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Assessment of industry data on pulmonary and immunosuppressive effects of IQOS

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ABSTRACT

Introduction Heated tobacco products are being touted as novel reduced-harm tobacco products by tobacco companies. In the USA, Philip Morris International submitted a modified risk tobacco product (MRTP) application to the US Food and Drug Administration in 2016 in which it purports that its heated tobacco product, I-Quit-Ordinary-Smoking (IQOS), is associated with reduced harm compared with conventional cigarettes.

Methods We reviewed Philip Morris International's MRTP application to assess the pulmonary and immune toxicities associated with IQOS use in both animal and human studies.

Results Among rats exposed to IQOS, there was evidence of pulmonary inflammation and immunomodulation. In human users, there was no evidence of improvement in pulmonary inflammation or pulmonary function in cigarette smokers who were switched to IQOS.

Conclusion IQOS is associated with significant pulmonary and immunomodulatory toxicities with no detectable differences between conventional cigarette smokers and those who were switched to IQOS in Philip Morris International's studies. Philip Morris International also failed to consider how dual use and secondhand aerosol exposure may further impact, and likely increase, the harms associated with these products.

INTRODUCTION

Conventional cigarettes have long been known to have numerous pulmonary toxicities. Cigarettes generate inflammation in the lung; over time, chronic inflammation contributes directly to the development of significant respiratory diseases including chronic obstructive pulmonary disease (COPD) and lung cancer.[1–3] In addition, cigarette smoke directly impacts immunity in the lung[4] and smoking is associated with an increased risk of respiratory infection,[5–7] a leading cause of mortality worldwide.[8 9] Driven by decades of data indicating the harms of cigarettes, public health campaigns have decreased the prevalence of cigarette smoking worldwide.[10]

In the setting of public awareness of the dangers of cigarettes and declining cigarette smoking in many parts of the world, tobacco companies have repeatedly attempted to develop 'safer cigarettes', including 'low-tar' cigarettes, electronic cigarettes and heated tobacco products (HTPs). HTPs heat tobacco to temperatures (~600°F) below the temperatures observed in conventional cigarettes (>900°F) to avoid combustion and produce a nicotine aerosol that is inhaled by the user. Given these

lower temperatures and the subsequent lack of combustion generated by these products, tobacco companies have argued that these products are healthier than conventional cigarettes and represent a harm reduction tool that could aid conventional cigarette smokers. However, to date, there has been little data that support HTPs as less harmful compared with conventional cigarettes.

On 5 December 2016, Philip Morris International (PMI) submitted an application to the US Food and Drug Administration (FDA) to market its HTP, I-Quit-Ordinary-Smoking (IQOS), as a 'modified risk tobacco product' (MRTP) in the USA. Section 911 of the Family Smoking Prevention and Tobacco Control Act requires the FDA to enforce rigorous standards that tobacco companies must meet before marketing a product as an MRTP. Section 911(g) mandates that the FDA may issue an MRTP order only if the applicant has demonstrated by substantial and objective scientific evidence that its product, as it is actually used by consumers, will '(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products'. These standards place the burden on the applicant to demonstrate that their product results in decreased harm, rather than merely equivalence. Such standards may often require a variety of studies, including invasive and/or longitudinal testing, in both animal and human models to provide evidence of reduced harm. This paper uses information and data from the publicly available PMI MRTP application to compare IQOS and conventional cigarettes in animal and human studies of pulmonary health and evaluate PMI's claim of harm reduction related to pulmonary health.

METHODS

In order to conduct this study, we searched PMI's publicly available MRTP application for data relevant to the pulmonary and immune toxicity of IQOS. In addition, when identified, publicly available raw data were downloaded from the FDA MRTP application to conduct independent statistical analyses.

Preclinical studies

Our analysis of PMI's preclinical studies focuses on data presented by Wong and colleagues,[11] which was published in Regulatory Toxicology and Pharmacology in 2016, and included in Module 7.2: Preclinical Studies of PMI's MRTP application. In order to compare the effects of IQOS emissions to

conventional cigarette smoke, PMI conducted a 90-day inhalation study in 10-week-old male and female Sprague-Dawley rats. Outcomes included markers of inflammation, histopathology, transcriptomics and standard toxicological endpoints, with comparisons of sham-exposed rats and rats exposed to the aerosol of IQOS and 3R4F research cigarettes. The IQOS product tested in these studies was the Tobacco Heated Systems (THS) V.2.2 tobacco stick which uses the FR1 tobacco blend. Rats were nose-exposed in flow-pass inhalation chambers for 6 hours per day to aerosols that were diluted with filtered air to obtain targeted nicotine concentrations ranging from 15 to 50 μg per litre aerosol. Unless otherwise stated, we focused on the highest level of aerosol nicotine for each product. Toxicants were measured at the breathing zone of the rats in the inhalation chambers and reported in ppm (carbon monoxide) or μg/litre (acetaldehyde, acrolein, formaldehyde).

Human studies

Our analyses of human clinical studies are based on the data presented in PMI's MRTP application's Executive Summary, Module 6: Summaries of all research findings, and Module 7.3.1: Scientific Studies and analyses (Studies in Adult Human Studies: Clinical Studies). The human data within these sections draw from two primary studies: ZRHR-REXA-07-JP, performed in Japan and ZRHM-REXA-08-US, performed in the USA. Briefly, both studies enrolled otherwise healthy adults who smoked at least 10 conventional cigarettes per day for the prior 3 years and randomised them into one of three groups: (1) those who smoked menthol conventional cigarettes, (2) those who quit completely and (3) those who switched to IQOS with menthol heatsticks. Participants were initially followed in confinement for 5 days of usage and then in the ambulatory setting for a total of 90 days. The goal of the 90-day ambulatory study period was to examine changes in biomarkers of exposure and clinical harm related to IQOS in near-real-world conditions. During the ambulatory study period, participants were discouraged from dual use. All participants kept a usage diary that documented their tobacco product usage. At the day 90-study visit, several clinical risk points were assessed including plasma white blood cell count (WBC), C reactive protein (CRP) and pulmonary function testing (PFT). Clinical risk endpoints were then compared between participants who continued smoking conventional cigarettes and those that were switched to HTPs.

Statistical analyses

PMI's main analyses included analysis of variance testing with baseline value, product exposure, sex and baseline cigarette consumption as fixed effect factors. We conducted independent analysis of publicly available raw data from PMI's MRTP application. We used Student's t test, analysis of variance testing and Pearson's χ^2 test to compare normally distributed variables. Non-normally distributed variables were compared using the Mann-Whitney Wilcoxon U-test or Kruskal-Wallis test. A p value ≤0.05 was considered statistically significant. Statistical analyses were performed with STATA V.15.0 (StataCorp).

RESULTS
Preclinical studies

A comparison of the toxicant profiles of IQOS, 3R4F cigarettes and sham exposure conditions revealed that, while containing generally lower toxicant levels than 3R4F smoke, IQOS emissions contain significant levels of volatile organic compounds, including known toxicants such as acrolein, acetaldehyde and

Table 1 Summary of preclinical pulmonary findings for I-Quit-Ordinary-Smoking (IQOS) compared with sham and 3R4F research cigarette groups

Parameter	Sham (n=10)	IQOS (n=8–10)	3R4F (n=9)
Lung weight (normalised to body weight)	35.8 (1.4)	40.3 (1.0)*	50.6 (1.4)*†
BAL cell count‡ (×10⁵/lung)	22.9 (3.4)	42.5 (7.1)*	116.4 (13.4)*†
BAL inflammatory markers MIP-1β, MCP-3, MPO, PAI-1		↑*	↑*†
Respiratory epithelial hyperplasia and metaplasia		↑*	↑*†

Unless otherwise specified, results signify those from male rats at the highest nicotine exposure levels for each group.
*Significantly increased compared with sham.
†Significantly increased compared with IQOS.
‡Female rats at targeted nicotine 23 μg/L.
BAL, bronchoalveolar lavage; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MPO, myeloperoxidase; PAI, plasminogen activator inhibitor.

formaldehyde. IQOS-exposed rats had impaired weight gain during the 90-day exposure compared with sham, but greater weight gain compared with animals exposed to 3R4F smoke. Similarly, IQOS-exposed rats had a trend towards increased numbers of inflammatory cells in bronchoalveolar lavage (BAL), but significantly less BAL cellularity than 3R4F-exposed rats (table 1). Respiratory histopathology demonstrated that IQOS caused significant epithelial hyperplasia and metaplasia compared with sham, though to a lesser extent than was observed following 3R4F exposure. Taken together, these data suggest that IQOS induces a significant inflammatory injury, but less severe than that observed with intense cigarette smoke exposure.

PMI's data indicate that IQOS exposure may be associated with substantial immunomodulatory effects (table 2). Animals exposed to IQOS developed systemic neutrophilia that trended nearly 75% higher than that observed in rats exposed to 3R4F smoke. Notably, blood neutrophil counts in female rats remained elevated compared with both sham and 3R4F exposed animals following a 6-week recovery period. Furthermore, IQOS-exposed animals had higher levels of thymic atrophy (by gross organ weight and histology) than both sham and 3R4F-exposed groups. Although functional immunological assays were not reported, thymic atrophy has previously been associated with decreases in host memory T cell populations[12] and reductions in the speed and sensitivity of host immune function.[13]

Table 2 Summary of preclinical systemic immune effects of I-Quit-Ordinary-Smoking (IQOS) compared with sham and 3R4F research cigarettes

Parameter	Sham (n=8–10)	IQOS (n=7–9)	3R4F (n=9–10)
Blood neutrophil count (10⁹/L)	1.3 (0.3)	4.8 (2.1)*	2.7 (0.4)*
Thymus weight	4.0 (0.4)	2.6 (0.6)*	2.5 (0.3)*
Histological thymic atrophy score	0.1 (0.1)	1.8 (0.4)*	1.1 (0.4)*

Unless otherwise specified, results signify those from male rats at the highest nicotine exposure levels for each group.
*Significantly different compared with sham; statistical comparisons between IQOS and 3R4F were not reported for blood neutrophil count or thymic atrophy score.

Table 3 Participant demographics and baseline data for Japan-based (ZRHR-REXA-07-JP) and US-based (ZRHM-REXA-08-US) studies

Japan-based study ZRHR-REXA-07-JP

Measurement	Conventional cigarettes (n=41)	Abstinence (n=37)	IQOS (n=70)	P values
Age	38±11	38±10	38±11	0.99
Male (%)	24 (59%)	22 (59%)	39 (56%)	0.92
Smoking history				
10 – 19 cig/day	23 (56%)	20 (54%)	36 (51%)	0.92
>19 cig/day	18 (44%)	17 (46%)	34 (49%)	
FEV1 (% predicted)	94±9	93±10	94±8	0.69
FEV1/FVC	0.81±0.05	0.81±0.06	0.82±0.07	0.73
WBC (GI/L)	5.8±1.4	6.4±1.9	5.9±1.2	0.12
CRP (mg/L)	0.1 (0.1–0.26)	0.1 (0.1–0.45)	0.1 (0.1–0.45)	0.81

US-based study ZRHM-REXA-08-US

Measurement	Conventional cigarettes (n=32)	Smoking abstinence (n=9)	IQOS (n=47)	P values
Age (years)	34±10	41±11	37±13	0.27
Male	20 (63%)	7 (78%)	28 (60%)	0.59
Smoking history				
10–19 cig/day	19 (59%)	6 (67%)	21 (45%)	0.29
>19 cig/day	13 (41%)	3 (33%)	26 (55%)	
FEV1 (% predicted)	97±14	96±11	93±13	0.46
FEV1/FVC	0.79±0.07	0.78±0.04	0.80±0.05	0.74
WBC (GI/L)	8.3±1.8	6.9±2.2	8.3±1.7	0.08
CRP (mg/L)	0.1 (0.1–0.2)	0.1 (0.03–0.2)	0.1 (0.1–0.3)	0.11

IQOS, I-Quit-Ordinary-Smoking; CRP, C reactive protein; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; WBC, white blood cell count.

Table 4 Difference (95% CI) in 90-day pulmonary function testing between I-Quit-Ordinary-Smoking users and conventional cigarette smokers as presented by Philip Morris International

Clinical endpoint	US-based study ZRHM-REXA-08-US* (n=77)	Japan-based study ZRHR-REXA-07-JP† (n=111)
FEV1 (% predicted)	0.53 (−2.09 to 3.00)	1.91 (−0.14 to 3.97)
FEV1/FVC	0.00 (−0.02 to 0.02)	N/A
MEF 25–75 (L/s)	−0.67 (−6.33 to 4.99)	N/A
DLCO (mL/min/mm Hg)	0.31 (−1.09 to 1.72)	N/A
KCO (mmol/min/kPa/L)	0.05 (−0.02 to 0.12)	N/A
TLC (L)	0.09 (−0.25 to 0.43)	N/A
FRV (L)	−0.09 (−0.31 to 0.13)	N/A
IC (L)	0.21 (−0.08 to 0.51)	N/A
VC (L)	0.10 (0.00 to 0.21)	N/A

*Without bronchodilator.
†With bronchodilator.
DLCO, diffusion capacity of lung for carbon monoxide; IC, inspiratory capacity; FEV1, forced expiratory volume in 1 s; FRV, functional residual volume; FVC, forced vital capacity; KCO, rate constant of carbon monoxide; MEF, mid expiratory flow; N/A, not conducted or reported by PMI; TLC, total lung capacity; VC, vital capacity.

Human studies
Japan-based study

The Japan-based study randomised 231 participants between two study sites. However, only one of these sites collected participant data at 90 days. After limiting the sample to participants who had samples drawn at 90 days (n=160), and excluding those who were lost to follow-up (n=12), 148 participants remained. At the day 0 baseline visit, we found no difference in age or sex between groups (table 3). We did not detect a difference between groups in baseline pulmonary function, CRP or WBC, although there was a trend towards increased levels of WBC in the smoking abstinence group.

At the 90-day study visit, PMI reported decreased plasma WBC in IQOS users compared with conventional cigarette smokers (6.14 GI/L vs 5.57 GI/L, difference: −0.57 GI/L, 95% CI: −1.04 to −0.10). Given that WBC had also been measured at the day 0 baseline visit, we compared the change in WBC from baseline to 90 days between groups, rather than only comparing the level at 90 days. We found that compared with cigarette smokers, participants using IQOS had a decrease in plasma WBC (difference: −0.63 GI/L, 95% CI: −1.1 to −0.2, p=0.006). There was no significant difference in the change in WBC between the IQOS and smoking abstinence group. PMI did not detect a difference in CRP levels at 90 days between cigarette smokers and IQOS users (95% CI for difference between groups: −40.75 to 37.77). In our analyses, we did not detect a significant difference in the change in CRP from baseline to 90 days between IQOS users (median:

0 mg/L) and either cigarette smokers (median: 0 mg/L, p=1.0) or the smoking abstinence group (median: 0 mg/L, p=0.74).

PMI also reported on forced expiratory volume in 1 s (FEV1) without bronchodilator administration and found no difference in FEV1 at 90 days between cigarette smokers and IQOS users (table 4). We independently studied the change in FEV1 from day 0 baseline to 90 days. We found no difference between the three groups in the change in FEV1 (cigarette smoking group: −0.3 % predicted, 95% CI: −2.3 to −1.7; smoking abstinence group: 1.5 % predicted, 95% CI: −0.3 to 3.3; IQOS group: 1.5 % predicted, 95% CI: 0.3 to 2.6, p=0.2).

US-based study

In the US-based study, 88 participants underwent testing at 90 days. At the day 0 baseline visit, we did not detect a difference between the three arms in age, sex, pulmonary function, WBC or CRP, although there was a trend towards increased CRP in the IQOS group and decreased WBC in the smoking abstinence group (table 3).

In the US-based study, PMI reported no difference in plasma WBC at 90 days between participants who continued to smoke conventional cigarettes and those who were randomised to IQOS (7.09 GI/L vs 7.26 GI/L, difference: 0.17 GI/L, 95% CI: - 0.47 to 0.81). Similarly, PMI reported no difference in CRP levels between conventional cigarette smokers and IQOS users (95% CI for difference between groups: −21.69 to 42.33). In our independent analyses, we did not detect a difference in the change in WBC from baseline to 90-day visit between the IQOS arm and either the conventional cigarette arm (difference: - 0.06 mg/L, 95% CI: −0.8 to 0.7, p=0.87) or the smoking abstinence arm (difference: - 0.5 mg/L, 95% CI: −1.6 to 0.7, p=0.43). Similarly, we did not detect a difference in change in CRP from baseline to day 90 visit between the IQOS group and either the conventional cigarette group (p=0.30) or the smoking abstinence group (p=0.50).

The US-based study conducted more extensive PFTs than the Japan-based study and notably these tests were performed following bronchodilator administration, which differed from the Japan-based study. At 90 days, PMI did not report a significant difference between the IQOS and conventional cigarette

Table 5 Changes in pulmonary function testing from day 0 to day 90 in the US-based study (ZRHM-REXA-08-US)

Clinical endpoint	Conventional cigarettes (n=30)	IQOS (n=47)	Smoking abstinence (n=9)	P values
FEV1 (% predicted)	−3.1 (−5.6 to −1.7)	−2.3 (−4.6 to −0.04)	−2.9 (−11.3 to 5.6)	0.72
FVC (% predicted)	−2.6 (−4.4 to 0.9)	−1.8 (−3.4 to −0.05)	−0.6 (−4.5 to 3.4)	0.57
FEV1/FVC	0.01 (−0.004 to 0.02)	−0.004 (−0.02 to 0.01)	0.04 (0.002 to 0.08)	0.01
MEF 25–75 (L/s)	−0.1 (−0.3 to 0.2)	−0.1 (−0.3 to 0.05)	0.2 (−0.8 to 1.1)	0.57
DLCO (mL/min/mm Hg)	0.2 (−1.0 to 1.3)	0.2 (−0.8 to 1.2)	−1.5 (−5.1 to 2.2)	0.40
TLC (L)	−0.3 (−0.6 to 0.1)	−0.02 (−0.3 to 0.2)	−0.6 (2.0 to 0.7)	0.15

DLCO, diffusion capacity of lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, mid expiratory flow; TLC, total lung capacity.

group for any of the pulmonary function tests that were assessed. We conducted independent analyses of the change in pulmonary function from baseline day 0 to 90-day visits between groups. We did not detect a difference in changes in pulmonary function over time between the three groups except for FEV1/FVC, which increased slightly in the smoking abstinence group relative to both the conventional cigarette group and the IQOS group (table 5). There were no other differences detected between the IQOS group and either the conventional cigarette or smoking abstinence groups.

DISCUSSION

The FDA requires that MRTP applicants demonstrate that their products, as actually used by consumers, will reduce harm in individuals and benefit the health of the public overall. PMI's data are incomplete as they lack adequate endpoints to specifically assess subclinical pulmonary toxicity in humans and do not incorporate enough longitudinal measures for the tests they do include. Additionally, PMI fails to account for real-world usage patterns and secondhand aerosol exposures that may negatively impact both individual and public health. However, even the data that are presented by PMI suggest that IQOS has significant potential to induce adverse pulmonary health effects in humans.

Data from PMI's MRTP application indicate that compared with conventional cigarettes, emissions from IQOS have lower levels of volatile organic compounds and are associated with decreased levels of pulmonary inflammation in rats after 90 days of exposure. However, compared with sham controls, IQOS induces significant changes in the respiratory epithelium and airspaces that are consistent with inflammatory injury. Furthermore, the two clinical studies of real-world usage cited by PMI do not definitively show evidence of reduced inflammation in IQOS users compared with conventional cigarette smokers. Although a very small reduction in plasma WBC was observed in IQOS users in the Japan-based study, there was no difference in plasma WBC in the US-based study. In addition, there was no difference in CRP levels between conventional smokers and IQOS users in either study.

While inflammation is an important toxic mediator in a number of respiratory diseases that have been linked to cigarette smoking, plasma WBC and CRP are not direct measures of pulmonary inflammation but rather non-specific measures of systemic inflammation. There was no difference in levels of these biomarkers at 90 days between conventional cigarette smokers and those who quit smoking, suggesting that these are poorly sensitive markers, particularly when measured over such a short period of time. There are several more specific measures that can assess pulmonary inflammation in humans, including studies of inflammatory biomarkers in sputum, airway tissue or BAL fluid.[14 15] Such tests directly sample lung tissue and thus more accurately reflect processes in the lung. However, despite presenting no human data directly from the lung, PMI concludes

that 'human clinical studies have confirmed that clinical markers of … inflammation show positive changes, similar to those seen following smoking abstinence' (PMI MRTP Application, Section 2.7, Executive Summary, p. 106) and that these changes indicate that 'smokers who switch to [IQOS] would have a lower risk of COPD compared with continued smoking' (PMI MRTP Application, Section 2.7, Executive Summary, p. 107). Thus, PMI not only fails to accurately assess pulmonary inflammation in their human studies, but also misleadingly concludes that their IQOS product reduces inflammation and the risk of COPD in humans, a claim that is simply not supported by their data.

Neither PMI's Japanese nor American ambulatory human clinical study shows any statistically significant improvement in any measure of PFT. In fact, after 3 months of usage, smokers who have transitioned to IQOS use have the same pulmonary function as those who continued to smoke conventional cigarettes. Notably, PMI reports several cases of worsening pulmonary function in IQOS users in their adverse event reports (Appendix A6.1.5.4 in the PMI MRTP application). However, PMI concludes that 'in the Japanese study (ZRHM-REXA-07-JP), smokers who switched to THS had an increase of 1.91 percent of predicted value (%Pred) in their FEV1 as compared with smokers who continued to smoke cigarettes' (PMI MRTP Application, Section 2.7, Executive Summary, p. 92) and that 'in the US study (ZRHM-REXA-08-US), the difference in FEV1 values between smokers who switched to THS and those who continued to smoke was smaller in magnitude as compared with in the Japanese study. Nonetheless, the results were consistent and trended in the expected direction following smoking abstinence' (PMI MRTP Application, Section 2.7, Executive Summary, p. 93). These conclusions are simply not supported by PMI's own actual data, which shows no statistically significant difference in pulmonary function between IQOS users and conventional smokers. Furthermore, the relatively short period of follow-up fails to address longer term effects of IQOS on pulmonary function. While prior studies have shown that there are small improvements in pulmonary function in the first year of smoking cessation,[16] a significant benefit arises from a slowing in the decline of lung function over many years.[16 17] A 90-day study period is simply not long enough to detect any meaningful changes in lung function, as evidenced by the lack of difference detected in pulmonary function between the smoking abstinence group and the conventional cigarette or IQOS groups for almost all tests of pulmonary function measured. Thus, the short follow-up period in PMI's studies is unable to assess the important clinical question of the long-term effects on IQOS on pulmonary health compared with both conventional cigarettes and complete smoking cessation.

Conventional cigarettes are known to directly impact immunity and are associated with increased rates of respiratory infection.[5–7] PMI's animal data suggest that IQOS may impact immunity, inducing thymic atrophy in exposed rats. Given that respiratory

infection represents a leading cause of morbidity and mortality worldwide,[8 9] this finding raises alarm that IQOS could increase the risk of infection in users and indicates that further studies of the immunomodulatory effects of IQOS are needed, including animal models of respiratory infection. Notably, PMI reports several cases of infection associated with human IQOS use in their adverse data reports (Appendix A6.1.5.4), which adds to the concern that these products may adversely affect immunity and predispose users to developing infection. The omission of additional studies on the immune effects of IQOS from PMI's MRTP application is significant and further clouds the picture on the true health risks of IQOS.

PMI's analyses focus on studying the harms associated with exclusive IQOS use. However, there is significant data that dual or poly use, the use of two or more tobacco products, will be a significant usage pattern among IQOS users. In PMI's US-based study, nearly one in four participants was still using conventional cigarettes after being switched to IQOS. Internationally, per PMI's own reports, it is estimated that up to 30% of IQOS users also use an additional tobacco product, including conventional cigarettes.[18] However, despite significant evidence of the potential for dual use among IQOS users,[19] PMI has failed to simulate dual use in their animal studies. Furthermore, in their human studies, PMI strictly prevented dual use during confinement study periods and strongly discouraged, although somewhat unsuccessfully, dual use in the ambulatory setting, resulting in less validity to their claims that it mimicked a 'real world' setting. In addition, no analyses are performed on the effects of dual use that was known to occur. Given that dual use is likely to impact any potential for harm reduction for individual users, its omission from PMI's study design and analyses on harm reduction potential is a glaring one.

Finally, PMI studies fail to account for the pulmonary health effects of secondhand aerosol exposure. A prior study of HTPs found that they do generate sidestream aerosol, the primary component of secondhand smoke exposure,[20] which comprises a large number of volatile organic compounds, polycyclic aromatic hydrocarbons and ultrafine particles.[21 22] Furthermore, a recent study found that people exposed to secondhand IQOS emissions experienced symptoms, including sore throat (20.6%), eye pain (22.3%) and feeling ill (25.1%).[19] Given that a number of public health organisations, including WHO, have deemed that no level of sidestream exposure is safe or acceptable,[23] these findings are clearly concerning and merit further study, which PMI has either failed to conduct or present.

In conclusion, PMI's IQOS MRTP application raises significant concerns about the pulmonary safety of IQOS. PMI ignores the effect of dual use and secondhand aerosol exposure in both study design and analyses; furthermore, no measurements of inflammation specific to the lung were made in any of the human studies presented, and the duration of follow-up does not allow for any meaningful study of pulmonary function. Any future studies of these products must include measurements specific to the lung, such as in sputum or BAL fluid, as well as additional longitudinal follow-up to more accurately assess the acute and chronic toxicities of these products. In addition, given that dual use is expected to be the predominant usage pattern, it is critical that future studies take into account dual use when assessing the public health impact of these products. However, even if these significant gaps were ignored, PMI's own data show that IQOS is associated with significant pulmonary and immune toxicity that does not appear to be significantly different from cigarette smoking in real-world human users.

What this paper adds

- ► Heated tobacco products are being touted as reduced harm tobacco products by tobacco companies across the world despite limited scientific evidence supporting this claim.
- ► Philip Morris's modified risk tobacco product (MRTP) application for I-Quit-Ordinary-Smoking (IQOS) shows that IQOS generates significant pulmonary and immunomodulatory harm, most notably in human studies.
- ► With regards to pulmonary and immunomodulatory harm, based on the limited available data to date, IQOS use does not appear to significantly differ from conventional cigarettes.

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