

Scientific evidence on heated-tobacco products. A narrative review

Evidencia científica sobre productos de tabaco calentado. Una revisión narrativa

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Received: 09/09/2020 · Accepted: 19/02/2021

Abstract

Given the impact of smoking on individuals and National Healthcare Systems, it has become necessary for the continuous evaluation of tobacco products, especially when they are claimed or perceived as being less harmful than conventional cigarettes (CCs), and coexisting conflict of interests. The objective of the present manuscript was to perform a complete and updated narrative review of scientific literature on the assessment of harmful and potentially harmful constituents (HPHCs) and the biological and clinical impact from the newest available heated-tobacco products (HTPs), in comparison with CCs. A total of 52 studies (46 from the review and 6 manually found) were finally analyzed. Despite some existing differences among the studies, most of them point to a reduction of the emissions of HPHCs as well as exposure to toxicants, and thus in the biological and clinical impact with HTPs when compared with CCs. In the scenario where individuals decide to continue smoking, HTPs seem to be a better option than CCs. Further prospective, independent studies should replicate the existing experiments in order to corroborate the conclusions raised in the original studies. Moreover, long-term investigations (decades) are also needed to obtain more compelling safety information of HTPs.

Key Words

Heated-tobacco products; narrative review; biological impact; biomarker; harmful constituents.

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Resumen

Dado el impacto del tabaquismo en las personas y en los Sistemas Nacionales de Salud, se ha vuelto una necesidad la evaluación continua de los nuevos productos de tabaco, especialmente cuando se afirma o se percibe que son menos dañinos que los cigarrillos convencionales (CC). El objetivo del presente manuscrito es presentar una revisión narrativa completa y actualizada de la literatura científica sobre la evaluación de los componentes dañinos y potencialmente dañinos (HPHC) y el impacto biológico y clínico de los productos de tabaco calentado (PTC), más novedosos, en comparación con los CC. Se analizaron un total de 52 estudios (46 de la revisión y 6 encontrados manualmente). A pesar de algunas diferencias existentes entre los estudios, la mayoría de ellos apuntan a una reducción de las emisiones de HPHC, así como a la exposición a sustancias tóxicas y, por lo tanto, en el impacto biológico y clínico con los PTC en comparación con los CC. En un posible escenario de personas que deciden seguir fumando, los PTC parecen ser una mejor opción que los CC. Estudios independientes prospectivos deberían replicar los experimentos existentes para corroborar las conclusiones planteadas en los estudios originales aquí presentados. De la misma manera, investigaciones a largo plazo (décadas) son necesarias para obtener información más completa sobre la seguridad de los PTC.

Palabras clave

Productos de tabaco calentado; revisión narrativa; impacto biológico; biomarcadores; constituyentes nocivos.

I. INTRODUCTION

Smoking is one of the major preventable causes of death. According to the World Health Organization, approximately 1.1 billion individuals worldwide smoked tobacco in 2015 (World Health Organization, 2019). Smoking is associated to serious conditions, such as cardiovascular disease, chronic obstructive pulmonary disease, and cancer (U.S. Department of Human Services, 2010). The path from exposure to tobacco smoke that contains the harmful constituents produced by combustion to the onset of disease are described as a chain of causally-linked key (biological) events, known as an Adverse Outcome Pathway (Sturla et al., 2014).

This pathway starts with the exposure to cigarette smoke and toxicants produced by burning tobacco, leading to molecular changes that cause interruption of biological mechanisms and, physiological changes that ultimately produce disease. National Healthcare Authorities strongly encourage the cessation of smoking, and have developed regulatory and educational initiatives. Despite documented increased risk, one billion individuals will continue smoking. Diverse alternative tobacco products have been commercialized in last decades, including electronic cigarettes and heated tobacco products (HTPs) (Glantz, 2018; Grana, Benowitz y Glantz, 2014; McNeill, Brose, Calder, Bauld y Robson, 2018). E-cigarettes do not contain tobacco, but an



e-liquid containing vegetable glycerin, propylene glycol and may contain nicotine, which is heated to generate an aerosol that is inhaled by the user. The HTPs do contain tobacco, which is heated rather than burned to generate a nicotine-containing aerosol. They are claimed to have reduced biological impact compared to conventional cigarettes (CCs). The scientific basis of the HTPs is associated to the absence of combustion, which leads to lower operating temperatures (below 400°C, versus 900°C in CCs), and the reduction of 90-95% of harmful and potentially harmful constituents (HPHCs) in the aerosol (Murphy et al., 2018; Schaller et al., 2016) in comparison with those present in the smoke of CCs. Given the impact of smoking on individuals and National Healthcare Systems, it has become necessary for the continuous evaluation of tobacco products, especially when they are claimed or perceived as being less harmful, and coexisting conflict of interests (Glantz, 2018; Wertz, Kyriss, Paranjape y Glantz, 2011). Therefore, the objective of the present manuscript was to perform a complete and updated narrative review of scientific literature on the assessment of HPHCs emissions and the biological and clinical impact from the newest available HTPs, in comparison with CCs. Based on results from this review, the question about whether HTPs have a less detrimental effect than CCs could be answered.

2. METHODS

This narrative review was carried out by using PubMed database, following PICO methodology: population (smokers), intervention (heated-tobacco), comparator (CCs), and outcome (biological impact,

combustion markers, harmful constituents) (Eriksen y Frandsen, 2018). Keywords used in the search were: "Tobacco products", "Tobacco", "heated", "heating", "modified risk tobacco product", "reduced risk product", "heat not burn", "heat-not-burn", "3T", "glo", "ifuse", "THP", "tobacco heating product", "IQOS", "THS", "tobacco heating system", "ismoke", "lil", "pax", "ploom", "zerostyle", "V2", and "Pro". The search was performed on 17th June, 2019. It focused on studies published from January 2010 to June 2019, written in English. The formula employed in PubMed was as follows: (((Tobacco products[MeSH Terms]) OR Tobacco[MeSH Terms]) AND ((heated OR heating OR (modified risk tobacco product) OR (reduced risk product) OR (heat not burn) OR (heat-not-burn) OR 3T OR glo OR ifuse OR THP OR (tobacco heating product) OR IQOS OR THS OR (tobacco heating system) OR ismoke OR lil OR pax OR plloom OR zerostyle OR v2 OR (v2 AND pro))) AND ("2010/01/01"[Pdat] : "2019/06/17"[Pdat])). Non-related studies (plant physiology, indoor air quality, menthol content, enamel discoloration, passive smoking, chewing-tobacco, perception/behavior of smokers, pharmacokinetics, protocols, politics/laws, n=523), meta-analyses/reviews/systematic reviews (n=16), short communications/commentaries (n=10), and non-English articles (n=15) were initially discarded out from the analysis. This selection of studies was done based on title and abstract of each reference. Additionally studies involving electronic cigarettes (n=14) or old version/prototypic/ no commercially available heated-tobacco devices (carbon heated tobacco product, CHTP; tobacco heating system, THS, 2.1, n=15) were also excluded. It is necessary to indicate that THS is a

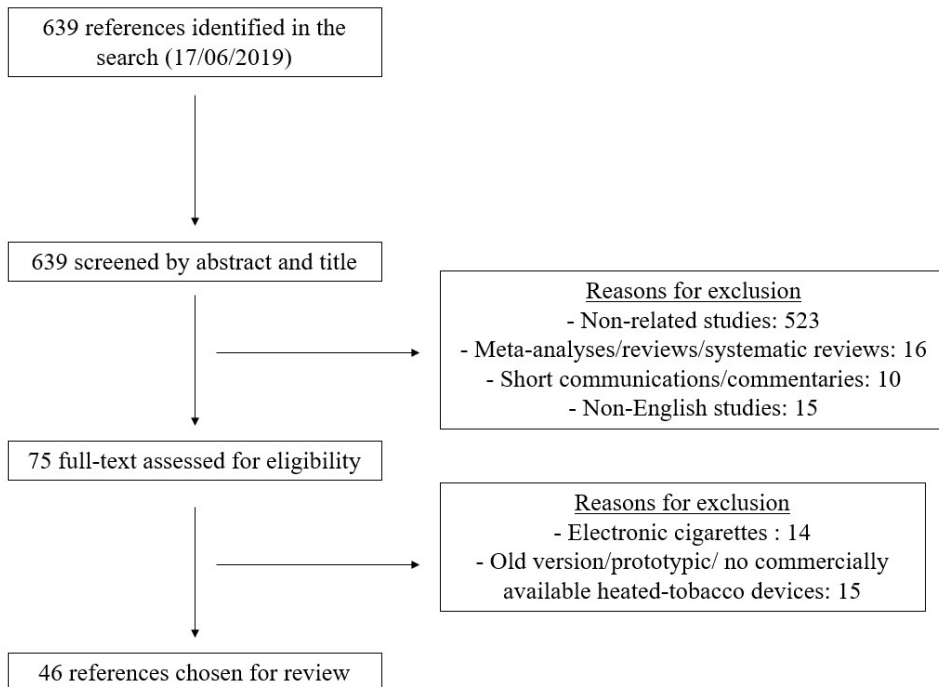


type of HTP. Only studies showing the level of emissions of HPHCs in the HTP aerosol and those related to the biological and clinical impact of HTPs were finally selected for review. Articles from *in vitro*, animals, and humans studies have been included. Most of the available references were for Philip Morris International (PMI)'s IQOS and/or British American Tobacco (BAT)'s glo, and thus the content of this review focuses on these products. The study design was in accordance with Equator network guidelines: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

3. RESULTS

A total of 639 studies were initially identified, however only 46 fell within the scope of this review (Figure 1). Additionally, four recent papers (Davis, Williams y Talbot, 2019; Gale et al., 2019; Li et al., 2019; Lüdicke et al., 2019), and two clinical studies that did not appear in the search were also analyzed (Lüdicke et al., 2018). The total number of references considered was 52. Of them, 42 were carried out by manufacturers (PMI, BAT, or Reynolds Tobacco Company).

Figure 1. PRISMA flow diagram





3.1. Emissions of harmful and potential harmful constituents

There are over 7,000 compounds identified in cigarette smoke, about a hundred have been identified as HPHCs (U.S. Department of Health and Human Services, 2010). A summary of studies characterizing HPHCs from HTPs are shown in Table I. A lot of studies (9 out of 12) were from manufacturers, and referred to THS 2.2. Most of studies (n=12) were focusing on aerosol chemistry tests, as well as laboratory tests involving physiology and histology together with lipidomics, proteomics, and transcriptomics. They showed reduced levels of HPHCs when using HTPs, compared with CCs. Jaccard, Kondylis, Gunduz, Pijnenburg y Belushkin (2018) evaluated levels of tobacco-specific nitrosamines (TSNA) in 1,000 commercially available tobacco products, including HTPs and CCs. The TSNA are

known carcinogens that can be generated in the tobacco plant during the curing process (Wang et al., 2017). The transfer of TSNA from tobacco to aerosol was 2–3 times lower with THS 2.2 than CCs, resulting in a significant reduction in HTP aerosol compared to cigarette smoke. Li et al. (2019) compared the chemical analysis and simulated pyrolysis between HTP and CCs. Authors concluded that, excepting some carbonyls, ammonia, and N-nitrosoanabasine, releases from HTP were 80% lower than CCs. Leigh, Palumbo, Marino, O'Connor y Goniewicz (2018) compared levels of TSNA in aerosol between HTP and electronic cigarettes and CCs, and found that levels from HTP are lower than CCs. On the other hand, Davis et al. (2019) evaluating performance of THS 2.2. in diverse conditions identified the release of the highly toxic, but not recognized currently as HPHC, formaldehyde cyanohydrin.

Table I. Summary of studies characterizing harmful constituents in heated-tobacco products

Reference	Heated-tobacco products	Methodology/ Procedure	Comparison with conventional cigarettes
Li et al. (2019)	THS 2.2	Simulation of pyrolysis with gas chromatography–mass spectrometry	- 80% lower releases (except carbonyls, ammonia, and N-nitrosoanabasine)
Davis et al. (2019)	THS 2.2	Gas chromatography-mass spectrometry	- Release of formaldehyde cyanohydrin
Gasparyan et al. (2018)	THS 2.2, THP 1.0	ISO 4387 standard	- Greater levels of humectants and water in dynamic equilibria between particulate and gaseous phases
Leigh et al. (2018)	THS 2.2	Liquid chromatography-tandem mass spectrometry	- Lower TSNA
Jaccard et al. (2018)	THS 2.2	Liquid chromatography-tandem mass spectrometry	- Lower (2–3 times) transfer of TSNA from tobacco to aerosol, compared with CCs
Buratto et al. (2017)	THS 2.2	Liquid chromatography tandem mass spectrometry	- Significant lower concentrations of carbonyl compounds than CCs
Eaton et al. (2018)	THP 1.0	Thermophysical studies, thermogravimetric analyses	- Significant lower levels of combustion markers in the aerosol than pyrolysis/combustion.



Reference	Heated-tobacco products	Methodology/ Procedure	Comparison with conventional cigarettes
Bekki et al. (2017)	THS 2.2	Liquid chromatography-tandem mass spectrometry	- 1/5 of TSNA concentration and 1/100 of CO, compared with CCs
Pratte et al. (2017)	THS 2.2	Dekati thermodenuder	- No formation and transfer of (80%) solid carbon particles, in contrast to CCs
Auer et al. (2017)	THS 2.2	Gas chromatography coupled to a flame ionization detector and polycyclic aromatic hydrocarbons using high-performance liquid chromatography coupled to a fluorescence detector	- Higher levels of acenaphthene (145 versus 49) - Smoke with same levels of other harmful constituents
Schaller et al. (2016)	THS 2.2	Isothermal gas chromatography	- >90% reduction of most of HPHCs - 90% decreased cytotoxicity and mutagenic potency in assays
Schaller et al. (2016)	THS 2.2	Labstat International analytical methods	- Significantly lower concentrations of HPHCs in aerosols from the 43 tobacco plug blends, compared to CCs - Significant variability in ammonia, TSNA, nitrogen oxides, PAHs, acrylamide and acetamide concentrations in the 43 tobacco plug blends

eCO, exhaled carbon monoxide; CCs, conventional cigarettes; THR, tobacco harm reduction; THS, tobacco heating system; TSNA, Tobacco-specific nitrosamines; THP, heated tobacco product; HPHCs, harmful and potentially harmful constituents; PAH, polycyclic aromatic hydrocarbon.

3.2. Biological and clinic impact

A summary of studies describing biological and clinical impact of HTPs are shown in Table 2. They have been performed with adult smokers (clinical trial, n=6), rodents (wildtype or transgenic ones, n=11), human or rodent cell lines (human bronchial epithelial cells, human gingival epithelial cells, human coronary arterial endothelial cells, monocytic and human coronary arterial endothelial cells, murine macrophage cells, murine bone marrow derived dendritic cells, and human monocyte dendritic cells, n=14), or they have employed diverse laboratory techniques (n=3). Most of studies show a reduced biological impact of HTPs compared to CCs, or when

switching to them. Main results from some of them are detailed below.

3.2.1. In vitro studies

Zanetti et al. (2017) by using human gingival epithelial cell, showed minor histopathological alterations and cytotoxicity (1% with HTPs versus 30% with CCs), significant alterations in 5/14 proinflammatory mediators (versus 11/14 with CCs). The biological impact with HTPs was reduced by 79%, compared with CCs. Leigh, Tran, O'Connor y Goniewicz (2018) evaluated the cytotoxic effects of HTPs on human bronchial epithelial cells, and concluded that cytotoxicity was reduced after using HTPs, compared with CCs.



Table 2. Summary of studies describing biological and clinical impact of heated-tobacco products

Reference	Heated-tobacco products	Study type	Subjects/cell line	Methodology/Procedure	Comparison with conventional cigarettes
Gale et al. (2019)	THP 1.0, THS 2.2	Clinical trial	182 adult humans	24-h urine samples	- Significant reduction in levels of biomarkers of toxicant exposure (excepting nicotine), comparable to cessation
Lüdicke et al. (2019)	THS 2.2	Clinical trial	984 adult humans	Bioanalytical methods	- Significant improvements in high-density lipoprotein cholesterol, white blood cell; FEV ₁ (% of predicted), carboxyhemoglobin, and total NNAL after switching to THS 2.2 - Biomarkers of exposure significantly reduced
Phillips et al. (2019)	THS 2.2, CHTP 1.2	Animal study	ApoE ^{-/-} mice	A systems toxicology approach combining physiology, histology and molecular measurements	- Significant lower effects on the cardiorespiratory system, lung inflammation, emphysematous changes, atherosclerotic plaque formation - Decreased effects when cessation/switching to CHTP 1.2
Choukralah et al. (2019)	THS 2.2	Animal study	ApoE ^{-/-} mice	A systems toxicology approach combining physiology, histology and molecular measurements	- Lower DNA methylation alterations in lung tissue - Reduced alterations when cessation/switching to THS 2.2
Adriaens et al. (2018)	THS 2.2	Clinical trial	30 adult humans	Physiological measures and subjective effect questionnaires	- Minimal increase of eCO (0.3 ppm) after overnight abstinence versus significant increase with CCs
Munakata et al. (2018)	THP	<i>In vitro</i> study	Human bronchial epithelial cell	Test concentrations of aqueous extracts	- Cytotoxicity EC ₅₀ value 10 times higher
Nabavizadeh et al. (2018)	THS 2.2	Animal study	Rats	Gas chromatography - tandem mass spectrometry	- Impairment of arterial flow-mediated dilation, similar that with CCs
Leigh et al. (2018)	THS 2.2	<i>In vitro</i> study	Human bronchial epithelial cells	Neutral red uptake and trypan blue assays and enzyme-linked immunosorbent assay	- Lower cytotoxicity (IL-1β: 13.7±5.1 versus 133.6±41.9; IL-6: 6.9±2.1 versus 65.5±21.7 pg/10 ⁷ cells)
van der Toorn et al. (2018)	THS 2.2	<i>In vitro</i> Human cells	Human bronchial epithelial cells	Gas chromatography	- Induced alterations in gene expression, anchorage independence, and epithelial to mesenchymal transition - Lower biological impact
Malinska et al. (2018)	THS 2.2	<i>In vitro</i> study	Human bronchial epithelial cells	Clark electrode, Seahorse phenotype test	- Lower effect on oxidative phosphorylation, and gene expression/proteins associated to oxidative stress



Reference	Heated tobacco products	Study type	Subjects/ cell line	Methodology/ Procedure	Comparison with conventional cigarettes
Haswell et al. (2018)	THP 1.0, THS	<i>In vitro</i> study	RNA-sequencing	Toxicogenomics assessments	- Reduced biological effect/impact on gene expression - No pro-inflammatory effect of the smoke, in contrast to CCs
Murphy et al. (2018)	THP 1.0, Glo	<i>In vitro</i> study	Multiple assays	Toxicogenomics assessments	- Significant lower responses to emissions - Potential reduced risk product
Taylor et al. (2018)	THP 1.0	<i>In vitro</i> study	Human bronchial epithelial cells	Luciferase-based reporter gene assay	- Lower increases in antioxidant response element activation - No activity or little in cellular acute response tests
Jaunky et al. (2018)	THP 1.0, THS	<i>In vitro</i> study	Human bronchial epithelial cells	Neutral red uptake assay	- Reduced biological response (cytotoxic response) and higher viability (87%)
Glantz (2018)	THS 2.2	Clinical trial	236 adult humans	Analysis of 24 biomarkers of potential harm	In American subjects (n=88), 23 out of 24 biomarkers of potential harm were similar than CCs - In Japanese subjects (n=148), 10/13 biomarkers were similar. Improvements in 4 out of 13 biomarkers
Lüdicke et al. (2018)	THS 2.2	Clinical trial	160 adult humans	Measurement of relevant risk markers	- Significant lower concentrations of carboxyhemoglobin (55%), 3-hydroxypropylmercapturic acid (49%), monohydroxybutenyl mercapturic acid (87%), and S-phenylmercapturic acid (89%)
Lüdicke et al. (2018)	THS 2.2	Clinical trial	160 adult humans	Measurement of relevant risk markers	- Reductions in levels of biomarkers of oxidative stress, platelet activation, and endothelial function - Increase in biomarkers of lipid metabolism and lung function
Caponnetto et al. (2018)	THS 2.2	Clinical trial	12 adult humans	Measurement of eCO at 5, 10, 15, 30, and 45 min after the first puff	- No elevations of eCO, in contrast to CCs
Brehehy et al. (2017)	THPs	<i>In vitro</i> study	<i>In vitro</i> assays	Ultra-performance liquid chromatography triple quad mass spectrometry	- Significant lower responses
Szostak et al. (2017)	THS 2.2	<i>In vitro</i> study	ApoE ^{-/-} mice	Transcriptomics determinations	- No downregulation of genes associated to contractile function of the heart and cytoskeleton organization, in contrast to CCs
Zanetti et al. (2017)	THS 2.2	<i>In vitro</i> study	Human gingival epithelial cells	Transcriptomic and metabolomic analysis	- Minor histopathological alterations and cytotoxicity - Significant alterations in 5 out of 14 proinflammatory mediators, versus 11/14 from CCs - 79% reduced biological impact



Reference	Heated-tobacco products	Study type	Subjects/cell line	Methodology/Procedure	Comparison with conventional cigarettes
Iskandar et al. (2017)	THS 2.2	<i>In vitro</i> study	Human bronchial epithelial cells	Immunohistochemistry analysis	- Lower cytotoxicity - Reduced levels of secreted pro-inflammatory mediators and miRNA alterations
Iskandar et al. (2017)	THS 2.2	<i>In vitro</i> study	Human nasal epithelial cells	Histology, cytotoxicity, secreted pro-inflammatory mediators, ciliary beating, and genome-wide profiles	- Lower impact in secretion of pro-inflammatory mediators, cytotoxicity, impaired ciliary function, and alterations in tissue morphology
Sewer et al. (2016)	THS 2.2	Animal study	Rats	Transformation of transcriptomic data into protein activity based on corresponding downstream gene expression	- Not caused downregulation and activation of microRNA levels in lungs, in contrast to CCs
Martin et al. (2016)	THS 2.2	Clinical trial	160 adult humans	Measurement of biomarkers of exposure	- Lower exposure response markers in peripheral blood when cessation/switching to THS 2.2
Oviedo et al. (2016)	THS 2.2	Animal study	Rats	Test atmosphere analysis	- Significant reduced alterations in the respiratory tract and systemic toxicity - Significant lower levels of pulmonary inflammation and changes in gene/protein expression
Kogel et al. (2016)	THS 2.2	Animal study	Rats	Transcriptomics and quantitative proteomics analyses	- Weaker molecular changes and adaptive response of the respiratory nasal epithelium
Haziza et al. (2016)	THS 2.2	Clinical trial	160 adult humans	Urine mutagenicity test, self-reported questionnaires	- Significant lower levels of biomarkers of exposure, in contrast to CCs
Haziza et al. (2016)	THS 2.2	Clinical trial	160 adult humans	Measurement of biomarkers	- Significantly decreased levels of exposure biomarkers to HPHCs when switching to THS 2.2 - Magnitude of exposure reduction similar than cessation for 5 days
Wong et al. (2016)	THS 2.2	Animal study	Rats	90-day nose-only inhalation study combined with classical and systems toxicology approaches	- Significant lower degree of lung inflammation, respiratory minute volume, and findings in organs from the respiratory tract - Less pronounced differential gene expression from nasal epithelium and lung parenchyma
Zanetti et al. (2016)	THS 2.2	<i>In vitro</i> study	Human oral epithelial cells	Cellular assays, measurements of secreted proinflammatory markers, and histopathological analysis	- Lower impact in morphological tissue alterations, secretion of inflammatory mediators, and cytotoxicity



Reference	Heated-tobacco products	Study type	Subjects/ cell line	Methodology/ Procedure	Comparison with conventional cigarettes
Lo Sasso et al. (2016)	THS 2.2	Animal study	ApoE ^{-/-} mice	Toxicological with molecular measurements and computational analyses	- Lower biological effects (proteomic and transcriptomic changes)
Poussin et al. (2016)	THS 2.2	<i>In vitro</i> study	Human coronary arterial endothelial cells	Measurement of inflammatory markers, transcriptome analysis	- Reduced effects on cell adhesion, and changes in endothelial and monocytic cells
Gonzalez-Suarez et al. (2016)	THS 2.2	<i>In vitro</i> study	Human bronchial epithelial cells	Multiparametric indicators of cellular toxicity	- Lower levels of HPHCs and biological impact
Phillips et al. (2016)	THS 2.2	Animal study	ApoE ^{-/-} mice	Toxicology approach, using physiology and histology combined with transcriptomics, lipidomics, and proteomics	- Not induced the inflammation or emphysema of lungs, the change in lipid profile or aortic plaque area, in contrast to CCs - Reversed inflammatory responses and stopped the progression emphysematous changes and aortic plaque area when switching to THS 2.2
Titz et al. (2016)	THS 2.2	Animal study	C57BL/6 and apoE ^{-/-} mice	Proteomics and lipidomics analyses	- No lipid response caused by transcription regulators, in contrast to CCs
Ogden et al. (2015)	HTP	Clinical trial	154 adult humans	Measurement of biomarkers	- Significant improvements in inflammation markers after switching to HTP
van der Toorn et al. (2015)	THS 2.2	<i>In vitro</i> study	Monocytic and human coronary arterial endothelial cells	Cytotoxicity and inflammation assays; Chemotaxis analysis	- 18 times less effective the inhibitory effects of chemotaxis and trans-endothelial migration
Ogden et al. (2015)	HTP	Clinical trial	154 adult humans	Measurement of biomarkers	- Lower exposure to HPHCs after switching to HTP

THS, tobacco heating system; FEV₁, forced expiratory volume in 1 second; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; CHTP, carbon heated tobacco product; eCO, exhaled carbon monoxide; CCs, conventional cigarettes; THP, heated tobacco product; EC₅₀, half-maximal effective concentration; IL, interleukin; HPHCs, harmful and potentially harmful constituents; DC, dendritic cells.



3.2.2. *In vivo* animal studies

Phillips et al. (2019) evaluated cardiovascular and respiratory effects of HTPs in ApoE^{-/-} mice for 6 months. Authors showed significant lower effects of HTPs on the cardiorespiratory system, lung inflammation, emphysematous changes, and atherosclerotic plaque formation, compared with CCs. Nabavizadeh et al. (2018) compared the vascular endothelial function between HTPs and CCs in Sprague-Dawley rats. The arterial flow-mediated dilation was similarly reduced by exposures to THS 2.2. aerosol (from 10.6% pre-exposure to 4.5% post-exposure) and CCs smoke (from 10.6% pre-exposure to 4.6% post-exposure). Authors concluded that HTPs produce impairment of arterial flow-mediated dilation, to the same extent that CCs.

3.2.3. Clinical studies

Adriaens, Van Gucht y Baeyens (2018) carried out a clinical study with 30 adult smokers and determined short-term effects after overnight abstinence. Exhaled carbon monoxide (eCO, after smoking a tobacco product for 5 minutes) was significantly increased with CCs, in contrast to a minimal increase (0.3 ppm) with HTP. Caponnetto, Maglia, Prosperini, Busà y Polosa (2018) in a randomized clinical study with 12 adult smokers compared levels of eCO between HTP and CCs. No elevations of eCO were shown after smoking HTPs (compared with a baseline), in contrast to elevations observed with CCs. Ogden, Marano, Jones, Morgan y Stiles (2015) evaluated a series of biomarkers of exposure in a randomized clinical study with 154 adult smokers after switching to HTP or SNUS. Authors demonstrated lower exposure to HPHCs after with HTP. Another group of studies evaluating biological and clinical impact of HTPs showed different re-

sults. Glantz (2018) re-analyzed data from a 3-month study (Lüdicke et al., 2018; Haziza et al., 2019) statistically powered to evaluate a reduction in HPHC exposure in smokers switching to CCs (clinical risk endpoints were also measured as exploratory objectives). This study was used in the PMI application to the FDA for modified risk tobacco product, and found no statistically significant differences between CCs and THS 2.2. groups, and between CCs and cessation groups. Glantz (2018) published a selected reporting of results from the 3-month exposure study, and stated that PMI data show no differences between THS 2.2. and CCs. Based on this study no detectable differences were found in 23/24 biomarkers of potential harm when using THS 2.2. or CCs in American subjects (n=88), and in 10/13 biomarkers in Japanese subjects (n=148). It is necessary to mention that Glantz (2018), did not consider that the original study was not designed to achieve statistical significance in those exploratory endpoints and that neither a difference was observed between cessation and CCs. Lüdicke et al. (2019) have recently published a randomized clinical study involving the largest cohort of adult humans (n=984). Authors primarily evaluated the impact of switching to THS 2.2 on biological parameters (high-density lipoprotein cholesterol, white blood cell, forced expiratory volume in 1 second, FEV₁, and carboxyhemoglobin), and HPHCs in urine such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), soluble intercellular adhesion molecule-1 (sICAM-1), 11-dehydrothromboxane B2 (11-DTXB2), and 8-epi-prostaglandin F2 alpha (8-epi-PGF₂α). After 6 months, levels of high-density lipoprotein cholesterol, white blood cell; FEV₁ (% of predicted), carboxyhemoglobin, and total NNAL significantly improved, compared with baseline and CCs.



4. DISCUSSION AND CONCLUSION

Considering information published in the 52 analyzed studies employing the newest available HTPs in the market, results point out to decreased levels of HPHCs in the aerosol from HTPs and a concomitant reduction in the biological and clinical impact. HTPs are being perceived as less harmful tobacco products compared with CCs and apparently focused on adults who continue smoking. One important aspect of this review is their great diversity in design of the studies (*in vitro* rodent and human cell lines, *in vivo* animals, or clinical studies), methodologies (laboratory assays and techniques), selected outcomes (biomarkers, oxidative stress, cytotoxicity, inflammation, changes in DNA, etc.), for determining biological and clinical impact of HTPs. At the same time, the lack of a unique procedure or technique might in part explain the differential results obtained. One limitation of the studies is the scarce number of clinical studies, and that they only evaluate short-term effects. None of the studies have determined long-term effects of HTPs in human populations. In the case of studies assessing levels HPHCs in the aerosol of HTPs, most of research points out a reduced exposure in comparison with CCs, although HPHCs are still present in the aerosol but at importantly lower levels than in CC smoke. Because they are still present, these products are not risk-free and not appropriate for non-smokers. Finally, another aspect of available scientific evidence on HTPs derives from the fact that most of studies have been carried out by the tobacco industry. Nevertheless, this situation might be considered as normal given the incipient development status of the HTPs. Additional independent studies

are needed to confirm if these new products have a lower impact than their former products, the CCs. Yet, there is a growing number of independent studies on HTPs, even if not all were of scope for this review.

Despite some studies show different results, most of studies point to a reduction of emissions of HPHCs as well as exposure to toxicants, and thus in the biological and clinical impact with HTPs when compared with CCs. Recently, the Food and Drug Administration (FDA) authorized the marketing of Philip Morris Products S.A.'s "IQOS Tobacco Heating System" as modified risk tobacco products (MRTPs). This MRTP product received from the FDA the exposure modification order which permits the marketing of a product as containing a reduced level of or presenting a reduced exposure to a substance or as being free of a substance when the issuance of the order (Food and Drug Administration, 2020). In the scenario where individuals decide to continue smoking, HTPs seem to be a better option than CCs. Further prospective independent studies should replicate the existing experiments in order to corroborate the conclusions raised in the original studies. Moreover, long-term investigations (decades) are also needed to obtain more compelling safety information of HTPs.

ACKNOWLEDGEMENTS

Authors would express gratitude to Meisys for helping in the elaboration of the manuscript.

CONFLICT OF INTEREST

This publication reflects only the view of the authors. Patricia Ortega is a consultant at Meisys (Madrid, Spain, <https://meisys.es>), a



company that was contracted by Philip Morris España for the literature search and the first draft of this article. The remaining authors have no financial relationship with Philip Morris and have not received any compensation. None of them has any conflict of interest related to this work.

FUNDING

Philip Morris España is the sole funding source and sponsor for this project.

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