Universidade de Lisboa
Faculdade de Farmácia

Traditional and New forms of Tobacco: Impacts on Health

Daniela Sofia Albernaz Reis Dias Moreira

Monografia orientada pela Professora Doutora Cristina Maria Leitão de Carvalho, Professora Associada

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Acknowledgments

I was eighteen and attending a friend's birthday party when someone asked me as a joke: ”How can an atom commit suicide? By throwing itself from an hydrogen bridge”. At that time, I was about to get into college for Business Administration and had quit studying Chemistry and Biology three years prior. Needless to say, I did not get the joke.

Regardless of its comedic potential, remembering this incident has put a smile on my face. Understanding this joke, encompasses a part of life and knowledge that I would have missed had it not been for the time spent at FFUL.

Pursuing Pharmaceutical Sciences at age twenty-five was, undoubtedly, the best family decision we ever made. It took my father's challenge to dream it, my mother's altruism in waiting on me to join the family business, my brother's insights and study notes, my grandmother's example and, last but certainly not least, my husband's motivation and pep talks every single time I felt like giving up. It took everyone of us. Nowadays, thankful for my family's input in this incredible journey, if nothing else, I am able to proudly say that I now get the joke. I still don´t find it funny, but I do get its point.

Declaração

Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

Resumo

Os novos produtos à base de tabaco são a resposta inovadora criada pelas tabaqueiras à alteração brusca registada nas preferências dos seus utilizadores que conduziu à descida acentuada da venda de cigarros de combustão. Este ponto de inflexão na ”epidemia do fumo” registou-se no início dos anos 50 quando começaram a ser publicitados estudos que correlacionavam o fumo de tabaco com patologias concretas, incluindo diferentes tipos de cancro. Tendo-se tornado crescentemente populares em anos recentes, os novos produtos à base de tabaco como os e-cigarros e os produtos à base de tabaco aquecido foram percecionados pelas massas como sendo preferíveis ao tabaco, tanto a nível social (estes dispositivos não emitem fumo e proporcionam uma experiência de uso mais limpa e discreta) como sobretudo ao nível do impacto na saúde (menos danosos que cigarros). Contudo, o verdadeiro impacto destas novas formas de tabaco na saúde tem sido publicitado de forma por vezes enganosa, navegando a ambiguidade entre ”risco minorado” e ”isento de risco”. Através de uma revisão literária detalhada, contrastando resultados obtidos por pesquisa promovida por empresas no sector e por fontes independentes, foi exposta e analisada a composição qualitativa e quantitativa dos aerósois formados por novos produtos à base de tabaco e o fumo de cigarros tradicionais. Devido a conteúdos qualitativamente semelhantes na composições destas emissões gasosas, são esperados efeitos secundários semelhantes aos induzidos pelo fumo de cigarros em novos produtos à base de tabaco, em especial no que toca a : dano endotelial e cardiovascular e imunosupressão pulmonar. A hepatotoxicidade é mecionada como um efeito colateral inesperado associado a produtos de tabaco aquecido. Dito isto, resultados obtidos entre as fontes literárias consultadas sugerem que, comparativamente aos cigarros, os cigarros eletrónicos são a categoria de novos produtos à base de tabaco que representam um menor risco para a saúde dos seus utilizadores, ressalvando contudo a necessidade de mais pesquisa neste tópico. Por último, o caso específico do IQOS foi descrito com maior destaque, não só pela sua prevalência a nível comercial mas também por se tratar de um exemplo flagrante do impacto pernicioso da investigação subsidiada e promovida pela indústria tabaqueira na manipulação da perceção dos seus consumidores. Dados gerados pela empresa, como resultados dos seus testes clínicos e as suas afirmações publicitárias foram contrastadas com resultados provenientes de projetos de pesquisa independentes.

Palavras Chave

Tabaco, Cigarros eletrónicos, HTPs, IQOS, Riscos para a Saúde

Abstract

New tobacco products are tobacco conglomerates' innovative response to a drastic shift in customers preferences which has ultimately triggered a decline in combustion cigarettes' sales. This pivotal point in the smoking epidemic began in the early 1950s as research correlating smoking with different diseases, including various types of cancer, started becoming widely publicized. Having become increasingly popular in recent years, new tobacco products as e-cigarettes and heated tobacco products have been perceived by the masses as being preferable to tobacco, both in social terms (this smoke free devices provide a more discreet and clean experience) and mostly heath wise (less harmful than traditional cigarettes). However, these new tobacco forms' true impact on health has been marketed in an at times misleading way, navigating the ambiguity between ”decreased” and ”null” impact on health. Through a thorough literature review, contrasting industry funded and independently generated research, the similar qualitative and quantitative composition in new tobacco forms' aerosols and traditional cigarettes' smoke was exposed and analysed. Due to similarities in its gaseous emissions' contents, expected side effects from new and traditional tobacco products were concluded to be coincident as far as endothelial and cardiovascular injury and pulmonary immunosupression were concerned. Hepatotoxicity was regarded as an unexpected side effect from heated tobacco products. With that said, results derived from consulted research papers suggest e-cigarettes to be the less harmful new tobacco product once compared to traditional cigarettes, despite acknowledging that further research is needed in this matter. Lastly, the case of IQOS was described in greater detail, not only for its commercial prevalence but also because it is a flagrant example of the pernicious impact from industry funded research on conditioning the users' perceptions. Company generated research, as results from its clinical studies were analysed and its marketing claims confronted with results from independent research on the topic.

Keywords

Tobacco, e-cigarettes, HTPs, IQOS, Health Risks

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Acronyms

CC	carbonyl compounds
COO	chief operating officer
FDA	Food and Drug Administration
FMD	flow-mediated dilation
HCI	Health Canada Intense - 55ml puff volume, 2s duration, 30s interval
HNB	heat not burn
HPHC	harmful and potentially harmful chemicals
HTPs	heated tobacco products
HTU	heated tobacco units
IARC	International Agency for Research on Cancer
ICAM	intracellular adhesion molecule
ISO	International Organization of Standardization
MRTP	modified risk tobacco product
PAH	polycyclic aromatic hydrocarbons
PMI	Philip Morris International
REX	reduced exposure
TPSAC	Tobacco Products Scientific Advisory Committee
TSNA	tobacco-specific nitrosamines

1

Introduction

Contents

1.1 The Smoking Epidemic

With the introduction of mass manufactured cigarettes in the late 20th century, cigarette smoking became a mass phenomenon in the developed world, as acknowledged by Richard Edwards [1]. This point is also reflected in Gary A Giovino's [27] research paper. According to the author, tobacco consumption "peaked in the early 1950s at approximately 13 pounds of tobacco consumed" *per capita* in the United States. By then, Giovino [27] estimates that 80% of all tobacco consumed in this market was attributable to cigarette consumption. Two main aspects justify this pivotal point in nicotine consumption at such time: shift to cigarettes from other tobacco products (i.e. chewing tobacco, cigars), as well as, additional tobacco consumption being driven by women who, by the beginning of 1920s, became more likely to engage in tobacco smoking as they became heavily targeted by marketing campaigns endorsing cigarettes' use. According to the author, four stages could be expected in a "smoking epidemic". A period of incremental smoking prevalence which steadily declines after its peak is reached, is followed by a similar trend in smoking attributable illnesses. The author calculates that a two to three decades lag time separates these two moments. See Figure 1.1 [1].

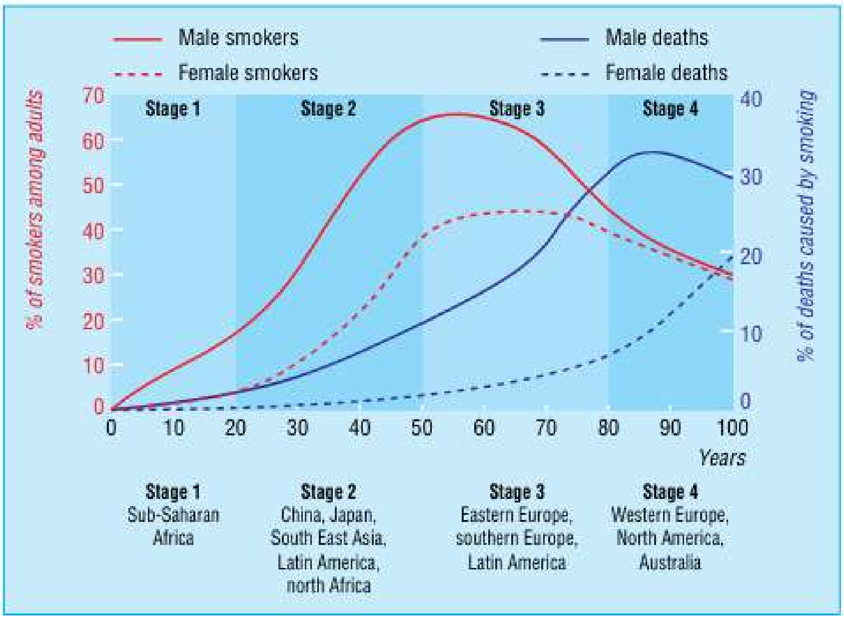


Figure 1.1: Stages of the "smoking epidemic" in developed countries as depicted in reference [1].

As highlighted by Kuper et al [2], "the first convincing report" linking smoking to lung cancer was attributable to Doll and Hill [28] in 1950 "and became the prototype for case-control studies". Following this lead, the inherit mechanism of smoking become known. Though combustion, nicotine is released together with other toxic compounds as ultrafine particles. These are then carried deep into the smokers' lungs. From there, nicotine is rapidly absorbed, becoming systemically available, and being carried on into the brain where its additive effect is performed, activating the brain's mesolimbic dopaminergic reward system. As detailed by Tiwari et al [29], nicotine's action in the brain stimulates both presynaptic acetylcholine receptors (enhancing acetylcholine's release and metabolism) and the dopaminergic system, which promotes the accumulation of dopamine in the nuclear accumbens (a property that Tiwari et al [29] attribute to possible re-enforcement of the behavioral changes associated to nicotine addiction).

However, as mentioned, the tail of the "smoking epidemic" has also become widely researched on from the 1950s onwards. As pointed out by Kuper et al [2], as of 2002, 15% of all cancers were attributable to smoking. In this statistic figured cancers with etiological associations with the respiratory track, as well as, urinary bladder, pancreatic, kidney and renal pelvis cancers. Given the multistage process that is carcinogenesis, there is no one all encompassing mechanism that can be attributable to tobacco-related carcinogenesis. The existing variety in tobacco products combined with differences attributable to their specific usage methods may impact the release of carcinogens in smoke or aerosols and influence the link between tobacco use and cancer causation. Furthermore, as acknowledged by Kuper et al [2], there is the role played by individual susceptibility as well as a random component that contribute to the event of carcinogenesis. On that note, a likely pathway that factors in tobacco's inhalation or ingestion (as is the case in smokeless tobacco products) is schemed out in Figure 1.2 [2].

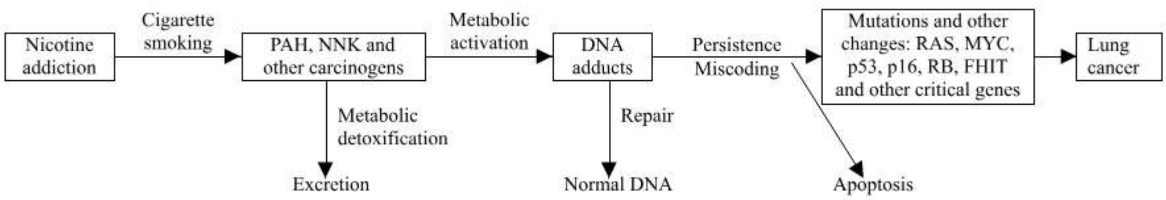


Figure 1.2: Scheme depicting the pathway through which tobacco smoke carcinogens can induce lung cancer through a series of mutations in critical genes, as showcased in [2].

Notes: As depicted, carcinogens present in tobacco products, once inhaled (or ingested, as is the case with smokeless tobacco products) undergo phase I oxidative reactions which enable the attachment of a conjugate by phase II inactivating enzymes. However, metabolites from phase I reactions have an increased potential for DNA damage, forming covalent bonds with it, thus creating DNA adducts. If these adducts escape cellular repair mechanisms and become persistant, they may lead to miscoding which, in turn, results in mutation. Specific mutations can result in the activation of an oncogene or the deactivation of a tumour suppressor gene, which can lead to uncontrollable cell division and, ultimately, cancer.

Accordingly, as studies begun to point out the overwhelming negative outline of this daily habit, multinational tobacco companies struggled to find a product that avoided burning, hence did not showcase the same toxicological profile (implying a differentiated risk profile). Such products included: low tar cigarettes, electronic cigarettes (e-cigarettes) and heated tobacco products (HTPs). Contrary to traditional cigarettes, the latter heats tobacco to a temperature that prevents combustion, whilst not requiring an e-liquid to operate. According to author Kate Lichtenberg [30], the first e-cigarettes' models began development in 1965, only to be first patented in 2003, and later introduced to the American market in 2007. This evidence is somewhat reflected in Dutra et al's [31] research, which indicates that the development of electronic nicotine delivery systems by tobacco companies started in 1963. However, these authors clearly attribute the modern electronic cigarette's invention to Chinese pharmacist Hon Lik, in 2003. With all the advancements and delays expected in the prosecution of an innovative products, it wasn't until January 2018, that the industry's efforts came to fruition as most manufacturers operating in the tobacco industry had developed (or were close to reaching their end goal in creating) a heated tobacco product under their respective label, as you can see in Table 1.1.

Table 1.1: Multinational tobacco companies with e-cigarette brands as presented in reference [17].

Company	E-cigarette brand
Altria (NuMark)	MarkTen, Green Smoke
Philip Morris International	Heat-not-burn, IQOS brand (Vape Ranks 2014) E-cigs, Nicolites by Nicocigs (Philip Morris International 2014)
Reynolds (Reynolds Vapor Company)	VUSE
Lorillard (Lorillard Vapor Company)	blu (until 2015)
Imperial Tobacco (Fontem Ventures)	Puritane (formerly Ruyan) blu (acquired in 2015)
British American Tobacco	Vype
Swisher	E-swisher
Japan Tobacco International (JTI)	E-Lites, offered in the United Kingdom by Zandera Ltd., which was acquired by Japan Tobacco Inc. in 2014 (Japan Tobacco Inc. 2014) Ploom (tobacco pods in heat-not-burn) and Ploom PAX (used for vaporizing marijuana) (Japan Tobacco Inc. 2015)

For cultural reasons, the Asian market became a natural early adopter for new tobacco products. Out of curiosity, it may be referenced that the first electronic cigarette was first commercialized in China. Accordingly, in their study of heat not burn (HNB) tobacco products in Japan, independent research conducted by Tabuchi et al [3] addressed the growing popularity of one of such products above its competitors. As evidenced in Figure 1.3 [3] weekly Google searches for IQOS have sky rocketed. Triggered by the product's marketing placement in a popular TV show "Ame-Talk" in April 2016, interest in IQOS has been sustained since then through promotional activities and the added incentive to circumvent the nationwide spread of smoke free environments.

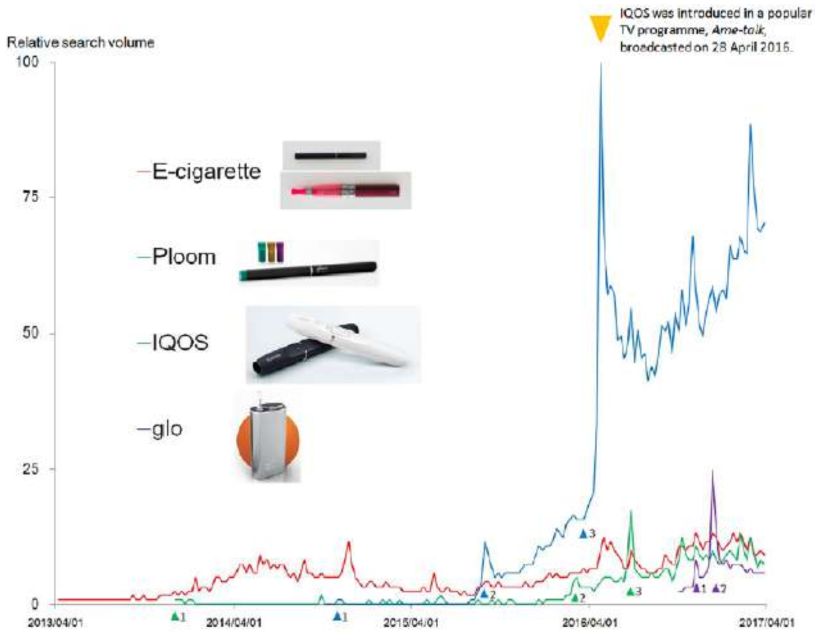


Figure 1.3: Weekly Google search volume for HNB tobacco/e-cigarette from 2013 to 2017 in Japan as contemplated in reference [3].

IQOS, Philip Morris International's answer to this market shock, was first market tested in 2015. One year later (in December 2016) Philip Morris International (PMI) submitted an application to the FDA to support its marketing claims and grant the product the label modified risk tobacco product (MRTP). According to what is stated in Section 911 (g) from the Family Smoking Prevention and Tobacco Control Act [32], the Food and Drug Administration (FDA) must only issue an MRTP order conditional to its applicant providing substantial and scientific evidence that its product, in its intended usage, will:

(A)" Significantly reduce harm and the risk of tobacco co-related disease to individual tobacco users";

(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".

As could be expected, PMI resorted to its own internally designed and conducted studies to backup IQOS's claims and meet the FDA's requirements in its MRTP application. Naturally, industry sponsored research faces a greater incentive to enhance or misconstrue conclusions in order to corroborate its desired outcome. Likewise, this process was involved in a degree of controversy as independent studies started to point out inconsistencies with the application itself, as well as, counter arguing conclusions reached in PMI funded research.

Throughout this timeline, Portugal played pivotal role in validating IQOS's business model and success as an early adopter. It was the fourth country in the world to allow its commercialization and, by 2020 it was estimated that this product was being used nationwide by approximately a quarter of a million smokers. See Figure 1.4.

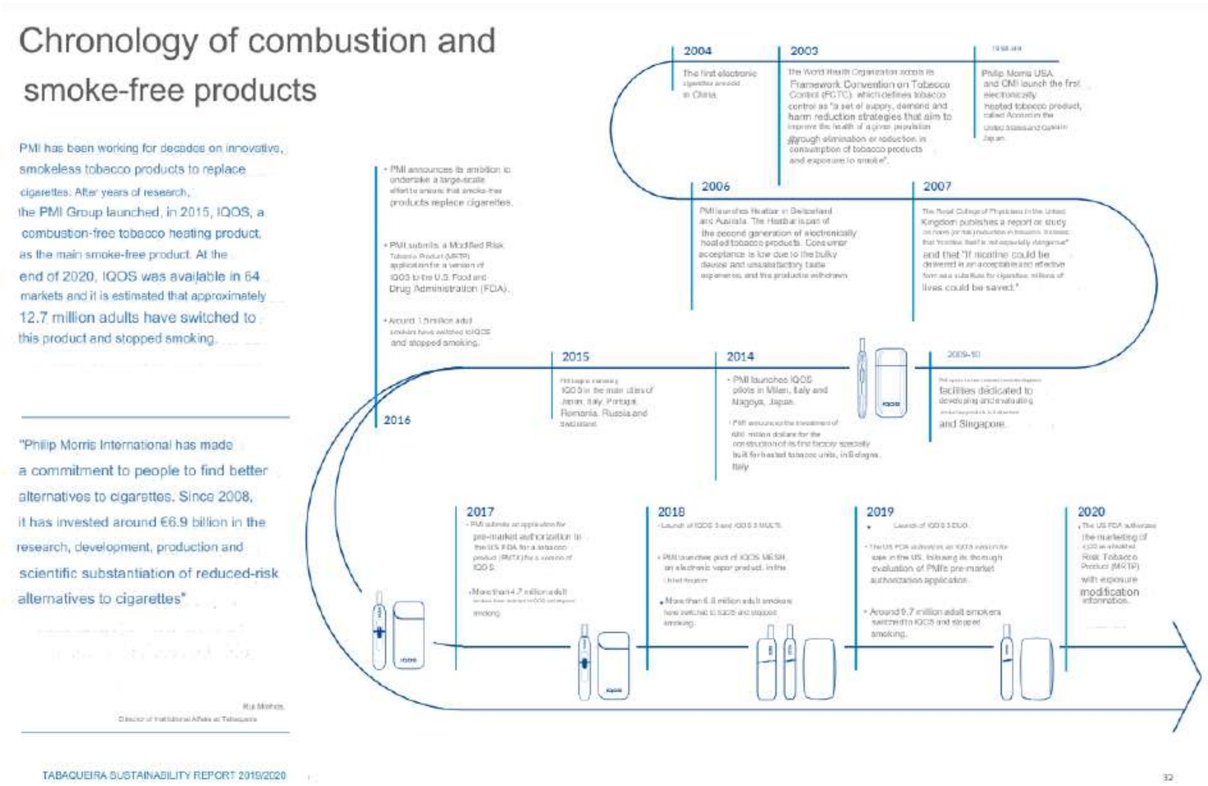


Figure 1.4: IQOS. Timeline of IQOS market introduction according to Tabaqueira, PMI's sales representative for the Portuguese market, in its 2019/2020 Sustainability Report depicted in [4]

At the end of the day, the 2016 efforts from PMI in obtaining the MRTP status for IQOS fell short on their initial purpose as this authorization was not granted by the FDA. It was only two years later, by 2020, that the company saw the green light from the agency and its application favourably closed.

1.2 Methods

Going in to this project, a manual search culminating in a short list of articles by the Financial Times aided in creating a schematic view of the information and data collecting methods to be undertaken in this literature review, as demonstrated in Figure 1.5 .

The search strategy was designed to first follow a chain on independent researchers, initiated with Dr Staton Glantz's available bibliography on the topic of ”new tobacco products” and, subsequently considering his co-authors and other referenced papers. Results depicted in these pool of research papers was then contrasted those obtained from industry funded papers (data from industry promoted clinical studies, an MRTP application and other company generated evidence was analysed). Research papers were mainly obtained through search engines, as PubMed and Google Scholar and were later complemented with the search of key words related to the topic at hand ("HTP" OR "IQOS" OR "Risks of new tobacco products" OR "new tobacco sources" OR "new nicotine delivery systems" OR "new tobacco forms" AND "nicotine"). Additionally, a complementary business perspective, intended to highlight the motivation and financial pressure from tobacco companies to invest in new tobacco products was included, by concentrating on PMI's example with IQOS. Information supporting this segment was obtained from PMI's sources mainly its: annual sales report, press briefing for quarterly results and its representative for the Portuguese market's sustainability report.

All in all, in constructing this literature review, 50 bibliographical sources were consulted. From these, 4 derived from news outlets, 5 were industry funded and generated (including Wong et al research paper) and 4 were pertained to governmental health agencies (EMA and the FDA). On that premise, 74% of all bibliographical sources cited are independent research papers, which critical view on new tobacco forms proved essential in ensuring that this project's main objective could be achieved : contrasting expectations created by the tobacco industry on new tobacco forms with scientific evidence supporting these products' true risk profile.

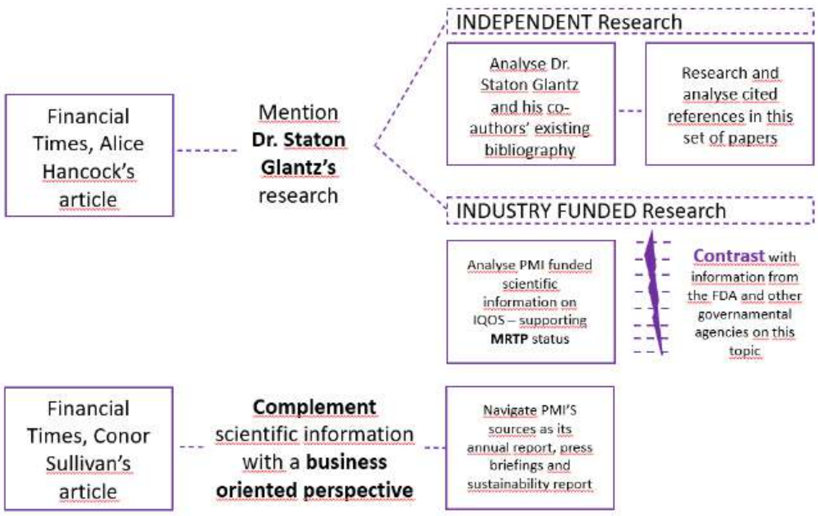


Figure 1.5: Scheme on information and data collection methods followed. Articles mentioned correspond to those found in references [5] and [6]

2

New Tobacco Forms

Contents

2.1 Heated Tobacco Products (HTPs)

As captured by Jankowski et al [33] in their research work, "Heated tobacco products (HTPs) are a form of nicotine delivery intended to provide an alternative to traditional cigarettes". These products display a patented heating technology incorporated in an internally placed metal component (which either penetrates the tobacco stick , as is the case of IQOS, or surrounds it, as is the case in glo - British American Tobacco's HTP brand). By activating this component, tobacco sticks are then heat up to a temperature inferior to combustion levels (350°C in IQOS and 240°C in glo).

As outlined in this systematic literature review on HTPs, the first market introduction of a product incorporating this technology took place in the USA in 1988, with R.J.Reynolds's "Premier". This step was only followed by PMI with "IQOS" in 2014 and in 2016 by British American Tobacco with "glo"."Ploom TECH", a hybrid between this technology and that of electronic cigarettes, developed by Japan Tabacco, also reached the market around this time. See Table 2.1 [18]. Whereas the first two contemplated similar technology in Ploom's case, the aerosol was formed by heating an inhalation solution (containing propylene glycol or glycerol).

Table 2.1: Availability of heated tobacco product by major cigarette company and country of availability (January 2018), as depicted in reference [18].

Company	Product	Year launched	Countries/comments
British American Tobacco	iFuse* glo	2015 2016	Romania, Japan, Switzerland, Canada, South Korea, Russia.
China National Tobacco Corporation/State Tobacco Monopoly Administration (STMA)	Not reported	Not launched	A few of the companies claim to have over 30 patents of HTP and continue to be engaged in research and development of these products. But none yet are in the market.
Imperial Brands	Not reported	Not launched	Focusing on e-cigarettes at the moment, claims to have options to launch when it deems that time is right.
Japan Tobacco International	Ploom TECH†	2016	Japan, Switzerland.
KT&G Corp	lil	2017	South Korea
Philip Morris International‡	IQOS TEEPS§	2014 Not yet launched	Canada, Guatemala, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Kazakhstan, Lithuania, Monaco, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Switzerland, Ukraine, United Kingdom, South Africa, South Korea, Japan, New Zealand.

†Ploom TECH is described as a hybrid between an HTP and a vaporiser. It is to be used with Mevius capsules. Mevius is one of JTI's best-selling cigarette brands. The capsules contain tobacco that are then heated by vapour. ‡PMI website states that it is developing a new heated nicotine delivery product that has no tobacco, STEEM, among other 'reduced risk' products.

Across the board, these products' marketing has focused on actively addressing two key issues: HTPs showcase reduced levels of harmful tobacco components making them less harmful than traditional cigarettes and HTPs are smoke and odour free. Under such strong claims, companies behind these products have made a conscious effort not only to appeal to potential customers, but also, as pointed out by Jankowski et al [33], to improve their position besides governmental power, striving to become perceived "as partners to address the tobacco epidemic rather than as the vectors causing it".

According to these authors (Jankowski et al [33]) there is even a more pressing matter: an overwhelming majority of industry funded research. Not only were independent projects considerably fewer in number but, more importantly, a clear contrast could be noted between tobacco companies' endorsed research goals and results obtained by independent sources. Considering its research scope, Jankowski et al [33] 2017 research project, indicates that 65% (20 out of 31) of all industry funded results available (at the time) tended to focus on the "nicotine delivery and mainstream emissions" as well as in isolating exposure to a pre-selected list of toxicants. Unfortunately, secondhand emissions were not discussed in these set of papers. The prevalence in industry or company funded studies comes as particularly alarming given tobacco companies track record in strategically positioning its research to prevent stricter regulations from being enforced. A clear example of such malpractices resulted in a group of studies conducted by PMI known as the Project MIX [34]. This set of papers concluded against the toxicity of additives found in cigarettes and pointed to the lack of evidence supporting this thesis. Later on, internal documents from PMI exposed that analytical protocols had been adapted, as early research had found a positive correlation between additives being present in the formula and increased cigarette's toxicity, as was the case for menthol for example. An example of a HTP device, IQOS is showcased in Figure 2.1 [7].

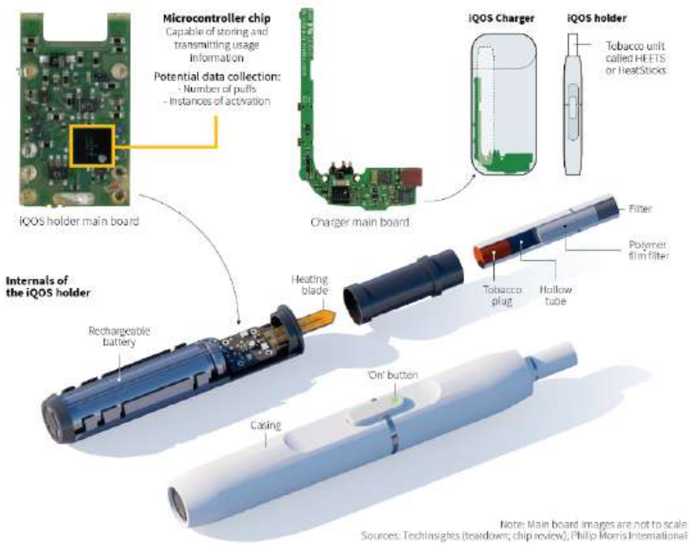
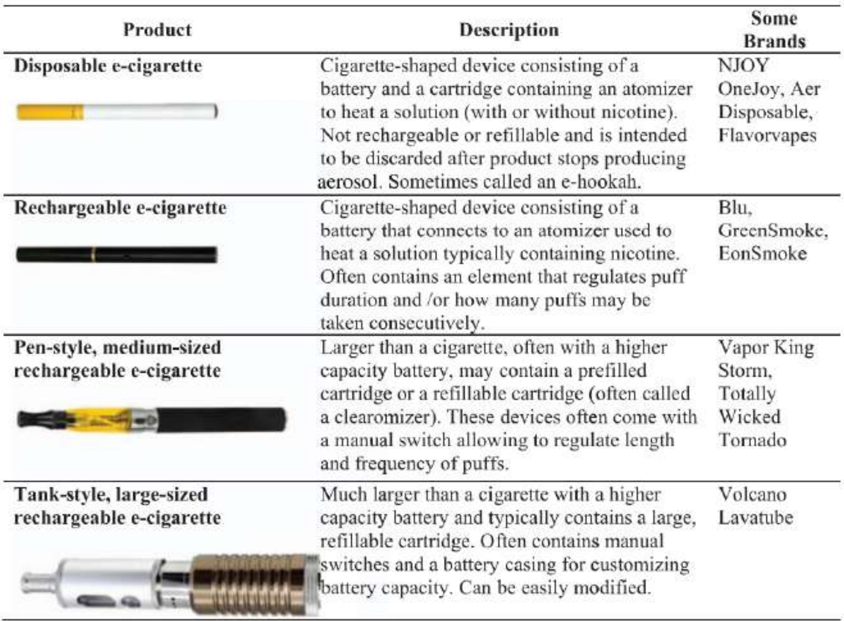


Figure 2.1: IQOS components and structure, as depicted in reference [7].

2.2 E-cigarettes

Contrary to HTPs, e-cigarettes are tobacco-free products in which nicotine delivery is ensured through heating a nicotine-based solution also containing propylene glycol, glycerol and flavouring agents. The temperature at which the aerosol is formed depends on the proportion of propylene glycol and glycerol present in this solution and ranges from 188.6°C to 292°C. Examples for such products can be seen in Figure 2.2 [8].



Product	Description	Some Brands
Disposable e-cigarette	Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing aerosol. Sometimes called an e-hookah.	NJOY OneJoy, Aer Disposable, Flavorvapes
Rechargeable e-cigarette	Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and /or how many puffs may be taken consecutively.	Blu, GreenSmoke, EonSmoke
Pen-style, medium-sized rechargeable e-cigarette	Larger than a cigarette, often with a higher capacity battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing to regulate length and frequency of puffs.	Vapor King Storm, Totally Wicked Tornado
Tank-style, large-sized rechargeable e-cigarette	Much larger than a cigarette with a higher capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified.	Volcano Lavatube

Figure 2.2: Examples of e-cigarettes available in the market, as depicted in reference [8].

Contrasts in : presence of tobacco, operating systems and peak temperatures are to be expected when comparing these two new electronic nicotine delivery systems, thus a brief summary commenting on these elements is showcased in Table 2.3.

Table 2.2: Summary of key contrasts between HTPs and E-cigarettes

	HTPs	E-Cigarettes
Tobacco content	Tobacco product	Tobacco free product
Operating mechanism	Tobacco is heated by an internal heating plaque (which can penetrate or soround the tobacco stick) promoting nicotine´s release.	E-liquid nicotine-based solution (containing propylene glycol, glycerol and flavouring agents) is heated by an internal heating mechanism, releasing nicotine.
Peak Temperatures	240 - 350ºC	188.6 - 292°C

As acknowledged by Grana et al [8] there is a generalized difficulty in establishing contrasts with this product category due to its internal variation. Differences in product engineering (i.e. battery voltage, volumes of e-liquid solution in the product) and e-liquid composition (varying nicotine concentrations, differences in compounds carried, additives and flavours) make up for discrepancies nicotine contents in the products aerosol and overall adjustments in each products' risk profile. Moreover, as reinforced by the authors, these products allow users to modify the product itself mainly by using them to deliver other types of drugs, for example marijuana. In spite of the aforementioned specificities, most e-cigarettes' e-liquids showcase propylene glycol and glycerin in their compositions. Dias et al [35] estimate that the e-liquids' propylene glycol content may vary between 50 and 95%. Considering these authors' premise of the average and most commonly reported e-liquid solution capacity being set at 1,5 ml of nicotine-based solution, this implies a maximum of 1,43 ml of propylene glycol per refill (of nicotine-based e-liquid solution). Once absorbed and available in the bloodstream, it is estimated that propylene glycol's bioavailability is set between 20 and 30%, as indicated in [36]. Moreover, this molecule is mainly metabolized in the liver through oxidation and conjugation with glucuronic acid, and its resulting byproducts are primordially excreted through urine (with that said they can also be excreted by sweat and feces). Dias et al [35] validate a two hour half life for this molecule. Given its irritative quality, once in direct contact with the skin or mucous membranes, this molecule may cause injury at cell level inducing the systemic release of inflammatory mediators as IL-6 and IL-8. Similarly, once inhaled, it can cause the irritation of the respiratory pathways, triggering symptoms as : dry mouth, soar throat and cough. Aside from these symptoms other toxicological effects can be expected from propylene glycol's exposure, as disclosed by EMA's (European Medicines Agency) Committee for Human Medicinal Products [19] and showcased in Table 2.3.

Table 2.3: Propylene Glycol's toxicological effects as mentioned in reference [19]

Toxicological Effects	Detailed description
Respiratory	Cough, respiratory depression, hyperventilation with respiratory alkalosis and acute pulmonary edema.
Reproductive	Some studies have pointed to teratogenicity, specifically craniofacial defects, neural tube closure and bone dysplasia.
Cardiological	Arrhythmias, Congestive Heart Failure (CHF), Systemic Arterial Hypertension (SAH) and circulatory collapse.
Metabolic	Propylene glycol metabolites produce severe metabolic acidosis (leading to brain, heart and kidney damage) and hypocalcemia, which can lead to tetany.
Renal	Tubular necrosis and renal failure may occur 24 to 48 hours after exposure, as a consequence of direct acid cytotoxicity and the deposition of calcium oxalate crystals in renal tubular capillaries.

Moreover, given the context of propylene glycol's application on e-cigarettes and as emphasized by Grana et al [8], once the e-liquid is heated in order for nicotine release to be enabled, propylene glycol may become metabolized into propylene oxide, an International Agency for Research on Cancer (IARC) classified class 2B carcinogen. Also, through the same process, glycerol forms acrolein a toxicant associated with upper respiratory track irritation. Thus, in order to monitor and control exposure to e-cigarettes e-liquid's components, as suggested by Dias et al [35], selected biomarkers must reflect both exposure to nicotine and propylene glycol. As far as nicotine is concerned, typically cotinine is selected as a biomarker, detectable in either blood, urine of saliva samples. Addicionally these authors comment on anabasine (an alkaloid found in tobacco products) and nornicotine's fit as possible nicotine's inhalation biomarkers, validating their choice when considering blood and urine samples. As for propylene glycol the molecule itself can be selected as its own biomarker, detectable in both blood and urine samples. Also it's metabolites, such as lactate and pyruvate, which can also be measured in urine and in the blood can be deemed as appropriate for this analysis. Since high levels of exposure to propylene glycol can induce liver damage,measuring the levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can also report on exposure to propylene glycol.

2.3 HTP vs E-cigarette vs Traditional cigarette

As addressed in Yuki Akiyama and Neil Sherwood's research [37], biomarkers of tobacco smoke exposure are, as expected, elevated in traditional cigarettes' smokers when compared with those showcased by HTPs or e-cigarettes 'users. This deviation from baseline levels in more recent tobacco forms become particularity noticeable in: nicotine, MHBMA, 3-HPMA, S-PMA, 1-OHP and NNAL. Other biomarkers, noted for their carcinogenic potential, such as butadiene, acrolein, benzene, toluidine, naphtylamine and methylnitrosamines are also reduced in the cases of HTP and e-cigarettes' users. Ultimately, in these authors' shared view, there seem to be "no major or consistent differences between e-cigarettes and HTPs. Other studies, however, have pointed at relevant differences between HTP and e-cigarettes' aerosol compositions.

2.3.1 Nicotine Content

According to Dusautoir et al [9], despite containing less nicotine and carbonyl compounds than traditional cigarettes, HTP aerosols' showcased higher levels of both compounds when confronted with electronic cigarettes' emission. Having fixed the e-cigarettes' e-liquid formulation at 16 mg/ml of nicotine, these authors measured the levels of nicotine delivered in the aerosols emitted from each tobacco product. Assuming a Health Canada Intense - 55ml puff volume, 2s duration, 30s interval (HCI) puffing profile to ensure comparable conditions, results demonstrated that HTPs accounted for 30% less nicotine (63 μg/puff) than the 3R4F cigarettes (95 μg/ puff). Moreover, regarding the two e-cigarette models considered by Dusautoir et al [9] (both pertaining to the same manufacturer, NHOSS®), conclusions varied slightly. The second generation "Lounge" model delivered significantly less nicotine levels than all the other tobacco products at 8 μg/ puff. The third generation model, "ModBox", derived its levels of nicotine delivered from the power setting selected. The lowest 18 W setting provided 60 μg of nicotine per puff, whereas the 30 W power setting delivered 137 μg/ puff, becoming the highest amount of nicotine per puff attributable in this experiment. See Figure 2.3 [9].

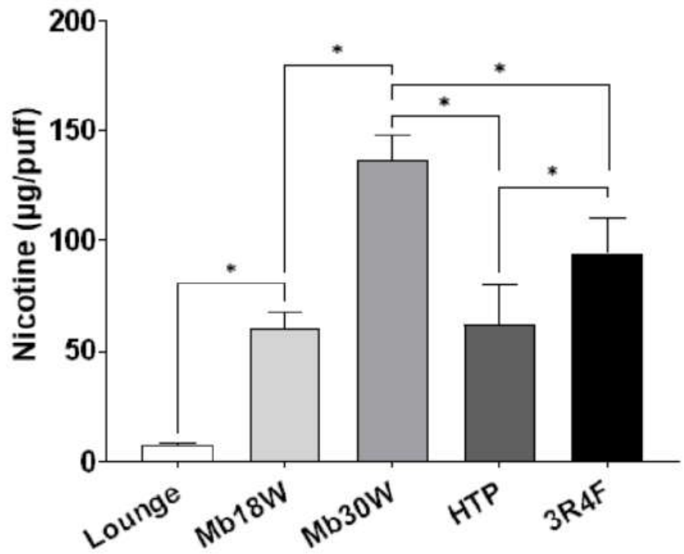


Figure 2.3: Nicotine levels (in μg/ puff) in e-cigarettes (Lounge, ModBox 18W or ModBox 30 W), HTP and 3R4F cigarette aerosols, as depicted in reference [9].

*Notes: Data represent the mean +/- SD of four independent measurements *p¡0.05*

This evidence highlights that there is a positive correlation between power supply and nicotine levels for e-cigarettes. It has been demonstrated by Talih et al [26] that increases in power supply in e-cigarattes translate into these devices' optimized efficiency in vaporizing its' e-liquid, thus increasing nicotine levels in vapour. On top of that, in order to compensate for lower baseline nicotine contents, these results suggest that when switching from conventional tobacco to other nicotine-delivering alternatives, smokers may " adopt a more intense "puffing regimens"and/or consume more puffs with HTP or e-cig", as outlined by Dusautoir et al [9].

In subscribing to nicotine delivery being affected by the users' smoking behavior Grana et al [8] highlights existing evidence supporting that nicotine's presence in e-cigarettes' aerosols is not significantly correlated with its e-liquid's nicotine content, in reality, it attributable to differences in engineering traits in these products. Additionally, these authors re-enforce that : ”a puff of the e-cigarete with the higherst nicotine content”, estimated at around 35 μg, ”contained 20% of the nicotine contained in a puff of conventional cigarette”.

2.3.2 Cytotoxicity

Through a comparison in vitro study on the impact of smoking aerosol on human bronchial epithelial cells, deriving from three different PMI tabacco products (the HTP IQOS, the e-cigarette MarkTen and Marlboro Red, the traditional cigarette), Leigh et al [10] concluded that IQOS showcased greater cytotoxicity than the e-cigarette but less than the traditional cigarette. In this study, the authors measured cytotoxicity in human bronchial epithelial cells (H292) after being separately exposed to smoking aerosols (from the aforementioned sources) for 2.5 hours. The level of cytotoxicity was inferred from two assays: the neutral red uptake (which offered a quantitative estimation of the number of metabolically active cells, these being the ones capable of incorporating the “supravital dye neutral red into lysosomes”) and the trypan blue assay (which provided a viability assay based on the premise that live cells showcase intact membranes therefore not permeable to certain dyes as is the example of trypan blue). Results demonstrated that, given the same time frame, the number of metabolically active cells after having been exposed to aerosols derived from IQOS was lower than the number of active cells which had in turn been exposed to MarkTen, by the end of the same time interval. This implies that the level of cytotoxicity in IQOS is likely higher than that of e-cigarretes. See Figure 2.4 [10]

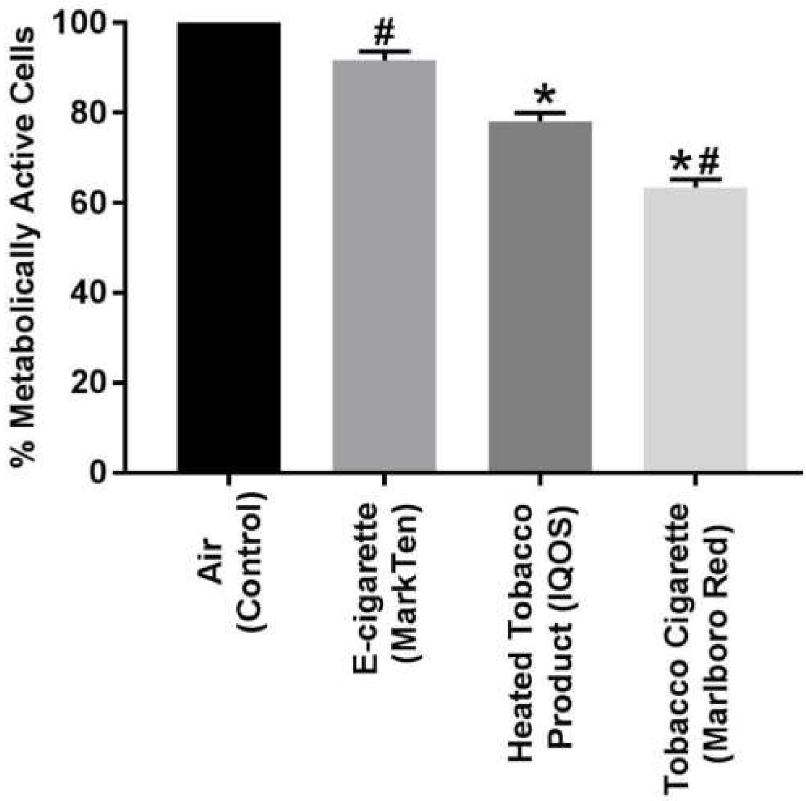


Figure 2.4: Metabolic activity (neutral red assay) from H292 bronchial epithelial cells directly exposed using an air–liquid interface to emissions from heated tobacco product (HTP), e-cigarette, combustible tobacco cigarette and air (controls), as depicted in reference [10].

In spite of Leigh et al's [10] results, corroborating a higher level of metabolically active cells after having been exposed to e-cigarette aerosol in contrast with other tobacco products, it is important to acknowledge Bahl et al's [38] findings. The latter focused their research on evaluating 41 e-cigarette refill fluids, which were testes in 3 cell types : human pulmonary fibroblasts, human embryonic stem cells, and mouse neutral stem cells. Results indicated that cytotoxicity in e-liquids is statistically attributable to the concentration and number of flavourings in such solutions. Also, human pulmonary fibroblasts were concluded to be the least sensitive cell type of the three in analysis, suggesting that adult lungs may not constitute the most effective system to assess the effects from e-cigarettes' aerosols from. Still on the topic of cytotoxicity, the cells inflammatory response was equally characterized in Leigh et al's [10] project. In doing so, these authors quantified six cytokines (interleukin (IL)-1β, IL-6, IL-10, CXCL1, CXCL2 and CXCL10) which were selected as a panel of inflammatory markers commonly used in in-vitro, in-vivo and clinical human studies. From this array of cytokines, only IL-1β (involved in cell proliferation, differentiation and apoptosis) and IL-6 (primarily produced at sited of acute and chronic inflammation) were detected and quantified, all others were found to be below the limit of quantitation. Regardless, both cytokines experienced an increased release after cells were exposed to traditional cigarettes. On the other hand, exposure to HTP translated into a reduced release of cytokines in contrast with combustible cigarettes (IL-1β: 13.7$\pm$5.1 vs 133.6$\pm$41.9; IL-6: 6.9$\pm$2.1 vs 65.5$\pm$21.7pg/10^7 cells) and differences in cytokines' levels resulting from isolated exposures to HTP and e-cigarettes were deemed not statistically significant.

2.3.3 Tobacco-specific nitrosamines

Moreover, Leigh et al ‘s [11] study points towards the majority of existing industry funded reports and research being solely focused on contrasting IQOS with combustible cigarettes, thus creating a knowledge gap in the evaluation of IQOS's health impact in absolute terms or its relative effects compared with e-cigarettes. Through its electrical heating component IQOS devices, as well as other HTPs, heat tabacco to 350ºC which in turn causes volatile compounds (some of which are untraceable in e-cigarettes aerosols) to be release and inhaled by its smoker. Amongst these are nitrosamines, a by-product of tobacco curing which are not generated through combustion thus potentially making HTPs a significant source of tobacco-specific nitrosamines (TSNA) as hypothesised by Leigh et al [11]. Applying an HCI protocol, the authors analysed the aerosols produced by: a single HeatStick (12 puffs), a single traditional cigarette (8 puffs) and e-cigarettes (55 puffs). Differences in the number of puffs per tobacco product were designed to ensure comparable nicotine levels across all products tested (the HTP IQOS – 12 puffs = 1.4+/- 0.2 mg nicotine, the e-cigarette MarkTen – 55 puffs = 1.3+/- 0.2 mg of nicotine, and Marlboro Red, the traditional cigarette– 8 puffs = 2.1 +/- 0.1 mg of nicotine). In order to strengthen the interpretation of these results, TNSA yields were normalised per nicotine delivery.

Conclusions reached support a statistically significant higher level of TSNA in HTP aerosols when compared to those emanating from e-cigarettes, albeit significantly lower than those found in combustible cigarettes' smoke. See Figure 2.5 [11].

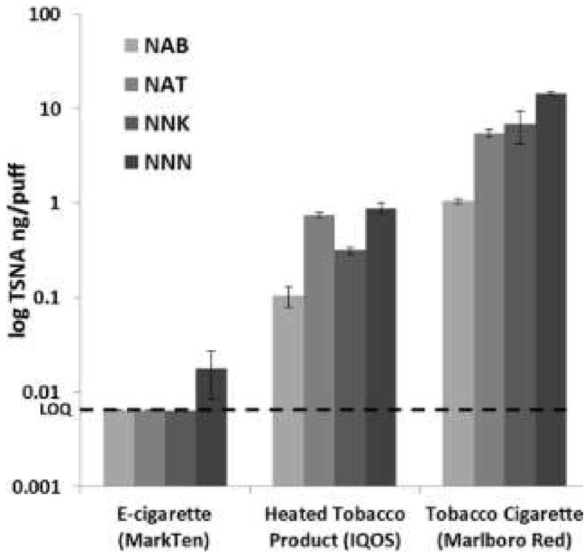


Figure 2.5: Yields of tobacco-specific nitrosamines (TSNA) (per puff) in aerosols generated from IQOS heated tobacco product (12 puffs/ HeatStick), MarkTen e-cigarette (55 puffs) and smoke from Malboro Red 100 combustible cigarettes (8 puffs/ cigarette), as depicted in reference [11].

2.3.4 PAH and carbonyl compounds

Distinct polycyclic aromatic hydrocarbons (PAH) such as benzo[a]pyrene and dibenzo[a,h]anthracene and carbonyl compounds as formaldehyde and acetaldehyde, are examples of carcinogenics that are released as a result from tobacco combustion. However, as outlined by Dusautoir et al [9] both carbonyls and PAHs can be found in e-cigarettes and HTPs' aerosols, as evidenced in Table 2.4 [9] and Table 2.5 [9], respectively.

Table 2.4: Carbonyl concentrations (in ng/puff) in aerosols from 3 models of e-cigarettes (Lounge, ModBox 18W and Modbox 30 W), HTP and 3R4F combustion cigarette, as depicted in reference [9].

	Lounge	Mb18W	Mb30W	HTP	3R4F
Formaldehyde	6.0 ± 0.7	25.8 ± 2.8	64.5 ± 23.7	156.9 ± 9.4	255.5 ± 60.8
Acetaldehyde	32.9 ± 5.4	63.0 ± 10.3	160.9 ± 46.4	26687.7 ± 657.8	166345.0 ± 59540.1
Propanone	3.9 ± 2.7	13.8 ± 3.0	28.5 ± 8.1	3132.3 ± 149.1	36075.8 ± 7896.5
Propanal	2.1 ± 0.7	8.4 ± 2.4	23.2 ± 5.6	1400.1 ± 205.8	6924.8 ± 1688.2
Methyl vinyl ketone	0.2 ± 0.1	6.4 ± 4.2	6.4 ± 2.1	443.1 ± 42.1	1341.1 ± 219.3
Crotonaldehyde	2.4 ± 0.1	16.1 ± 3.3	38.8 ± 8.1	139.9 ± 10.2	1697.4 ± 794.5
Methyl ethyl ketone	0.8 ± 1.6	34.7 ± 23.6	23.5 ± 9.5	625.6 ± 26.9	9005.1 ± 1097.8
Methylpropenal	~ ± ~	~ ± ~	~ ± ~	334.8 ± 20.6	842.4 ± 350.7
Butanal	0.1 ± 0.1	2.0 ± 0.1	2.4 ± 0.1	985.9 ± 94.7	3653.9 ± 1055.0
Benzaldehyde	0.5 ± 0.1	2.5 ± 0.3	3.2 ± 0.1	58.9 ± 2.8	63.6 ± 59.3
Isopentanal	0.7 ± 0.1	7.9 ± 1.1	11.5 ± 0.6	391.3 ± 37.6	2084.9 ± 599,0
Pentanal	0.5 ± 1.1	1.0 ± 0.2	0.4 ± 0.1	25.2 ± 1.4	172.0 ± 50.5
Glyoxal	0.6 ± 0.4	0.6 ± 0.0	0.7 ± 0.0	40.7 ± 9.2	308.2 ± 92.0
o-Tolualdehyde	0.7 ± 0.1	2.9 ± 0.5	2.8 ± 0.5	6.3 ± 0.4	29.0 ± 2.8
m-Tolualdehyde	~ ± ~	1.0 ± 0.6	1.1 ± 0.8	~ ± ~	~ ± ~
p-Tolualdehyde	1.7 ± 0.4	0.9 ± 0.6	0.6 ± 0.7	115.0 ± 26.4	291.8 ± 195.8
Methylglyoxal	25.2 ± 3.1	12.2 ± 1.1	44.1 ± 10.9	490.1 ± 69.8	982.0 ± 249.0
Hexanal	0.5 ± 0.1	1.5 ± 0.1	1.8 ± 0.1	22.1 ± 11.8	10.4 ± 12.1
2,5-Dimethylbenzaldehyde	~ ± ~	0.6 ± 0.1	0.7 ± 0.1	~ ± ~	~ ± ~
Total carbonyl compounds	**79 ± 10**	**201 ± 48**	**415 ± 63**	**35056 ± 825**	**230083 ± 70153**

Table 2.5: PAHs (in ng/puff) in aerosols from 3 models of e-cigarettes (Lounge, ModBox 18W and Modbox 30 W), HTP and 3R4F combustion cigarette, as depicted in reference [9].

	Lounge	Mb18W	Mb30W	HTP	3R4F
Naphthalene	61.5 ± 9.5	75.9 ± 5.6	92.2 ± 6.2	71.2 ± 38.8	3598.6 ± 735.4
Acenaphthene	0.2 ± 0.1	2.6 ± 1.1	5.0 ± 1.4	12.5 ± 13.6	1318.2 ± 397.5
Fluorene	6.7 ± 3.3	6.7 ± 1.5	5.0 ± 1.3	26.0 ± 22.4	1976.7 ± 387.6
Phenanthrene	7.2 ± 0.7	25.2 ± 8.2	22.8 ± 3.5	55.9 ± 34.7	2829.4 ± 533.3
Anthracene	0.6 ± 0.1	1.7 ± 0.4	2.8 ± 3.7	4.7 ± 2.3	1356.2 ± 266.7
Fluoranthene	9.2 ± 1.4	20.1 ± 11.8	11.5 ± 11.8	131.0 ± 79.0	1463.5 ± 288.7
Pyrene	17.9 ± 4.3	30.9 ± 9.2	30.9 ± 10.9	153.0 ± 98.6	1752.4 ± 304.4
Benzo(c)phenanthrene	1.9 ± 0.6	4.5 ± 2.1	3.1 ± 4.4	10.2 ± 6.9	1.5 ± 0.6
Benzo(a)anthracene	0.2 ± 0.0	2.6 ± 0.8	3.2 ± 4.0	43.8 ± 23.3	542.5 ± 150.1
Chrysene	0.4 ± 0.3	1.6 ± 0.2	2.5 ± 4.0	26.3 ± 13.8	471.7 ± 72.5
5-Methylchrysene	1.5 ± 0.4	1.0 ± 0.7	0.6 ± 0.4	1.7 ± 1.0	1130.5 ± 293.9
Benzo(e)pyrene	1.9 ± 0.2	6.1 ± 2.5	5.3 ± 3.6	22.9 ± 17.1	1343.9 ± 303.1
Benzo(b)fluoranthene	0.3 ± 0.1	1.2 ± 0.2	4.2 ± 7.1	18.9 ± 8.9	358.9 ± 125.6
Benzo(k)fluoranthene	0.2 ± 0.1	0.5 ± 0.1	1.4 ± 2.2	18.4 ± 11.1	99.6 ± 28.1
Benzo(a)pyrene	0.6 ± 0.2	0.6 ± 0.2	1.1 ± 0.3	25.6 ± 13.8	457.6 ± 114.5
Dibenzo(a,l)pyrene	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.3 ± 0.1	0.6 ± 0.2
Dibenzo(a,h)anthracene	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.3	0.8 ± 0.4	38.4 ± 11.8
Benzo(g,h,i)perylene	1.5 ± 0.7	0.9 ± 0.2	4.8 ± 3.1	16.6 ± 8.9	276.2 ± 55.9
Indeno(1,2,3-c,d)pyrene	0.3 ± 0.1	0.2 ± 0.0	1.5 ± 2.0	6.6 ± 5.6	214.0 ± 81.4
Dibenzo(a,e)pyrene	0.1 ± 0.0	0.0 ± 0.0	0.2 ± 0.3	0.5 ± 0.3	92.4 ± 43.5
Anthanthrene	0.3 ± 0.1	0.2 ± 0.1	0.4 ± 0.1	11.7 ± 6.7	233.9 ± 52.6
Coronene	0.3 ± 0.1	0.5 ± 0.1	2.8 ± 1.0	5.5 ± 1.8	25.6 ± 5.4
Cyclopenta(c,d)pyrene	~ ± ~	~ ± ~	~ ± ~	~ ± ~	~ ± ~
Total PAHs	**113 ± 16**	**183 ± 29**	**202 ± 57**	**664 ± 389**	**19582 ± 400**

From their experimental work in comparing the chemical composition of aerosols formed by different tobacco products, Dusautoir et al [9] concluded that, as a general trend, the HTP showcased a 84.7% decrease in carbonyl compounds' emissions when contrasted with traditional cigarettes. On the other hand, the same levels for e-cigarettes were, on average, 98.5% weaker than in HTP aerosols. As explained by the authors this fact may be justifiable given that traditional cigarettes, e-cigarettes and HTPs generate this byproducts through different processes. In the case of traditional cigarettes, when smoking, carbonyl compounds are formed *via* pyrolysis of the carbohydrates contained in tobacco. Since in HTPs' peak temperature is kept below 350°C, users' exposure to this carcinogenic toxicants is minimized. However, as verifiable in Figure 2.5 [9], several of these compounds, as is acetaldehyde and formaldehyde, are still detectable in these products' aerosols. Regardless, in the case of HTPs, carbonyl compounds are formed as a direct result of tobacco's thermal degradation. Contrastingly, in the case of e-cigarettes, carbonyl compounds result from glycerol and propylene glycol's thermal degradation. As was the case with nicotine release, a correlation can be derived from carbonyl concentrations and operating power in e-cigarettes. Interestingly, Dusautoir et al [9] draw out the possibility of some studies reporting high amounts of aldehydes in these products' emissions. In such cases, the authors advert, that study premises are operating under overheating scenarios. In real-life settings that happening would generate an unpleasant taste that would unable those emissions.

On the case of PAHs, Dusautoir et al [9] established that HTP emissions contained, on average, 96.2% less PAHs than 3R4F cigarettes. Similarly to what had been concluded for carbonyl compounds, the pyrolysis process was most limited for e-cigarettes. In such cases, a 64.9 to 78,2% decrease in PAHs was verifiable from the levels registered for HTP. Adding to the lower temperatures reached by e-cigarette devices, most PAHs precursors are contained in tobacco which, the majority of e-cigarettes, do not carry in their e-liquids' compositions.

3

IQOS - I Quit Ordinary Smoking

Contents

3.1 Business Case – market expansion and business model

From the golden age of traditional cigarettes, Philip Moris International (PMI) had established itself as a world renowned corporation operating in the tobacco industry. However, much to its competitors liking, by 2017 it was tasting the fall from grace of an once exponentially profitable business, smoking. In just one year, its sales in the expanding Japanese market had fallen by a quarter as its customer base was speedily shifting to from combustible cigarettes to "heat not burn sticks". PMI's net income dipped 0.4 per cent to 1.78 billion dollars, or 1.14 dollars a share, missing Wall Street's forecast which in turn had predicted a rise to 1.9 billion dollars, or 1.22 dollars a share [6]. Not only had these "reduced risk" products taken a toll on PMI's market valuation, they were permanent damage to the company's market share as it became evident that they portrayed a structural change in customer demand preferences, even more so in Japan than other markets. This shift in demand was clearly depicted in the tendency captured by the company's revenue stream for that year. Roughly 9% of PMI's worldwide revenues were lead by "reduced risk products", contrasting with the mere 1.8% reported in the previous year.

It seemed like investing in research and development for a heated tobacco product and getting on board with the inconvenient truth that was once the declared gravestone for the smoking industry, "Smoking kills", was now ironically PMI's best hope of keeping up with its track records in sales. In a way it could be argued there was a silver lining to be taken advantage of, conditional on PMI's ability to incorporate dynamic capabilities in its business model and pivot its revenue sources. After all, sales of Marlboro-branded tobacco sticks (which users inserted into PMI's now star product, the HTP, IQOS) registered an unprecedented growth in sales, having reached 5.7 billion units sold. More than "an absolute game changer" as Peter Nixon, PMI's UK chief, chose to address IQOS, PMI's 2014 product launch materialized a new perception of smoking as a virtually "risk free" daily activity [39]. By 2019, PMI went as far as to launch a worldwide campaign with the moto: "Make a change today, unsmoked your world". See Figure 3.1 [12].

Figure 3.1: PMI's advertisement campaign: "Make a change today. Unsmoke your world" campaign, as depicted in reference [12].

On that same note, Jacek Olczak, PMI's chief operating officer (COO), even admitted to IQOS having become the company's target for its marketing and research budgets' allocation. As acknowledged in its annual report, 92% of the 383 million dollars expenses in R&D had already been assigned to this IQOS's product range.

In that same year (2019) sales forecast indicated that the "reduced-risk segment" was expected to account for 30% of PMI's shipment volume by 2025 [5]. Fast-forward to PMI's 2023 Annual Report, which conclusively indicates that the company is well on its way to achieve this milestone, as shipments from this category already account for 16.97% of the total shipments volume for the company. Additionally, as indicated by Table 3.1 [20], there was a 14.7% increase in heated tobacco units (HTU) shipments across all regions and a 1.4% decline in traditional cigarettes shipments, within the same time frame.

Table 3.1: PMI's Shipments and Market Share as stated in its 2023 annual report, as depicted in reference [20].

			PMI Shipments (billion units)						PMI Market Share (%)[2]			
Market	Total Market (billion units)		Total		Cigarette		Heated Tobacco Unit		Total		Heated Tobacco Unit	
	2023	2022	2023	2022	2023	2022	2023	2022	2023	2022	2023	2022
Total [1][2]	2,579.9	2,621.5	738.2	731.1	612.9	621.9	125.3	109.2	28.3	27.7	4.7	4.1

As for the present year, PMI's 2024 First-Quarter Conference Call also unveils encouraging news for the company which, paraphrasing the words of its COO (Jacek Olczak), has renewed its smoke free vision and ambition in having two thirds of its total net revenue deriving directly from smoke-free products by 2030. First Quarter projections for 2024 regarding HTU shipments were surpassed the total of 33.1 billion units was reached, representing a 20.9% positive variation from the previous year. See Figure 3.2 [13]. This fluctuation attested to IQOS strong momentum, which can partially be attributed to: its growth in the Japanese market, the positive contribution of new markets such as Indonesia and the prevalence of good results in the European market.

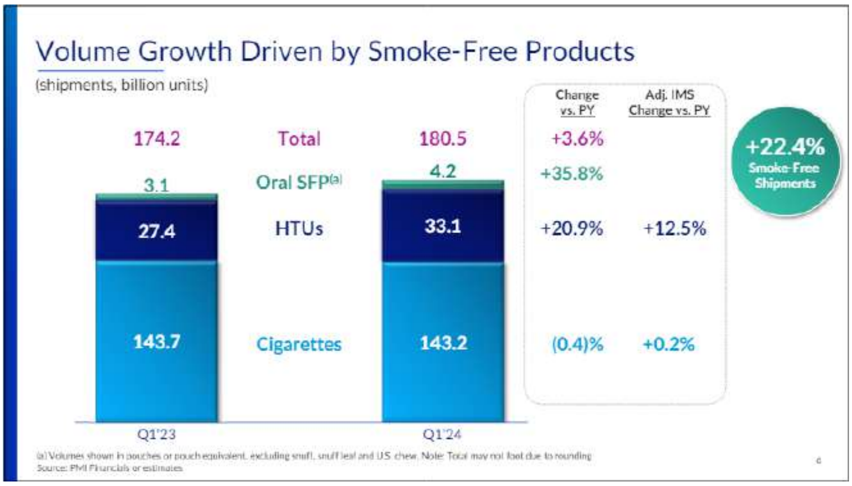


Figure 3.2: Volume growth driven by smoke-free products, as stated in PMI's 2024 press briefing, as depicted in reference [13].

Due to its growing trajectory in sales worldwide, with PMI was able to establish the IQOS brand as the second largest nicotine brand in markets where it has commercial presence. Even reaching the pole position in 11 of those markets. Not only has IQOS single handedly surpassed Marlboro (in a 10 year timeframe) in net revenues, but also, together with the other PMI products in the HTU range, it has now exceed the 10% market share mark. See Figure 3.3 [13].

Figure 3.3: IQOS market share for the first quarter of 2024, as stated in PMI's 2024 press briefing, as depicted in reference [13].

Encouraged by these stellar results, PMI is still eager to offer innovation to its trusted customer base. To mark the 10 th anniversary of IQOS (first launched in Nagoya, Japan, in 2014), the company has once more chosen the Japanese market to launch its newest creation, the IQOS

ILUMA i . See Figure 3.4 [14]. After all, it is calculated that, in Japan, one in every three adult smokers use IQOS. This new range includes three different devices (the IQOS ILUMA iPrime, iqos iluma i and the IQOS ILUMA i One), all promising a more flexible and customizable experience of the star product.

Figure 3.4: PMI Japan's latest launch: IQOS ILUMA i series, launched March 13 0f 2024, as showcased in reference [14].

In a nutshell, IQOS could really have stood for: "I Quit Ordinary Smoking", after all, it poses as an innovation in both the presentation of the act of smoking itself, but also, in the mutation of the associations and concerns tied up with this activity. Thus, the more pressing question seems to be how ordinary is IQOS when compared to traditional cigarettes? Is IQOS smoke-free world a healthier option to the one we now know?

3.2 Confronting PMI's claims

As previously disclosed in chapter one, it wasn't until 2020 that the FDA granted IQOS the MRTP status. In doing so, there was a final FDA's [40] in print recognition that the following three claims were valid:

1. IQOS system heats tobacco and does not burn it.

2. IQOS's heating mechanism significantly reduces the production of harmful and potentially harmful chemicals (HPHC).

3. Scientific studies have proven that switching from combustible cigarettes to the IQOS system significantly reduced the body's exposure to harmful or potentially harmful chemicals.

Unfortunately, PMI's research supporting its application can be argued to have been conditioned to fulfil its desired outcome. Such is the thesis presented by Gideon et al [21]. Out of the total 58 constituents PMI reported results on ("PMI-58"), 40 (43%) were cherry picked out of 93 harmful and potentially harmful constituents (HPHC) that featured on the FDA's original HPHC list. Constituents that fell out from this list (the remaining 18 out of 58) included : water, total particulate matter, pyrene and nitrogen oxides. Naturally, the prevalent majority of constituents encompassed in the PMI-58's list, portrayed better results for IQOS than for the 3R4F cigarette it was being studied up against.

Interestingly, after the FDA's approval, its Center for Tabacco Products came out with an addendum to the briefing document regarding a preceding meeting of the Tobacco Products Scientific Advisory Committee (TPSAC) which had taken place back in 2018. As a direct result from this update, additional data from PMI's studies was released. Information that was then put forward included data on 56 out of the 58 constituents in PMI's 58 list (leaving out total particulate matter and nicotine-free dry particulate matter) plus fifty-seven more constituents that were not commented on prior. Contrary to what had happened before, results presented for the added constituents did not paint IQOS under the same favourable light as the ones provided by the PMI-58 shortlist did. Fifty-six out of the new fifty-seven added new constituents scored higher in IQOS aerosols than they did in 3R4F smoke. For 22 parameters out of this added set, results for IQOS were at least 200% higher, and from those, seven went as far as presenting a 1000% increase. On average, added constituents showcased 154% higher results in IQOS emissions when compared to the combustible cigarette smoke. The added list of constituents and its respective measurements in IQOS aerosols and 3R4F cigarette smoke are showcased in Table 3.2 [21].

Table 3.2: Quantification of compounds non PMI-58 in mainstream aerosol from IQOS Heatsticks and 3R4F traditional cigarette, as depicted in reference [21].

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
1,2,3-Propanetriol, diacetate (diacetin)	µg/stick	No	1.23	0.381	↑ 223
1,2-Propanediol, 3-chloro-	µg/stick	No	9.94	5.93	↑ 68
1,4-Dioxane, 2-ethyl-5-methyl-	µg/stick	No	0.055	0.0004	↑ 13650
12,14-Labdadiene-7,8-diol, (8a,12E)	µg/stick	No	1.43	0.064	↑ 2134
1 hour-Indene, 2,3-dihydro-1,1,5,6-tetramethyl-	µg/stick	No	0.026	0.014	↑ 86
1-Hydroxy-2-butanone	µg/stick	No	0.947	0.465	↑ 104
1-Hydroxy-2-propanone(1,2-Propenediol)	µg/stick	No	162	96.8	↑ 67
2 (5H)-Furanone	µg/stick	No	5.32	1.99	↑ 167
2,3-Dihydro-5-hydroxy-6-methyl-4 hour-pyran-4-one	µg/stick	No	0.231	0.135	↑ 71
2,4-Dimethylcyclopent-4-ene-1,3-dione	µg/stick	No	0.333	0.193	↑ 73
2-Cyclopentene-1,4-dione	µg/stick	No	3.8	0.764	↑ 397
2-Formyl-1-methylpyrrole	µg/stick	No	0.128	0.064	↑ 100
2-Furancarboxaldehyde,5-methyl-	µg/stick	No	11.1	2.94	↑ 278
2-Furanmethanol	µg/stick	No	39.2	7	↑ 460
2-Furanmethanol, 5-methyl-	µg/stick	No	0.123	0.029	↑ 324
2 hour-Pyran-2-one,tetrahydro-5-hydroxy	µg/stick	No	4.45	3.11	↑ 43
2-Methylcyclobutane-1,3-dione	µg/stick	No	2.78	0.71	↑ 292
2-Propanone, 1-(acetyloxy)-	µg/stick	No	16.9	8.01	↑ 111
3 (2H)-Furanone, dihydro-2-methyl-	µg/stick	No	0.326	0.119	↑ 174
3-Methylvaleric acid	µg/stick	No	5.1	3.63	↑ 40
4(H)-Pyridine, N-acetyl-	µg/stick	No	0.296	0.112	↑ 164
5-Methylfurfural	µg/stick	No	0.995	0.632	↑ 57
Anhydro linalool oxide	µg/stick	No	0.457	0.291	↑ 57
Benzene, 1,2,3,4-tetramethyl-4-(1-methylethenyl)-	µg/stick	No	0.006	0.005	↑ 20
Benzenemethanol, 4-hydroxy-	µg/stick	No	0.011	0	↑
Benzoic acid, 2,5-dihydroxy-methyl	µg/stick	No	4.55	2.18	↑ 109
Butylated hydroxytoluene	µg/stick	No	0.132	0.007	↑ 1786
Butyrolactone	µg/stick	No	4.08	0.728	↑ 460
Cis-sesquisabinene hydrate	µg/stick	No	0.061	0	↑
Cyclohexane, 1,2-dioxo-	µg/stick	No	0.083	0.046	↑ 80
Cyclohexane-1,2-dione, 3-methyl-	µg/stick	No	0.101	0.073	↑ 38
Eicosane, 2-methyl-	µg/stick	No	0.05	0.014	↑ 257
Ergosterol	µg/stick	No	3.18	1.58	↑ 101
Ethyl 2,4-dioxohexanoate	µg/stick	No	6.73	3.57	↑ 89
Ethyl dodecanoate (ethyl laurate)	µg/stick	No	0.023	0	↑
Ethyl linoleate	µg/stick	No	0.135	0.008	↑ 1588
Ethyl linolenate	µg/stick	No	0.614	0.153	↑ 301
Furfural	µg/stick	No	31.1	25.9	↑ 20
Glycerol	mg/stick	No	5.02	2.08	↑ 141
Glycidol	µg/stick	No	5.71	1.76	↑ 224
Heneicosane, 2-methyl-	µg/stick	No	0.063	0.021	↑ 200
Hexadecanoic acid, ethyl ester	µg/stick	No	0.491	0.008	↑ 6038
Isolinderanolide	µg/stick	No	4.99	1.85	↑ 170
Isoquinoline, 3-methyl	µg/stick	No	6.29	4.99	↑ 26
Labdane-8,15-diol, (13S)	µg/stick	No	0.143	0.015	↑ 853
Lanost-8-en-3-ol, 24-methylene-, (3beta)	µg/stick	No	6.3	1.61	↑ 291
Maltoxazine	µg/stick	No	0.077	0.038	↑ 103
Methyl furoate	µg/stick	No	0.147	0.029	↑ 407
Phenylacetaldehyde	µg/stick	No	1.41	0.529	↑ 167
p-Menthan-3-ol	µg/stick	No	0.786	0.322	↑ 144
Propylene glycol	µg/stick	No	175	23.7	↑ 638
Pyranone	µg/stick	No	6.54	5.07	↑ 29
Pyranone	µg/stick	No	9.26	5.84	↑ 59
Pyridoxin	µg/stick	No	0.699	0.526	↑ 33
Stearate, ethyl-	µg/stick	No	0.074	0.003	↑ 2367

Reporting back to the 93 HPHCs list provided by the FDA, within the 53 compounds that were left out from PMI's-58 featured 50 carcinogenic compounds, among which stand the following four: 2,6-dimethylaniline, benz[j]aceanthrylene, ethylbenzene and furan. Therefore, assuming that reduced exposure to some toxicants is enough to backup IQOS's strong claims of supposed health benefits in this tobacco form seems to be a short-sighted mistake. Even more so when considered that the prevalence of other substances, some known to have significant toxicity (α,β,-unsaturated carbonyl compounds – 2-cyclopentene-1,4-dione; 1,2-dicarbonyl compounds – cyclohexane, 1,2-dioxo-; furans – 2(5H)-furanone; epoxides- anydro linalool oxide) is greatly increased in the case of this HTP's aerosols. Gideon et al [21] speculate that some of the compounds found in IQOS' aerosols are flavour additives or result from thermal degradation. A few might even be flavouring additives that can be found in other products where they are regarded as safe but might present a different toxicity profile once they undergo thermal degradation from IQOS internal heating mechanism. Such is the case of annydro linalool oxide or 2-Furanmethanol (which has been associated with skin, eye, nose and throat irritation and linked to central nervous system effects). Other examples are disclosed in Table 3.3.

Table 3.3: Flavouring agents and food additives found in IQOS aerosol and their effects, as reflected in [21].

Compound found in IQOS aerosol	Category	Effect
Anydro linalool oxide	Flavouring ingredient (safe for oral ingestion)	Unknown when subject to heat
2 (5H)-Furanone	Food additive (suppress appetite)	Induce cellular DNA damage in vitro
2-Furanmethanol	Flavouring ingredient	Unknown when subject to heat. Nose, eye and skin irritation. Central nervous system effects
3-Chloro-1,2-propanediol	Food contaminant	Mutagenic activity if in high concentrations in vitro. Increased incidence of kidney and testicular tumours in male rats.

If on one hand it is true that tobacco smoke has been widely characterized, the same cannot be said about IQOS, or any other HTP's aerosols. The process through which each component is generated or released in tobacco smoke goes as follows: through distillation, which occurs below 300ºC, nicotine and aromas are transferred from the tobacco stick to it's smoke, after that, this product undergoes pyrolysis, between 300 and 700ºC. At this stage biopolymers, proteins and other organic materials are decomposed whilst a few other compounds are generated. It so happens that IQOS Heatsticks reach peak temperature at around 350ºC, a temperature that is high enough to allow pyrolytic decomposition of some of its organic components. Considering e-cigarretes, in many aspects directly comparable to IQOS, this is the exact temperature point at which toxic volatile organic compounds are formed. Amongst such components stand:

formaldehyde, acetaldehyde, acrolein (which result from dehydration), as well as propylene, glycol and glycerine (which result from the oxidation of the humectants). All these components have been proven to be present in e-cigarettes' aerosols. Thus, due to its similar function, heating mechanism and composition, it is reasonable to consider that they might also be found in IQOS aerosols. The same reasoning applies to flavouring chemicals which, through thermal degradation, are release and cause for the increased toxicity of aldehydes emitted through smoke.

Adding to the point of the need to thoroughly characterize IQOS risk profile, the FDA has provided important feedback on evaluation of the clinical studies supporting IQOS, in what concerns the adequacy of biomarkers of exposure for HPHC's pre-selected by PMI for its four reduced exposure (REX) studies [22]. As verifiable in the list presented below, previously mentioned HPHCs such as acrolein (a byproduct of glycerol thermal degradation) and benzo[a]pyrene (a potentially carcinogenic PAH) are mentioned, as well as, their recommended biomarkers of exposure : 3-hydroxypropylmercapturic acid and Total 3-hydroxybenzo[a]pyrene, respectively. Regardless, in this same document, the FDA discloses that on top of possible undetectable variations in these biomarkers given the short duration of the REX studies, it is not yet clear how appropriate these selected biomarkers of exposure may be at predicting long-term tobacco-related disease risk.

Table 3.4: PMI's pre-selected HPHCs and their respective biomarkers of exposure as evidenced in reference [22].

BoExp	HPHCs	Abbreviation (BoExp)
Monohydroxybutenyl-mercapturic acid	1,3 Butadiene	MHBMA
3-Hydroxypropylmercapturic acid	Acrolein	3 HPMA
S-Phenylmercapturic acid	Benzene	S-PMA
Carboxyhemoglobin	Carbon monoxide (CO)	COHb
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol	4 (Methylnitrosamino)-1-(3-pyridyl)-1butanone (NNK)	Total NNAL
Total 1-hydroxypyrene	Pyrene #	1-OHP
Total N-nitrosonornicotine	N-nitrosonornicotine	Total NNN
4-Aminobiphenyl	4-Aminobiphenyl	4-ABP
1-Aminonaphthalene	1-Aminonaphthalene	1-NA
2-Aminonaphthalene	2-Aminonaphthalene	2-NA
o-Toluidine	*o*-Toluidine	*o*-Toluidine
2-Cyanoethylmercapturic acid	Acrylonitrile	CEMA
2-Hydroxyethylmercapturic acid	Ethylene oxide	HEMA
Total 3-hydroxybenzo[a]pyrene	Benzo[a]pyrene	3-OH-B[a]P (or B[a]P)
3-Hydroxy-1-methylpropyl-mercapturic acid	Crotonaldehyde	HMPMA
S-Benzylmercapturic acid	Toluene	S-BMA

3.3 Limitations on IQOS clinical studies

As evidenced by Glantz's [23] research, these PMI sponsored studies, were conducted in two different population sets, one in Japan (ZRHR-REXA-07-JP) and the other in the Unites States (ZRHM-REXA-08-US). In each study, smokers were randomly assigned to one of three groups, labelled and controlled for the following internal criteria: IQOS menthol smokers, smokers using their current preferred brand of cigarettes and smokers that completely quit smoking from that point on (smoking abstinence). Data was collected on day 0 of this three-arm parallel group studies, prior to randomisation. After that point, participants were held in confinement for 5 days, followed by their release to an ambulatory setting. The total duration of these studies was 90 days (+/- 3 days) counting from the moment of randomisation. At this point (the 90th day) data was once more collected. Throughout the confinement period, product compliance was closely monitored with smokers assigned to both the IQOS and the traditional cigarette groups being granted *ad libitum* access to their respective assigned products, for 16 hour time frames each day. At this stage, dual use was not allowed, meaning that smokers could not use both combustion cigarettes and IQOS. This behaviour (dual use) was only accounted for in the ambulatory phase that followed. Regarding the sample subject to this study, it was conceived to characterise what PMI deemed as "the optimal effect", meaning the maximum exposure reduction achievable in the group whose condition was to solely or at least predominantly use IQOS. Naturally, this implies that the characterization of a heterogeneous exposure to the product (i.e. non-compliance to the assigned product) fell outside the studies' scope. As for the study itself, it focused mainly on indicators of health, the so-called "biomarkers", selected or agreed to by PMI, that were able to capture and quantify: inflammation, cholesterol, triglycerides and other physiological parameters that were deemed as indicators of heart disease, as well as measures concerned with lung function. For the American section, Glantz [23] critiques that the registered difference in results seeking to contrast IQOS with traditional cigarettes was not statistically significant for 23 out of the 24 biomarkers considered. On top of that, given that results were validated within 95% confidence intervals, it is only statistically likely to expect 5% of tests to yield false positives. Moreover, in 24 parameters subject to testing, 1.2 would most probably be a false positive. Hence, given that only one out of 24 parameters tested yielded a positive outcome, it could be argued that such result could very well be a false positive (this parameter being soluble intracellular adhesion molecule (ICAM)). Regarding the Japanese segment, results were more enthusiastic for PMI. In this case, 4 out of the 13 parameters subject to testing, registered a positive result (these being : white cell count, prostaglandin F2 alpha and soluble ICAM; two indicators of inflammation and one measure for cholesterol, respectively). Contrary to what occurred with the American based study, this results would not be expected by mere randomness. See Table 3.5 [23].

Table 3.5: Changes in biomarkers in IQOS users compared with traditional cigarette smokers, as depicted in reference [23].

	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
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<0.5).
**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, DLCO and KCO.
‡n=30 for FEV, FEV/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.

These results could offer valued context into the voting that took place in the aforementioned TPSAC meeting, back in January 2018, scheduled to discuss PMI's MRTP application for IQOS [41]. In said meeting, 9 TPSAC members were allowed to vote on one of three possible answer : 1) yes, 2) no and 3) abstain when presented with an array of questions, designed to capture their views on IQOS and support the FDA's decision to grant the MRTP status or not. When asked to vote on the validity of PMI's claim that "scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.", 8 out of 9 committee members voted favourably (yes – 8, no – 1, abstain – 0). This overwhelming majority of positive votes contrasted with the position undertaken by voting members when the question subject to voting change to "scientific studies have shown that switching completely form cigarettes to IQOS system can reduce the risks of tobacco-related diseases?". In that case, the great majority (8 out of 9) voted negatively (yes -0, no – 8, abstain – 9). This shift in voting can be explained by existing knowledge that much like traditional cigarettes, IQOS also produces an aerosol of ultrafine particles that convey nicotine to be absorbed in the lungs. Such particles are known to cause heart and lung disease and their toxicity is not dose dependent, implying that even low levels of exposure can be dangerous. Therefore, despite not having reported on potential carcinogenic effects on its studies, PMI nor any other institution can disprove this causality. Despite conveying a lower level of exposure to carcinogens, IQOS does not proportionately reduce cancer risks as this outcome dependents on both the intensity and duration of the exposure. In capturing the intensity and frequency in usage of these products Tingting Yao et al [42] suggest that e-cigarette expenditures work as a better proxy for this purpose rather than 30-day e-cigarette use. The same could be assumed for other HTPs. Acknowledging a clear disparity in opinions regarding the health gain in switching from traditional cigarettes to IQOS, committee members were more aligned in their unenthusiastic views regarding the little likelihood they attributed to the sustainability of this switch and their estimation that, in due time, IQOS smokers would eventually become dual users. Interestingly these experts' views are conflicting with those proposed by PMI's own Population Health Impact Model.

The Population Health Impact Model was the result of PMI's own study derived from the application of its internally developed computation model. The study proposed following its subject population for 20 years and aimed to capture IQOS marketing's impact on public health, choosing to focus on mortality as the outcome measure.

According to results inferred from this model, and contrary to TPSAC committee members' views, after one year of IQOS use , switching to cigarette smoke or adopting dual use is virtually impossible, with an estimation of 10% of dual users becoming strictly cigarette smokers on a monthly basis. More than that, this PMI study goes as far as stating that merely less than 0.02% of non-smokers and less than 0.04% of former smokers will become dual users. Despite existing evidence indicating that dual users may face greater risks of negative health outcomes than strictly tobacco smokers, PMI undervalues the Relative Risk (RR) of dual use by establishing it as the midpoint between the RR attributed to IQOS and the RR that refers to traditional cigarettes. Likewise mortality attributable to dual use is grossly misrepresented in this model. Moreover the model estimates that, due to IQOS usage, between 0.4 and 1.5% of smokers will completely quit smoking on a monthly basis. This statement is directly contra pointed by Esther F. Afolalu et al [43]. In this research paper, authors resorted to the analysis of repeated cross-sectional surveys conducted in two population sets: one designed to be representative of the general adult Japanese population, and the other of adult (Japanese) IQOS users. The latter generated evidence that supported that 36,6% of IQOS user engage in dual smoking and, of those, 20.6% select traditional cigarettes as their alternative tobacco product of choice. Adding to this Japanese sourced data, Kim et al [44] conducted an online survey targeting young adults aged 19 to 24 years in Korea, three months after IQOS was launched in this market. Despite acknowledging a lower awareness of the IQOS brand in this market (48% in Japan vs 38.1% in Korea), the authors run this analysis based on similar percentages of current IQOS users in both the Japanese and Korean cases (3.6% in Japan vs 3.5% in Korea). As a result from their experiment, researchers found that 100% of IQOS users in their 228 elements sample were current conventional cigarettes and e-cigarettes users, thus dual smokers. Additionally, their conclusions outlined that none of the IQOS current users in this sample had switched to IQOS from conventional cigarettes. Hence, one can be left wondering what is the real net effect on smoking cessation attributable to e-cigarettes' introduction in the market. As matter of fact, Kim et al [44] advance the hypothesis that " IQOS might possibly be a gateway product for tobacco use among never smokers". Supporting this observation the research team makes reference to Liu X et al's paper citing the Italian example. According to the latter, 45% of Italian IQOS current users and 51% of Italian people who revealed interest in IQOS were never conventional tobacco smokers.

4

Health hazards to be expected in new tobacco products

Contents

4.1 Endothelial and cardiovascular injury

In testing the hypothesis that endothelial function can be altered, and to an extent impaired, through exposure to e-cigarettes' aerosols, much to the liking of what is known to occur with traditional tobacco smoke, Matthew L Springer et al [15] constructed an in vivo animal model in which variations in arterial flow-mediated dilation (FMD) were observed as a result of the subjects' exposure to smoke emanated from combustion cigarettes (1R6F) and aerosols emitted by IQOS. Considering the parameter of choice for the study at hand, FMD, that may be defined as "the per cent by which arteries vasodilate in response to an increased blood flow", for which reason its validity as an indicator for cardiovascular health effects has become widely accepted. The design of this experiment was drafted in response to PMI's claims in support of its MRTP application filing, which seemed too eager to imply that due to a decreased exposure to (selected) toxic compounds, IQOS would cause less endothelial dysfunction than conventional cigarettes. Considering that conclusions reached by PMI on the potential impact of IQOS on endothelial function were solely based on cultured cell models and measurements for circulating sICAM-1 protein (which indirectly depicts quality of vascular function), thus lacking a physiological based approach and contextualization, the afore mentioned team of researchers felt the need to further research the validity of PMI's claims on this topic.

In Matthew L Springer et al's [15] study, eight male Sprague-Dawley rats were exposed "via nose cone to IQOS aerosol, Malboro cigarette mainstream smoke or clean air as a control". "The exposure regimen consisted of a series of consecutive 30 cycles, each consisting of 15 or 5 seconds exposure followed by removal of the nose cone for the rest of the 30 seconds interval". In following through with this premise, rats were exposed to either 10 cycles over 5 minute time frames or 3 cycles over 1.5 minutes intervals. See Figure 4.1 [15].

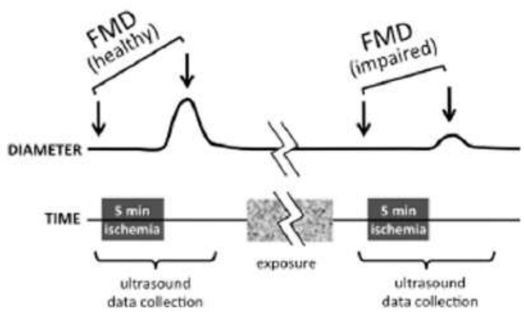


Figure 4.1: Impact of aerosol exposure in arterial FMD (flow-mediated dilation), as depicted in reference [15].

A previous model designed by this research team, also for an in vivo rat model to quantify FMD measurements before and after exposure through high-resolution ultrasound and microsurgical techniques was used in this new experiment for the same purpose. Since researchers selected the common iliac artery as the blood vessel to run measurements on, a 5 minute transient limb ischemia was induced and ultrasound image obtained immediately after re-perfusion occurred. FDM computed as the per cent increase in diameter of said artery after ischemia was induced. This process was repeated before and after exposure to smoke or IQOS aerosols. Complementary to this testing experiment, in order to strengthen the analysis in place, serum nicotine and cotinine (nicotine's metabolite) were also collected from the blood stream immediately before and 20 minutes after each exposure. See Figure 4.2 [15].

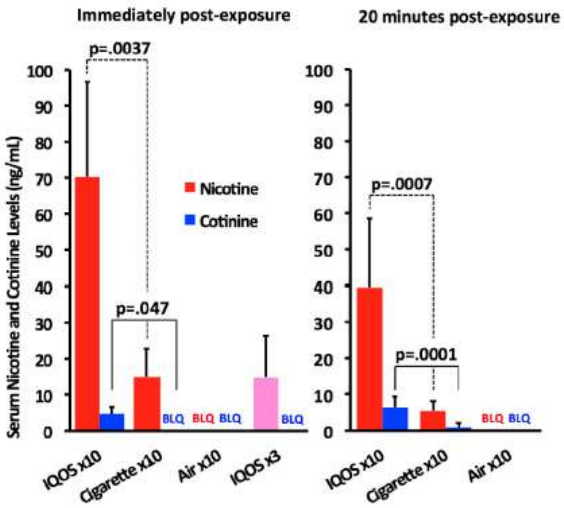


Figure 4.2: Serum nicotine and cotinine levels immediately and 20 minutes post-exposure. Subjects were exposed to 10 cycles of 5s exposure + 25s break. As referenced in [15].

As a result from this experiment, authors were able to demonstrate that cardiovascular effects from the exposure to a single Heatstick are comparable to those triggered by traditional cigarette smoke. In both cases acute effects derived from either tobacco sources' smoke are able to lead to rapid impairment of vascular endothelial function. See Figure 4.3 [15].

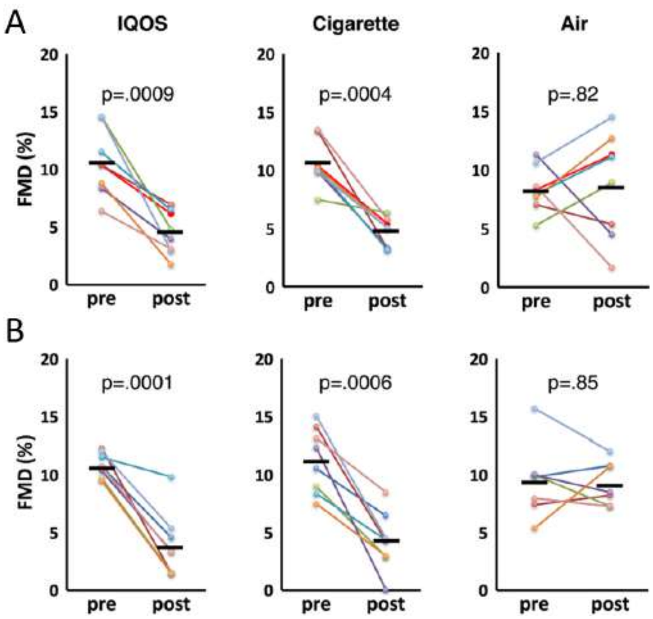


Figure 4.3: Arterial FMD was impacted by both traditional cigarette smoke and IQOS aerosol. In A subjects were exposed for 10 cycles of 15s exposure + 15s break. In B subjects were exposed for 10 cycles of 5s exposure + 25s breaks. As referenced in [15].

Therefore, assuming that long term exposure to IQOS aerosol will lead to less aortic plaque being formed in comparison to what is verifiable under traditional cigarettes' use, contrast with this study's findings which clearly outline rapid adverse cardiovascular effects in both cases. The first data set resulting from this analysis attributed no statistical significance to the per cent FMD impairment verifiable between groups exposed for 5 or 15 seconds to either smoke source, thus being independent from type or duration of exposure and, naturally, implying that "endothelial response was saturated with a single HeatStick or Cigarette". However, adjustments were made to the initial conditions established for the experiment by reducing the number of exposure cycles in IQOS exposures from 10 to 3 due to disparities detected in serum nicotine measurements. When analysing this data, researchers detected that serum nicotine in the "IQOS-exposed group under identical conditions was more the four times higher than in the cigarette group". When confronting these initial results with existing literature, authors confirmed that nicotine content was equivalent in both tobacco sources be it in filler or aerosol form. Thus conditions were altered and re-instated to ensure the same level of nicotine absorption in both models. Still, conditional on the same level of serum nicotine, FDM impairment in the IQOS group remained comparable to the one verified in the cigarette group. Though the theoretical support for the initial empirical results was not conclusively outlined, authors advanced on possible explanation for it, particle size. It is established that particle size determines the extent to which particles are able to reach different respiratory zones. Hence, studying particle size in each aerosol and how it affects absorption and ultimately nicotine concentrations in the blood stream, would be a starting point to consider in future research.

4.2 Pulmonary immunosuppression

In their study, Farzard Moazed et al [24] resorted to PMI's own data to run their independent analysis on IQOS's impact on pulmonary and immunosuppressive effects. Both animal and human models, the first of which based on Wong et al's [45] findings, were considered by these group of researchers.

PMI's preclinical studies were based on an animal model which took as subjects10-week-old male and female Sprague-Dawley rats. These animals where randomly assigned to one of three groups according to whether they were being exposed to: IQOS's aerosols, 3R4F cigarette smoke or clean air (as a control group). Systemic immune effects based on "markers of inflammation, histopathology, transcriptomics and standard toxicological endpoints" were measured and compared amongst the three groups.

Compared to the controlled group rats placed in the IQOS group showcased impaired weight gain increased number of inflammatory cells in bronchoalveolar lavage, as well as, respiratory epithelial hyperplasia and metaplasia. When confronted with results from the cigarette group, however, these results could indeed be perceived as "better". With that said, regardless of relative effects, in absolute terms IQOS these results support that IQOS causes significant inflammatory injury which could trigger substantial immunomodulatory effects. On this topic, results directly derived from PMI's own data demonstrates that subject in the IQOS group presented systemic neutrophilia, approximately 75% higher than in the group exposed to traditional cigarette smoke. This tendency was kept in female subjects following a 6 week recovery period. Additionally within the IQOS exposed group, subjects showcase higher levels of thymic atrophy in contrast to what is detected in traditional cigarette or the control group. Considering a physiopathological context, this event is closely connected to the reduction in host T cell populations as well as a weakening in the host's immune function. See Table 4.1 [24].

Table 4.1: Contrast in preclenical systemic immune effects between IQOS and traditional cigarette, as referenced in [24].

Parameter	Sham (n=8–10)	IQOS (n=7–9)	3R4F (n=9–10)
Blood neutrophil count (10^9/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.*

As for PMI's clinical studies' reports, both the American and Japanese research projects neglect to clearly present evidence on reduced inflammation in IQOS users when confronted with traditional cigarette smokers. In both settings, white blood cell count and c reactive protein measurements were conducted and confronted with those reported by the conventional smokers' group in each corresponding study. No variations were detected with the exception of a slight decrease in plasma white blood cells noted in IQOS users restricted to the Japanese-based study. Despite PMI's misleading interpretation of this fact, falsely extrapolating from it that IQOS "reduces inflammation and the risk of COPD (chronic obstructive pulmonary disease) in humans", it most be emphasized these biomarkers lack of specificity to pulmonary inflammation. Plus, as reported by Fazard Moazed et al [24] "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.". In this research group's understanding, "studies of inflammatory biomarkers in sputum, airway tissue or BAL fluid" could offer more robust analysis in terms of specificity and selectivity to pulmonary track inflammation.

4.3 Hepatotoxicity

Focusing on PMI's previously discussed preclinical studies conducted by Wong and colleagues in Sprague Dawley rats, Chun et al [25] theorized on possible hepatotoxicity in IQOS. According to results from PMI's scientists (Wong et al [45]), after 90 days of exposure, ALT levels within the subjects' group exposed to IQOS aerosols showcased a significant increase, contrastingly to those reported by group exposed to traditional cigarette smoke. ALT, alanine aminotransferase is widely accepted indicator for acute liver injury as, it is known to be released by hepatocytes as a direct result of hepatocellular injury. Additionally, it was reported evidence on liver weight gain in female animals placed in the IQOS exposed group.: On top of that, this subset of study subjects equally showcased hepatocellular vacuolisation a complementary sign of acute liver injury, which was not present in female (nor male) elements of the cigarette exposed group. See Table 4.2 [25].

Table 4.2: Liver parameters in test subjects after 90 days of exposure, as referenced in [25].

	Female			Male		
	Sham	IQOS	3R4F	Sham	IQOS	3R4F
ALT levels (IU/L)	51.0±4.4	73.0±3.2**,****	54.0±2.6	57.0±6.5	75.0±6.7*	68.0±5.8
Liver weight†	339.6±6.6	442.6±10.2***,****	386.7±15.1*	329.3±5.1	381.7±13.2**	373.0±7.9***
Hepatocellular vacuolisation	0.7±0.4	1.5±0.2*	1.2±0.3	1.4±0.3	0.8±0.4	1.8±0.8

Data are from Wong et al [45] and are presented as mean±SEM.
$*P < 0.05$ relative to sham; $**P < 0.01$ relative to sham; $***P < 0.001$ relative to sham; $****P < 0.01$ relative to 3R4F.
†Normalised to body weight and reported as $\times 10^{-4}$.
ALT, alanine aminotransferase.

Liver weight gain was later contested by another research group, Granata et al [46], whose work was published in August 2023, three years after the FDA's formal classification of IQOS as a MRTP. In this experiment project male Sprague Dawley rats were exposure to IQOS (4 sticks per day) was monitored and controlled for 5 days a week for a total of 4 weeks. In such conditions, investigators concluded that "comparison of liver weights showed an absence of statistical differences, although a downward trend could be observed". This results, however may be connected to the shorter timeframe considered in the study's design. Also in their research paper Granata et. al [46] concluded that "IQOS boosted reactive radicals and generated oxidative stress". This pathological response to elevated ROS levels is characterized in literature as causing chronic inflammation and liver damage, which is then reflected in diseases such as steatosis and cirrhosis. By damaging oxidative phosphorylation, elevated ROS, can also activate biogenesis which, in turn, triggers mitochondrial proliferation in a tissue's mass. This reasoning validates Granata et al's [46] results showcasing an increase in the number of liver mitochondria. Besides that, ROS overgeneration as a source of oxidative stress is a promoter of protein carbonylation and lipid perodixation, both irreversible steps in the oxidative reaction and a critical point in assessing oxidative damage. As a response to increased oxidative stress, variations in antioxidant biomarkers, that conjecture a post-oxidative defense, could have been expected as a result of the reported overflow in ROS. Interestingly, this was not the case in general terms, with the exceptions of DT diaphorase and catalase which values were significantly higher. Regardless, consistent with conclusions outlined in conventional cigarettes' studies, Granata et. al [46] concluded that, not only did IQOS exposed elementes experience a significant decrease in GSH, possibly due to radical stress, as is typically found in chronic liver disease patients, but also, their UDPGT levels varied in the opposite direction, once more in line with the established tendency in traditional cigarettes' results . Lastly, still based on Granata et al's [46] animal model findings, IQOS exposed rats' registered decreased Nrf2 expression in the liver in combination with increased levels of p38. The contrasting tendency in these parameters being simultaneously verified has been suggested to imply tabacco smoke caused liver damage, regardless of its combustion method, as it is believed that Nrf2's downregulation activates p38. All in all, as far as IQOS potential hepatotoxicity in animal models is concerns, both Chun and Granata et al's [46] research teams showcase results that support the conclusion that IQOS exposure induces impairment in homeostatic liver function in a way similar to that triggered by tobacco smoke.

As for PMI's available human studies, Chun. et al [25] reviewed existing information focusing the scope of their analysis on the potential hepatotoxicity of IQOS in humans. Results were deemed as distressful across the studies dissected by the research team. Two different 5 day exposure three armed experiments were considered and analysed, each focusing on a different liver injury related biomarker. The first 5 day exposure project concluded that plasma bilirubin was elevated in the IQOS group, potentially implying "cholesteric liver injury with impaired hepatic bile flow, accelerated red blood cell destruction, or decreased bilirubin metabolism" (increased by 8.8% in this study's group, contrasting with 0% in the abstinence group and 2.6% in the combustion cigarette group).Even though it is well documented that smoking cessation may trigger slight increases in unconjugated bilirubin, averaging 0.06 mg/dL, these reported elevations were clearly above what could be initially expected (less than 1.0 mg/dL) and its rate of increased drastically higher than was detected in smoking cessation groups (tending to be three times higher; 8,8% vs 2,6% increases). The following study under the same duration, pointed at ALT being elevated in IQOS exposed subjects when compared with elements belonging to the abstinence or traditional cigarette groups (value of 4.5 IU/L in the IQOS group, contrasting with 1.6 IU/L in the abstinence group and 2.9 IU/L in the combustion cigarette group). Conclusions derived from this data were also confirmed by another PMI run experiment, this time within a wider timeframe: 90 days. This study which contrasted results in groups exposed to either: mentholated IQOS, mentholated cigarettes or smoking abstinence, concluded that subjects placed in the IQOS group experienced grade 2 (moderate) increases in ALT. Contrary to bilirubin, shifts in ATL levels are not to document in literature, thus are not expectable to occur in the case of smoking cessation.

5

Moving Forward - points in future research

Contents

5.1 Mandatory "non-targeted" analysis for all manufacturers

As pointed out by Klupinski et al [47] with their comparative study contrasting little cigars and mainstream cigarettes, different tobacco products showcase unique chemical fingerprints, each entailing specific exposure risks and a distinctive toxicological profile. Taking into consideration the case at hand, deriving from the authors' conclusions, one might argue that "non-targeted" analyses are more suitable in future studies of HTP such as IQOS, as unique substances with inherit characteristics are expected to be present. This methodology should be standardized and enforced by the FDA, forcing HTPs' manufacturers incorporate this level of testing in their testing protocols. This would allow manufacturers to test for and duly quantify the presence of potentially toxic compounds that are specific to HTPs' aerosols. Additionally, regarding PMI's studies' structure and methodology, it must emphasized that smoking machine studies, despite their practicality in use and adequacy in examining the different constituents of each tobacco products' aerosols, are not able to provide a reliable estimate of usage patterns and the systematic exposure to toxicants those might entail.

5.2 IQOS's impact in the smoke naïve

For their brief report, Talih et al [26] resorted to florescence, high-performance liquid chromatography, and gas chromatography to respectively quantify total and free-base nicotine, carbonyl compounds (CC) and ROS in IQOS aerosols. In doing so, two different puffing regimens were applied: ISO (used for nicotine and ROS measurements) and HCI (used in quantifying nicotine and CC). Researchers imprinted a pack-a-day equivalence to their obtained results. By doing so, conclusions outlined IQOS users approximately doubling their exposure to formaldehyde (IARC group 1, carcinogenic to humans) and total ROS in regards to solely being exposed to background air alone (naturally IQOS results become cumulative with those depicted in background air).Also, exposure to acetaldehyde (IARC group 2B, possibly carcinogenic to humans, and group 1 if in combination with alcohol) was notably above 100 times higher in IQOS aerosols than in urban breathing air. Despite the absolute risk associated with these measurements, there was a somewhat positive undertone that could be exploited if one were to analyse results relative terms. As acknowledged by this study's authors, IQOS aerosols depict a "reduction in daily intake of formaldehyde and acetaldehyde of 70% and 65%, respectively, and an 85% reduction in ROS" when compared with traditional cigarette smoke. See Table 5.1 [26].

Table 5.1: Toxicological content in aerosols, as referenced in [26].

	IQOS		Marlboro Red		
Device	ISO	HCI	ISO	HCI	IQOS (previous reports)
TPM (mg/cigarette)	12.93 (0.25)	27.17 (2.08)	10.03 (0.65)	37.5 (2.96)	44–55.85[4,6]
Nicotine (mg/cigarette)	0.77 (0.06)	1.50 (0.2)	0.80 (0.05)	1.80 (0.11)	0.5–1.4[4,6,8]
%FB	13.6 (1.4)	5.7 (2.2)	14.5 (1.9)	5.8 (1.7)	NR
pH	6.66 (0.12)	5.87 (0.17)	6.11 (0.05)	5.69 (0.06)	NR
PG/VG		8/92			14/86[6]
ROS (nmol H_2O_2/cigarette)					
Gas phase	1.93 (0.95)	2.25 (0.74)	22.10 (0.74)		NR
Particle phase	4.34 (1.8)	7.78 (1.46)	24.74 (4.18)		NR
Total	6.26 (2.72)	10.04 (2.12)	46.83 (9.6)		NR
Carbonyls (µg/cigarette)					
Formaldehyde		0.85 (0.28)		3.17 (0.33)	3.2–21.87[1,5,6]
Acetaldehyde		301.46 (15.8)		1059 (9.03)	133–210[1,5,6]
Acetone		48.37 (2.73)		775.6 (28.42)	12–26.59[1,6]
Acrolein		ND		0 (0)	0.9–10.8[1,5,6]
Propionaldehyde		22.25 (0.6)		47.89 (1.04)	7.8–12.8[1,5]
Crotonaldehyde		5.52 (0.55)		40.42 (0.69)	0.7–6.42[1,5,6]
Methacrolein		6.53 (0.37)		85.46 (3.85)	NR
Butyraldehyde		30.73 (1.89)		22.19 (2.91)	NR
Valeraldehyde		20.11 (1.48)		0 (0)	NR
Glyoxal		3.11 (0.18)		0 (0)	NR
Methyl glyoxal		33.51 (1.23)		0 (0)	NR
Sum of carbonyls		472.4 (19.35)		2033 (35.72)	NR

Blank entry = not analyzed, FB = free-base, ND = not detected, NR = not reported, PG = propylene glycol, ROS = reactive oxygen species, TPM = total particulate matter, VG = vegetable glycerin. Puffing regiments used in citations: [1]ISO; [4]HCI; [5]HCI; [6]HCI, ISO; [8]HCI.

On that premise, there is, unfortunately, one piece of evidence that may become extremely naïve when considering the affect of IQOS in the smoking naïve. As stated by the authors from this research paper "IQOS and combustible cigarettes had nearly identical total nicotine yields and free based fractions under both HCI and International Organization of Standardization (ISO) puffing regimens". This becomes relevant when considering this specific subset of the population because, as established in literature, free based nicotine is considered as the component in tobacco smoke responsible for its addicting "kick", a crucial attribute in smokers' satisfaction. Thus, comparable levels of nicotine and free base nicotine in IQOS and traditional cigarettes imply a similar sensory experience and addicting potential in both tobacco forms. Naturally, previously nicotine naïve individuals may become as easily addicted to IQOS as they would be if experimenting with traditional cigarettes. As part of the nicotine-naïve stands a particular group to whom nicotine stands as a threat to its developing (adolescent) brain, young adults. This risk was clearly acknowledged in the U.S. Department of Health and Human Services' 2016 publication of "E-cigarette use among youth and young adults: a report of the Surgeon General" [17]. In this publication, IQOS is mentioned and treated as an e-cigarette. Moreover, among its findings, this reports states that since 2011 the number of middle and high school students who have either admitted to have tried or who have experienced e-cigarette use in the last 30 days, has more than tripled. More specifically, data concerning the 18 to 24 year old group showcases that this age group has more than doubled in self-reported ever users (from 2013 to 2014) and has presented a prevalence of past-30-day use of e-cigarettes of approximately 13.6%, a statistic that is only surpassed by high school students which showcase a 16% prevalence. Among the reasons cited for e-cigarette experimentation and usage within youth and young adults stand: curiosity, flavouring/taste, and low perceived harm in comparison to other tobacco products. If anything else, the novelty and appeal in e-cigarette seems to be placing this option as a new entry gate for smoking in this particular age group. According to the Surgeon General in 2015, past-30-day exclusive e-cigarettes' use has outweighed the exclusive use of traditional cigarettes registered within the same 30 day timeframe for 8th, 10th and 12h grade students (6.8% vs 1.4%, 10.4% vs 2.2%, 10.4% vs 5.3%, respectively), with flavoured varieties in e-cigarettes being consumed at higher rates by 18 to 24 year olds than verifiable for older adults (25 years old and older). It is even reported that the majority of youth used flavoured varieties in their first e-cigarette experience. Regrettably this does not translate into youngsters not experimenting in dual use. This is, in reality, an added reason for concern approached in this document. As stated, e-cigarettes' use among youth and young adults' e-cigarettes is commonly associated with other tobacco products' consumption, namely combustible cigarettes. In 2015, 58.8% of high schoolers in the US who were pre-established traditional cigarettes' smokers also reported concomitant use of e-cigarettes. Unfortunately, this shortcoming in accurately predicting consequences inherit to this real-world scenario usage pattern transcends this age group and is a point to be made in future research on its own.

Adding to the already established risks derived from nicotine dependency and exposure to harmful and potentially harmful compounds contained in heated tobacco products as IQOS, in its technical report from 2023, Brian P. Jenssen et al [48], have alerted to tobacco and/or nicotine use may, in time, become an added risk of engaging in other heavier drugs' and alcohol use. As stated in this document". Cohort studies reveal that tobacco use often precedes the use of other drugs in adolescents". In other alarming news addressed in this document, a "nationwide outbreak of severe lung injury cases" is directly attributed to e-cigarettes' use. As of February 2020, in the United States, 2800 hospitalizations and 68 related deaths had been reported to the Centre for Disease Control and Prevention (CDC), as a result from this crisis. The patients' average age was 24 years, and a subset of 15% were younger than 18.

All in all, characterizing the impact of IQOS in the nicotine-naïve, more specifically in younger aged groups is a valid point in independent research to be carried out in the future, especially if PMI's dismissal of this matter is considered. This statistic has been purposely underreported by PMI, according to which, IQOS uptake is expected to be limited among youth due to its relatively high initiation cost. This assumption becomes easily refutable. Not only is the price effect result of coupons not equated, but more importantly, the trend of shared use among users is greatly overlooked. As reported by Pepper JK et al [49] given their pre-set 1729 sample of teens aged 15 to 17 who vaped (or used e-cigarettes) in the past 30 days, over 70% of teenagers (72.8%) reported using someone else's e-cigarette. More than a purchasing decision, this tendency was assumed by participants in this study as part of the user's social experience, a behaviour that demands further research in other to be better understood.

5.3 Secondhand smoking in IQOS

According to O'Connell et al [16] there is enough evidence to suggest the generation of side-stream emissions during and prior to puffing, once an IQOS is merely switched on. In their research, the authors conducted a Proton Transfer Reaction -Mass Spectrometry (PTR-MS) analysis. In doing so, the PTR-MS device ionized volatile organic compounds (VOCs) present in the aerosol stream through their reaction with H_3O^+ to form protonated species (VOCH+) which can be detected by a mass spectrometer. As confirmed by this research group's results, a wide number of different VOC species (as well as toxicants such as Acetaldehyde and Nicotine) varying in their respective masses were detected in the airspace, confirming the generation of side-steam both when the IQOS device was only switched on and at use.See Figure 5.1 [16].

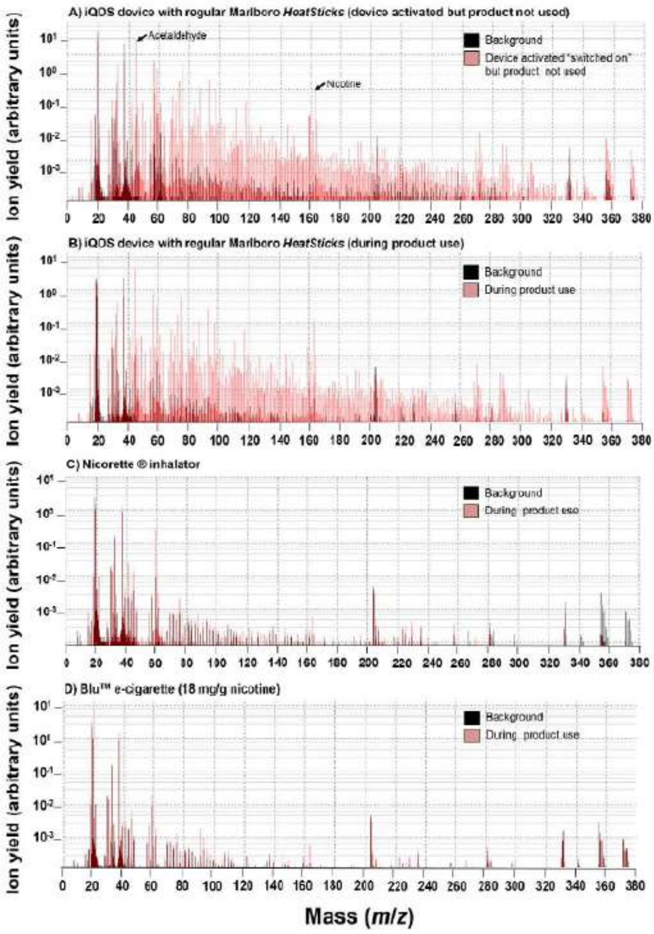


Figure 5.1: Results from PTR-MS analysis showcasing the VOCs released from IQOS regular Heatsticks once "switched on" but not actively puffed, in A, during consumption, in B, during consumer use of a Nicorette inhalor, in C, and as released during use of Blu's e-cigarette, in D. Specific compound peaks at m/z 45 regards protonated acetaldehyde and m/z 163 represents protonated nicotine. As referenced in [16].

It is perhaps useful to remember WHO's (World Health Organization) statement, according to which " there is no safe level of exposure to secondhand tobacco smoke". Given that several toxicants are common to tobacco smoke and IQOS aerosols, no level of sidestream exposure should be deemed safe or acceptable. Thus far independent research conducted on the impact of second hand smoking in IQOS has been limited. Having said that, a study by Tabuchi et al [3] , based on an internet longitudinal survey of 8240 individuals aged 15 to 69 conducted from 2015 until 2017, allowed researchers to map out frequent symptoms experienced by those who are exposed to secondhand IQOS aerosol. Two questions were posed in order to obtain this data:

1. "Have you ever inhaled the aerosol of HNB (heat not burn) tobacco (Ploom Tech, IQOS and/or glo) that other people were using?" (answering options : yes or no)

2. "Have you ever experienced symptoms due to the aerosol of HNB tobacco that other

people were producing?" (options given as referral: sore throat, eye pain, feeling ill, other injuries or symptoms; answering options to each referral option : yes or no)

Answers revealed that 12% (n=997) of all respondents considered to have been exposed to secondhand HNB tobacco aerosol. From these, 37% reported to have experienced at least one symptom as a direct result from such exposure. The most popular symptom reported was "feeling ill" (25.1%), followed by "eye pain" (22.3%) and sore throat (20.6%). Another conclusion drawn out of this data set had to do with the increased tendency in reporting at least one symptom from subjects who identified as smoke naïve (49.2%) in comparison with former users (41%) and current users (26%). See Table 5.2 [3].

Table 5.2: Symptoms reported as being connected to third party aerosol emission from HNB tobacco products, as referenced in [3].

	Among total sample, n=8240	Among those exposed to aerosol of HNB tobacco, n=977				
Characteristics	Exposed to aerosol of HNB tobacco, n (%)	Sore throat, %	Eye pain, %	Feeling ill, %	Other injury or symptom, %	Any symptom, %
Total	977 (11.9)	20.6	22.3	25.1	13.4	37.0
Sex						
Men	582 (14.1)	19.7	24.0	24.3	18.6	31.4
Women	395 (9.6)	21.9	19.9	26.3	5.7	45.3
Age groups, years*						
17–29	179 (10.6)	27.9	37.3	39.7	14.5	56.3
30–39	310 (18.5)	22.3	25.0	24.0	13.6	42.1
40–49	227 (12.0)	22.4	22.3	25.1	11.0	28.8
50–59	169 (12.2)	11.6	5.7	12.0	18.8	24.4
60–71	93 (5.8)	13.0	14.9	24.8	6.6	26.1
Combustible cigarette and HNB tobacco/e-cigarette use*						
Never/never†	294 (6.9)	23.1	28.7	38.0	9.6	49.2
At least one former and no current‡	272 (13.1)	21.1	20.9	22.9	10.6	41.2
At least one current§	412 (21.5)	18.6	18.7	17.4	18.0	25.6

**Status in 2017.*
†Never/never means persons who never smoke (combustible tobacco) and never used HNB tobacco/e-cigarette
‡Former/former, former/never or never/former
§Current/never, current/former, current/current former/current or never/current.
HNB, heat-not-burn.

As a particularly exposed group to second and thirdhand smoking stand pregnant woman and infants. As is well documented in existing literature, nicotine and other toxins found in tobacco can cross the placenta and cause harm to the fetus. This exposure can derived from maternal smoking habits as well as absorption or inhalation of toxic particles being emanated from third party smoking. Consistent with what has been stated throughout this paper, the American Academy of Paediatrics acknowledges in its report the harmful nature of particles contained in e-cigarettes aerosols, namely: nicotine, volatile organic compounds, heavy metals, tobacco-specific carcinogens, ultrafine particles and other toxicants. In doing so, this organization emphasizes the Surgeon General's report conclusion in recommending smoke and e-cigarette aerosol-free spaces, re-enforcing the need to legislate against its use in enclosed spaces.

Moreover, on the issue of paediatrics' applied research, Richmond et al [50] conducted a onetime survey on e-cigarette exposure (both through inhalation and ingestion) in the last 12 months in children and adolescents, which targeted paediatricians in Canada. In replying, the 520 surveys that were completed and sent in (corresponding to 220 cases) by paediatricians provided a detailed report on: the number of injuries and symptoms experienced by their e-cigarette exposed patients, as well as, complementary information on their age, sex, treatment settings, conditions under which the product was accessed and validated whether its usage was intentional. With a 20.5% response frequency (520 completed surveys out of 2533 sent) data gathered through this research method indicated that the majority of incidents with e-cigarettes were related with inhalation cases. From the 135 surveys describing such events, the best part concerned male patients, aged 15 to19 years old, who sought medical assistance for nausea and/or vomiting, persistent cough, throat irritation or acute nicotine toxicity. In most cases, patients had been exposed to e-cigarettes aerosols 2 to 3 days per week. All in all, an extensive characterization of the health hazards in secondhand IQOS aerosols is yet to be accomplished through research. This is a necessary step in ensuring better risk communication for this product category and it is crucial in ensuring that legislator activity is undertaken in order to protect IQOS users and bystanders.

6

Conclusion

All in all, the rise of new tobacco products is a lifeline for an otherwise declining industry. Increasingly health conscious and informed audiences, powered by overwhelming evidence on the harmful health effects associated with smoking have pushed key players in the industry to seek out other revenue streams in the form of alternative products that respond to the same need as traditional cigarettes: nicotine craving. Hence, as combustible cigarette sales began to decline, the inverse tendency was registered for new tobacco products. With that said, electronic cigarettes were followed by heated tobacco products, as well as hybrid options, in reaching the market place. At different paces, by 2018 all major tobacco conglomerates had been successful in identifying and marketing alternative nicotine delivery systems. More than directly responding to the change in costumer preferences as providers of a seemingly healthier alternative to smoking, tobacco conglomerates sought to exploit a lobbying opportunity at a governmental level, pushing for more lenient regulations to be implemented regarding this innovative products and naturally expecting to take commercial benefits from this. Having been the last category of new tobacco products to reach the market, one could expect HTPs to be the option to score the furthest from conventional cigarettes, as far as parameters depicting the hazardous nature of smoking are concerned. On the contrary, conditional on acknowledging existing variations within its category and its impact on risk profiles, electronic cigarettes are suggested by different research papers as: conveying the least amount of nicotine (conditional on fixing the e-liquids formulation at comparable nicotine concentrations) per puff, having the mildest level of cytotoxicity, emitting the lowest levels of tobacco specific nitrosamines, as well as, PAHs and carbonyl compounds. All things considered, despite its comparatively less hazardous nature, e-cigarettes' impact was also proven to be greatly altered and affected by product engineering, specifically power settings, as well as its users' personal smoking behaviour. On top of falling in the less favourable end of this comparison with e-cigarettes, HTPs still offer an added cause for concern. In spite of acknowledging the need for further research on this matter, evidence is clear in outlining that these products only need to be ”switched on” (need not be actively puffed on) in other for toxicants to be emitted, implying that side stream emissions and thus secondhand smoking are implicated in the use of HTPs. The extent to which this influences bystanders' health is yet to be characterized in detail. Given HTPs growing popularity, especially in what concerns a younger population, it is also important to further research these products' impact on the smoke naive, not only in terms of clarifying how it may become a recruitment path to smoking, creating much needed independent research on the ”dual smoking phenomenon”, but also understanding whether it may encourage other drugs engaging behavior in the future. At the end of the day, ensuring relatively lower levels of exposure to toxicants does not imply a risk free experience. Exposure to carcinogenic compounds is still a relevant part of the e-cigarette or HTP users' experience. As a matter of fact, similar symptoms from smoking are to be expected as far as pulmonary immunosupression and endothelial and cardiovascular injury are concerned. After all, some toxicants' effects are not dose dependent and the frequency of exposure may become optimized as some of the less user friendly aspects of traditional smoking become circumvented with these new nicotine products.

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