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Evaluation and meta-analysis of HTP testing methods in harm reduction

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Abstract

This paper presents a comprehensive literature review to evaluate and synthesize heated tobacco product (HTP) testing methodologies and quantify differences in aerosol emissions versus conventional cigarettes to inform harmonized, health-relevant standards. The review systematically examines scientific publications, regulatory documents, and industrial reports published over the past decade to assess current practices in the mechanical, chemical, and toxicological evaluation of HTPs A systematic review and meta-analysis following PRISMA searched Scopus/Google Scholar through July 2025, screened studies against predefined inclusion criteria, and extracted analytes, instruments, and outcomes; 26 eligible studies were analyzed using Review Manager and JASP with random-effects modeling (REML). Based on studies, HTP aerosols showed large reductions in harmful and potentially harmful constituents relative to cigarette smoke, frequently exceeding 80–90% for key classes; the pooled effect size indicated an ≈88.18% reduction with moderate heterogeneity, and funnel-plot symmetry suggested low publication bias. HTPs consistently produce lower toxicant emissions than conventional cigarettes. However, cross-study variability in devices, puffing regimens, and collection/analytic methods limits direct comparability, underscoring the need for standardized, validated HTP-specific protocols. The findings recommend that regulators and labs could elaborated to adopt harmonized HTP puffing and aerosol-collection methods based on product used specificity to improve product emission robustness and eventual the risk assessment for consumer protection.

Keywords: Heated Tobacco Products, Standardized, Testing Method, Tobacco.

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1. Introduction

The development of heated tobacco product (HTP) technology has become a significant innovation in the global tobacco industry. These products were developed with the claim of being a potentially risk-reducing alternative to conventional cigarettes because they eliminate the combustion process [1-3]. Heated tobacco products (HTPs) are engineered to lower the concentrations of harmful and potentially harmful constituents (HPHCs) by heating, rather than combusting, tobacco. Harmful and potentially harmful constituents (HPHCs) refer to chemicals or chemical compounds present in tobacco products or tobacco smoke that are known or suspected to cause adverse health effects in both smokers and nonsmokers [4-7]. Heated tobacco products thermally generate inhalable aerosol without sustained combustion and, overall, produce significantly lower yields of harmful and potentially harmful constituents than combustible cigarettes. However, effect sizes are device-, analyte-, and regimen-dependent, underscoring the need for methodological harmonization to enable robust cross-study comparability and exposure assessment [8]. In Indonesia, HTP consumption has shown an increasing trend, aligning with shifting consumer patterns and market penetration by multinational manufacturers [9].

HTP devices vary widely in their heating mechanisms, ranging from induction and blade heating (e.g., IQOS) to hybrid systems that employ e-liquids and tobacco, and are sold in over 60 countries, with sales expected to reach nearly USD 68 billion by 2027 [10]. These mechanical and design differences, coupled with region-specific regulatory requirements, complicate attempts to standardize testing procedures.

Nevertheless, the long-term potential health profile of HTPs remains to be explored, offering opportunities for continued scientific evaluation. Several studies have shown that although the content of harmful compounds in HTP aerosols is generally lower than in cigarettes, some compounds are still found in significant levels, including carbonyls such as formaldehyde and acrolein, as well as residual nicotine, which still has an addictive effect [3, 11, 12]. Therefore, laboratory-based analysis is essential to measure exposure to harmful substances and assess whether HTPs can potentially be categorized as lower-risk tobacco products.

Currently, most HTP evaluations adapt protocols from combustible cigarette testing, such as ISO 3308 or Health Canada Intense (HCI), which may not accurately reflect HTP-specific puffing patterns, device turn-off systems, or aerosol generation dynamics [13, 14]. Differences in puff volume, frequency, and filter ventilation can significantly affect HPHC yields and the interpretation of comparative risk assessments [15].

Building on the analyte- and regimen-dependence noted above, the HTP testing standards landscape is fragmented: beyond ISO 3308 and Health Canada Intense, documents such as ISO 20778 (intense cigarette) and ISO 20768 (vaping-machine) are applied inconsistently to HTPs. A harmonized framework mapping device class to machine regimen, collection media, and a consensus analyte panel would strengthen reproducibility and regulatory comparability. Remaining heterogeneity—heater set-point/ramp control, stick matrix (water/humectants), puff-count termination, battery stability—and uneven reporting of study-quality domains (measurement traceability, lab accreditation, funding transparency) argue for coordinated inter-laboratory studies and routine proficiency testing [8].

This study aims to evaluate current HTP testing methods through a meta-analysis approach (including machine inhalation protocols, aerosol collection techniques, and chemical and toxicological analyses). Through a meta-analysis approach, this study aims to assess the effectiveness, reliability, and consistency of testing methods used in scientific literature. This study is also expected to analyze laboratory test results for various key parameters of harmful compounds in HTP aerosols in Indonesia and compare them with results from conventional cigarettes and global reference sources. This approach is expected to provide a scientific basis for the development of regulations, consumer protection, and the assessment of risk reduction claims frequently made by the HTP industry.

2. Material and Method

2.1. Search Strategy

This study conducted a literature search using the Scopus and Google Scholar databases to identify relevant publications. The literature search used the keywords "Heated Tobacco Product" and "Heat not Burn Tobacco." This meta-analysis adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in compiling references. PRISMA consists of a four-phase flow diagram (Identification, Screening, Eligibility, and Inclusion) [16-19]. PRISMA aims to improve the quality and transparency of reporting in systematic reviews and meta-analyses [17]. The search was repeated until no further relevant articles were found (as of July 2025). Reviews, opinion proposals, editorial articles, commentaries, and conference abstracts were not included in this review.

2.2. Inclusion Criteria

Before conducting a study on HTP testing methodologies (covering machine puffing protocols, aerosol collection techniques, chemical and toxicological analyses), criteria were established for the analysis. These criteria are: (1) The study refers to the use of testing methods for HTP products; (2) The study is experimental with a control group consisting of subjects who receive and do not receive treatment, selected from design-based or natural samples; (3) The study is an empirical study that uses quantitative analysis; (4) The study must present sample sizes and other relevant information that supports the conclusions; (5) The studies used are only studies that use English.

2.3. Data extraction

Based on the study collection, a total of 31 studies were identified related to testing methods for HTP products. A total of 5 studies were excluded from the study because, after reviewing the title, abstract, and content, they did not meet the established inclusion criteria. Therefore, by using the inclusion criteria, a total of 26 relevant studies were obtained and could be analyzed further. The 26 studies that met the criteria are presented in Table 1. Information extracted from the studies was: author, year of publication, country where the study was conducted, type of Heated Tobacco Products (HTP) and Conventional Tobacco Cigarettes (CTG), parameters, methods, statistical analysis used, and remarks. Data analysis used correlation meta-analysis.

2.4. Statistical Analysis

All statistical analyses were conducted using Review Manager software (version 5.1, Oxford, UK) and JASP (version 16.0, College Station, TX) to evaluate the data. Statistical significance was determined using a P-value threshold of 0.05 for all applied tests and models.

3. Result

A total of 26 studies from various countries (Switzerland, Japan, the USA, the UK, Greece, and others) were searched through NCBI, Elsevier, and ResearchGate websites to create a systematic literature review using the PRISMA format. These studies were used to compare the chemical emission profiles of Heated Tobacco Products (HTPs) and Conventional Tobacco Cigarettes (CTCs) and to identify effective and validated testing methods for analyte identification and quantification in e-cigarettes compared to conventional cigarettes. All studies primarily employed descriptive statistical analysis, reporting mean values and standard deviations. Some studies, however, employed ANOVA, t-tests, or Principal Component Analysis for further comparison. Based on the results of the search analysis of each study, most studies consistently report a significant reduction in Hazardous and Potentially Hazardous Constituents (HPHC) in HTP aerosols compared to conventional cigarette smoke (Table 1).

The reviewed literature indicates that HTPs emit significantly fewer toxicants than conventional cigarettes, with reported average reductions often exceeding 80–90%, particularly for nicotine, carbonyls, and VOCs. However, inconsistencies in device types, testing methods, and measurement parameters limit the comparability and generalizability of the results, underscoring the need for standardized testing protocols and further research into the relationships and correlations between each component in the two currently available tobacco stick types.

A quantitative analysis of the types of analytes investigated in HTP studies reveals significant variation in research focus. As depicted in Figure 1, the most frequently investigated analytes are formaldehyde and acrolein, each accounting for 12.5% of the total reported analytes. These two analytes are known toxicants and common markers of combustion-related emissions, indicating strong research interest in assessing the toxicological risks associated with HTP aerosols. Other important categories include TSNAs (tobacco-specific nitrosamines) and carbonyls, each accounting for 8.3% of the studies. NNK compounds, a specific TSNA, were investigated in 4.2% of cases. In addition, CO/NOx emissions and TSNAs (on average) were each addressed in 4.2% of the studies, suggesting broader concerns regarding oxidative stress and nitrosamine exposure (Figure 2).

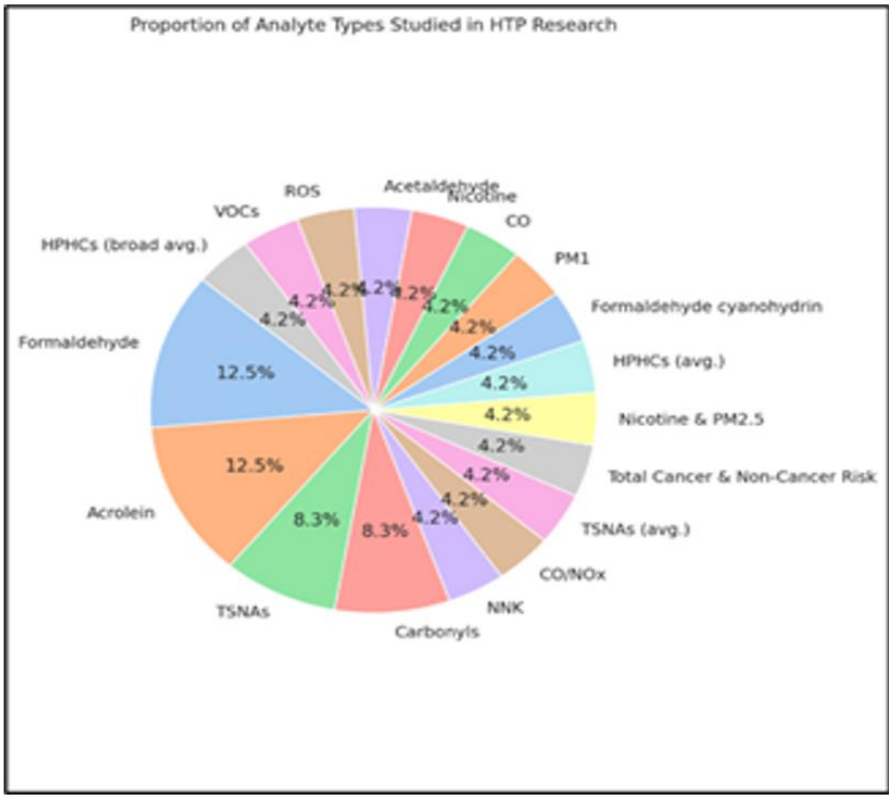

Figure 1.
Proportion of analyte types studied in HTP research. Pie chart show the share of studies (%) focusing on each analyte type; labels indicate exact percentages. Data reflect the distribution across included studies.

Less frequently analyzed compounds include formaldehyde cyanohydrin, HPHC (average), nicotine & PM2.5, body toxicity, PM1, CO, acetaldehyde, nicotine, ROS (reactive oxygen species), and VOCs (volatile organic compounds)—each contributing 4.2% or less to the analyte distribution. Importantly, HPHC (broad average), which represents a common class of hazardous and potentially hazardous constituents, constitutes 4.2% of the analyte profile, suggesting a holistic view in some studies despite its lower frequency. Overall, the results indicate that HTP research to date has prioritized tobacco-specific carbonyl compounds and nitrosamines, with less emphasis on particulates, oxidative stress markers, and volatile organics (Figure 2).

Appropriate methods for identifying HTP components must have an adequate level of accuracy and precision according to standards. This is shown in Figure 1, which highlights the most applied analytical techniques for quantifying HPHCs in tobacco aerosol research. The prevalence of a specific method reflects its reliability, sensitivity, and regulatory acceptance, as determined by several studies. Gas Chromatography–Mass Spectrometry (GC-MS) is widely used to detect volatile organic compounds (VOCs) and carbonyls due to its elevated sensitivity and capacity to differentiate structurally similar compounds. This is followed by Liquid Chromatography–Mass Spectrometry (LC-MS/MS) for TSNAs and other polar compounds. Gravimetric analysis is often used to measure Total Particulate Matter (TPM) and reduce tar values. Non-Dispersive Infrared Spectroscopy (NDIR) and Chemiluminescence are applied to detect CO and NOx gases (Figure 2).

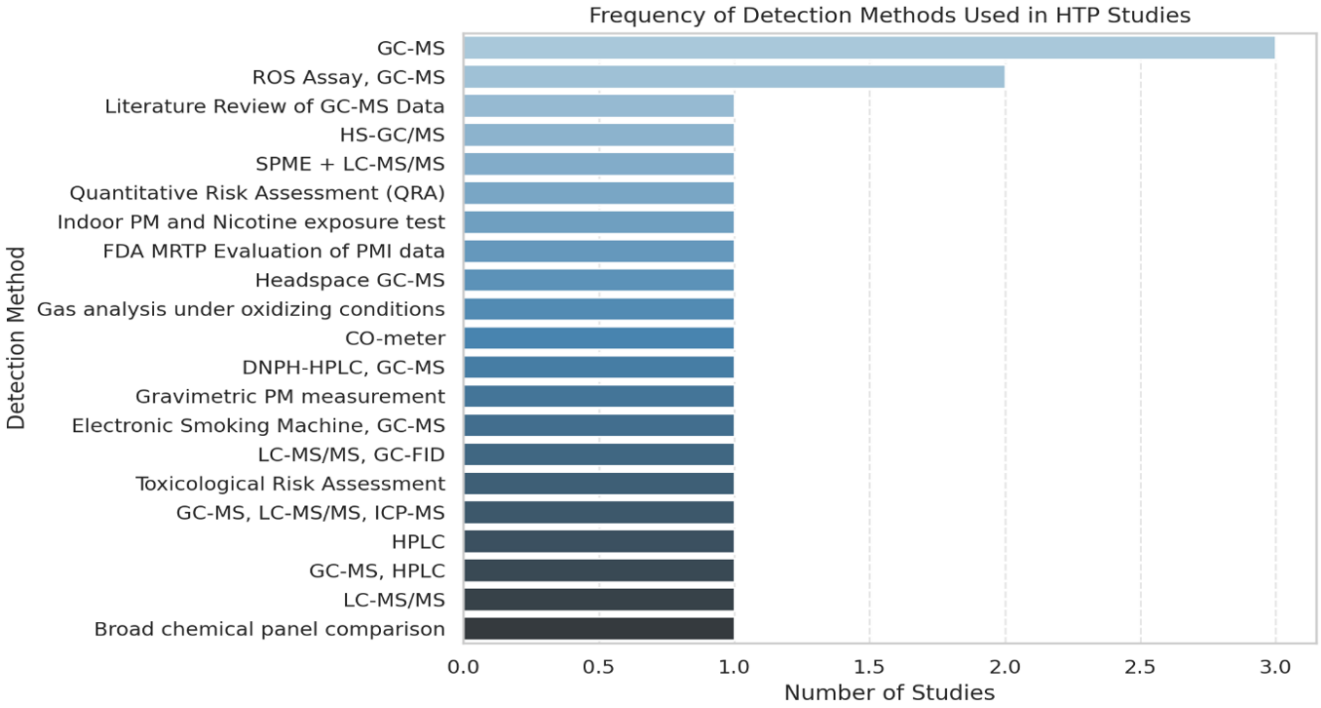

Figure 2.
Frequency of detection/analytical methods used in heated tobacco product (HTP) studies.

Horizontal bars show the number of included studies that applied each method; categories are ordered by frequency. GC-MS was most common, followed by ROS assays paired with GC-MS and literature syntheses of GC-MS datasets. See Methods for study selection and counting rules.

Furthermore, a meta-analysis was conducted using a random-effects model, estimated through Restricted Maximum Likelihood (REML), to synthesize the effect sizes of reductions in harmful and potentially harmful constituents (HPHCs) from multiple studies evaluating heated tobacco products (HTPs) compared with conventional cigarettes.

Table 1.
Characteristics of research included in a systematic review.

Author, year	Ref	Country	Heated Tobacco Products (HTPs)	Conventional Tobacco Cigarettes (CTG)	Parameter	Methods	Statistical analysis	Remark
Schaller, et al. [20]		Switzerland	THS 2.2	3R4F	ISO Parameters and product-specific constituents	Borgwaldt linear smoking machine type LM20X Machine-smoking regimen. Generation of THS2.2 Generation of THS2.2 aerosol under alternative puffing regimens.	Descriptive (mean and standard deviation) Quantitative by ANOVA	THS2.2's leads to over 90% reduction in most HPHCs
Smith, et al. [21]		Switzerland	THS 2.2	Combustible cigarette	Acetaldehyde, acetamide, acetone, acrolein, acrylamide, acrylonitrile, 3-aminobiphenyl, 4 aminobiphenyl, 1-aminonaphthalene, 2-aminonaphthalene, ammonia, benz [a]anthracene, benzene, 1,3-butadiene, butyralde hyde, carbon monoxide, catechol, m-cresol, o-cresol, p-cresol, ethylene oxide, formaldehyde, hydroquinone, isoprene, methyl ethyl ketone, mercury, nicotine, nitric oxide, nitrogen oxides, NAB, NAT, NNK, NNN,phenol,propionaldehyde, propyleneoxide,pyrene, pyridine, styrene, toluene, and	Combine the machine smoking regimen and LC-MS/MS for specific components.	Descriptive and Principal Component Analysis	THS2.2 tobacco had much lower HPHC levels than 3R4F smoke.

					o-toluidine			
Bekki, et al. [22]		Japan	IQOS regular IQOS menthol	3R4F 1R5F	Nicotine, tobacco-specific nitrosamines (TSNA), CO, Tar	LC-MS/MS (TSNAs) NDIR, IR200 (CO) TPM (tar)	Descriptive (mean and standard deviation)	The concentration of hazardous compounds in IQOS mainstream smoke are substantially lower.
Farsalinos, et al. [23]		Greece	HnB/IQOS regular HnB/IQOS menthol E-cigarettes (ECs) of (ciga-like, eGo-style and variable wattage)	Tobacco cigarette	Nicotine	GC-NPD	Comparison by t-test ANOVA	HnB delivers less nicotine in aerosol form compared conventional cigarettes under the tested puffing regimes.
Auer, et al. [24]		Switzerland	IQOS (IQOS Holder, IQOS Pocket Charger, Marlboro HeatSticks [regular], and Heets, Philipp Morris SA)	Conventional cigarettes (Lucky Strike Blue Lights)	VOC, nicotine, polycyclic aromatic hydrocarbons	GC/FID HPLC-FD/UV/separation column nucleodur	Descriptive	IIQOS emits harmful substances similar to cigarette smoke, but most are reduced in comparison.
Jaccard, et al. [25]		Switzerland	THS2.2	3R4F	HPHC: nitrosamine, polycyclic aromatic hydrocarbons	LC-MS GC-MS	Descriptive	A significant decrease is observed on average across a broad range of chemical compounds when compared against 3R4F reference cigarettes and commercial cigarettes

Caponnetto, et al. [26]		Italy	IQOS Glo	Own brand conventional cigarettes	Exhaled breath CO (eCO) level	CO-meter	ANOVA	Significant differences were found between IQOS/GLO and CT.
Davis, et al. [27]		USA	IQOS tobacco heating system kits, manufactured by Philip Morris Products S.A.	-	ε-caprolactone, Lactide, 1,2-Diacetin, Formaldehyde cyanohydrin (glycolonitrile)	GC MS Headspace	Descriptive	The IQOS appears to be well-manufactured
Farsalinos, et al. [28]		Greek	HnB-regular menthol e-cigarettes	Conventional cigarette	Formaldehyde, acetaldehyde, acrolein, propionaldehyde, crotonaldehyde	HPLC GC-NPD	Descriptive	IQOS emitted significantly lower levels of potentially harmful carbonyl emissions compared to combustible cigarettes.
Forster, et al. [29]		UK	THP1.0	3R4F	Carbonyls: formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl ethyl ketone, n-butyraldehyde, isobutyraldehyde, glyoxal, methylglyoxal, acetyl-propionyl, diacetyl, acetoin, allyl alcohol, nicotine, carbon monoxide, carbon dioxide, water, glycerol, propylene glycol, diethylene glycol, ethylene glycol, glycidol TSNAs: NAB, NAT, NNK, NNN	HPLC/conductivity detector AAS GC-MS SIM GC-FID GC-TCD NDIR HPLC-MS/MS, chemiluminescence ICP-MS HPLC/selectiv Fluorescence detection GC-TEA UPLC-MS/MS HPLC-UV	Descriptive	THP1.0 emissions were significantly reduced across all chemical classes.

					Nicotine-related impurities Nornicotine, Anatabine, Anabasine, Myosmine, Nicotine-N-Oxide, Cotinine, b Nicotyrine	NCI GC-MS (SIM)		
Helen, et al. [30]		USA	IQOS HeatSticks regular IQOS HeatSticks menthol	3R4F	HPHC. Philip Morris Internationa (PMI) lists 58 constituents (which PMI refers to as 'PMI-58') including nicotin, methyl etc	Borgwaldt linear smoking machine type LM20X Burghart rotary smoking machine type RMB 20 (Burghart Tabaktechnik GmbH, Wedel, Germany) for elements	Descriptive	IQOS emits lower levels of several harmful chemicals than cigarettes and reduces users' exposure to some toxins.
Leigh, et al. [31]		USA	HTP aerosols (IQOs, Amber, Tobacco flavor)	Tobacco cigarettes	Tobacco-specific nitrosamines (TSNA): N'-nitrosoanabasine, N'-nitrosoanatabine, 4 (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine Nicotine.	LC-MS (TSNA) GC-NPD (nicotine)	ANOVA t-test	HTPs emit lower amounts of TSNA than combustible cigarettes.
Uchiyama, et al. [11]		Japan	IQOS Glo Ploom TECH	CM6 3R4F IR5F Traditional cigarettes	VOCs Nicotine Carbonyls Water TGPM	GC/MS: VOCs are detected in the eluates from the mainstream smoke of HTPs and traditional cigarettes HPLC: carbonyl compounds GC/TCD: water in	Descriptive	Overall, no significant differences were observed between HTP and traditional cigarettes in terms of total gaseous and particulate compounds. A decrease is observed

						the eluate from mainstream smoke		on average across a broad range of chemical compounds when compared against reference cigarettes
Li, et al. [2]		China	THS 2.2	3R4F	TPM water Nicotine Tar propylene glycol glycerin Carbon monoxide VOCs: 1,3-butadiene, Isoprene, Acrylonitrile, Benzene, Toluene; Carbonyls: Formaldehyde, Acetaldehyde, Acetone, Acrolein, Propionaldehyde, Crotonaldehyde, Butanal, 2-Butanone; Aromatic Amines: 1-Aminonaphthalene, 2-Aminonaphthalene, 3-Aminobiphenyl, 4-Aminobiphenyl; Hydrogen Cyanide, Ammonia, N-nitrosamines: NNN, NNK, NAT, NAB; Phenol, PAH	Gravimetry GC/TCD GC/FID NDIR GC-MS HPLC	Fisher ratio	The study shows that most chemicals in THS 2.2 aerosol are reduced compared to 3R4F.
Salman, et al. [32]		Lebanon	IQOS (tobacco-flavored, balance-labeled Heets)	Marlboro Red combustible cigarettes	TPM, Carbonyls, Nicotine, pH, VGP G	Gravimetry HPLC-UV GC/FID	Descriptive	IQOS delivers nicotine levels similar to cigarettes.

						pH meter		
Bentley, et al. [33]		UK	The mainstream aerosol produced by THS 2.2 (IQOS)	3R4F in mainstream smoke	529 compounds	GCxGC TOF MS LC+HRAM MS (untargeted screening)	Descriptive	THS 2.2 decreases in both the number and the number of chemicals.
Cancelada, et al. [34]		USA	IQOS (Philip Morris) Glo (British American Tobacco)	3R4F	Volatile Organic: Acetaldehyde Acrolein, formaldehyde, benzene, toluene, styrene, 1,3-Butadiene, isoprene, acetone, propionaldehyde, crotonaldehyde Total Particulate Matter (TPM) in aerosol Emission rate per puff (ng/puff and µg/stick) Predicted Indoor Air Concentration (IAQ)	Health Canada Intense (HCI) Regimen machine HS-GC/MS	Descriptive	The impact of IQOS is likely lower than that of conventional cigarettes, but not negligible
Le Godec, et al. [35]		UK	THS 2.2	3R4F	HPHCs (nicotine & Tar) NFDPM (Tar) Carbonil Formaldehide, Aceltadehide, Acrolein, Crotonaldehida VOCs Benzene, Toluene, 1,3-Butadiene, Isoprene TSNA NNK, NNN (Tobacco-specific nitrosamines) PAH Benzo[a]pyrene, Fluorene, Phenanthrene, Pyrene Arsen (As), Cadmium (Cd),	Health Canada Intense (HCI) Regimen GC-MS, LC-MS/MS, ICP-MS, UV-Vis Cascade Impactor (Marple 8-stage), MMAD, Mass Distribution Tar & TPM, Cambridge Filter Pad (CFP)	Descriptive	The reduction of measured toxicants in Neostik emissions is consistent

					(Pb), Crom (Cr), (Ni) CO, NO, NO_2 Glycerol, propylene glycol, ammonia Total Particulate Matter (TPM)	Glycerol & nicotine, Gravimetri		
Ishizaki and Kataoka [36]		Japan	iQOS, GALO, Ploom TECH	Conventional cigarette	Volatile Organic Compounds (VOCs): Benzene - Toluene - Styrene - 1,3-Butadiene - Isoprene 2 Carbonyl Compounds: - Formaldehyde - Acetaldehyde - Acrolein - Propionaldehyde - Crotonaldehyde	Smoking Regimen LCMS/MS	Descriptive	TSNAs in smoke samples can be accurately and precisely determined using a TPG cigarette at a 1 level.
Cozzani, et al. [37]		Italy	THS2.2	3R4F	CO TPM Nicotine Water Glycerol HPHCs	FTIR Gravimetry GC-TCD GC-FID	Descriptive	EHTP devices, tobacco undergoes mainly drying, evaporation, and mild pyrolysis (torrefaction), with no self-sustained combustion.
Group, et al. [38]		Austria, Canada, China, Cuba, France, Germany, India, Japan, Korea, Spain,	Electrically Heated Tobacco Products (eHTPs) Aerosol Heated Tobacco Products (aHTPs or hybrids) &	not specify brand/model of conventional cigarettes, but uses standardized regimes (e.g., ISO, Health	Harmful and Potentially Harmful Constituents (HPHCs)	Aerosol Generation Regimes: HTPs: Based on ISO 20778:2018 (modified HCI regime) aHTPs: Based on ISO 20768:2018	Replicates for test consistency Pre-tests for puff number determination Contamination checks Device calibration and	Report provides standardized [39]

		Switzerland, UAE, UK, USA		Canada T-115) for comparative emission testing		(vaping machine method) cHTPs: Based on Health Canada T-115 and ISO 20778:2018 (intense smoking regime) Cambridge Filter Pads (CFP) Gravimetric determination for Aerosol Collected Mass (ACM) Analytical chemistry for priority constituents (toxicants)	validation	
Hirano, et al. [39]		Japan	IQOS (Philip Morris Products S.A. Neuchâtel, Switzerland) Glo (British American Tobacco plc., London, UK) PloomTECH (Japan Tobacco Inc., Tokyo, Japan)		Particulate matter (PM) Nicotine Carbon monoxide (CO) Glycerol Propylene glycol Total volatile organic compounds (TVOCs) Formaldehyde Acetaldehyde Acrolein	PM: Real-time aerosol monitor Nicotine, CO, aldehydes: Sorbent tubes and DNPH cartridges TVOCs: Real-time total hydrocarbon analyzer Formaldehyde and other aldehydes: HPLC with UV detection	Mean values and standard deviations (SD), ANOVA, comparative analysis.	Exposure levels of environmental tobacco aerosol (ETA) from HTPs were significantly lower than those from conventional cigarettes.

Kim, et al. [40]		Korea	Three unnamed commercial HTP devices (HTP-1, HTP-2, HTP-3)		Formaldehyde (FA) Acetaldehyde (AA) Acrolein (ACR) Acetone (AT) Propionaldehyde (PA) Crotonaldehyde (CA)	DNPH, Analysis by, High-Performance Liquid Chromatography (HPLC) with UV detection	One-way ANOVA	This highlights the need to include non-tobacco components in safety evaluations of HTPs.
Protano, et al. [41]		Switzertland	HTP	3R4F	Aerosol concentrations (μg m−3) for PM10, PM4, PM2.5, PM1 on indoor air	Labstat International ULC Smoke and aerosol were generated by machine smoking using the ISO	Descriptive	QRA assessments on an HTP versus the 3R4F reference cigarette using aerosol
Bitzer, et al. [42]		US	e-cigarettes HnB	Conventional cigarettes	Nicotine Particulate-Phase Radicals Total Gas-Phase Radicals Non-Polar Characteristic Gas-Phase Radicals Polar Characteristic Gas-Phase Radicals	GC/FID EPR spectroscopy	Brown-Forsythe and Welch ANOVA tests	Heat-not-burn (HnB) products produce significantly fewer free radicals than conventional cigarettes.
Maeder and Jeannet [43]		Canada	THS2.2 regular THS 2.2 menthol	3R4F	108 HPHC, including nicotine, covering the FDA 93 constituents.	NA (All analysis was conducted by Labstat International ULC)	Descriptive	THS 2.2 contained significantly lower levels of harmful and potentially harmful constituents HPHCs) compared to smoke from conventional cigarettes (3R4F)

Component identification in HTPs and conventional cigarettes has been extensively conducted using various methods. However, in these studies, the majority of component identifications were conducted using GC-MS/MS and LC-MS/MS methods, given the excellent validity of these two methods, yielding high concentrations and levels of each identified analyte (Table 2).

Table 2.
Instruments and analytical methods used to detect priority constituents in aerosols from heated tobacco products (HTPs), e-cigarettes, and conventional cigarettes.

Type of Cigarette	Parameter	Method	Process	Ref
Tobacco Heating System 2.2. Part 2 3R4F	ISO SR-1 SR-5 HCl SR-4 SR-6 LR-3	A Cerulean SM450RH smoking machine (Cerulean Molins PLC, Milton Keynes, UK)	It is designed to simulate standardized human smoking behavior according to ISO 3308, FTC, Canadian, and Massachusetts protocols. It allows precise control over puff parameters such as volume, duration, and interval, and is commonly used for testing conventional cigarettes, heated tobacco products (HTPs), and other tobacco-related devices. Smoke is drawn through each port and collected on Cambridge filter pads for particulate analysis, while volatile and gaseous components can be captured in gas bags or analyzed using additional attachments.	Schaller, et al. [44]
	NO, NOx	Borgwaldt linear smoking machine type LM20X (Borgwald tKCGmbH, Hamburg,Germany)	It is a multi-port linear smoking machine (usually up to 20 ports) used to generate mainstream smoke or aerosol under standardized puffing regimes such as ISO 3308, Health Canada Intense, or CORESTA e-cigarette protocols. It operates using an airflow-controlled piston pump (PM1 series) and is compatible with diverse trapping systems, including Cambridge filter pads for particulate matter and gas collection setups for volatile constituents and carbon monoxide	Schaller, et al. [20]
	Nicotine, tobacco-specific nitrosamines (TSNA), CO, Tar	Liquid Chromatography Mass Spectrometry, Mass Spectrometry	It is an analytical technique that combines liquid-phase separation with two-stage mass spectrometric detection. Analytes are first separated based on their physicochemical properties via liquid chromatography, then ionized and introduced into the first mass analyzer (MS1) to select precursor ions.	Bekki, et al. [22]
	CO	Non dispersive infrared analyzer (NDIR)	This technique relies on the vibrational motions of atoms within a molecule. An infrared spectrum is typically acquired by transmitting infrared radiation through a sample and measuring the proportion of radiation absorbed at specific energy levels.	Bekki, et al. [22]
	Tar	The total particulate matter (TPM)	It is a standardized gravimetric technique employed to quantify tar yields in mainstream cigarette smoke. During controlled smoking under specified regimes (e.g., ISO 3308 or Health Canada Intense), the particulate phase of the smoke is collected on a Cambridge glass fibre filter pad. The mass of the retained material, defined as TPM, is determined by weighing the filter both before and after use. Tar is calculated by subtracting the measured quantities of water and nicotine from the TPM, in accordance with regulatory definitions, where Tar = TPM – (Water + Nicotine). This approach enables consistent and reproducible estimation of the condensed non-volatile constituents of cigarette smoke	Uchiyama, et al. [11]
	Nicotine	Gas	A selective detector used in Gas Chromatography	Farsalinos, et

		Chromatography Nitrogen – Phosphorous Detector (GC-NPD)	(GC) to detect compounds containing nitrogen and/or phosphorus. It works by generating plasma from a heated thermionic bead (often coated with alkali metals) in the presence of hydrogen and air. This plasma selectively ionizes nitrogen and phosphorus-containing compounds, and the resulting current is measured.	al. [28] and Leigh, et al. [31]
	Glycerol	Gas Chromatography- Flame Ionization Detection (GC-FID)	Separates volatile compounds in a gas stream using a chromatographic column. As each compound elutes from the column, it is burned in a hydrogen-air flame at the FID detector. The combustion produces ions and electrons, generating an electrical current proportional to the number of carbon atoms present. This current is measured and recorded as a peak on a chromatogram, allowing for quantitative analysis of organic compounds	Forster, et al. [29] and Cozzani, et al. [37]
	Polycyclic aromatic hydrocarbons	High-performance liquid chromatography-fluorescence detector/Ultra violet (HPLC-FD/UV/separation column nucleodur)	An upgraded version of liquid chromatography is based on the same principle of separating mixtures of chemicals.	Auer, et al. [24]
	Polycyclic aromatic hydrocarbons Volatile organic compounds Carbonyls	Gas Chromatography Mass Spectrometry (GC-MS)	Separates volatile compounds via gas chromatography, then identifies and quantifies them based on their mass-to-charge (m/z) ratios using a mass spectrometer. Ionization (e.g., EI or CI) fragments molecules, and the resulting ions are analyzed based on m/z in a mass analyzer (e.g., quadrupole or TOF)	Li, et al. [2] and Jaccard, et al. [25]
	eCO	CO-meter	Measures CO concentration by detecting electrochemical changes or infrared absorption. In electrochemical sensors, CO oxidizes at an electrode, generating a current proportional to CO levels.	Caponnetto, et al. [26]
IQOS	ε-caprolactone, Lactide, 1,2-Diacetin, Formaldehyde cyanohydrin (glycolonitrile)	Gas Chromatography Mass Spectrometry (GC MS) Headspace	A headspace sampler extracts volatile compounds from a sample's gas phase, which are then introduced into GC-MS. It enables the analysis of volatiles without direct sample injection, reducing matrix effects.	Davis, et al. [27]
THP1.0 3R4F	Potassium permanganate	Atomic Absorption Spectroscopy (AAS)	Detects metal ions by atomizing a sample in a flame or graphite furnace and measuring the absorption of light at specific wavelengths corresponding to the metal's electronic transitions.	Forster, et al. [29]
Tobacco Heating	Water	Gas chromatograp	Measures changes in thermal conductivity between the carrier gas and eluting analytes.	Cozzani, et al. [37]

System 2.2. Part 2 3R4F		hy-thermal conductivity detector (GC-TCD)	Compounds with lower thermal conductivity than the carrier gas (usually helium) alter the detector signal.	
THP1.0 3R4F	NO NOx	Chemiluminescence	Detects compounds based on light emission from a chemical reaction. Commonly used for NOx or ozone, where the target gas reacts to form an excited state that emits photons measured by a photomultiplier.	Forster, et al. [29]
	Gaseous-phase metals	Inductively Coupled Plasma–Mass Spectrometry (ICP-MS)	Ionizes elements using a high-temperature argon plasma and detects them by mass spectrometry. Capable of trace-level elemental analysis with high sensitivity and multi-element capacity.	Forster, et al. [29]
	HPHC	Gas Chromatography–Thermal Energy Analyzer (GC-TEA)	Detects nitrogen- or sulfur-containing compounds by pyrolysis and chemiluminescence. After GC separation, compounds are thermally decomposed and react to emit light, which is detected.	Forster, et al. [29]
	Cambridge filter pad constituent detection	Ultra-Performance Liquid Chromatography–Tandem MS (UPLC-MS/MS)	Uses high-pressure UPLC for fast, high-resolution separation, coupled with tandem mass spectrometry (MS/MS) for structural identification and quantification based on specific precursor-product ion transitions.	Forster, et al. [29]
	Cambridge filter pad constituent detection	NCI GC-MS (SIM)	soft ionization technique in GC-MS that uses low-energy electrons to ionize electronegative compounds (e.g., halogenated). SIM mode improves sensitivity by focusing on specific m/z values	Forster, et al. [29]
Electrically Heated Tobacco Product (EHTP)	The total particulate matter constituents	Gravimetry	A classical analytical method where the analyte is converted to a stable, weighable form (precipitate, residue), and measured by mass. High accuracy but low sensitivity compared to modern techniques.	Salman, et al. [32] and Cozzani, et al. [37]
THS 2.2 3R4F	529 compounds that were Present in THS2.2 (unidentified target)	Comprehensive Two-Dimensional Gas Chromatography–Time-of-Flight MS (GCxGC TOF MS)	Employs two sequential GC columns with differing polarities for enhanced separation, coupled with TOF-MS that measures ion flight time to determine m/z with high speed and resolution.	Bentley, et al. [33]
	529 compounds that were Present in THS2.2 (unidentified target)	Liquid Chromatography + High-Resolution Accurate Mass Spectrometry (LC+HRAM MS)	Combines LC with high-resolution MS (e.g., Orbitrap, TOF) to provide accurate mass determination, allowing identification of unknowns and precise quantification in complex matrices.	Bentley, et al. [33]
	CO CO2	Fourier Transform	Analyzes molecular vibrations by measuring the absorption of infrared radiation across a broad	

		infrared spectroscopy (FTIR)	spectrum of wavelengths. The resulting IR spectrum represents functional group-specific fingerprinting of molecules.	

The forest plot (Figure 3) presents the average exposure reductions across different analyte types in studies comparing emissions from heated tobacco products (HTPs) with conventional cigarettes. Overall, the majority of analytes showed substantial reductions in exposure levels, with average reductions varying widely across studies and analyte categories. The most prominent finding, formaldehyde a well-known toxic carbonyl compound showed consistent and significant reductions across several studies [20, 21, 39] with average exposure reductions exceeding 70%. Similarly, acrolein showed significant emission reductions in studies by Le Godec, et al. [35], Cancelada, et al. [34] and Auer, et al. [24] all of which reported average reductions approaching or above 80% [23, 33, 34].

Reductions were also consistently observed for TSNAs (tobacco-specific nitrosamines), including NNK, with exposure reductions reported by Farsalinos, et al. [28] and Leigh, et al. [31] both exceeding 60%. Carbonyls and Reactive Oxygen Species (ROS), as measured in studies such as Salman, et al. [32] also showed significant reductions, often exceeding 60%. Additional analytes such as nicotine, acetaldehyde, CO/NOx, PM1, VOCs, and HPHCs (broad or average), were included in several studies, typically showing average exposure reductions above of 50%, although with some variability in confidence intervals. Notably, formaldehyde, cyanhydrine [27] and total cancer and non-cancer risk estimates [13] were also assessed, with both showing significant reductions in exposure levels or modeled risks.

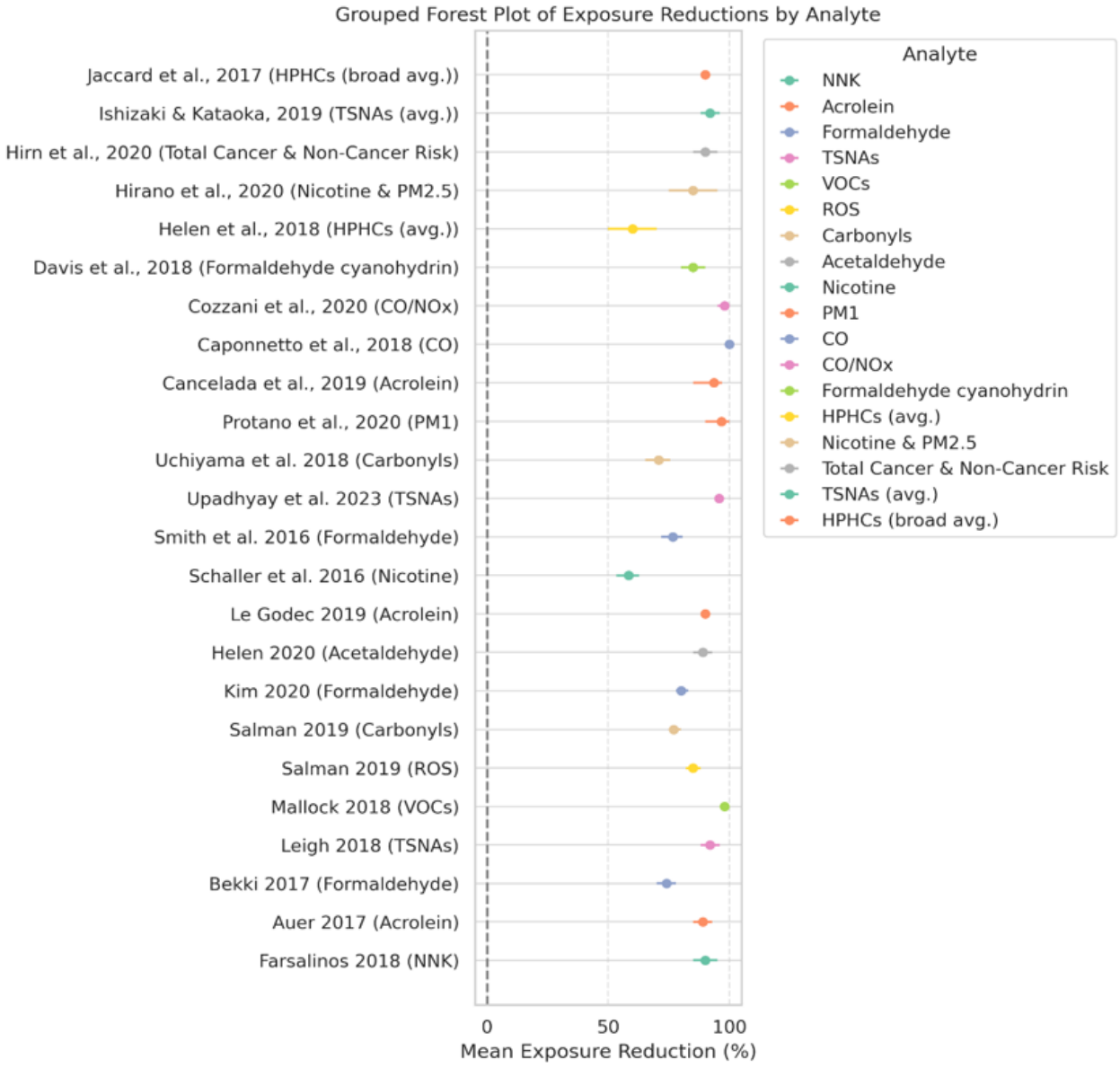

Figure 3.
Grouped forest plot of exposure reductions by analyte for heated tobacco products (HTPs) versus conventional cigarettes.
Source: Jaccard, et al. [25]; Ishizaki and Kataoka [36]; Hirano, et al. [39]; Helen, et al. [30]; Davis, et al. [27]; Cozzani, et al. [37]; Caponnetto, et al. [26]; Cancelada, et al. [34]; Protano, et al. [41]; Uchiyama, et al. [11]; Upadhyay, et al. [7]; Smith, et al. [21]; Schaller, et al. [20]; Le Godec, et al. [35]; Helen, et al. [30]; Kim, et al. [40]; Salman, et al. [32]; Mallock, et al. [8]; Leigh, et al. [31]; Bekki, et al. [22]; Auer, et al. [24] and Farsalinos, et al. [3].

These findings underscore a general trend of decreased analyte emissions in HTP aerosol compared to conventional cigarette smoke. However, variations in the magnitude of the reductions between analytes and between studies suggest that the reductions are compound-specific and may be influenced by the analytical method, product type, and study design.

This study assessed potential publication bias in the included studies on exposure reduction from heated tobacco products (HTPs) using a funnel plot analysis (Figure 4). The funnel plot displays the distribution of effect sizes against their corresponding standard errors. The plot shows a generally symmetric distribution of studies around the pooled effect size (centered near an effect size of approximately 90), indicating a low risk of publication bias. Most data points fall within the 95% confidence limits (represented by the dashed triangle region), and there is no obvious asymmetry or clustering on one side of the plot.

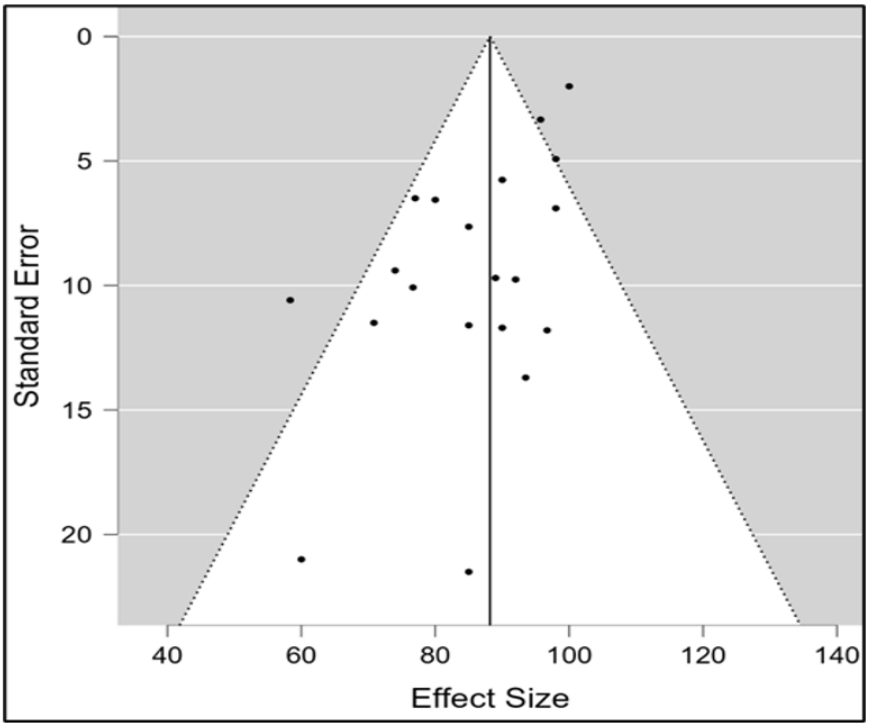

Figure 4.
Funnel plot assessing small-study effects in the meta-analysis.

A meta-analysis employed a random-effects model to address heterogeneity among studies. The resulting pooled effect size demonstrated statistical significance, indicating a consistent association across the included research (estimate = 88.18, SE = 2.24, z = 39.38, $p < .001$), indicating a strong and consistent overall effect. Heterogeneity was moderate (I^2 = 52.5%, τ^2 = 48.42), with a significant test of residual heterogeneity (Q = 50.87, df = 23, $p < .001$), suggesting that variability among the studies is not solely due to sampling error and likely real differences in study characteristics.

4. Discussions

Conventional cigarette smoke contains tar, carbon monoxide, and a wide spectrum of harmful carbonyl compounds formed during burning. HTP aerosol delivers nicotine effectively but contains drastically reduced levels of harmful carbonyl compounds and carbon monoxide. Analysis of 26 studies selected following the PRISMA guidelines, to assess and compare chemical emissions from HTPs and conventional tobacco cigarettes (CTCs), indicates that HTPs demonstrate significantly reduced emissions of numerous toxicants compared to conventional cigarettes. The notable reductions in are Carbon monoxide (CO) emissions, typically below detectable levels carbonyl compounds such as formaldehyde and acrolein reduced by 80-90%, tobacco-specific nitrosamines (TSNAs) and nitrogen oxides reduced by more than 85%, toxic aromatic hydrocarbons (e.g., benzene, toluene) reduced by over 90%, dan volatile organic compounds (VOCs) and other harmful volatile substances substantially decreased. Statistical analyses reveal consistent and significant reductions in HPHCs across multiple studies, with an average reduction of approximately 88.18% ($p < 0.001$) in harmful constituent emissions in HTP aerosols relative to conventional cigarette smoke. Despite this, meta-analyses report moderate heterogeneity (I^2 = 52.5%), which is attributed to variations in study design, tobacco heating systems, and analytical methodologies.

The results of this research are also consistent with those of studies conducted in Indonesia, as shown in Table 3. An analysis of HTP in the Indonesian market, comparing emissions from a representative Heated Tobacco Product (IQOS) with three types of conventional cigarettes, focuses on chemical analysis using standardized testing procedures. The data includes measurements of nicotine, carcinogenic polycyclic aromatic hydrocarbons, carbonyl compounds, volatile organic compounds, tobacco-specific nitrosamines, and carbon monoxide.

Table 3.
Comparison of chemical components between HTP and conventional cigarettes.

Chemical Toxicant	HTP	Conventional Cigarette Standard	Conventional Cigarette Type 1	Conventional Cigarette Type 2
Nicotine (mg/puff)	0.10	0.22	0.12	0.19
Benzo[a]pyrene (ng/puff)	0.05	1.76	2.04	2.6
Formaldehyde (µg/puff)	0.43	9.51	4.40	7.69
Acetaldehyde (µg/puff)	10.38	154.89	62.19	111.84
Acrolein (µg/puff)	0.46	17.52	7.97	11.9
1,3-Butadiene (µg/puff)	0.06	11.76	5.4	9.6
Benzene (µg/puff)	0.08	9.81	4.77	8.23
N-Nitrosonornicotine (NNN) (ng/puff)	0.52	24.54	5.42	4.95
NNK (Methylnitroso-amino compound) (ng/puff)	0.73	19.73	5.71	5.48
Carbon monoxide (CO) (mg/puff)	0.02	3.51	2.08	2.08

As shown in the table, benzo[a]pyrene levels in HTP (0.05 ng) are significantly lower than those in conventional cigarettes (1.76-2.6 ng), indicating a significant reduction in this potent carcinogen. Carbonyl compounds (formaldehyde, acetaldehyde, acrolein) show >90% reduction in HTP compared to conventional cigarettes. Volatile organic compounds (1,3-butadiene, benzene) are near negligible in HTP emissions. Tobacco-specific nitrosamines (NNN, NNK) are significantly lower in HTP aerosol compared to cigarettes. Carbon monoxide levels from HTP are almost negligible (0.02 mg) compared to conventional cigarettes (2.08-3.51 mg).

The data demonstrate that HTPs generate substantially lower yields of multiple HPHCs compared to conventional cigarettes. This is consistent with the fundamental design difference: HTPs heat tobacco without combustion, thereby avoiding the chemical processes that produce toxicants found in cigarette smoke. The sharp reduction in carcinogens (benzo[a]pyrene, NNN, NNK) is particularly notable as these compounds are strongly linked to cancer risk. Reductions in aldehydes and VOCs mitigate risks for respiratory and cardiovascular diseases. The near elimination of CO in HTP emissions distinguishes them from conventional cigarettes regarding cardiovascular toxicity.

Indonesia has established an Indonesian National Standard (SNI) for heated tobacco products, SNI 8946:2021. This standard, developed by Technical Committee 6519 on Tobacco Products, encompasses terminology and definitions, quality requirements, sampling procedures, test methods, packaging, and labeling. Based on the test results in Table 3, the nicotine and carbon monoxide contents met the SNI requirements. Although the current national standard does not specify limits for some constituents (exp carbonyl compounds), the concentration observed here are in line with the World Health Organization guidelines. This alignment offers reassurance that the results meet internationally recognized health standards, reinforcing confidence in the product's safety and overall quality.

Although the literature study of HTP products and data analysis in Indonesia shows significant reduction results in terms of toxicants from HTP compared to conventional cigarettes, there are still notable limitations that should be considered for future research. There are variabilities in study design, tobacco heating system models, and testing protocols that produce heterogeneity, impacting the comparability of results. In addition, the variable standardized test methods for HTP emissions also added challenges to such cross-study synthesis. Moreover, this product is relatively new to the market, and as such, long-term epidemiological data on health outcomes related to heated tobacco products (HTPs) remain limited.

This comparative analysis demonstrates that Heated Tobacco Products (HTPs) generate significantly lower levels of harmful and potentially harmful constituents than conventional cigarettes. These findings indicate that HTPs may present a reduced health risk as an alternative to traditional tobacco products. However, HTPs are not risk-free; the substantial reductions in toxicant emissions suggest HTPs may present reduced health risks for smokers who switch completely from conventional cigarettes.

For continuous improvement of the role of HTP in harm reduction, it is necessary that potential exposure to residual harmful constituents in HTP aerosol necessitates continued careful monitoring and regulatory oversight. Regulatory frameworks should prioritize science-based product regulation, ongoing research on the long-term health effects, and residual risks associated with HTP use. Integration of standardized testing protocols will enhance data comparability and support informed policy making.

5. Conclusions

This study has identified the method used for evaluating analytes in the aerosol of a heated tobacco product (HTP), which includes harmful and potentially harmful constituents (HPHC), as well as other substances such the total particulate matter (TPM), carbon monoxide (CO), and nicotine. The most widely used method for analyzing HPHC in the HTP is the official Health Canada method, which incorporates liquid chromatography in tandem with mass spectrometry (LC-MS/MS), gas chromatography-mass spectrometry (GC-MS), or both analytical instruments. This method has been proven to be able to detect analyte yield in HTP products with up to 95% lower concentrations than the original analytes found in conventional cigarettes. Further research on best practices in testing methods for HPHC in HTP products is required to decrease variability and improve comparability among research reports. Underlining the discrepancies in preparation of the

samples, such as the humidity or water content in the HTP stick samples, the number of puffs, battery or current stability during aerosol sampling, and even the temperature used for heating the samples. Improved and standardized methods will help others to replicate the work in future research.

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