Toxicology Mechanisms and Methods

ISSN: 1537-6516 (Print) 1537-6524 (Online) Journal homepage: https://www.tandfonline.com/loi/itxm20

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To cite this article: Paulina Natalia Kopa & Rafał Pawliczak (2019): IQOS - a heat-not-burn (HnB) tobacco product – chemical composition and possible impact on oxidative stress and inflammatory response. A Systematic Review, Toxicology Mechanisms and Methods, DOI: 10.1080/15376516.2019.1669245

To link to this article: https://doi.org/10.1080/15376516.2019.1669245

Accepted author version posted online: 18 Sep 2019.

IQOS - a heat-not-burn (HnB) tobacco product – chemical composition and possible impact on oxidative stress and inflammatory response. A Systematic Review

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IQOS - a heat-not-burn (HnB) tobacco product – chemical composition and possible impact on oxidative stress and inflammatory response. A Systematic Review

Abstract

Objectives: This work attempts to summarize current knowledge about IQOS, the heat-not-burn tobacco products, their chemical composition and possible impact on oxidative stress and inflammatory response.

Materials and Methods: The literature search was performed between January and April 2019 by a combination of terms: 'IQOS smoking', 'IQOS cigarette', 'I quit original smoking cigarette', 'heat-not-burn products', 'HnB tobacco products'.

Results: The aim of IQOS system is to minimalize the exposure of its smokers to dangerous substances present in cigarette smoke and to lower the probability of development of tobacco-related diseases. As current studies suggest, this new heat-not-burn tobacco product emits significantly lower concentrations of tar, carbonyls, VOCs, CO, free radicals or nitrosamines when compared to conventional cigarette, and thus it may reduce health risk for smokers. However, it does not eliminate this risk of development of tobacco-related diseases.

Discussion: For conventional tobacco smokers the IQOS products may be an alternative option, which helps to reduce exposure to hazardous and potentially hazardous constituents. However, for never-smokers using the IQOS cigarettes may develop addiction or increase exposition to some substances, which may increase probability of tobacco-related diseases. Moreover, emission of unexpected substances depends on device cleaning strategy and puff regiments.

Conclusions: There is only limited data about IQOS effect on smokers' health. Future investigation, especially comparison with healthy never-smokers or study of chronic exposure to IQOS, is needed.

Keywords: *smoking; heat-not-burn tobacco product; IQOS; oxidative stress; inflammatory response*

Introduction

Smoking is a global problem. According to the „*WHO report on the global tobacco epidemic, 2015: raising taxes on tobacco*", about 28% of European population (38% male and 19% female) currently smoke tobacco products (World Health Organization, 2015). Both active and passive exposure to tobacco smoke causes increased risk of cancer and cardiovascular or respiratory disease development (Lee, 2013). Moreover, tobacco smoking is classified as a one of the leading causes of death around the world. For people of age ≥ 30 year-old, tobacco smoking is currently responsible for about 16% of all deaths in Europe. This number for European region is higher than global average of deaths caused by smoking (12%) (World Health Organization, 2015). In 20th century, tobacco-related diseases were the cause of deaths of over 100 million people and this number is still increasing (World Health Organization, 2013).

Tobacco cigarettes contain about 5000 different chemicals, such as: tar, carbon monoxide (CO), nicotine, tobacco-specific nitrosamines (TSNAs), volatile organic compounds (VOCs) or polyaromatic hydrocarbons (PAHs) (Harris, 1996; Talhout et al., 2011). A great number of publications confirmed that these substances emitted to cigarette aerosol have an negative effect on the smoker's body. Moreover, a huge number of free radicals released to cigarette aerosol leads to oxidative stress activation in the respiratory tract, which corresponds to inflammatory response and airways remodeling (Gometz, 2011; Sherman, 1991). To reduce consumer exposition to these hazardous substances emitted in the main-stream and a side-stream cigarette aerosol, alternative smoking devices, such as electronic cigarettes and heat-not-burn tobacco products (McKelvey et al., 2018b, 2018a), are introduced on the market.

After 15 years from introducing the electronic cigarettes to the market, their chemical composition and the effects on consumers' bodies have often been researched. However, there

is only limited data for the second alternative smoking method - the IQOS (I quit original smoking) system. This new heat-not-burn product has been made by Philip Morris International (PMI) to reduce consumers exposure to harmful and potentially harmful constituents (HPHCs) emitted during burning tobacco. Less exposure to toxic chemicals released in IQOS cigarette smoke may reduce potential toxicological effects. Moreover, huge amount of hazardous chemicals that increase the risk of development of tobacco-related diseases present in conventional tobacco cigarette smoke could be reduced after switching to new heat-not-burn IQOS system. However, there is only limited number of trials corresponding to health effects of this alternative method of smoking and future investigations are needed (Liu et al., 2018a; Tabuchi et al., 2016; Adriaens et al., 2018; Elias et al., 2018; Popova et al., 2018).

The following work attempts to summarize current knowledge about the new heat-not-burn IQOS system, its chemical composition, and analyze current data about its potential effect on oxidative stress and inflammatory response, when compared to tobacco cigarettes (TCs) and electronic cigarettes (ECs). The authors have no links to any branch of tobacco industry, and none of the authors has had any relationship with Philip Morris International in the past or present. Therefore, the following work provides a completely independent systematic review of current research results about IQOS system.

Methods

This literature review focuses on a new alternative tobacco product – the heat-not-burn IQOS cigarettes. In the article we summarized current knowledge about chemical composition of these products and their potential effect on oxidative stress and immune response induction. Searching strategy of article identification, as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement, is shown in Figure 1.

The literature search was performed between January and April 2019 by the combination of terms: 'IQOS smoking', 'IQOS cigarette', 'I quit original smoking cigarette', 'heat-not-burn products', 'HnB tobacco products' in the PubMed database. Initial 48 articles in the topic of IQOS were further analysed by title and abstract. Reference list of review articles gave additional 5 more literature positions. Articles which summarized chemical composition of IQOS were also included to this systematic review. Other inclusion criteria were: original data, publications which discussed the effect of smoking IQOS on immune response and oxidative stress parameters and articles published in English language.

Basing on primary analysis of articles by title and abstracts, the initial number of 53 publications was reduced to 43 articles, which were additionally analysed. At this step, 10 articles were excluded from further review, because they did not meet the inclusion criteria. The exclusion criteria were: no direct connection to smoking IQOS (i.e. marketing or legislation issues), other manuscript language than English, publications which discussed new methods of determining chemical composition of HnB products or subjective opinions about their effect on customers' health. At this step, the total number of publications used in this systematic review was reduced to 20, and divided into two parts, based on type of findings, for further discussion in the Results section.

Results

Chemical Composition of IQOS

IQOS system generates temperature necessary for heating the tobacco plug to produce aerosol, which is inhaled by smokers. The temperature oscillates between 330-349 ^{0}C. During heating process there is no tobacco combustion and thus the emission of toxic chemical compounds is reduced. This way IQOS provide lower exposition to the HPHCs and reduced adverse health effects of smoking. Moreover, above 350 ^{0}C these electronic devices are

automatically switched off (Adriaens et al., 2018; Davis et al., 2019; Farsalinos et al., 2018a, 2018b; Gale et al., 2018). Another important aspect connected with IQOS system is a limited smoking cycle. The devices work maximally for 6 minutes and after this time they need to be charged. Moreover, in order to achieve the highest smoking efficiency, each puff should be taken within 25 sec intervals. With these conditions the maximal number of puffs taken in 6 min is 12-14 (Davis et al., 2019; Lee et al., 2018; Pacitto et al., 2018) (IQOS system elements are shown in Figure 2).

Lower temperature of heating tobacco in IQOS system, compared to conventional tobacco cigarettes, should be assumed to reduce smokers' exposition to HPHCs. According to the GC-MS study by *Davis et al*, the non-used heat stick contains 1,2-diacetin, lactide and Ɛ-caprolactone (in the polymer-film filter part of heat stick). Authors of the study also observed melting of the polymer-film filter during device usage. Moreover, presence of formaldehyde cyanhydrin (starting from 90 ^{0}C) was observed within operating temperatures generated by IQOS, inhalation of which may be dangerous for consumers. *Davis et al* discussed some possibilities of tobacco pyrolysis which occurred between 200 - 600 ^{0}C and emission of some volatile organic compounds (VOCs) or some constituents of tobacco, which boiling points are estimated between 70 – 300 ^{0}C (Davis et al., 2019).

Comparison of chemicals in mainstream smoke of tobacco cigarette and IQOS presented by *Bekki et al* show that the heat-not-burn products contained similar content of nicotine in mainstream smoke compared with conventional cigarette (1R5F) – 1.1 – 1.2 mg/cigarette vs. 1.0 – 1.7 mg/cigarette, respectively for IQOS and TC. Moreover, the HnB products emitted about 50% less tar and about 99% less carbon monoxide (0.44 mg/cigarette vs 32mg/cigarette) than tobacco cigarettes (Bekki et al., 2017). *Kaur et al* also highlight presence of nicotine, tar, carbonyl compounds and nitrosamines in IQOS aerosol. Therefore, heat-not-burn products do not eliminate, but only reduce exposure to hazardous constituents

of tobacco smoke, despite being used as an alternative, low-risk products to exchange conventional cigarettes (Kaur et al., 2018).

Farsalinos et al summarized IQOS content of main carbonyls in 3 different puffing regiments. This study showed that heat-not-burn products in their aerosol emit significantly less formaldehyde, acetaldehyde, acrolein, propionaldehyde and crotonaldehyde (at range between 72-95% for all carbonyls and puffing regiments) when compared with conventional tobacco cigarettes. However, when compared with electronic cigarettes, aerosol composition of IQOS contained higher concentrations of these carbonyls (at a range 82-99% for formaldehyde, acetaldehyde and acrolein in different puff regimen; propionaldehyde and crotonaldehyde were not present in EC aerosol) (Farsalinos et al., 2018b). Similar results were obtained by *Li et al*, where tar and nicotine contents were similar and some carbonyls, ammonia and N-nitrosanabasine (NAB) were about 80% lower for IQOS when compared with standard cigarette (3R4F) (Li et al., 2019). *Leigh et al* study showed that conventional tobacco cigarettes contained 7 – 17 times higher amount of TSNAs (N'-nitrosoanabasine, N'-nitrosoanatabine, 4-(-methylnitrosamino)-1-(-3-pyridyl)-1-butanone (NNK) and N'-nitrosononicotine) than the IQOS HeatStick with the similar nicotine content (1.3±0.2 mg from conventional cigarette vs. 1.4±0.2 mg from HeatStick) (Leigh et al., 2018a).

Protano et al measured deposition of submicronic particles in smokers' respiratory tract, when generated by conventional cigarettes, electronic cigarettes and IQOS. This study showed that exposition to SMPs occurred for e-cigarettes and IQOS and they can be inhaled to the alveolar region. However, for the alternative products this exposure is presented only during their usage and was reduced when the devices were turn off. For conventional cigarettes and hand-rolled cigarettes, SMPs deposition in the respiratory tract remined elevated also after finishing smoking. One hour exposition to a conventional cigarette, a hand-rolled cigarette, an e-cigarette or a heat-not-burn product was a source of submicronic

particles comparable to 49, 39, 12 and 10 min presence in heavy traffic area (Protano et al., 2016). Another study by *Protano et al* suggested that electronic devices: e-cigarettes and heat-not-burn IQOS products are responsible for deposition of significantly lower number of particles ($1.6*10^8$ particles/kg body weight) in the respiratory tract of a 3-month individual (second-hand smoke) when compared with conventional tobacco products ($9.88*10^8$ particles/kg body weight) (Protano et al., 2017). Moreover, a study done by *Pacitto et al* showed that IQOS emitted no more than $1*10^8$ particles/cm^3, especially for temperatures > 300 ^{0}C in mainstream aerosol (Pacitto et al., 2018) (Summarized in Figure 3).

Schober et al summarized passive exposure to pollutants from IQOS, conventional cigarettes and e-cigarettes in passenger cars. The authors showed an increased number of particles with diameter 25-300 nm for IQOS cigarettes ($1.6 – 12.3*10^4$/cm^3), and $PM_{2.5}$ for e-cigarettes (75 – 490 µg/m^3) and conventional cigarettes (64 – 1988 µg/m^3) in most of investigated cars. Furthermore, elevated levels of propylene glycol (50 – 752 µg/m^3) for electronic cigarettes and formaldehyde (18.5 – 56.5 µg/m^3), acetaldehyde (26.5 – 141.5 µg/m^3) and acetone (27.8-75.8 µg/m^3) for conventional cigarettes were observed inside the cars (Schober et al., 2019).

IQOS vs. Oxidative Stress and Inflammatory Response

Huge amount of free radicals present in cigarette smoke contributes to damaging of oxidative-antioxidative balance. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are responsible for peroxidation of specific structural components, such as lipid proteins or DNA, and cause changes in activity of different molecules, which consequently leads to activation of secretions of cytokines and chemokines. This inflammatory response is responsible for starting structural changes in respiratory tracks, which may affect the development of smoking-related diseases (Cai and Wang, 2017; Williams et al., 2013).

Salman et al analysis of aerosol of tobacco products by high-performance liquid chromatography and gas chromatography showed that IQOS, heat-not-burn products generated significantly lower concentrations of ROS and carbonyls than conventional Marlboro Red tobacco cigarettes. Moreover, both tobacco products emitted similar concentrations of nicotine and free base (FB). When the authors compared obtained results to the concentrations of investigated compounds in urban air, 1 pack/day of smoking IQOS generated 2-fold higher concentration of formaldehyde and ROS and 100-fold higher concentration of acetaldehyde than in urban air. However, when smoking IQOS 1 pack/day was to be compared with smoking 1 pack/day of conventional tobacco cigarettes, daily intake of formaldehyde and acetaldehyde may be reduced by about 70% and 65% and ROS generation about 85% (Salman et al., 2018). Despite the fact that switching from tobacco cigarettes to IQOS may reduce customers' exposition to ROS and carbonyls by 85%, these substances may be harmful even in small doses for never-smokers. As various data suggest, free radicals like ROS and RNS, and some toxic substances, such as TSNAs, VOCs and PAHs irradiate airways and disrupt oxidative-antioxidative balance. Secretion of chemokines and cytokines consequently leads to inflammatory response and remodeling respiratory tracts, which is characteristic for chronic respiratory diseases. For this reason, it is very important to determine the effect of free radicals and some harmful and potentially harmful substances emitted during smoking IQOS on health parameters of never-smoking customers (Cai and Wang, 2017; Farsalinos et al., 2018b; Leigh et al., 2018a; Salman et al., 2018; Sharman et al., 2018).

Kaur et al review of current literature also suggested that presence of components such as tar and volatile organic compounds in IQOS aerosol increases exposure to free radicals and activation of oxidative stress and inflammatory response in the airways. Therefore, heat-not-burn tobacco products may activate a mechanism of airway remodeling similar to

conventional cigarettes, which may lead to increased risk of smoking-related diseases, such as asthma, COPD or stroke (Kaur et al., 2018). *Leigh et al* showed that IQOS smoke provided higher cytotoxicity (trypan blue staining and neutral red uptake assays, 2.5 h exposure) to bronchial epithelial cells than control air sample and e-cigarette aerosol. However, conventional cigarette smoke is responsible for the highest cytotoxic effect on these cell lines, when compared to control, IQOS and e-cigarette group. Moreover, only for conventional cigarette there was a significant increase in cytokines production (ELISA test, 2.5 h exposure) by bronchial epithelial cells after exposition to any cigarette smoke (Leigh et al., 2018b). *Sohal et al* study on human bronchial epithelial cells, Beas-2B and primary human airway smooth muscle (ASM) cells, showed similar cytotoxicity (MTT and LDH tests, 72 h exposition) of 1, 5 and 10% extracts of IQOS and conventional cigarettes and also in dose-dependent manner induction of chemokine release (CXCL8, ELISA test, 72 h exposure) in both cell line types. Moreover, the authors observed that only the 10%-e-cigarette extract induces enhanced chemokine release. In a concentration-dependent manner, conventional cigarette, e-cigarette and IQOS extract exposure increased collagen 1 and fibronectin release (ELISA test, 72 h exposure), extracellular acidification rate and proton leak from mitochondria (extracellular acidification rate (ECAR) analysis, 72 h exposure), in both cell types (Sohal et al., 2019).

Study of *Moazed et al* on Philip Morris International (PMI) application of IQOS as a modified risk tobacco product (MRTP) for US FDA summarized and discussed results obtained for animal model and human participants who switched to IQOS. In the study 10-week-old rats that exposed to 90-day inhalation of heat-not-burn product aerosol (6 h/day, nicotine dose 15-50 µg/L of aerosol) were characterized by increased level of inflammatory cells in airways, which may suggest activation of inflammatory response. However, the number of inflammatory cells after exposition to IQOS smoke were significantly lower than

after exposition to conventional cigarette aerosol. Clinical studies discussed by *Moazed et al* were performed on adult smokers (at least 10 cigarettes smoked/day for 3 years) for up to 90 days for participants who continued smoking conventional cigarettes, quit smoking and switched to IQOS. For the study on participants who switched to heat-not-burn products smoking, there was only a reduction in white blood cells (WBC) level when compared to cigarette smokers group. Other parameters of pulmonary function: C-reactive protein (CRP) and Forced Expiratory Volume in one second (FEV_1) remained similar for both groups of participants. A second study, with US participants, show that switching to IQOS does not change pulmonary function compared with cigarette smoking group (Moazed et al., 2018).

Discussion

Philip Morris International introduced a heat-not-burn IQOS products on the market in 2014, therefore we acquired only limited data about their chemical composition and possible impact on health of their consumers. The literature provides some studies about chemical composition of HeatSticks and IQOS aerosol and their effect on pulmonary function. As the available data suggests, IQOS emits lower concentrations of harmful and potentially harmful constituents when compared with conventional tobacco cigarettes, which may reduce probability of development of smoking-related diseases. Therefore, switching from conventional cigarettes to HnB products may reduce customers' exposure to these toxic substances and in this way improve health outcomes (Glantz, 2018; Sohal et al., 2019). However, most of the studies compared the aforementioned parameters only for smokers who had switched from conventional to IQOS tobacco products, and there is no data about health effects of IQOS for never-smokers or for prolonged usage of IQOS system. For customers who have never been smoking, using IQOS, which contain similar nicotine concentrations as other standard tobacco products, may lead to increased risk of developing addiction. As data suggested, IQOS smokers who smoke 1 pack/day of are exposed to two times more

formaldehyde and ROS, and 100-times more to acetaldehyde than if they were inhaling urban air only. (Liu et al., 2018; McKelvey et al., 2018a; Salman et al., 2018).

Another important aspect is the effect of irregular cleaning of IQOS and puffing regiments on emission of hazardous chemicals during product usage. For the IQOS device, there are two cleaning protocols: first, per use cleaning protocol, which recommends cleaning the device after each use of the HeatStick; second, the manufacturer's recommended cleaning instruction, where cleaning is needed after each 20 uses (1 pack) of the HeatStick. Cleaning regiments may affect subsequent emission of hazardous or potentially hazardous substances in IQOS smoke. After each HeatStick usage a part of the tobacco plug or substances from filter remain in the IQOS chamber. During next usage without cleaning, unremoved tobacco particles may be burned and emit unexpected toxic substances which negatively affect customers' body (Davis et al., 2019). Puffing regiment may also affect exposition of customers to hazardous substances. As data suggests, number of puffs, duration and volume may increase customers' exposition to toxic substances, such as carbonyls. More intense puffing regime enhanced inhalation of formaldehyde, crotonaldehyde, acetaldehyde or propionaldehyde (Farsalinos et al., 2018b).

The currently performed *in vitro* and *in vivo* tests show the chemical characteristic of IQOS aerosol, and indicate presence of small amounts of free radicals or HPHCs. Moreover, these studies also determine cytotoxic effect of HnB products to airway cells. Therefore, these results suggest that IQOS may induce oxidative stress and inflammatory response in the airways. However, other pre-clinical and clinical studies highlighted that IQOS induces lower number of inflammatory mediators than conventional cigarettes and lead to improvement of respiratory parameters. However, these clinical trials were carried out with smokers who switched to HnB products and compared to conventional tobacco smokers. Moreover, there is no data about IQOS smoking impact on health outcomes for never-smokers or some specific

groups of people, such as children, pregnant women and fetuses, older people or people suffering from chronic diseases. Therefore, to clearly define safety and benefits of IQOS as an alternative smoking method, further investigations are needed. First of all, studies of possible impact of HnB products on chronic respiratory diseases development among healthy never-smokers should be carried out, which is highly important due to growing interest of this new tobacco product. As a *Liu et al* Italy data suggested, about half of respondents who want to try IQOS products are never-smokers (Liu et al., 2018) . Another focus point of studies should be the impact of chronic exposure of IQOS on exacerbation of chronic respiratory diseases (for IQOS only-smokers) or the health effects of long-term use of IQOS. *Sharman et al* to determine IQOS effect on respiratory symptoms of COPD, exacerbation frequency and lung function suggested a 5-year cohort observational study with adult IQOS or conventional cigarette smokers (Sharman et al., 2018). We suggest that *Sharman et al* scheme of study or similar observational study for at least 2 years for IQOS-only and TCs-only smokers should be optimal. An important issue is also to determine the prenatal impact of heat-not-burn tobacco products on fetus and child respiratory system development and possibility of appearance of chronic diseases or the effect on gene expression. Currently available data may suggest that IQOS products are a safer smoking option than conventional tobacco products, therefore, basing on information currently available, may potentially be used during pregnancy. However, as data shows, fetal abnormalities are significantly affected by nicotine, which content is similar in IQOS and conventional cigarettes (McEvoy and Spindel, 2017). Moreover, there is no pre-clinical or clinical data about the impact of these HnB products on fetus development. For this reason, initial study with animal models would be helpful to determine possible effects of IQOS aerosol on fetus or gene expression. Such model for e-cigarettes was suggested by *Lauterstein et al*, where pregnant mice were exposed to

e-cigarette aerosol and their effects on fetus development were investigated in 1-month offsprings (Lauterstein et al., 2016).

Conclusions

IQOS heat-not-burn products were introduced by Philip Morris International on the market in 2014, therefore only limited data about their impact on the customers health is currently available. Compared to conventional tobacco cigarettes, IQOS devices reduce customers' exposition to hazardous and potentially hazardous constituents. In this fact, HnB products seems to be an alternative option for smokers. However, IQOS do not eliminate probability of development of tobacco-related diseases. Moreover, there is no data about their impact on the never-smokers or exacerbation of chronic disease for these customers. Therefore, to clarify safety of the IQOS, future investigations are needed.

Acknowledgements

This work was supported by a Medical University of Lodz Grant: 503/0-149-03/503-01-004 and 503/0-149-03/503-01-005

Declaration of interest statement

Disclosure of interest: The authors report no conflict of interest. The authors report no declaration of interest.

Authors' contributions: PK searched the literature, analysed the data, interpreted the results, and wrote the manuscript; RP supervised overall study, analysed the data and critically reviewed the manuscript. All the authors have read and approved the final manuscript.

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