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PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes

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ABSTRACT

Introduction New 'heated tobacco products' are being marketed in several countries with claims that they expose users to lower levels of toxins than conventional cigarettes which could be read as being less likely to cause health problems than conventional cigarettes. In the USA, Philip Morris International (PMI) has submitted an application to the Food and Drug Administration for permission to market its heated tobacco product, IQOS, with reduced exposure and reduced risk claims.

Methods Analysis of detailed results on 24 biomarkers of potential harm in PMI studies of humans using IQOS compared with humans using conventional cigarettes.

Results Among American adults, there is no statistically detectable difference between IQOS and conventional cigarette users for 23 of the 24 biomarkers of potential harm in PMI's studies. In Japan, there were no significant differences between people using IQOS and conventional cigarettes in 10 of 13 biomarkers of potential harm. It is likely that some of the significant differences are false positives.

Conclusion Despite delivering lower levels of some toxins than conventional cigarettes, PMI's own data fail to show consistently lower risks of harm in humans using its heated tobacco product, IQOS, than conventional cigarettes.

INTRODUCTION

Nicotine is the addictive drug in tobacco. Burning the tobacco generates an aerosol of ultrafine particles that carries nicotine deep into smokers' lungs, where it is absorbed and rapidly reaches the brain. That burning yields toxic chemicals that cause disease. Ever since people started understanding in the 1950s that smoking kills, millions have struggled to stop smoking. The tobacco companies, desperate to keep and expand their customers, have been trying to make 'safer cigarettes' since the 1960s.[1] They have also developed products that avoided burning, including e-cigarettes,[2] nicotine replacement therapy,[3] and products that heat the tobacco without setting it on fire. As of January 2018 all the major multinational tobacco companies had developed, or were in the process of developing, so-called 'heated tobacco products' (HTP; also called 'heat-not-burn' tobacco products). Because these devices generate their nicotine aerosols by heating a stick of ground tobacco and chemicals without setting the tobacco on fire, they generally produce fewer toxic chemicals than a conventional cigarette, which is promoted as meaning or implying that these products are not as dangerous as conventional cigarettes.

In 2015, Philip Morris International (PMI) started test marketing its IQOS HTP outside the USA on the grounds that it is not as bad as a cigarette because 'the tobacco is heated and not burned, the levels of harmful chemicals are significantly reduced compared to cigarette smoke.'[4]

Because IQOS is a new tobacco product, PMI needs to obtain premarket authorisation from the US Food and Drug Administration (FDA) to sell it in the USA. In particular, PMI wants to market IQOS with reduced risk claims, what US law calls a 'modified risk tobacco product' (MRTP). To obtain authorisation to market IQOS with reduced risk claims, PMI submitted an application to the FDA in December 2016.[5] As required by law, FDA has made most of the application available for the public to review. The application includes comparisons of the levels of 24 biomarkers of potential harm in human smokers, including comparisons with people who smoke conventional cigarettes. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure and lung function. This paper uses information in the PMI application to evaluate this comparison and concludes that in people who actually use IQOS, the levels of these biomarkers of potential harm are not detectably different from conventional cigarettes.

METHODS

The results analysed in this paper are from PMI's 'Three-month Reduced Exposure in a confined and ambulatory setting' studies (ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA) that present human clinical studies of non-cancer biomarkers of potential harm presented in PMI's MRTP application's[5] 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), specifically the data on 24 biomarkers of potential harm *in human users* derived from two of their 'Reduced Exposure' studies: ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA.

As described in Section 6.1.4.3.2 of the application, cigarette smokers were randomised, controlled, open-label, three-arm parallel group studies in which smokers were randomised to IQOS (menthol), continued smoking their current brand of cigarettes or smoking abstinence. Baseline data were collected on day 0 immediately before randomisation, people were held during a 5-day confinement period then released to the ambulatory setting and observed at 90 (±3 (range)) days

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after randomisation. (Some variables were measured during confinement and before 90 days, but are not considered in this analysis.) During the confinement period, product use was directed and monitored by the study staff and participating smokers were controlled for product compliance. Subjects assigned to conventional cigarettes or IQOS used the products without restriction (ad libitum) during an extended daily time window (16 hours); dual use of conventional cigarettes and IQOS was not permitted. The 3-month ambulatory phase was designed to reflect a near real-world environment where dual use of IQOS and conventional cigarettes or other tobacco products could occur. PMI selected a 3-month extended ambulatory follow-up period so that the study would be long enough to assess the initial changes in some of the clinical risk endpoints that have been shown to be reversible within 2 weeks to 3 months.

The final sample (table 1) consisted of people who were adherent with their assigned study product and without major protocol deviations that impacted the validity of the evaluation of the study results. This sample was designed to assess the maximum exposure reduction achievable (what PMI characterised as the 'optimal effect') in subjects who were using IQOS ad libitum and exclusively or at least predominantly, rather than the effect in the full population representing a heterogeneous exposure (eg, as mixed product use, or non-use of the assigned product).

The point estimates and 95% confident intervals (CIs) at day 90 were computed using least squares means from an analysis of covariance with study arm as a factor adjusting for baseline value, sex and average daily conventional cigarette consumption over the last 4 weeks as reported during screening. (Thus, the width of the CIs for the differences between IQOS and conventional cigarette use in table 1 benefits from the information in the smoking abstinence group even though those subjects are not directly involved in the point estimates being compared.) Endpoints that were not normally distributed were log-transformed (base e) prior to analysis, then back-transformed to calculate least squares means ratios to compare IQOS with conventional cigarettes.

Both trials were registered with ClinTrials.gov.

Specific results are based on measures of inflammation in Section 6.1.4.4.2; cholesterol, triglycerides and physiological measures related to heart disease in Section 6.1.4.4.4; and lung function in Section 6.1.4.4.5.

RESULTS

Among American adults, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 biomarkers of potential harm in PMI's studies (table 1). This is indicated by the fact that 23 of the 95% CIs include zero (ie, no statistically significant difference). Moreover, when using the conventional 95% confidence standard for statistical hypothesis testing, one would expect 5% of the tests to yield false positives. Five per cent of 24 tests is 1.2 tests, which means that one would expect one false positive result. PMI had one positive result (soluble intercellular adhesion molecule (ICAM)), which is what one would expect by chance.

PMI also reported the results on 13 biomarkers of potential harm among Japanese people (table 1). There were significant improvements in 4/13 of these biomarkers, 3 markers of inflammation (white cell count, prostaglandin F2 alpha and soluble ICAM) and 1 measure of cholesterol (high-density lipoprotein cholesterol). When using the conventional 95% confidence standard one would expect 0.65 positive tests, which means one would expect one false positive test.

Table 1 Summary of Philip Morris studies of changes in biomarkers in IQOS users compared with conventional cigarette smokers after 90 days of product use (95% CIs in parenthesis)

	Japan	USA
Inflammation (6.1.4.4.2**)		
White cell count	**−0.57 GI/L (−1.04 to −0.10)**	0.17 GI/L (−0.47 to 0.81)
C-reactive protein (CRP)	6.41% ↓ (−40.75 to 37.77)	16.23% ↓ (−21.69 to 42.33)
Soluble ICAM (sICAM-1)	**8.72% ↓ (2.05 to 14.94)**	**10.59% ↓ (4.03 to 16.71)**
Fibrinogen	5.42% ↓ (−1.80 to 12.13)	1.63% ↓ (−6.42 to 9.08)
Oxidative stress (6.1.4.4.3)		
Prostaglandin F2 alpha (8-epi-PGF2α)	**12.71% ↓ (2.55 to 21.81)**	13.46% ↓ (−1.95 to 23.61)
11-dehydrothromboxane B2 (11DTXB2)	5.42% ↓ (−1.80 to 12.13)	3.56% ↓ (−23.31 to 24.57)
Cholesterol and triglycerides (6.1.4.4.4)		
High-density lipoprotein cholesterol (HDL-C)	**4.53** mg/dL **(1.17 to 7.88)**	1.4 mg/dL (−2.3 to 5.0)
Low-density lipoprotein cholesterol (LDL-C)	0.87 mg/dL (−6.55 to 8.30)	−3.3 mg/dL (−12.0 to 5.4)
Total cholesterol	2.00 mg/dL (−6.68 to 10.67)	−4.0 mg/dL (−13.3 to 5.2)
Triglycerides	−6.25 mg/dL (−21.20 to 8.69)	0.9 mg/dL (−12.8 to 14.6)
Apolipoprotein A1 (apoA1)	NA	3.1 mg/dL (−4.6 to 10. 7)
Apolipoprotein B (apoB)	NA	−1.6 mg/dL (−7.24 to 4.03)
Physiological measures		
Systolic blood pressure	−0.59 mm Hg (−3.80 to 2.62)	−0.7 mm Hg (−4.5 to 3.1)
Diastolic blood pressure	−0.68 mm Hg (−3.04 to 1.69)	0.2 mm Hg (−3.7 to 4.0)
Lung function (6.1.4.4.5)		
Forced expiratory volume in 1 s (FEV_1)	1.91 %Pred (−0.14 to 3.97)	0.53 %Pred (−2.09 to 3.00) 0.05 L (−0.06 to 0.15)
FEV_1/FVC (forced vital capacity)	NA	0.00 (−0.02 to 0.02)
Mid-expiratory flow (MEF 25–75) (L/s)	NA	−0.67 (−6.33 to 4.99)
Diffusion capacity for lung CO (DLCO) (mL/min/mm Hg)	NA	0.31 (−1.09 to 1.72)
Rate constant of CO (KCO) (mmol/min/kPa/L)	NA	0.05 (−0.02 to 0.12)
Total lung capacity (TLC) (L)	NA	0.09 (−0.25 to 0.43)
Functional residual volume (FRV) (L)	NA	−0.09 (−0.31 to 0.13)
Inspiratory capacity (IC) (L)	NA	0.21 (−0.08 to 0.51)
Vital capacity (VC) (L)	NA	0.10 (0.00 to 0.21)
Summary		
Number of biomarkers tested	13	24
Number significantly improved	3	1
Number expected by chance	1	1

Continued

Table 1 Continued

	Japan	USA
Sample sizes		
IQOS	70	47†
Conventional cigarettes	41	32‡
Smoking abstinence	37	9§

The results are either IQOS:CC or IQOS-CC (conventional cigarettes).
Bold results are statistically significant differences (p<05).
*Section of Philip Morris International's Modified Risk Tobacco Product application.
†n=45 for fibrinogen, 8-epi-PGF2α, 11DTXB2, systolic blood pressure, diastolic blood pressure, DCLO and KCO.
‡n=30 for FEV_1, FEV_1/FVC, MEF 25–75, DLCO, KCO, TLC, FRV, IC and VC.
§n=8 for DLCO and 7 for KCO.
ICAM, intercellular adhesion molecule; NA, not applicable.

DISCUSSION

These human data are important information because they represent direct evidence on how IQOS affects people who use the product. They show that, despite the evidence that PMI submitted that the levels of some toxins in IQOS aerosol are lower than in conventional cigarettes,[5] fewer toxic chemicals, however, do not necessarily translate into lower harm when people use the product.

In its MRTP application, PMI did not discuss the results of the conventional statistical tests described in the Results section, which are routine for such scientific analysis. Rather, they simply emphasise the direction of changes while ignoring the fact that these differences are within what would be expected based on simple randomness. No tobacco company would tolerate such assertions made by the FDA or other public health authorities.

The results reported in PMI's application (and in a published paper[6]) for Japan are slightly more positive for IQOS, with 4 of 13 biomarkers showing differences from conventional cigarettes (where one would expect one false positive by chance). These results are not strong enough to warrant drawing a conclusion of reduced risk. The conclusion of no significant difference on biomarkers of potential harm is based on taking PMI's results at face value despite the tobacco companies' (including Philip Morris) long record of manipulating the design, analysis and presentation of their published scientific studies <<ED: Citation should be "7-12" no "7-13".>>.[7–13]

Like cigarettes (and e-cigarettes), IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease. The adverse health effects of these particles and many of the other toxins do not drop in proportion to reducing the dose, so even low levels of exposure can be dangerous.[13] This effect is why smoke-free environment laws are followed by big drops in heart attacks and other diseases despite the fact that secondhand smokers breathe in much less smoke that the smokers.[14] In addition, while the IQOS does not set the tobacco stick on fire, it heats it to 350°C (660°F), which is still hot enough to cause pyrolysis. There is already independent evidence that IQOS compromises functioning of arteries,[15] a key risk factor for heart disease and heart attacks, as badly as a cigarette.

The clinical studies that PMI reported appropriately did not include cancer because carcinogenic effects take much longer to be manifest than cardiovascular and pulmonary effects. Even if the levels of carcinogens delivered by IQOS are lower than conventional cigarettes on a per-puff basis, these lower exposure levels may not yield proportionately lower cancer risks because both the intensity and duration of exposure impact cancer risk.[16–18]

The purpose of this paper is to assess the data on biomarkers of potential harm of the Philip Morris IQOS HTP system in people who were actually using the system compared with people who smoke conventional cigarettes based on the information submitted to the US FDA in PMI's MRTP application for IQOS. On 31 March 2018, the author conducted a PubMed search using the search term '(IQOS or 'heat not burn' or 'heated tobacco product') and (health or harm) and (human or clinical)'. This search returned 33 papers, none of which reported on comparisons of in vivo biomarkers of potential harm in people using IQOS (or any other HTP system) compared with conventional cigarettes. Thus, as of 9 July 2018, the data in the PMI MRTP application remained the only publicly available evidence on the in vivo human clinical effects of IQOS compared with conventional cigarettes.

While this analysis is limited to the data presented in PMI's IQOS MRTP application to the FDA, it is likely that the effects of other HTPs being developed by other tobacco companies will have similar effects because the fundamental principles behind all these products are the same.

On 15 June 2018, PMI issued a press release, 'Philip Morris (PM) Announces Positive Results from New Clinical Study on IQOS,'[19] that said, 'all eight of the primary clinical risk endpoints moved in the same direction as observed for smoking cessation in the group who switched to IQOS, with statistically significant changes in five of the eight endpoints compared with on-going smoking.' While PMI did not release any detailed results, examining the protocol (on ClinicalTrials.gov) revealed that this new study only examined six clinical measures, compared with the 24 in MRTP application (table 1). (The other two were biomarkers of exposure.) PMI did not say which of the changes were statistically significant, raising the possibility that the protocol and analysis were manipulated to achieve positive results.[8 9] PMI increased the sample size from 88 in the original US study to 984. While bigger studies are better, the fact is that making the sample size big enough will increase the power to the point that almost any difference will reach statistical significance regardless of whether it is clinically significant or not. The true measure of reduced risk would be statistically significant changes that were large enough to be clinically significant in enough biomarkers of potential harm to be meaningful.

PMI's failure to show significant improvements in these biomarkers of potential harm is consistent with the data PMI reported on the levels of toxicants in IQOS mainstream aerosol compared with mainstream smoke of 3R4F reference cigarettes.[20] While many toxicants were lower in IQOS aerosol, 56 others were higher in IQOS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher.

In short, PMI's results in humans failed to meet the legal requirement that IQOS 'as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users' that US law requires before the FDA can approve a reduced risk claim. In the USA, PMI wants to sell IQOS with claims that 'Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases' and 'Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes'[5]; these claims are not substantiated by PMI's own data.

On 25 January 2018, based in part on the information in this paper (which had been submitted to FDA as a public comment) showing gaps in PMI's scientific evidence, the FDA's Tobacco Products Scientific Advisory Committee voted that PMI had failed to demonstrate that its proposed modified (reduced) risk labelling and advertising claims for IQOS were demonstrated by scientific evidence.[21]

Based on the data in the PMI MRTP application for IQOS, neither the US FDA nor comparable authorities elsewhere in

What this paper adds

- Heated tobacco products are being marketed in several countries with claims of reduced exposure to toxins compared with conventional cigarettes.
- Studies conducted in people using Philip Morris International's IQOS heated tobacco product did not reveal detectably better measures of biomarkers of potential harm than conventional cigarettes in human tests.
- These products should not be permitted to be marketed with claims that state or imply reduced risks compared with conventional cigarettes.

the world should permit such claims to be made. All companies wishing to market HTPs with reduced risk claims should be held to the same standard, and their claims independently verified.

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