific disease risks, a value of 1 indicating no information and a value of 0 indicating the set fully characterizing the risks. In spite of the extensive set of biomarkers of exposure and clinical risk markers, the conservative assumption of the total set of these endpoints

characterizing the smoking exposure-related disease risks by no more than half was made by assuming the value of the lack of sufficiency parameter to be 0.5. The assumed value for the second parameter, necessity, was also set to 0.5, the parameter again having a theoretical range from 0 to 1. By setting the necessity parameter to 0.5, the minimal effect required to be observed in the biomarker or clinical risk endpoint upon switching from smoking to the novel product had to be at least half of that observed upon smoking cessation to reduce the effective dose. Based on the set of biomarkers and clinical risk markers analyzed, as well as given the conservative assumptions regarding the lack of sufficiency and necessity parameters, it appears very unlikely that the posterior distribution of the F-factor so derived would overestimate the reduction of the effective dose achieved by switching from cigarette smoking to THS use. As the sensitivity analysis results indicate, the posterior distribution was found to be robust with regard to small changes in the sufficiency and necessity parameters. Generally, and in line with the theoretical expectations, the narrowness of the posterior distribution and thus the credibility of the F-factor estimation increased as the parameter values increased. Omission of any single biomarker did not materially change the results, which points at the robustness of the information provided by the set of biomarkers of exposure and clinical risk markers.

With the present methodological development a practical method of estimating the disease risk potential of a novel modified risk tobacco product has become available. The necessary assumptions are justifiable and, when parameters are set conservatively and a comprehensive set of biomarkers and clinical risk marker data is available, the resulting evidence-based approach appears to provide a solution for bridging the gap to health impact assessment, until eventually epidemiological data become available.

In addition to data from clinical studies, *in-vivo* and *in-vitro* data could be integrated. Further sensitivity analyses can include factors like sex, age, and variables related to smoking history, including smoking duration and intensity. At present, it appears important to note that the methodology is probabilistic and results in a posterior distribution rather than in a point estimate. This uncertainty should be considered whenever the results are used, as for example in estimating disease-specific population health impacts upon introducing a novel tobacco product on the market.

5. Conclusion

A methodology is described that allows for translating biomarker measurements into excess risks by estimating a product-specific risk-modulating effective dose (F-factor). In a first step, relative changes for the biomarkers of exposure and clinical risk markers and related uncertainties are derived. Based on parsimonious and justified assumptions the set of biomarkers is linked to the F-factor by introducing the parameters lack of sufficiency and necessity, to account for the lack of knowledge regarding the "true" link function. This allows for updating non-informative "prior" beliefs regarding F by data obtained in clinical studies. Sensitivity analyses support the robustness of the results with regard to variations of the lack of sufficiency and necessity parameters and to the omission of individual biomarkers. The methodology bridges the gap between the need for quantitative disease- and product-specific health impact assessment on the one hand, and the lack of epidemiological data on the other, for novel tobacco products.

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Declaration of interest

Acknowledgments

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2017.12.011.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2017.12.011.

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