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Heated tobacco product aerosol emission compared to cigarette smoke: A scoping review

Stefano Bellosta [a,*], Alberto Corsini [a], Gabriele Catena [b]

[a] Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", Università degli Studi di Milano, via Balzaretti 9, Milan 20133, Italy
[b] Società Italiana Scienze Mediche ets (SISMED) – Viale Giulio Cesare, 71, Rome, Italy

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ABSTRACT

Heated tobacco products (HTPs) are promoted as reduced-risk alternatives to combustible tobacco cigarettes (TCs), yet toxicant exposure reduction and associated health benefits remain uncertain. We evaluated preclinical and interventional clinical studies comparing HTPs with TCs, focusing on aerosol composition, toxicological exposure, and harm biomarkers. A systematic PubMed search identified 1105 peer-reviewed articles published between January 2017 and October 2024. Studies were screened using validated MeSH terms and commercial brand names. Forty-three articles met inclusion criteria, reporting standardized aerosol characterization, *in vivo* or *in vitro* toxicology, or biomarker assessments. Data were extracted by independent reviewers. Clinical studies were categorized by exposure duration (acute, short, medium, or long-term). HTP aerosols contained up to 95 % lower levels of regulated toxicants and exhibited substantially reduced mutagenic, toxic, genotoxic, carcinogenic, and proinflammatory activities (85–95 % reduction) compared with TC smoke. Among 24 interventional clinical studies, 20 reported 40–97 % reductions in toxicant biomarkers of exposure (BoE)—including tobacco-specific nitrosamines, carboxyhemoglobin, volatile organic compounds, and mutagenic metabolites—among smokers who switched completely to HTPs. These reductions were observed from minutes to 24 months and occurred largely independently of systemic nicotine concentrations. Four independent studies reported no significant improvement or detected adverse effects. International health authorities acknowledge that HTP aerosols contain carcinogenic and mutagenic constituents, albeit at substantially lower concentrations than TC smoke, suggesting a potential—though unconfirmed—risk reduction. Overall, HTP users experience lower toxicant exposure than TC smokers; however, additional independent, long-term investigations are required to determine the actual health impact of sustained HTP use.

1. Introduction

Tobacco use is a preventable cause of morbidity and mortality worldwide, accounting for eight million deaths annually [1]. Of these, nearly 90 % are attributable to cigarette smoking [2]. In the United States, 50.9 million individuals use tobacco products, with 23 % of the population aged ≥ 12 years and 7.3 % of adolescents reporting usage in the past month [3]. Globally, tobacco use was associated with over 3 million cardiovascular deaths and 7.4 million all-cause deaths in 2021 [4].

In combustible tobacco cigarettes (TCs), tobacco burns at temperatures up to 700–900°C producing more than 7000 chemical compounds, including carbon monoxide (CO), nicotine, tobacco-specific-N-nitrosamines (TSNAs), volatile organic compounds, and polycyclic aromatic hydrocarbons [5] which exert numerous deleterious health effects. Additionally, cigarette aerosol induces oxidative stress in the respiratory epithelium, leading to inflammation and airway remodeling [6].

In response to growing public health concerns, alternative nicotine delivery systems have emerged, such as electronic cigarettes (Ecigs) and heat-not-burn tobacco products, or heated tobacco products (HTPs) [7, 8]. By avoiding combustion, these devices aim to reduce user exposure to harmful and potentially harmful constituents (HPHCs, such as TSNAs) found in TC smoke. HTPs function by heating reconstituted tobacco material to a much lower temperature (250–350°C), below the combustion threshold but still sufficient for aerosol generation. As combustion is a principal source of many toxic and carcinogenic compounds, HTPs are marketed as reduced-risk alternatives [9]. However, the true

* Corresponding author.
E-mail addresses: stefano.bellosta@unimi.it (S. Bellosta), alberto.corsini@unimi.it (A. Corsini), segreteria@sismed-it.com (G. Catena).

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long-term health effects of HTPs remain under-explored, and clinical outcome data are slowly emerging [10].

HTPs have been developed by major tobacco companies with the objective of reducing user exposure to combustion-related toxicants. Theoretically, reduced exposure to such toxicants could translate into a lower disease risk, although this relationship is not yet definitively established.

Manufacturers describe HTPs as lower-risk alternatives to conventional cigarettes, with the aerosol containing significantly lower concentrations of toxicants compared to cigarette smoke [11,12]. The U.S. Food and Drug Administration (FDA) emphasized that:" IQOS (an HTP) heats tobacco but does not burn it, significantly reducing the production of HPHCs. Switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to HPHCs." In 2023, the FDA authorized the marketing of three new tobacco-flavored HTPs stating that "the marketing of these products should be authorized because, among other things, the net population-level benefits to adult smokers outweigh the risks to youth" [13].

Although switching from conventional cigarettes to HTPs may reduce exposure to HPHCs, few clinical trials have examined the corresponding health effects. Additional research is needed to elucidate the long-term implications of HTP use on respiratory, cardiovascular, and systemic health outcomes [14].

The present review aims to synthesize current scientific evidence regarding the chemical composition and toxicological effects of aerosols generated by HTPs in comparison to TCs. Given that none of these products are risk-free, this review seeks to identify and evaluate potential differences in toxicological risk profiles associated with HTP use relative to TC smoking.

We analyzed published literature regarding the emission of HPHCs from HTPs, aerosol composition, *in vitro* and *in vivo* toxicological data, and interventional studies evaluating clinical biomarkers of harm. Finally, we briefly summarized the positions of international health authorities on the new tobacco products.

2. Methods

2.1. Information sources and search terms

- We interrogated the PubMed database to identify all potentially relevant peer-reviewed articles, published between January 1st, 2017 and October 31st, 2024, relating to HTP aerosol physical and chemical characterization, toxicology and exposure in animal models and in humans. The following Medical Subject Heading (MeSH) were considered: "heat-not-burn," "heated tobacco", "tobacco heating", "heat tobacco", "tobacco heating system", "heated tobacco product*", and brand names ('IQOS', 'Ploom', 'Heets', 'glo'). The interrogation was limited to the title and/or abstract of the journal article and resulted in a list (n = 1105) representing the initial starting point. Two reviewers screened titles and abstracts of initially included studies, and the same two reviewers screened full-text papers.

2.2. Study eligibility criteria

- *Inclusion criteria*: The first list of paper included peer-reviewed studies that focused on HTP aerosol physical and chemical characterization (target and untargeted), toxicology (*in vitro* cell studies and *in vivo* animal studies) and exposure in humans. We considered the following article types according to PubMed Article type: English language, Classical Article, pre-Clinical study, Clinical Study, and Clinical, Comparative, Controlled Clinical Trials, Methodological, Multicenter, Observational Studies, Randomized Controlled Trial, Meta-Analysis, and Systematic Reviews. Both independent and sponsored studies by the tobacco industry were included.
- *Exclusion criteria*: Studies which were not peer-reviewed or conference abstract. Publications without a) comparison to cigarettes smoking; b) analytical data to support study conclusions; c) standardized aerosol characterization and exposure methodologies.

3. Results

The preliminary evaluation identified 1105 articles. The title and abstract of these papers were then manually screened to select studies. After the application of the specific timeframe, article type, and inclusion criteria, n = 122 articles were identified. After a further final in-depth analysis applying the exclusion criteria listed above, we excluded 79 records thus reducing to 43 the number of reviewed publications (Fig. 1). These papers were then divided by topics and discussed in detail as shown below.

3.1. Reduction of emissions of HPHCs

To analyze the evidence about the HPHCs present in HTP aerosols, we analyzed papers regarding the chemical-physical characterization of TC smoke and HTP aerosols. Toxicological studies assessing aerosol toxicity, mutagenicity, genotoxicity, capacity to induce oxidative stress, and the *in vivo* effects in animal models, were also considered.

3.1.1. Physical characterization of the aerosol

HTP aerosol and TC smoke contain respirable particles of similar size. Cigarette smoke consists primarily of a gaseous phase, droplets, and non-water-soluble solid particles. HTPs heat tobacco without triggering combustion, thereby they drastically reduce the formation of solid, non-water-soluble particles [15,16].

3.1.2. Targeted chemical analysis of the aerosol

Based on the WHO list of priority HPHCs, a substantial reduction (on average, about 95–97 %) [9,15–19] in the levels of these components has been observed in HTP aerosols compared to reference TCs (3R4F or 1R6F, Kentucky Reference Cigarettes) [20].

3.1.3. Non-targeted chemical analysis of the aerosol

Unlike targeted methods, non-targeted analysis investigates the full spectrum of compounds present. HTP aerosol contains a significantly lower number of chemical compounds (529 substances) compared to TC smoke (approximately 4268 substances generated by combustion) [21]. Furthermore, the concentration of these compounds in HTP aerosols is substantially lower (about 95 %) than in cigarette smoke [22]. Additionally, among the three compounds found exclusively in HTP aerosol (cis-sesquisabinene hydrate, ethyl dodecanoate, and benzenemethanol, 4-hydroxy) [21], all were present at very low concentrations, below the No Observed Effect Level, a toxicological benchmark for substances without observed adverse effects [23].

Although the presence of nicotine in HTP aerosols is similar to what is observed with TCs, the transfer of TSNAs from tobacco to HTP aerosol was 2–3 times lower than in cigarettes. Most probably this was caused by the fact that the tobacco is not burnt but only heated, thus causing a smaller transfer of toxicants by distillation with a limited contribution from pyrosynthesis or pyrorelease [24].

3.2. Reduction in toxicity

3.2.1. Cytotoxicity (Neutral Red Uptake (NRU) Test) in vitro

NRU assays indicate that the cytotoxic potential of HTP aerosol is reduced by approximately 85–90 % compared to TC smoke [25]. HTP aerosols caused significantly less toxicity compared with reference TC smoke. However, repeating the experiments in other cell types, including cells from the respiratory system, and with higher concentrations of aerosols, cytotoxicity equivalent to that of TC smoke was observed also with HTP aerosols [18].

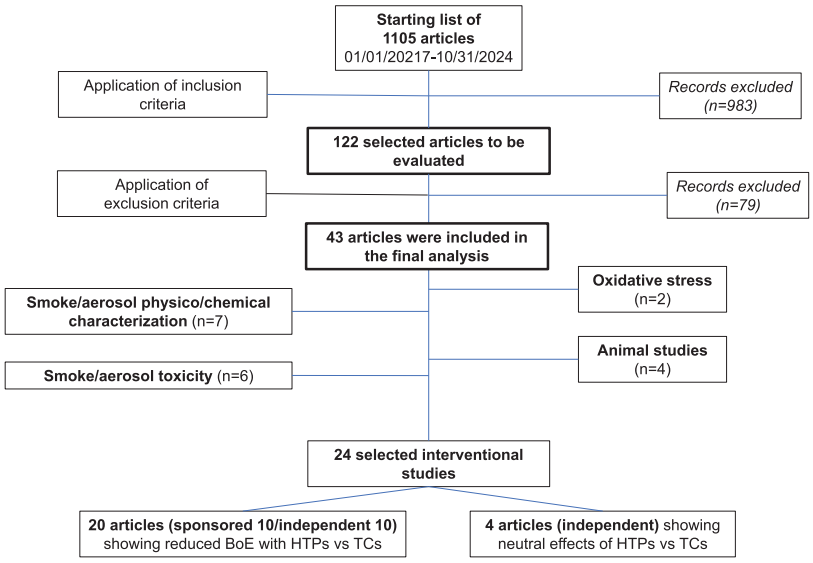

Fig. 1. Article selection process.

HTP aerosol caused only little histopathological toxicity and minimal cytotoxicity compared to TC in human gingival epithelial organotypic cultures. A general reduction (-79 %) in the impact of HTP aerosol-exposed samples with respect to TC was observed in transcriptomic and metabolomic analyses. This study suggests that exposure to TC smoke has a higher impact than HTP aerosol [26].

Similar assays showed that HTPs had higher levels of cytotoxicity than air controls but lower levels than TCs. HTPs showed significantly higher cytokine levels compared to air controls after exposure to TC smoke but not after exposure to HTP aerosol. [27].

Concordantly, in a mechanistical study applying both proteomic and interactomic approaches, we recently showed *in vitro* that HTPs effectively mitigate some negative effects of TC on human smooth muscle cells, although HTP's potential to affect genes and proteins involved in proatherogenic processes, such as neointimal hyperplasia, fibrosis, and calcification, necessitate further investigation to evaluate their long-term cardiovascular implications [28].

3.2.1.1. Mutagenicity. Fractions of the HTP aerosol were found to be either non-mutagenic [25], or at least tenfold less mutagenic than the TC smoke [22].

In another study, the authors assessed cytotoxicity, mutagenicity, and tumor-promoting activity of TC and HTP *in vitro*. They observed a positive response with TC smoke, and a negative response to HTP at doses equivalent to or higher than in cigarette smoke tests [29].

TC negatively affects transcriptome and miRNA-mediated gene expression regulation due to a substantial number of toxicants produced. HTP has a reduced effect on miRNA profile although still higher than with air-control [30].

3.2.1.2. Genotoxicity (Micronucleus Assay). The genotoxic potency of HTP aerosol was at least seven times lower than that of TC smoke [25].

3.2.1.3. Carcinogenicity. The evaluation of the changes in cumulative exposure (CCE) is used to assess the risk of combined exposures to multiple compounds and to evaluate the health impact of an individual who completely switches from smoking TCs to HTPs. Slob et al. applied the method to 8 carcinogens occurring both in HTP aerosols and TC smoke. CCE was 10- to 25-fold lower when using HTPs instead of TCs. This resulted in a smaller reduction in expected life span, based on available dose-response information in smokers [31].

3.2.2. Oxidative stress

Free radical exposure poses a potentially significant health risk [32]. HTP aerosol contains 50-fold lower levels of free radicals than conventional TC smoke [33,34].

3.2.3. Animal studies

TC smoke mostly caused hypermethylation of candidate enhancers in mice lungs, and slightly affected promoters. Upon cessation or switching to HTP the effect was strongly reduced. Chronic exposure to HTP smoke had only a limited effect on DNA methylation at both promoters and enhancers in mice [35].

In a rat model, inhalation of HTP aerosol led to a lower exposure to HPHCs and induced less respiratory tract irritation and pathological effects compared with TC [36].

In a different rat study, exposure to TC smoke, but not to HTP aerosol, caused inflammatory and cellular stress responses. At matched nicotine concentrations, HTP aerosol exposure was associated with an 80 %–100 % reduction of the molecular and tissue/organ effects, probably due to a 94 % reduction of HPHCs in the aerosol, and resulting in a 93 % reduction of exposure markers in plasma [37].

However, in an *in vivo* rat model, mainstream HTP aerosol rapidly and substantially caused endothelial dysfunction comparably to TC smoke [38], possibly due to the nicotine content.

3.3. Interventional clinical studies

Among the 24 selected articles regarding interventional studies, 20 articles (10 sponsored by a tobacco company and 10 independent studies), reported a significant reduction of biomarker of exposure (BoE) in smokers using HTPs compared to TCs. Four others, all independent studies, reported no significant reduction of BoEs or detected adverse effects in people using HTPs compared to TC smokers. The results of these studies are summarized in the Table 1.

3.4. Studies reporting significant reduction of BoE with HTP

Biomarker studies have shown a significant exposure reduction to HPHCs in individuals who switched from combustible cigarettes to HTPs. These findings clinically substantiate the emission reduction data reported [9,25]. The 20 selected articles have been divided based on the time of exposure to smoke in acute (5 up to 45 min), few days or chronic

Table 1
Summary of the results of the included interventional studies.

Study	Intervention length	Total participants	Summary of the results
Reporting reduction of BoE with HTP vs TC			
[39]	5 min	20	HTPs impact less than TC on clinically relevant features
[40]	5–45 min	12	No eCO elevation in HTP smokers
[41]	5 min	30	Smaller increase in eCO in HTP smokers
[42]	5 days	89	The reduction in BoE observed in the HTP groups was like that observed in the group that quit smoking
[43]	5 days	90	HTP use reduced exposure to most of the selected BoE
[44]	5 days	180	Nicotine levels and BoE and eCO levels were significantly reduced in all HTP groups or quitting tobacco use
[45]	5 days	n.a.	Individuals using HTP or TC were exposed to similar plasma levels of nicotine; switching to HTP reduced all urinary and blood BoE
[46]	90 days		HTP delivers similar levels of nicotine, but reduced levels of HPHCs compared to TC
[66]	5–85 days	160	Similar levels of nicotine, bur reduced BoE with HTP
[47]	5–85 days	160	HTP use reduced cardiovascular risk factors, effect more pronounced in normal weight subjects
[48]	5–85 days	160	HTP use reduced respiratory BoE up to day 90
[49]	90 days	377	Sustained reductions of BoE in smokers using HTP or undergoing smoking cessation
[50]	180 days	466	HTP users' BoE were similar to people abstaining from smoking
[51]	5 days up to 6 months	1766	HTP delivered less nicotine and reduced BoE
[52]	5 days up to 6 months	n.a.	HTP delivered similar levels of nicotine, but less carcinogen exposure, although higher than never smokers. Higher bladder cancer unchanged.
[53]	6 months	984	HTP delivered similar levels of nicotine, but reduced BoE
[54]	6 months	672	Baseline nicotine levels and reduction of BoE were maintained up to 12 months. Follow up of previous study
[55]	24 months	n.a.	HTP reduced BoE
[56]	n.a.	n.a.	HTP improved clinical BoE
[57]	n.a.	n.a.	HTP improved cardiovascular BoE
Reporting no reduction of BoE with HTP vs TC			
[58]	120 min	20	HTP increased systolic blood pressure and heart rate like TC
[59]	120 min	40	HTP increased endothelial dysfunction, arterial stiffness and proinflammatory BoE like TC
[60]	3 months	n.a.	HTP use mildly reduced non-cancer, inflammatory, oxidative stress and thrombotic BoE
[61]	n.a.	n.a.	HTP use reduced flow-mediated vasodilation like TC

Abbreviations used: BoE, biomarkers of exposure; eCO, exhaled breath carbon monoxide; HPHC, harmful and potentially harmful constituents; HTP, heated tobacco product; TC, tobacco cigarette; n.a., not available.

(from 3 up to 24 months) use.

3.4.1. *Acute exposure effects*

One cross-over, randomized trial in 20 healthy TC smokers, evaluated the effects of a single use of HTPs and TCs. Acute effects of HTP and TC differed on numerous platelet functions, oxidative stress, cardiovascular markers, and antioxidant reserve, with TCs showing the most detrimental changes in clinically relevant features [39].

In another randomized cross-over acute exposure study, the levels of exposure to carbon monoxide in the exhaled breath (eCO, a combustion marker) were measured in 12 healthy smokers after use of two HTPs, compared with participants' own brand of TCs [40]. In contrast to TCs, HTP use did not elevate eCO levels in exhaled breath.

Similarly, in a randomized, cross-over behavioral trial, 30 smokers, after being overnight smoking-abstinent on three consecutive days, used TC or a HTP. After smoking a TC for 5 min, a significant increase of eCO was observed, whereas using HTP caused only a minor increase [41].

3.4.2. *Few days of exposure (5 days)*

In a longer exposure intervention, 89 smokers were followed for 5 days in a randomized, controlled, six-arm parallel group, open-label study, analyzing 15 BoEs in urine and breath [42] (listed in Suppl. Table).The nicotine uptake in the TC group between baseline and the end of the investigational period was stable, while the nicotine uptake in the HTP groups either did not change or decreased from baseline on day 5 (change ranged between 3 % and −50 %). No changes in BoE were observed in the TC group, while the reduction in HPHC exposure in the HTP groups was similar to that observed in the group that stopped smoking.

The same group followed ninety adult TC smokers who switched to using novel HTPs in a similar controlled, randomized, open-label, study to assess changes in exposure to selected cigarette smoke constituents [43]. In the 5-day exposure period, the same BoEs to selected HPHCs as in the previous study were measured and assessment of nicotine pharmacokinetics was performed. Significant exposure reductions were observed for most of the HPHCs as compared to continuing smoking TCs, similar to the reductions observed after smoking cessation. The authors concluded that switching from smoking TC to HTP use reduced exposure to HPHCs. No differences were observed regarding the measurements obtained from different HTPs.

In a randomized, controlled study in 180 Japanese smokers, on day 5 after switching from smoking TCs to using HTPs, nicotine levels were reduced by up to 40 %, while urinary BoE (Suppl. Table) and eCO levels dropped by 21 % and 92 %, respectively, in all HTP groups or quitting tobacco use [44].

A randomized, open-label, two-arm, parallel-group, short-term confinement study, tested the hypothesis that BoE levels in subjects switching to HTP for 5 days are lower relative to those continuing to smoke TCs [45]. Different BoE (Suppl. Table) were measured in blood and/or 24-h urine samples during *ad libitum* product use. Nicotine exposure plasma levels were similar in individuals using HTP or TC. However, switching to HTP markedly decreased urinary BoE (by 56–97 %), carboxyhemoglobin (by 59 %), urinary mutagenic activity of nitroso-compounds, PAHs, and heterocyclic amines, and CYP1A2 activity (by 24 %) compared with continued TC smoking (see Suppl. Table).

3.4.3. *Months of exposure*

Simonavicius et al. analyzed 14 randomized controlled trials (cross-over) + 1 case report on active smokers, evaluating nicotine delivery and BoEs (Suppl. Table) for up to 3 months [46]. Using distinct types of HTPs, they showed that HTP delivers up to 85 % of nicotine, and reduced levels of HPHCs by at least 62 %, and particulate matter by at least 75 % compared to TC.

In back-to-back publications, Haziza et al. described a randomized, three-arm parallel group, controlled clinical study in which 160 healthy adult US smokers either switched to menthol-flavored HTP, continued smoking menthol TC or quit smoking. After 5 days, both exposure groups showed similar nicotine uptake, while BoE (MHBMA, 3-HPMA, S-PMA and COHb; Suppl. Table) levels from exposure to other HPHCs were reduced by 51 %–96 % in the HTP group compared with the TC group, and the effect was maintained for further 85 days to levels

approaching those observed in subjects who did not smoke for the entire study [47]. Favorable changes in HPHCs in the HTP group were related to lipid metabolism, endothelial dysfunction, oxidative stress, and cardiovascular risk factors. Some of the benefits were more pronounced in normal weight subjects [47].

Adult Japanese smokers were enrolled in a study with 5-day confinement and 85 days in ambulatory settings. They smoked TC, HTP or were asked not to smoke. On day 5, the HTP group had lower concentrations of biomarkers retaled to toxicants (COHb −55 %, 3-HPMA −49 %, MHBMA −87 %, and S-PMA −89 %, $p < 0.001$) (Suppl. Table) than in the TC group. The reductions were maintained up to the end of the study, like the group that quit smoking [48].

A randomized, controlled, parallel-group, open label, ambulatory clinical study investigated whether switching from smoking TCs to using HTPs reduces BoEs from toxicants. After 90 days, in the presence of similar nicotine levels, significant and sustained reductions in BoE for smoking-related disease toxicants (such as MHBMA, S-PMA, 3-HPMA, eCO, NNAL, and CEMA; Suppl. Table) were observed in subjects switching to using HTP or quitting smoking [49].

3.4.4. Chronic exposure

A randomized, controlled, parallel group, open label, ambulatory clinical UK study, showed that at day 180 nicotine levels did not change and HTP users' levels of most BoE were reduced to levels similar to those present in controls that quit smoking [50].

Ten randomized, controlled studies involving 1766 participants were analyzed by Drovandi et al. who assessed 12 BoEs (Suppl. Table) from day 5 up to 6 months. In comparison to TC, HTP delivered less nicotine (-37 %), and HTP users had significantly less BoEs [51].

Svendsen et al. concentrated their attention to eleven randomized controlled studies assessing 29 BoEs (Suppl. Table) present in the urine of HTP users, among which also 14 carcinogens (10 linked to bladder cancer), from 5 days up to 6 months of exposure. With similar nicotine levels in HTP and TC users, HTP users had lower exposure to carcinogens than TC smokers, but higher than in never-smokers. However, chronic urothelial exposure to bladder carcinogens was still concerning [52].

Ludicke et al. enrolled 984 smokers in a randomized controlled, 2-arm parallel group, multicenter, open-label, ambulatory trial to evaluate biological and functional changes in healthy smokers who switched to HTP use compared with those who continued to smoke TCs for 6 months. At the end of the 26th week, with equal nicotine levels in HTP and TC smokers, a statistically significant improvement in 5 out of 8 biomarkers of effect (HDL-C, WBC count, COHb, FEV1, NNAL) was observed when smokers switched to HTP compared with those who continued to smoke combustible cigarettes [53]. In a six-month follow-up study reported by Ansari et al., 672 smokers continued into an extension study [54]. Measured nicotine levels were similar across the groups and maintained throughout the 12 months. Although the authors stated that they could not make a strict comparison between the results observed in the extension study and the first 6-month study [53], since not all of the initial study's subjects were enrolled in the extension study, the positive effects of switching to HTPs, either partially or fully, were maintained [54].

Comparing levels of BoE collected in clinical studies which lasted up to 24 months, the use of HTPs led to a significantly reduced exposure to HPHCs compared to TCs [55].

Finally, a review of twenty-five independent and sponsored studies analyzing BoEs, cardiovascular disease (CVD) and respiratory risk showed differences between TC smokers and people using HTPs with improvement of clinical risk biomarkers [56].

Similarly, another study reported significant reductions in BoE and biological effects related to CVD, such as inflammation, oxidative stress, lipid metabolism, platelet function, and endothelial dysfunction [57].

The reduction of BoEs observed in smokers switching to HTPs, compared to those that kept smoking TCs, could be explained by the observation that smoke of a conventional TC contains much higher levels of TSNAs than the aerosol of a HTP with similar nicotine content. HTP produce significantly lower amounts carbonyls, VOCs, CO, free radicals or nitrosamines when compared to TC [14]. However, there is still not enough data showing that this equates to reduced long-term harm.

Altogether, the selected interventional studies consistently showed a reduced exposure to chemicals as indicated by their corresponding biomarkers (up to 40–97 % reduction) after smoking HTP as compared to TC (**Table**). The effect is detected already after acute exposure and is maintained after a longer-term exposure. Interestingly, the benefit of HTP appears to be independent of nicotine plasma levels. In addition, it is worthwhile to mention that only 10 out of the 20 studies were sponsored by tobacco companies, thus supporting the clinical unbiased value of the presented data (Fig. 2).

3.5. Studies reporting no reduced emissions of HPHCs with HTPs

We found also four independent studies reporting no reduction in the emission of HPHCs in smokers using HTPs compared to TCs.

3.5.1. Two-hour exposure

CVD risk was investigated in 20 young smokers followed for 2 h after smoking, in a partly double-blinded randomized, cross-over trial [58]. Peripheral systolic blood pressure increased in both TC and HTP groups by more than + 3 % ($p < 0.05$) and returned to baseline after 1 h. Similar effects were observed for mean arterial pressure. Heart rate initially increased by more than 9 % in the HTP groups ($p < 0.01$) and returned to baseline after 45 min. Numerically more pronounced changes in arterial stiffness were observed after TC smoking, while HTP showed a non-significant trend. These variable alterations of hemodynamics and arterial stiffness are most probably caused by nicotine and increased local and circulating catecholamines [58]. However, the study was only partially randomized, and baseline information regarding lifestyle habits, physical fitness levels, and chronic CVDs was incomplete.

Inflammation, endothelial dysfunction, blood samples and arterial stiffness were analyzed in 40 active smokers during and 2 h after smoking an HTP or TC, with or without nicotine [59]. An increase in white blood cell counts and in proinflammatory cytokines were observed for HTPs and TCs. Nicotine-independent endothelial dysfunction was shown with both HTPs and TCs so that an increased CV risk for the corresponding consumption was postulated.

3.5.2. Chronic exposure

Glantz et al. analyzed two randomized, controlled, open-label, three-arm parallel group studies in which smokers used an HTP, continued smoking their current brand of TC or underwent smoking abstinence for 3 months [60]. The results show that 24 non-cancer biomarkers of potential harm, including inflammatory, oxidative stress, and thrombotic markers were mildly reduced after HTP use. In addition, levels of some toxins in HTP aerosol were lower than in TCs. However, reduced toxicants levels do not necessarily translate into lower harm [60].

Magna et al. analyzed the effects of chronic exposure to HTPs on endothelial function, assessed by brachial flow-mediated dilation (FMD). The study found a significant reduction in nitric oxide (NO) levels and FMD in both HTP and TC users, compared to non-smokers, at comparable nicotine levels [61]. However, the study was not randomized, and the age of TC smokers was younger than those using HTPs.

Altogether, these independent studies show that HTP consumption can cause arterial stiffness, probably related to reduced NO production followed by endothelial dysfunction. These effects appear to be partially independent of nicotine levels.

3.6. Summary of the positions from International Health Authorities

Several international health authorities issued guidance about their

Strengths

- **Focused Design**: The review is focused on aerosol composition, toxicological exposure, and interventional studies evaluating clinical biomarkers of harm, and reviewed also the positions of some international health authorities. This enhances the relevance of its findings.
- **Clear Inclusion Criteria**: The authors explicitly describe how they compared HTPs with TCs, filtering for only those studies that include quantitative data and standardized protocols.
- **Comprehensive Literature Search**: Over 1,100 articles were screened using robust MeSH terms and brand names, showing methodological thoroughness.
- **Diverse Timeframes**: Interventional human studies were stratified by exposure length (acute, short-term, medium, and long-term), allowing a nuanced temporal interpretation of biomarker changes.

Limitations

- **Bias Risk perceived**: Some of the included interventional studies (10 out of 20) were industry-sponsored.
- **Lack of Meta-Analysis**: The absence of quantitative synthesis (e.g., meta-analytic pooling of BoE reductions) reduces the statistical power and limits generalizability.
- **Limited Independent Long-Term Data**: There remains a scarcity of independent, multi-year longitudinal studies assessing actual disease outcomes.

Fig. 2. Strengths and limitations of this review.

positions regarding HTPs and their impact on human health. Below, we summarize few of these:

- **United States (U.S. Food and Drug Administration, FDA)** FDA concluded that although some of the chemicals produced by HTPs may have cytotoxic or genotoxic potential, their low concentrations and the substantial reduction in total HPHCs offer significant harm reduction [9]. The FDA authorized the marketing of an HTP system under its Modified Risk Tobacco Product framework since the product "significantly reduces the production of HPHCs compared to cigarette smoke". Furthermore, "complete switching from cigarettes to this HTP system significantly reduced exposure to potential carcinogenic and other chemical toxicants acting on respiratory and developmental systems" [9,15,22]. In 2023, the FDA authorized the marketing of three new tobacco-flavored HTPs stating that "the marketing of these products should be authorized because the net population-level benefits to adult smokers outweigh the risks to youth" [13].

- **Greece (Greek Ministry of Health)** In July 2020, the Greek government permitted scientifically substantiated claims related to the reduced health risks of smoke-free alternatives. In March 2023, the Greek Ministry of Health approved a scientifically substantiated health claim concerning reduced exposure to toxic substances from a specific HTP. Thus, Greece became the second country, after the U.S., to permit such a claim [62].
- **United Kingdom (UK Committee on Toxicity, COT)** In 2017, COT concluded that HTP aerosol contains HPHCs, some of which are mutagenic and carcinogenic, and therefore there will be some risk to health from use of these products. However, "since the exposure to toxic substances in HTP aerosol is lower than in cigarette smoke, a reduction in health risks is likely, though not absolute, for smokers who completely switch to HTPs." [25]. In 2018, the Agency Public Health England noted that "it is likely that HTPs expose users and bystanders to lower levels of particulate matter and toxic substances compared to cigarette smoke". The agency also concluded that "HTPs are likely to be considerably less harmful than cigarettes." [63]
- **Germany (German Federal Institute for Risk Assessment, BfR)** BfR stated that "the significant reduction (>99 %) of key carcinogens and the overall decrease in toxicants are likely to have positive implications for health risks, provided users abstain from other tobacco products". Nicotine levels absorbed after using HTPs were found to be comparable to those of conventional cigarettes, limiting the risk of relapse to smoking [15,22].
- **Netherlands (Dutch National Institute for Public Health and the Environment, RIVM)** In 2018, RIVM estimated that the cumulative exposure when using HTPs was lower than with TCs. Overall, the agency concluded that the use of HTPs could be harmful to health, but probably less harmful than smoking TCs [23].

- **Norway (Norwegian Institute of Public Health, NIPH)** NIPH reported that HTPs deliver levels of nicotine comparable to cigarettes while significantly reducing levels of nitrosamines, formaldehyde, CO, and various other HPHCs. Therefore "… novel tobacco and HTPs may be less harmful to health than TCs. Nevertheless, all tobacco and nicotine products involve some health risks, especially for vulnerable groups like children and young people, and people with cardiovascular problems" [64].

4. Conclusions

Most of the papers we analyzed clearly confirm that HTP aerosol contains significantly lower levels (up to 95 %) of toxicants, probably thanks to the fact that tobacco is not burnt but heated, resulting in a reduced impact of the tobacco combustion process. These results were obtained with both *in vitro* and *in vivo* approaches showing a reduction of toxic, mutagenic, genotoxic, carcinogenic and proinflammatory potentials of HTP aerosol by approximately 85–95 % compared to TC smoke.

On the same line, interventional studies in humans (both sponsored and independent) support the fact that switching to HTPs effectively reduces the risk of exposure to toxicants with significant reductions in corresponding BoE (from 40 % to 97 %). These reductions were observed within minutes and maintained up to 24 months of exposure, with nicotine delivery remaining largely unchanged. Interestingly, reductions in toxicants were comparable to those seen in smoking cessation arms of some trials.

Similarly, a recent sponsored cross-sectional study compared 974 smokers, who switched to HTP for at least 2 years, to those who continued to smoke TC. The study showed, independently of nicotine levels, favorable differences in biological pathways such as inflammation, oxidative stress, oxygen delivery, genotoxicity, lipid metabolism, endothelial function and clotting, as well as improvement in arterial stiffness and lung function [10].

We found also few studies showing that HTP aerosol in some experimental conditions causes similar toxic effects as TC smoke. A recent Cochrane metanalysis analyzed 13 studies involving 2666 participants [65]. The conclusion of the metanalysis was that "there was insufficient evidence to determine whether the risk of serious adverse

events differed between groups due to very serious imprecision and risk of bias". There was moderate-certainty evidence for lower NNAL and COHb at follow-up in HTP than TC smoking groups. There was moderate-certainty evidence that HTP users have lower exposure to toxicants/carcinogens than cigarette smokers and very low- to moderate-certainty evidence of higher exposure than those attempting abstinence from all tobacco. Independently funded research on the effectiveness and safety of HTPs is clearly needed [65].

Based on a review of the published data, several international health authorities issued guidance regarding their positions on HTP impact on human health. They reported that the aerosol generated by HTPs contains some toxicants, but at a much lower level compared to TC smoke. Therefore, if a TC smoker completely switches from cigarettes to HTPs this will greatly reduce exposure to harmful chemicals and consequently it will also have positive implications for health risks.

In conclusion, considering the strengths and limitations of our review (Fig. 2), the evidence available so far suggests that HTPs effectively reduce toxicant exposure relative to TCs, but there is still not enough data showing that this equates to reduced long-term harm. Further independent, multi-year-long longitudinal studies assessing actual disease outcomes are still needed to assess the complete potential health harm of HTPs [41].

CRediT authorship contribution statement

Gabriele Catena: Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Alberto Corsini:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Stefano Bellosta:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.toxrep.2026.102209.

Data availability

Data will be made available on request.

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