Analysis of mainstream emissions, secondhand emissions and the environmental impact of IQOS waste: a systematic review on IQOS that accounts for data source

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ABSTRACT

Objective To highlight the general features of IQOS literature focusing on the chemical analysis of IQOS emissions.

Data sources PubMed, Web of Science and Scopus databases were searched on 8 November 2021 using the terms 'heated tobacco product', 'heat-not-burn', 'IQOS' and 'tobacco heating system' with time restriction (2010–2021). The search yielded 5480 records.

Study selection Relevant publications on topics related to IQOS assessment were retrieved (n=341). Two reviewers worked separately and reached agreement by consensus.

Data extraction Data on author affiliation and funding, article type and date of publication were extracted. Publications were categorised depending on their focus and outcomes. Data on IQOS emissions from the chemical analysis category were extracted.

Data synthesis Of the included publications, 25% were published by Philip Morris International (PMI) affiliates or PMI-funded studies. PMI-sponsored publications on emissions, toxicology assessments and health effects were comparable in number to those reported by independent research, in contrast to publications on IQOS use, market trends and regulation. Data on nicotine yield, carbonyl emissions, other mainstream emissions, secondhand emissions and IQOS waste were compared between data sources to highlight agreement or disagreement between PMI-sponsored and independent research.

Conclusions Our analysis showed agreement between the data sources on nicotine yield from IQOS under the same puffing conditions. Also, both sources agreed that IQOS emits significantly reduced levels of some emissions compared with combustible cigarettes. However, independent studies and examination of PMI's data showed significant increases in other emissions from and beyond the Food and Drug Administration's harmful and potentially harmful constituents list.

INTRODUCTION

Tobacco use is the leading cause of preventable disease and death worldwide.[1] The WHO states that the tobacco epidemic kills more than 8 million people annually.[2] In the USA, the 1964 Surgeon General Report linked smoking cigarettes to deleterious health effects, such as lung cancer.[3] This landmark in the history of tobacco research and policy transpired, although slowly, into more research and regulations on tobacco in the following decades.[4] On the other hand, it also triggered faster adaptation from the industry, which introduced filtered, low-tar, light, ultralight and mentholated cigarettes as supposedly safer alternatives[5] that were not, in fact, safer than their predecessors.[6–8]

More recently, the tobacco industry has promoted alternative products, like electronic cigarettes and heated tobacco products (HTPs), with a claimed potential of reduced risk and harm.[9–11] Analogous with other industries,[12 13] tobacco companies promote 'safer' products as a narrative directed towards health-conscious consumers and policymakers.[14] A remarkable example was the introduction of IQOS, an HTP branded by tobacco giant Philip Morris International (PMI), into the US market after securing a premarket tobacco application from the US Food and Drug Administration (FDA).[15 16] A year later, the FDA authorised the advertisement of IQOS as a modified risk tobacco product (MRTP),[17 18] with 'modified exposure' but not 'modified risk' claims.[18] The MRTP application relies on a theoretical benefit of tobacco harm reduction based on data presented by the industry.[19–21] However, researchers affiliated with or supported by the industry have communicated risks in a way that minimises harm,[22] created a false impression of unbiased research,[23] highlighted favourable results[24] and ignored unfavourable ones,[25 26] concealed industry support[27 28] or published in industry-dominated journals.[29] These tactics jeopardise research integrity,[30–33] and scepticism is warranted when dealing with industry-sponsored data.[14 34] Moreover, recently publicised industry documents indicated that industry research was several years ahead of independent research.[34] These observations highlight the need to scrutinise industry data and emphasise the importance of independent research to verify emissions, health effects and public health impact of newly introduced tobacco products.[35–37]

In this paper, we report a systematic literature review conducted to assess the distribution of published data on IQOS between PMI-sponsored research (affiliated authors or funded studies) and independent research. We focused on publication type, topic(s) and date. We extracted data on chemical analysis of IQOS mainstream emissions including nicotine, carbonyls and other harmful and potentially harmful constituents (HPHCs). We also discussed data on the impact of IQOS use on indoor air quality and the environmental impact of

IQOS waste disposal. This work emphasises the importance of independent evidence in tobacco control.

METHODS

Literature search strategy and study selection

PubMed, Web of Science and Scopus databases were searched on 8 November 2021 using the keywords 'heated tobacco product', 'Heat-not-burn', 'IQOS' and 'Tobacco Heating System' (THS). The search was limited to publication between 2010 and 2021 to avoid collecting data on an HTP previously marketed by PMI, a precursor to IQOS.[17] Two reviewers (AE-H and ME-K) worked separately to screen the databases. EndNote V.X9 was used to record all hits and remove duplicates. Once the two reviewers removed duplicates and independently screened the titles and abstracts of included publications, they met and reached consensus. The same agreement was reached after a full-text review and data were collected in a common Excel file.

Inclusion criteria

The systematic review included peer-reviewed publications in English on any topic related to IQOS or THS (a premarket designation with a model code: 2.1, 2.2 or 2.4).

Exclusion criteria

A publication was excluded if it is not peer reviewed, not related to HTPs, talks about HTP in general without mentioning IQOS (or THS 2.1, 2.2 or 2.4) or focuses on HTPs other than IQOS (eg, Glo, Ploom) without testing IQOS for comparison.

Data extraction

Data on author affiliation, conflict of interest and/or study funding were retrieved from the respective sections of each publication. The type and date of publication were recorded. Publications were categorised into six categories based on topic or focus. The chemical analysis category includes assessments of IQOS mainstream emissions, sidestream emissions, particle size distribution, impact of IQOS use on indoor air quality and environmental impact of IQOS waste. The toxicity assessment category includes in vitro, in vivo and systems toxicology studies.[38] The human health category includes clinical studies that assessed the pharmacokinetics of nicotine, biomarkers of exposure and biomarkers of potential harm following IQOS use. The category related to perception, awareness and prevalence includes studies related to IQOS use trends and population appeal. One category related to marketing strategies and trends and another related to the regulation of IQOS were also included. Categorisation decision on publications that could be classified into two or more categories was reached by consensus.

Data synthesis

Data on authors' relation to PMI, publication type and date of publication were used to discuss the general features of IQOS literature. Research was classified as PMI sponsored if the authors were PMI affiliated or the study was funded by PMI. Spearman's rank-order correlation was run to assess the strength and direction of association between the annual number of publications and data source. Chi-sqaure (X^2) analysis was performed to test for differences in publication type between data sources. For chemical analysis, data on mainstream nicotine and carbonyl emissions were compared across studies and statistical analyses were performed to highlight the impact of puffing parameters on emissions. The association between outcome measures with product flavour, data source, puffing duration (seconds), number

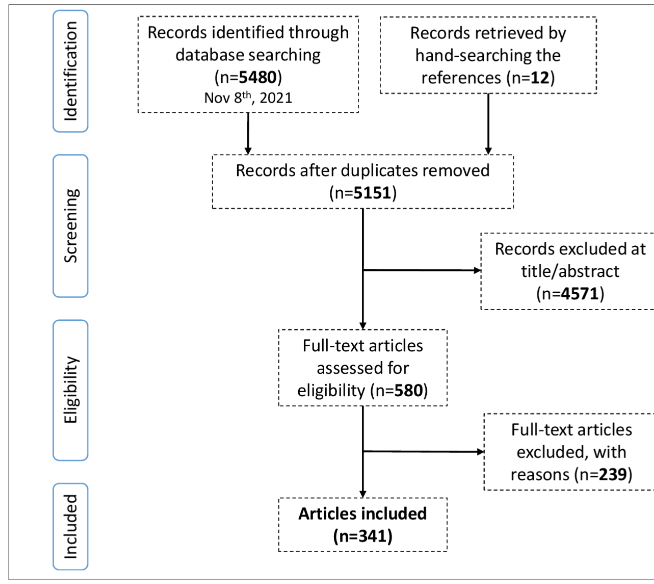

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the systematic review. Reasons for exclusion of a publication: not peer reviewed, not related to heated tobacco products (HTPs), discusses HTP in general or focuses on HTPs other than IQOS (eg, Glo, Ploom) without testing IQOS for comparison.

of puffs and flow rate (L/min) was analysed using a general linear model regression analysis. Because the IQOS battery lifetime is limited, we calculated the number of puffs based on puff duration and interpuff interval, and the flow rate from the puff volume and total puffing duration. Statistical analyses were performed using SPSS V.25.0 (significance at $p<0.05$). A narrative synthesis summarises data on other toxicants in mainstream emissions, sidestream emissions and other topics covered in the chemical analysis category. The content of publications listed in the other five categories will be discussed in follow-up reports.

RESULTS

Included studies

The search resulted in 5480 hits (online supplemental table S1), and 12 publications were manually retrieved (figure 1). Duplicate checking removed 341 hits, while title and abstract screening removed 4571 hits. After a thorough review of the full texts of the remaining records (n=580), 341 publications were deemed relevant (online supplemental table S2). Of the included publications, 86 were published by researchers affiliated with or supported by PMI (25%), 246 by independent researchers (72%) and 9 by competing manufacturers (3%).

General features of IQOS literature

Categorisation of included publications

We categorised the literature into six categories (figure 2). Independent and PMI-sponsored research reported close contributions in chemical analysis (56% and 43%, respectively) and toxicity assessment (38% and 57%, respectively). Two-thirds of publications in the human health category were published by independent research. PMI-sponsored research constitutes 3% of the three categories related to use, marketing and regulation, which constitute 44% of the published literature on IQOS. In the context of comparing IQOS to their HTPs, competing manufacturers reported on chemical analysis (1%), toxicity assessment (5%), human health (3%) and perception and use of IQOS (3%).

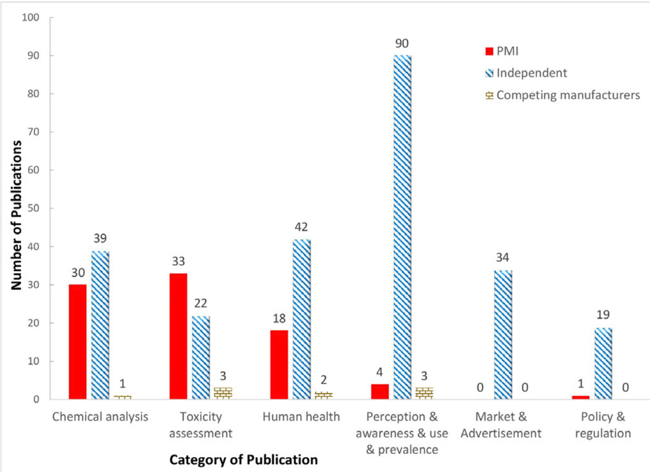

Figure 2 Categorisation of publications on IQOS according to the main topic covered. This includes publications by Philip Morris International (PMI)-affiliated or sponsored researchers, independent researchers and researchers affiliated with or supported by competing manufacturers of heated tobacco products (HTPs).

Date of publication

Figure 3 illustrates the temporal distribution of IQOS literature. The number of independent research publications on IQOS surpassed PMI-sponsored publications beginning in 2018.[39 40] From 2016 to 2021, PMI published a steady number of annual reports (14.2±3.9); however, for the same period, the number of independent annual publications varies widely (4 in 2016 to 74 in 2020). From 2018 to 2021, other HTP manufacturers reported data on IQOS for comparison.

Publication type

The assessment of publication type showed more independent (66%) than PMI-sponsored original investigations. PMI-sponsored research reported no brief reports, one literature review and five publications characterised as letters, commentaries, protocols, opinions and industry watch type (table 1). Brief reports, reviews and opinion letters constituted 25% of the IQOS literature. Independent researchers published seven literature reviews on IQOS in 2019 and six in 2020. Several independent opinion letters were published annually in the last 5 years (8.2±3.1). Manufacturers of other HTPs published eight original articles (3%) and one review (6%) that included IQOS data.

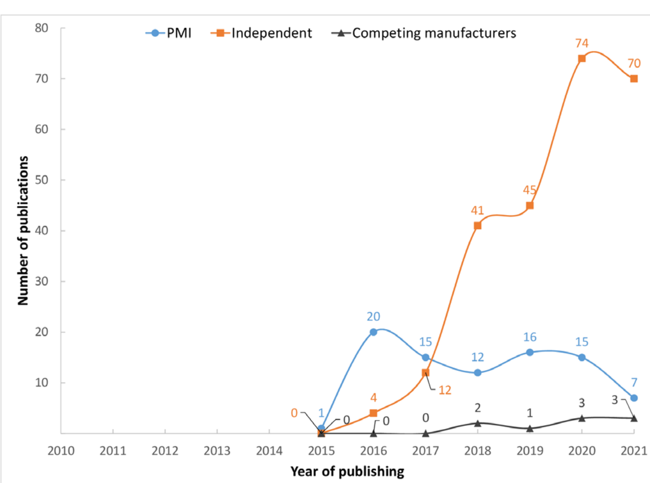

Figure 3 The temporal distribution of publications on IQOS starts from its introduction into the global market in 2014 and extends to 2021. PMI, Philip Morris International.

Table 1 Type of publication per data source; number of publications (% of total from each source type)

Type of paper	PMI	Independent	Competing manufacturers
Original research	80 (93)	168 (68)	8 (89)
Brief report	0 (0)	23 (9)	0 (0)
Review	1 (1)	14 (6)	1 (11)
LCPOI	5 (6)	41 (17)	0 (0)

Number of publications (% of total from each source type).
LCPOI, letters, commentaries, protocols, opinions and industry watch; PMI, Philip Morris International.

Chemical analysis

In this section, IQOS emissions will be compared with those from combustible cigarettes generated under the Health Canada Intense (HCI) puffing regime conditions. Any other puffing conditions used in the comparison will be clearly stated.

Nicotine yield in IQOS aerosols

PMI data

Five PMI studies showed that nicotine yield from IQOS with tobacco flavour (hereafter IQOS regular (IQOS-R)) varies widely under different puffing regimes (range: 0.49–2.19 mg/stick).[9 41–44] PMI data showed that nicotine yield from IQOS-R (1.27±0.10 mg/stick) was 64% of the average yield of 3R4F reference cigarette smoke (1.97±0.17 mg/cigarette).[9 44] Nicotine yield of IQOS menthol flavour (IQOS-M; 1.21 mg/stick) was reported in one study to be similar to IQOS-R (online supplemental table S3).[41]

Independent data

Fifteen studies reported nicotine yield from IQOS-R under different puffing regimes (range: 0.30–1.46 mg/stick).[36 45–58] The collected data showed that the average nicotine yield from IQOS-R (1.19±0.20 mg/stick) was equal to 65% that of 3R4F.[51 55 58] Six studies reported on nicotine yield of IQOS-M (1.09±0.25 mg/stick).[45 46 51 52 54 58] Eleven studies used cigarette comparators other than 3R4F, with two studies showing that IQOS-R nicotine yield is equivalent to that of 1R5F reference cigarette (1.1 mg/cigarette).[36 45 47–54 56] Two independent studies found nicotine mainly in salt form in IQOS-R aerosols.[47 56] Table 2 shows the wide range of nicotine yields from IQOS-R generated under different puffing parameters as reported by all data sources (0.30–2.19 mg/stick).[59]

Levels of carbonyls in IQOS aerosols

PMI data

Three PMI studies quantified carbonyls in IQOS-R emissions under different puffing regimes.[9 41 42] For eight carbonyls (formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl ethyl ketone and butyraldehyde), the data showed a significant reduction (70%–95%) in IQOS-R aerosols compared with 3R4F cigarette smoke.[9 41 42] Three studies highlighted the robustness of HPHC reductions (including carbonyls) in IQOS aerosols compared with 3R4F under different puffing regimes and climatic conditions.[59–61] A comprehensive chemical characterisation using non-targeted

Table 2 Nicotine yield (mean±SD) in IQOS-R aerosols under different puffing regimes

Reference	Affiliation/funding	Puffing regime (PR)	Puff duration (s)	Interpuff interval (s)	Puff volume (mL)	Nicotine yield (mg/stick)
Schaller *et al*[41]	PMI	HCI	2.0	30	55	1.32±0.16
		ISO	2.0	60	35	0.49±0.08
		PR1	2.4	25	60	1.64±0.22
		PR2	2.4	25	80	1.8±0.41
		PR3	4.5	22	110	2.19±0.43
		PR4	2.4	30	40	0.76±0.19
		PR5	2.4	30	80	1.13±0.11
Schaller *et al*[42]	PMI	HCI	2.0	30	55	1.38±0.20
Jaccard *et al*[9]	PMI	HCI	2.0	30	55	1.14±0.03
Poget *et al*[43]	PMI	HCI	2.0	30	55	1.36±0.09
		ISO	2.0	60	35	0.49±0.04
		PR1	2.4	25	60	1.64±0.10
		PR2	2.4	25	80	1.8±0.19
		PR3	4.5	22	110	2.19±0.20
		PR4	2.4	30	40	0.76±0.09
		PR5	2.4	30	80	1.13±0.05
Ibañez *et al*[44]	PMI	HCI	2.0	30	55	1.15±0.02
Gasparyan *et al*[110]	BAT	HCI	2.0	30	55	1.23±0.05
Auer *et al*[36]	Ind	ISO	2.0	60	35	0.30±0.21
Bekki *et al*[51]	Ind	HCI	2.0	30	55	1.10
Farsalinos *et al*[45]	Ind	HCI	2.0	30	55	1.40±0.16
		PR6	4.0	30	55	1.41±0.08
Farsalinos *et al*[52]	Ind	HCI	2.0	30	55	1.20
		PR7	3.0	30	80	1.31
		PR8	3.0	25	90	1.60
Leigh *et al*[50]	Ind	HCI	2.0	30	55	1.40±0.20
Mallock *et al*[53]	Ind	HCI	2.0	30	55	1.1±0.10
Uchiyama *et al*[54]	Ind	HCI	2.0	30	55	1.2±0.13
		ISO	2.0	60	35	0.40±0.07
Cancelada *et al*[46]	Ind	HCI	2.0	30	55	0.99±0.10
Li *et al*[55]	Ind	HCI	2.0	30	55	1.35±0.07
		ISO	2.0	60	35	0.50±0.03
Meehan-Atrash *et al*[56]	Ind	PR9	3.0	30	55	1.22±0.12
Salman *et al*[47]	Ind	HCI	2.0	30	55	1.50±0.20
		ISO	2.0	60	35	0.77±0.06
Bitzer *et al*[48]	Ind	PR10	2.5	30	75	1.47±0.12
Wang *et al*[49]	Ind	ISO	2.0	60	35	0.55±0.01
Dusautoir *et al*[57]	Ind	HCI	2.0	30	55	0.76
Perezhogina *et al*[58]	Ind	HCI	2.0	30	55	1.10±0.03

BAT, British American Tobacco; HCI, Health Canada Intense puffing regime; Ind, independent; IQOS-R, IQOS regular; ISO, International Organization for Standardization; PMI, Philip Morris International.

analysis and semiquantification reported similar reductions in the above-mentioned carbonyls.[62] However, the same data showed a lower reduction in 5-hydroxymethylfurfural (28%) and 2,3-pentanedione (62%) and increases in hydroxyacetone (226%), furfural (125%), 5-methylfurfural (270%) and 2(5H)-furanone (332%) levels in IQOS-R aerosols compared with 3R4F cigarette smoke.

Independent data

Nine independent studies reported on carbonyl emissions from IQOS-R under different puffing regimes.[36 46 47 49 52–55 57] Data showed significant reduction in carbonyl levels compared with 3R4F smoke (69%–97%) except for one study that showed a moderate decrease for some carbonyls (formaldehyde (26%), methylglyoxal (40%) and methacrolein (52%)) and increases for others (benzaldehyde (11%) and hexaldehyde (155%)).[57] Two studies reported a slightly lower reduction in carbonyl emissions when IQOS-R and 3R4F were smoked under International Organization for Standardization (ISO) conditions (eg, butyraldehyde was reduced by 75% and 42% under HCI and ISO conditions, respectively).[54 55] One study reported similar reductions when IQOS was compared with CORESTA Monitor 6 reference cigarette which is reported to have similar toxicant emissions as 3R4F.[54 63] However, this study showed that IQOS-R emissions were slightly lower than 1R5F reference cigarette smoke for formaldehyde (33%) and acetaldehyde (6%) but higher for butyraldehyde (72%), isovaleraldehyde (91%) and glyoxal (64%) under ISO conditions.[54] Other studies used different cigarette comparators like Marlboro Red, Lucky Strike Blue Lights and ultralight cigarettes. Reduction of carbonyl levels in comparison to Marlboro Red was similar to 3R4F but much lower when IQOS was compared with Lucky Strike Blue Lights (eg, formaldehyde (25%) and acrolein (18%)).[36 47] Acetone, acrolein and methyl ethyl ketone were reduced by 50% in comparison with emissions from an ultralight cigarette; however, formaldehyde, acetaldehyde, propionaldehyde, crotonaldehyde and butyraldehyde were increased by 109%, 29%, 29%, 33% and 160%, respectively.[49] Moreover, a study reported higher furanic carbonyl emissions in IQOS-R aerosols in comparison to 3R4F smoke (furfural (13%) and 5-methylfurfural (175%)).[64] Similarly, another study reported higher acetol emissions in IQOS-R aerosols (188%); the acetol level was even higher with IQOS-M (288%).[54]

Other HPHCs, radicals and particles

PMI data

Three studies reported no solid particles emissions in IQOS aerosols in contrast to 3R4F smoke, indicating that no combustion took place.[65–67] Combustion was also ruled out by another study that showed a similar chemical composition of IQOS aerosols generated under oxidative and non-oxidative atmospheres (air and nitrogen, respectively).[68]

One study showed that the transfer of tobacco-specific nitrosamines (TSNAs) from IQOS tobacco filler to the aerosol was two to three times lower than combustible cigarettes due to the lower operating temperature,[69] resulting in more than 90% reduction in TSNA yields. PMI data also showed more than 90% reduction of aromatic amines, gases (like nitrogen oxides and hydrogen cyanide), TSNAs, phenols, polycyclic aromatic hydrocarbons (PAHs) and metals, but lower reductions (60%–80%) in other HPHCs like ammonia, catechol, mercury, acetamide and acrylamide.[9 41 42] A study showed the same reduction of HPHC yields including phenols, volatile organic compounds (VOCs) and TSNAs when comparing IQOS to 1R6F reference cigarette, which has similar toxicant emissions as 3R4F.[70] The comprehensive chemical characterisation mentioned previously reported data on 529 constituents including alcohols, carbonyls, acids, furans, terpenes, pyridines and other chemical classes, showing moderate to high reductions (6%–99%) yet sometimes high increases (13%–6330%) in IQOS-R emissions compared with 3R4F.[62 71]

Independent data

One study reported presence of a non-volatile fraction of aerosol particles.[72] Another study reported observation of charring on used IQOS HeatSticks (ie, HEETS) and detection of an IQOS-specific toxicant (formaldehyde cyanohydrin).[40 73]

Two studies reported more than 90% reduction in PAH emissions in IQOS aerosols compared with 3R4F,[57] except for acenaphthene which was higher by 196% in IQOS aerosols under ISO conditions.[36] A study reported at least 80% reduction in IQOS emissions of carbonyls, VOCs, TSNAs, aromatic amines, phenol and Benzo[a]pyrene but not in N-nitrosoanabasine, ammonia gas or some carbonyls compared with 3R4F under HCI and ISO conditions.[55] Unlike carbonyls, VOCs and TSNAs were lower and aromatic amines and PAHs were not present in IQOS aerosols compared with smoke from an ultralight cigarette under ISO conditions.[49] Two studies reported more than 95% reduction in 1,3-butadiene, benzene and toluene in IQOS emissions compared with a range of cigarette smoke levels.[53 58] A study showed 76%–84% lower pyridine emissions in IQOS-R aerosols compared with 3R4F smoke.[64] However, the same group reported lower reduction under ISO conditions (58%) and increases when IQOS-R was compared with 1R5F cigarette (264%).[54] One study comparing emissions from JUUL (a leading e-cigarette brand) to IQOS and 3R4F showed 400% higher glycidol in IQOS aerosols than in 3R4F cigarette smoke generated under an intense puffing regime compared with HCI.[74]

TSNA emissions were reduced by 85%–95% in IQOS-R aerosols compared with 3R4F and a similar reduction compared with 1R5F smoke.[51 75] In a per-puff comparison, TSNA levels were reported to be 8–22 times lower in IQOS-R aerosol than in Marlboro Red cigarette smoke.[50]

One study reported more than 99% and 95% reductions in gas phase radical and nitrogen oxide emissions, respectively, in IQOS aerosols compared with 3R4F smoke.[76] Another group reported similar reductions in gas phase radicals, in addition to the absence of particle-phase radicals.[48] One study showed that reactive oxygen species emissions are 91% and 82% lower in the gas phase and particle phase of IQOS aerosols compared with Marlboro Red cigarette smoke under ISO conditions.[47]

IQOS secondhand emissions

PMI data

Two studies on the impact of IQOS use on indoor air quality reported background concentrations of constituents including suspended particles (particulate matter, PM2.5), VOCs, carbonyls, carbon monoxide and nitrogen oxide. Only acetaldehyde and nicotine concentrations were above background levels and much lower compared with those from Marlboro Gold cigarettes.[77 78] Another study reported similar results, finding benzene, toluene and solanesol in addition to nicotine and acetaldehyde above background levels, but 77%–99% lower than Marlboro Gold.[79] In contrast, a chamber study showed that IQOS use resulted in a statistically significant increase in particle number concentration (PNC), PM2.5, nicotine and acetaldehyde compared with background levels, but significantly lower (12%, 4%, 6% and 12%, respectively) than those from cigarette smoking.[80] However, IQOS formaldehyde emissions were 51% those from combustible cigarettes. A study showed that IQOS use in a nightclub increased the background number and mass concentration of particles that exhibited high volatility but did not significantly affect the concentrations of formaldehyde, acetaldehyde and 3-ethenyl pyridine.[81] A study on TSNAs (1′-demethyl-1′-nitrosonicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)) in indoor air showed that NNN and NNK emissions in IQOS aerosols were 10% and 2% of those from Marlboro Gold.[82]

A comprehensive analysis of airborne constituents emitted from IQOS quantified 31 constituents and targeted screening of 30 compounds in the gas phase and 36 compounds in the particle phase.[83] Data showed that only nicotine, glycerol, menthol and acetaldehyde levels were above background levels. Ultrafine particles increased on IQOS use but quickly returned to baseline. The reported data showed that indoor IQOS emissions are substantially lower than combustible cigarettes or incense, consistent with a review on the impact of IQOS emissions on indoor air quality compared with everyday activities.[84] This review highlighted the challenges of assessing secondhand exposure from IQOS in real-life scenarios.

Independent data

An independent study simulating secondhand exposure to submicron particles (SMP) showed four times lower emissions from IQOS in comparison to cigarettes, but a return to background levels immediately after use termination, implying that IQOS use is not a persistent indoor air pollutant.[85] In contrast, another study showed that although SMP emissions from IQOS are one order of magnitude lower than cigarette smoke, levels were still higher than baseline values 1 hour after IQOS use.[86] Two studies showed that IQOS emitted the least PNC of ultrafine, fine and coarse particles in an indoor environment compared with an e-cigarette and a combustible cigarette.[87 88] The conclusion that IQOS is the least indoor air pollutant was confirmed by another study that nevertheless estimated concerning acrolein levels.[46] Moreover, a study showed significantly lower secondhand VOC and PM emissions from IQOS compared with combustible cigarettes and e-cigarettes.[89] A study indicated that IQOS has significantly less intense and persistent impact on indoor air quality compared with combustible cigarettes, and significantly lower than a competing HTP from British American Tobacco (ie, Glo) and a leading e-cigarette (JUUL).[90] This study found some differences in IQOS secondhand emissions depending on flavour. In contrast, another study showed that IQOS emitted comparable PM1 levels to Glo and higher than JUUL.[91] In a chamber study, IQOS emitted significantly lower PM2.5 than a combustible cigarette or Glo but equivalent to ploomTECH tobacco product.[92]

A study showed that IQOS emitted 0.7%, 1–2%, 22–24%, 5% and 7% of black carbon, PM2.5 and PM10, PMnm, acetaldehyde and formaldehyde levels, respective to those from cigarette smoking. PAHs were undetectable in IQOS secondhand emissions and metal emissions from IQOS were much lower than from cigarettes but comparable to background levels. Nevertheless, the authors computed statistically significant emission factors of certain n-alkanes, organic acids and carcinogenic aldehydes that warrant restriction of indoor IQOS use.[93]

A study showed that IQOS use in passenger cars markedly increased the number concentration of ultrafine particles and nicotine levels.[94]

Environmental impact of IQOS waste

PMI data

A study discussed the impact of improper disposal of IQOS HeatSticks and combustible cigarettes on the environment with a comprehensive analysis of metal leachates from IQOS waste as water contaminants.[95] Another study focused on the development of a photolysis method to treat nicotine leachates in water.[96]

Independent data

No independent research addressed the impact of improper IQOS waste disposal on the environment.

DISCUSSION

Researchers affiliated with or funded by PMI reported a considerable share of IQOS literature (25%), exceeding the contribution of independent researchers in the first 4 years after the introduction of IQOS into the global market.[36 39] However, it should be noted that financial connections to PMI may be concealed in some publications.[97 98] There was no significant Spearman correlation between research funding and the temporal distribution of the number of publications (rs=0.072, p=0.878).

PMI-sponsored researchers focused their efforts on chemical analysis and toxicity assessment, and studies related to health benefits for smokers switching to IQOS, generating data to support the IQOS MRTP application.[11 18] The industry used exposure reduction as a feature to promote IQOS as a safer tobacco product than combustible cigarettes.[99 100] On the other hand, independent research published 90 articles on perception, awareness, use and prevalence to highlight IQOS use trends and directions in the population.[101–103] Tobacco control experts are concerned with the widespread use of IQOS and its impact on individual and public health,[104] so they reported comprehensively on IQOS emissions, toxicity assessment, health impact, and marketing and regulation.

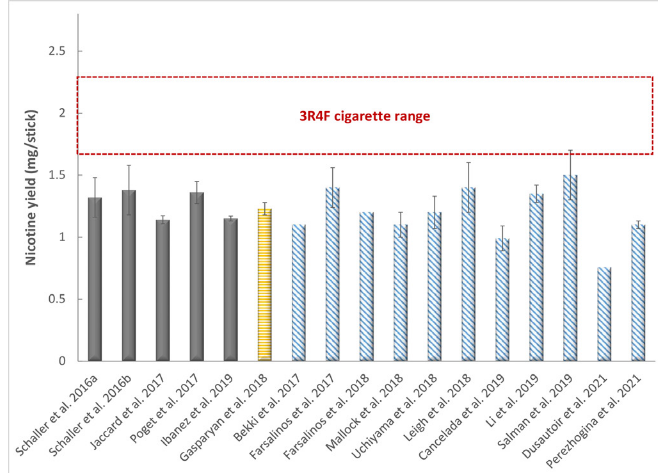

Figure 4 Nicotine yield in IQOS-R (regular tobacco flavour) aerosols generated under Health Canada Intense (HCI) regime. The dashed box represents the range of 3R4F cigarette smoke (1.70–2.26 mg/cigarette) obtained from data presented by five independent and five Philip Morris International (PMI)-sponsored studies. Filled columns represent data from PMI-sponsored research, horizontal stripes from a competing manufacturer and oblique stripes from independent research. The error bars are the SDs reported in the corresponding articles.

Of interest was the number of brief reports, reviews and opinion pieces published mainly by independent researchers (25%), suggesting a high interest and concern regarding this novel tobacco product.[105–109] A χ^2 test of independence showed a significant relationship between publication type and data source ($p<0.001$).

Figure 4 summarises data on nicotine yield from IQOS-R smoked under HCI puffing regime with no statistical difference between independent and PMI data ($p=0.36$). Data from a competing manufacturer also reported a similar nicotine yield.[110] Regardless of the data source, the averaged ratio of nicotine yield from IQOS-R was ~65% of 3R4F reference cigarette, which is representative of the most popular cigarettes in the US market. However, IQOS-R nicotine yield was similar to a 1R5F reference cigarette, which is designed to deliver lower nicotine yield.[111] Also, IQOS-M yielded the same nicotine level as IQOS-R under HCI conditions ($p=0.35$).

Online supplemental table S3 summarises data on nicotine, formaldehyde, acetaldehyde and acrolein emissions for all tested products under different puffing regimes. Under HCI conditions, data on the common carbonyls in IQOS-R aerosols showed no significant difference that could be attributed to affiliation or funding. However, both data sources showed higher emissions of furanic carbonyls in IQOS aerosols compared with 3R4F cigarettes, which could be attributed to the high concentration of sugar additives in IQOS HeatSticks (Talhout *et al*, unpublished data, 2021). Independent data highlighted the impact of puffing conditions on toxicant levels in IQOS aerosols when compared with combustible cigarettes with lower reductions in ISO conditions than in HCI, although PMI affiliates reported a robust reduction in carbonyls under different puffing conditions.[59 60] Independent research further highlighted the influence of cigarette comparator when assessing carbonyl reduction in IQOS

Table 3 Statistical analysis of the impact of puffing parameters and IQOS flavour on IQOS nicotine and carbonyl emissions

	Nicotine (mg/item)		Formaldehyde (µg/item)		Acetaldehyde (µg/item)		Acrolein (µg/item)	
Tobacco product	IQOS	Cigarette (3R4F)	IQOS	Cigarette (3R4F)	IQOS	Cigarette (3R4F)	IQOS	Cigarette (3R4F)
Puff duration (s)	0.35±0.07***	0.35±0.13*	3.00±1.85	3.86±16.70	−2.59±7.15	164.60±555.60	1.48±0.77	39.48±18.56
Number of puffs (/session)	0.06±0.02**	−0.01±0.02	0.35±0.51	−0.58 ±2.64	2.09±1.95	−9.51±87.90	0.44±0.22	0.00±2.90
Flow rate (L/min)	0.68±0.16***	2.10±0.20***	3.55±4.25	48.40±26.46	37.60±16.39*	1507.31±879.90	3.40±1.77	133.20±29.42**
IQOS flavour/cigarette type (categorical)		***		**	*			
Affiliation (categorical)	*			*	***			

Data on combustible cigarettes were analysed for comparison.
B (unstandardised regression coefficient)±SE, statistical significance at: *p<0.05; **p<0.01; ***p<0.001.

aerosol, as some carbonyls were higher in IQOS-R aerosols than in 1R5F or ultralight cigarette smoke.[47 49 54]

To assess the impact of puffing conditions on nicotine and carbonyl emissions, we combined and analysed data from independent and PMI studies.[9 36 41–58] Table 3 shows that puff duration, number of puffs and flow rate are significantly associated with IQOS nicotine emissions. In contrast, puff duration, flow rate and cigarette type were significantly associated with combustible cigarette nicotine emissions. This finding is in partial agreement with a recent study showing that puff volume and puff frequency significantly affected nicotine emissions from cigarettes and continuously heated HTPs like IQOS.[112] In terms of carbonyl emissions, in general, we found no significant correlations between puffing parameters and carbonyl emissions. IQOS flavour had a significant effect on acetaldehyde emissions while cigarette type affected formaldehyde emissions. Our group recently found a significant correlation between all puffing parameters and carbonyl emissions (El-Hellani *et al*, unpublished data). Data source had a significant effect on nicotine yield and acetaldehyde emissions from IQOS and formaldehyde emissions from cigarettes when different puffing conditions are considered.

Our statistical analysis highlighted the need to monitor IQOS emissions under different puffing regimes,[9 46 47 54] as there are no standard IQOS smoking regimes and the only puffing data collected from users were reported by PMI.[41 43] Moreover, PMI used the HCI regime in their studies which could lead to overestimated reductions, as HCI is considered an intense regime for cigarettes.[55] Independent research should compare IQOS to other cigarette comparators[49] and other available tobacco products before accepting reduced exposure or reduced risk claims.[57 84]

PMI and independent data agreed that IQOS emits nicotine efficiently,[45 55] while reducing exposure to certain HPHCs compared with combustible cigarettes.[9 41] However, PMI data showed increases in some emissions from IQOS aerosols compared with cigarette smoke as reported in the comprehensive chemical characterisation.[62] Notably, not all these emissions are listed in the FDA's HPHC list (n=93), which was recently criticised for its limited scope ignoring compounds with cardiovascular and pulmonary impact (eg, radicals and particles).[113] Moreover, an independent report reviewed the IQOS MRTP application and found that data on 53 of FDA's HPHC list were missing, of which 50 are carcinogens, while 56 other constituents with limited toxicity data (not in the FDA list) were higher in IQOS emissions (eg, up to 13 650% for 2-ethyl-5-methyl-1,4-dioxane) compared with 3R4F.[37] The authors noted that this selective reporting of data supports PMI's claim of reduced exposure to HPHCs.

Independent studies reported similar reductions to TSNAs, VOCs, PAHs and other emissions under HCI conditions, but sometimes lower reductions under ISO conditions or when compared with cigarettes other than 3R4F (eg, pyridine was higher by 264% compared with 1R5F). One study reported 400% higher glycidol in IQOS aerosols; glycidol was identified as a probable carcinogen by the International Agency for Research on Cancer and others suggested adding it to the FDA's HPHC list to highlight the toxicity of alternative tobacco products.[113] Another study reported emission of an IQOS-specific acute toxicant (formaldehyde cyanohydrin).[73] This result highlights the need for independent analysis of the complex matrix of the IQOS aerosol,[37] including non-targeted analysis to identify unknown constituents of toxicity potential.[71] It is important to note that reduced exposure to some HPHCs does not necessarily translate into reduced risk, as there could be different types of effects, varying potency (dose related) and varying severity of disease between different tobacco products.[114–116] Also, reduction in some emissions may be associated with increases in others, which complicates any head-to-head comparison of tobacco products.

Independent research, in contrast to PMI data, showed that particle emissions in indoor spaces do not return to baseline values soon after IQOS use termination, indicating that IQOS is an indoor air pollutant.[46 80 86] However, both data sources agreed that IQOS is a lesser indoor air pollutant compared with other sources of emissions like cigarettes, waterpipe, e-cigarettes, other HTPs, incense or mosquito coils.[84 89 90] Nevertheless, both sources showed emission levels higher than background levels of some constituents (eg, PM and acetaldehyde) that could negatively impact bystanders' health in the long term, urging independent researchers to call for restricting indoor IQOS use.[93]

Notably, in contrast to Accord, an HTP previously marketed by PMI, IQOS has been marketed as a safer alternative to cigarettes with reduced risk claims,[17] although IQOS increased users' exposure to several emissions compared with Accord (eg, catechol, formaldehyde and styrene). In July 2020, the US FDA authorised marketing IQOS as a reduced exposure (but not reduced risk) product based on data reported by PMI mainly in an industry-dominated journal.[11 29 117] Independent reports expressed concern about PMI's data[35 37 73 106 118] and scepticism about the net public health benefit of issuing this authorisation before independent evidence is available, especially given that such a label may impact harm perceptions in the population.[15 16 18 119] Moreover, PMI's MRTP application relies on smokers switching completely from cigarettes to IQOS (to be discussed in a follow-up report).[106 120–125] .[16 18]

A good public health approach should not rely only on data from the manufacturer to decide whether a new tobacco product has reduced risk potential.[14] One possible solution is to recruit a third party to replicate the data and ensure that harm reduction claims are valid.[21 113] Analysing data from both the manufacturer and independent researchers likely results in a more comprehensive and objective assessment of novel tobacco products. Procedural changes are needed to diminish the privileged position of the tobacco industry in regulation such as the current MRTP application mechanism in the USA.[126] Also, special care should be given to the language of risk communication related to any novel tobacco product.[127 128] To shorten the time between the introduction of a novel tobacco product into the market and building evidence-based regulation, a proactive approach might be to require a premarket notice of 1 or 2 years.[129] During this period, prototypes are made available for independent researchers to analyse emissions, toxicity and short-term health impact.

CONCLUSION

This review assessed the distribution of reported data on IQOS between PMI-affiliated or supported researchers and independent researchers. Comparable contributions on chemical analysis, toxicity assessment and health effects were highlighted; however, independent research dominated studies on IQOS use, marketing and regulation. Our analysis showed agreement between data sources on nicotine yield and reductions in some IQOS emissions compared with combustible cigarettes, while independent studies and examination of PMI's data showed increases in other emissions from and beyond the FDA's HPHC list.

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REFERENCES

1 CDC. Burden of cigarette use in the U.S, 2020. Available: https://www.cdc.gov/tobacco/campaign/tips/resources/data/cigarette-smoking-in-united-states.html#:~:text=Cigarette%20smoking%20kills%20more%20than,%24156%20billion%20in%20lost%20productivity
2 WHO. Tobacco, 2020. Available: https://www.who.int/news-room/fact-sheets/detail/tobacco
3 Brawley OW, Glynn TJ, Khuri FR, *et al*. The first surgeon General's report on smoking and health: the 50th anniversary. *CA Cancer J Clin* 2014;64:5–8.
4 Schroeder SA, Koh HK. Tobacco control 50 years after the 1964 surgeon General's report. *JAMA* 2014;311:141–3.
5 Blum A. Blowing Smoke: The Lost Legacy of the 1964 Surgeon General's Report on Smoking and Health, 2014. Available: https://www.cancernetwork.com/view/blowing-smoke-lost-legacy-1964-surgeon-generals-report-smoking-and-health
6 Lin S, Fonteno S, Weng J-H, *et al*. Comparison of the toxicity of smoke from conventional and harm reduction cigarettes using human embryonic stem cells. *Toxicol Sci* 2010;118:202–12.
7 Gendreau PL, Vitaro F. The unbearable lightness of "light" cigarettes: a comparison of smoke yields in six varieties of Canadian "light" cigarettes. *Can J Public Health* 2005;96:167–72.
8 Hoffman AC. The health effects of menthol cigarettes as compared to non-menthol cigarettes. *Tob Induc Dis* 2011;9 Suppl 1:S7.
9 Jaccard G, Tafin Djoko D, Moennikes O, *et al*. Comparative assessment of HPHC yields in the tobacco heating system THS2.2 and commercial cigarettes. *Regul Toxicol Pharmacol* 2017;90:1–8.
10 Martin F, Talikka M, Ivanov NV, *et al*. Evaluation of the tobacco heating system 2.2. Part 9: application of systems pharmacology to identify exposure response markers in peripheral blood of smokers switching to THS2.2. *Regul Toxicol Pharmacol* 2016;81 Suppl 2:S151–7.
11 Smith MR, Clark B, Lüdicke F, *et al*. Evaluation of the tobacco heating system 2.2. Part 1: description of the system and the scientific assessment program. *Regul Toxicol Pharmacol* 2016;81 Suppl 2:S17–26.
12 Brownell KD, Warner KE. The perils of ignoring history: big tobacco played dirty and millions died. How similar is big food? *Milbank Q* 2009;87:259–94.
13 Casswell S. Vested interests in addiction research and policy. why do we not see the corporate interests of the alcohol industry as clearly as we see those of the tobacco industry? *Addiction* 2013;108:680–5.
14 Capps B, van der Eijk Y, Krahn TM. Conflicts of interest in e-cigarette research: a public good and public interest perspective. *Bioethics* 2020;34:114–22.
15 Lempert LK, Glantz S. Analysis of FDA's IQOS marketing authorisation and its policy impacts. *Tob Control* 2021;30:413–21.
16 Lempert LK, Glantz SA. Heated tobacco product regulation under us law and the FCTC. *Tob Control* 2018;27:s118–25.
17 Elias J, Dutra LM, St Helen G, *et al*. Revolution or redux? assessing IQOS through a precursor product. *Tob Control* 2018;27:s102–10.
18 Lempert LK, Bialous S, Glantz S. Fda's reduced exposure marketing order for IQOS: why it is not a reliable global model. *Tob Control* 2022;31:e83–7.
19 Henningfield JE, Rose CA, Giovino GA. Brave new world of tobacco disease prevention: promoting dual tobacco-product use? *Am J Prev Med* 2002;23:226–8.
20 Zeller M, Hatsukami D, Strategic Dialogue on Tobacco Harm Reduction Group. The strategic dialogue on tobacco harm reduction: a vision and blueprint for action in the US. *Tob Control* 2009;18:324–32.
21 Berman ML, Connolly G, Cummings KM, *et al*. Providing a science base for the evaluation of tobacco products. *Tob Regul Sci* 2015;1:76–93.
22 Bero LA. Tobacco industry manipulation of research. *Public Health Rep* 2005;120:200–8.
23 Muggli ME, Forster JL, Hurt RD, *et al*. The smoke you don't see: uncovering tobacco industry scientific strategies aimed against environmental tobacco smoke policies. *Am J Public Health* 2001;91:1419–23.
24 Yano E. Japanese spousal smoking study revisited: how a tobacco industry funded paper reached erroneous conclusions. *Tob Control* 2005;14:227–33. discussion 33-5.
25 Neeley EE, Glantz SA. RJ Reynolds has not published a negative randomised clinical trial of camel Snus for smoking cessation. *Tob Control* 2017;26:357–8.
26 Neilsen K, Glantz SA. A tobacco industry study of airline cabin air quality: dropping inconvenient findings. *Tob Control* 2004;13 Suppl 1:i20–9.
27 Barnes DE, Bero LA. Industry-funded research and conflict of interest: an analysis of research sponsored by the tobacco industry through the center for indoor air research. *J Health Polit Policy Law* 1996;21:515–42.
28 Diethelm PA, Rielle J-C, McKee M. The whole truth and nothing but the truth? The research that Philip Morris did not want you to see. *Lancet* 2005;366:86–92.
29 Velicer C, St Helen G, Glantz SA. Tobacco papers and tobacco industry ties in regulatory toxicology and pharmacology. *J Public Health Policy* 2018;39:34–48.
30 Brandt AM. Inventing conflicts of interest: a history of tobacco industry tactics. *Am J Public Health* 2012;102:63–71.
31 Tong EK, Glantz SA. Tobacco industry efforts undermining evidence linking secondhand smoke with cardiovascular disease. *Circulation* 2007;116:1845–54.
32 van der Eijk Y, Bero LA, Malone RE. Philip Morris International-funded 'Foundation for a Smoke-Free World': analysing its claims of independence. *Tob Control* 2019;28:712–8.

33 Pisinger C, Godtfredsen N, Bender AM. A conflict of interest is strongly associated with tobacco industry-favourable results, indicating no harm of e-cigarettes. *Prev Med* 2019;119:124–31.
34 Parascandola M. Tobacco harm reduction and the evolution of nicotine dependence. *Am J Public Health* 2011;101:632–41.
35 Glantz SA. Heated tobacco products: the example of IQOS. *Tob Control* 2018;27:S1–6.
36 Auer R, Concha-Lozano N, Jacot-Sadowski I, *et al*. Heat-Not-Burn tobacco cigarettes: smoke by any other name. *JAMA Intern Med* 2017;177:1050–2.
37 Jacob Iii P, Jacob Iii P, Nardone N, *et al*. IQOS: examination of Philip Morris international's claim of reduced exposure. *Tob Control* 2018;27:s30–6.
38 Sturla SJ, Boobis AR, FitzGerald RE, *et al*. Systems toxicology: from basic research to risk assessment. *Chem Res Toxicol* 2014;27:314–29.
39 Simonavicius E, McNeill A, Shahab L, *et al*. Heat-not-burn tobacco products: a systematic literature review. *Tob Control* 2019;28:582–94.
40 Kopa PN, Pawliczak R. IQOS - a heat-not-burn (HnB) tobacco product - chemical composition and possible impact on oxidative stress and inflammatory response. A systematic review. *Toxicol Mech Methods* 2020;30:81–7.
41 Schaller J-P, Keller D, Poget L, *et al*. Evaluation of the tobacco heating system 2.2. Part 2: chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. *Regul Toxicol Pharmacol* 2016;81 Suppl 2:S27–47.
42 Schaller J-P, Pijnenburg JPM, Ajithkumar A, *et al*. Evaluation of the tobacco heating system 2.2. Part 3: influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the tobacco heating system 2.2 aerosol. *Regul Toxicol Pharmacol* 2016;81 Suppl 2:S48–58.
43 Poget L, Campelos P, Jeannet C, *et al*. Development of models for the estimation of mouth level exposure to aerosol constituents from a Heat-Not-Burn tobacco product using Mouthpiece analysis. *Beiträge zur Tabakforschung International/Contributions to Tobacco Research* 2017;27:42–64.
44 Ibañez MP, Martin D, Gonzálvez AG, *et al*. A comparative study of non-volatile compounds present in 3R4F cigarettes and iQOS Heatsticks utilizing GC-MS. *Am J Analyt Chem* 2019;10:76–85.
45 Farsalinos KE, Yannovits N, Sarri T, *et al*. Nicotine delivery to the aerosol of a Heat-Not-Burn tobacco product: comparison with a tobacco cigarette and e-cigarettes. *Nicotine Tob Res* 2018;20:1004–9.
46 Cancelada L, Sleiman M, Tang X, *et al*. Heated tobacco products: volatile emissions and their predicted impact on indoor air quality. *Environ Sci Technol* 2019;53:7866–76.
47 Salman R, Talih S, El-Hage R, *et al*. Free-Base and total nicotine, reactive oxygen species, and carbonyl emissions from IQOS, a heated tobacco product. *Nicotine Tob Res* 2019;21:1285–8.
48 Bitzer ZT, Goel R, Trushin N, *et al*. Free radical production and characterization of Heat-Not-Burn cigarettes in comparison to conventional and electronic cigarettes. *Chem Res Toxicol* 2020;33:1882–7.
49 Wang L, Liu X, Chen L, *et al*. Harmful chemicals of heat not burn product and its induced oxidative stress of macrophages at air-liquid interface: comparison with ultra-light cigarette. *Toxicol Lett* 2020;331:200–7.
50 Leigh NJ, Palumbo MN, Marino AM, *et al*. Tobacco-Specific nitrosamines (TSNA) in heated tobacco product IQOS. *Tob Control* 2018;27:S37–8.
51 Bekki K, Inaba Y, Uchiyama S, *et al*. Comparison of chemicals in mainstream smoke in Heat-not-burn tobacco and combustion cigarettes. *J Uoeh* 2017;39:201–7.
52 Farsalinos KE, Yannovits N, Sarri T, *et al*. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. *Addiction* 2018;113:2099–106.
53 Mallock N, Böss L, Burk R, *et al*. Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. *Arch Toxicol* 2018;92:2145–9.
54 Uchiyama S, Noguchi M, Takagi N, *et al*. Simple determination of gaseous and particulate compounds generated from heated tobacco products. *Chem Res Toxicol* 2018;31:585–93.
55 Li X, Luo Y, Jiang X, *et al*. Chemical analysis and simulated pyrolysis of tobacco heating system 2.2 compared to conventional cigarettes. *Nicotine Tob Res* 2019;21:111–8.
56 Meehan-Atrash J, Duell AK, McWhirter KJ, *et al*. Free-Base Nicotine Is Nearly Absent in Aerosol from IQOS Heat-Not-Burn Devices, As Determined by ^{1}H NMR Spectroscopy. *Chem Res Toxicol* 2019;32:974–6.
57 Dusautoir R, Zarcone G, Verriele M, *et al*. Comparison of the chemical composition of aerosols from heated tobacco products, electronic cigarettes and tobacco cigarettes and their toxic impacts on the human bronchial epithelial Beas-2B cells. *J Hazard Mater* 2021;401:123417.
58 Perezhogina TA, Gnuchikh EV, Faizullin RI, *et al*. Investigation of Volatile Organic Compounds and Benzo[a]pyrene Contents in the Aerosols of Cigarettes and IQOS Tobacco Heating System Using High-Performance Gas Chromatography/Mass Spectrometry. *Bionanoscience* 2021;11:939–45.
59 Belushkin M, Esposito M, Jaccard G, *et al*. Role of testing standards in smoke-free product assessments. *Regul Toxicol Pharmacol* 2018;98:1–8.
60 Goujon C, Kleinhans S, Maeder S, *et al*. Robustness of HPHC reduction for THS 2.2 aerosol compared with 3R4f reference cigarette smoke under high intensity puffing conditions. *Contributions to Tobacco Nicotine Research* 2020;29:66–83.
61 Poget L, Goujon C, Kleinhans S, *et al*. Robustness of HPHC reduction in THS 2.2 aerosol relative to 3R4F reference cigarette smoke under extreme climatic conditions. *Contributions to Tobacco Nicotine Research* 2021;30:109–26.
62 Bentley MC, Almstetter M, Arndt D, *et al*. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. *Anal Bioanal Chem* 2020;412:2675–85.
63 Ticha J, Wright C. Rapid detection of toxic compounds in tobacco smoke condensates using high-resolution ^{1} H-nuclear magnetic resonance spectroscopy. *Analytical Methods* 2016;8:6388–97.
64 Bekki K, Uchiyama S, Inaba Y, *et al*. Analysis of furans and pyridines from new generation heated tobacco product in Japan. *Environ Health Prev Med* 2021;26:89.
65 Pratte P, Cosandey S, Goujon Ginglinger C. Investigation of solid particles in the mainstream aerosol of the tobacco heating system THS2.2 and mainstream smoke of a 3R4F reference cigarette. *Hum Exp Toxicol* 2017;36:1115–20.
66 Pratte P, Cosandey S, Goujon Ginglinger C. Innovative methodology based on the thermo-denuder principle for the detection of combustion-related solid particles or high boiling point droplets: application to 3R4F cigarette and the tobacco heating system THS 2.2. *J Aerosol Sci* 2018;120:52–61.
67 Kärkelä T, Ebinger J-C, Tapper U, *et al*. Investigation into the presence or absence of solid particles generated from thermal processes in the aerosol from an electrically heated tobacco product with and without filter elements. *Aerosol Air Qual Res* 2021;21:200667.
68 Cozzani V, Barontini F, McGrath T, *et al*. An experimental investigation into the operation of an electrically heated tobacco system. *Thermochim Acta* 2020;684:178475.
69 Jaccard G, Kondylis A, Gunduz I, *et al*. Investigation and comparison of the transfer of TSNA from tobacco to cigarette mainstream smoke and to the aerosol of a heated tobacco product, THS2.2. *Regul Toxicol Pharmacol* 2018;97:103–9.
70 Jaccard G, Djoko DT, Korneliou A, *et al*. Mainstream smoke constituents and *in vitro* toxicity comparative analysis of 3R4F and 1R6F reference cigarettes. *Toxicol Rep* 2019;6:222–31.
71 Hofer I, Gautier L, Sauteur EC, *et al*. A screening method by gas chromatography-mass spectrometry for the quantification of 24 aerosol constituents from Heat-Not-Burn tobacco products. *Beiträge zur Tabakforschung International* 2019;28:317–28.
72 Pacitto A, Stabile L, Scungio M, *et al*. Characterization of airborne particles emitted by an electrically heated tobacco smoking system. *Environ Pollut* 2018;240:248–54.
73 Davis B, Williams M, Talbot P. iQOS: evidence of pyrolysis and release of a toxicant from plastic. *Tob Control* 2019;28:34–41.
74 Chen X, Bailey PC, Yang C, *et al*. Targeted characterization of the chemical composition of juul systems aerosol and comparison with 3r4f reference cigarettes and iqos heat sticks. *Separations* 2021;8:168.
75 Ishizaki A, Kataoka H. A sensitive method for the determination of tobacco-specific nitrosamines in mainstream and sidestream smokes of combustion cigarettes and heated tobacco products by online in-tube solid-phase microextraction coupled with liquid chromatography-tandem mass spectrometry. *Anal Chim Acta* 2019;1075:98–105.
76 Shein M, Jeschke G. Comparison of free radical levels in the aerosol from conventional cigarettes, electronic cigarettes, and Heat-Not-Burn tobacco products. *Chem Res Toxicol* 2019;32:1289–98.
77 Mitova MI, Campelos PB, Goujon-Ginglinger CG, *et al*. Comparison of the impact of the tobacco heating system 2.2 and a cigarette on indoor air quality. *Regul Toxicol Pharmacol* 2016;80:91–101.
78 Mitova MI, Bielik N, Campelos PB, *et al*. Air quality assessment of the tobacco heating system 2.2 under simulated residential conditions. *Air Qual Atmos Health* 2019;12:807–23.
79 Mottier N, Tharin M, Cluse C, *et al*. Validation of selected analytical methods using accuracy profiles to assess the impact of a tobacco heating system on indoor air quality. *Talanta* 2016;158:165–78.
80 Meišutovič-Akhtarieva M, Prasauskas T, Čiužas D, *et al*. Impacts of exhaled aerosol from the usage of the tobacco heating system to indoor air quality: a chamber study. *Chemosphere* 2019;223:474–82.
81 Kaunelienė V, Meišutovič-Akhtarieva M, Prasauskas T, *et al*. Impact of using a tobacco heating system (THS) on indoor air quality in a nightclub. *Aerosol and Air Quality Research* 2019;19:1961–8.
82 Gómez Lueso M, Mitova MI, Mottier N, *et al*. Development and validation of a method for quantification of two tobacco-specific nitrosamines in indoor air. *J Chromatogr A* 2018;1580:90–9.
83 Mitova MI, Cluse C, Correia D, *et al*. Comprehensive air quality assessment of the tobacco heating system 2.2 under simulated indoor environments. *Atmosphere* 2021;12:989.
84 Kaunelienė V, Meišutovič-Akhtarieva M, Martuzevičius D. A review of the impacts of tobacco heating system on indoor air quality versus conventional pollution sources. *Chemosphere* 2018;206:568–78.
85 Protano C, Manigrasso M, Avino P, *et al*. Second-Hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system. *Ann Ig* 2016;28:109–12.

86 Protano C, Manigrasso M, Avino P, *et al*. Second-Hand smoke generated by combustion and electronic smoking devices used in real scenarios: ultrafine particle pollution and age-related dose assessment. *Environ Int* 2017;107:190–5.
87 Loupa G, Karali D, Rapsomanikis S. The trace of airborne particulate matter from smoking e-cigarette, tobacco heating system, conventional and hand-rolled cigarettes in a residential environment. *Air Qual Atmos Health* 2019;12:1449–57.
88 Savdie J, Canha N, Buitrago N, *et al*. Passive exposure to pollutants from a new generation of cigarettes in real life scenarios. *Int J Environ Res Public Health* 2020;17:3455.
89 Gallart-Mateu D, Dhaouadi Z, de la Guardia M. Exposure of heat-not-burn tobacco effect on the quality of air and expiratory plume. *Microchemical Journal* 2021;170:106733.
90 Peruzzi M, Cavarretta E, Frati G, *et al*. Comparative indoor pollution from Glo, Iqos, and Juul, using traditional combustion cigarettes as benchmark: evidence from the randomized SUR-VAPES air trial. *Int J Environ Res Public Health* 2020;17:6029.
91 Protano C, Manigrasso M, Cammalleri V, *et al*. Impact of electronic alternatives to tobacco cigarettes on indoor air particular matter levels. *Int J Environ Res Public Health* 2020;17:2947.
92 Hirano T, Shobayashi T, Takei T, *et al*. Exposure assessment of environmental tobacco aerosol from heated tobacco products: nicotine and PM exposures under two limited conditions. *Int J Environ Res Public Health* 2020;17:8536.
93 Ruprecht AA, De Marco C, Saffari A, *et al*. Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products, and conventional cigarettes. *Aerosol Science and Technology* 2017;51:674–84.
94 Schober W, Fembacher L, Frenzen A, *et al*. Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (IQOS, e-cigarette) in passenger cars. *Int J Hyg Environ Health* 2019;222:486–93.
95 Koutela N, Fernández E, Saru M-L, *et al*. A comprehensive study on the leaching of metals from heated tobacco sticks and cigarettes in water and natural waters. *Sci Total Environ* 2020;714:136700.
96 Alberti S, Sotiropoulou M, Fernández E, *et al*. UV-254 degradation of nicotine in natural waters and leachates produced from cigarette butts and heat-not-burn tobacco products. *Environ Res* 2021;194:110695.
97 Bero LA, Glantz S, Hong M-K. The limits of competing interest disclosures. *Tob Control* 2005;14:118–26.
98 Hendlin YH, Vora M, Elias J, *et al*. Financial conflicts of interest and stance on tobacco harm reduction: a systematic review. *Am J Public Health* 2019;109:e1–8.
99 Chen-Sankey JC, Kechter A, Barrington-Trimis J, *et al*. Effect of a hypothetical modified risk tobacco product claim on heated tobacco product use intention and perceptions in young adults. *Tob Control* 2023;32:42–50.
100 Yang B, Massey ZB, Popova L. Effects of modified risk tobacco product claims on consumer comprehension and risk perceptions of IQOS. *Tob Control* 2021. doi:10.1136/tobaccocontrol-2020-056191. [Epub ahead of print: 09 Mar 2021].
101 Caputi TL, Leas E, Dredze M, *et al*. They're heating up: Internet search query trends reveal significant public interest in heat-not-burn tobacco products. *PLoS One* 2017;12:e0185735.
102 Stoklosa M, Cahn Z, Liber A, *et al*. Effect of IQOS introduction on cigarette sales: evidence of decline and replacement. *Tob Control* 2020;29:381–7.
103 Gottschlich A, Mus S, Monzon JC, *et al*. Cross-Sectional study on the awareness, susceptibility and use of heated tobacco products among adolescents in Guatemala City, Guatemala. *BMJ Open* 2020;10:e039792.
104 Edwards R. Lest we forget: Harm-Reduction research is important and increasing, but other facets of tobacco control research remain a high priority. *Nicotine Tob Res* 2018;20:145–6.
105 Bialous SA, Glantz SA. Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control. *Tob Control* 2018;27:s111–7.
106 Gilmore AB, Braznell S. Us regulator adds to confusion around heated tobacco products. *BMJ* 2020;370:m3528.
107 Churchill V, Weaver SR, Spears CA, *et al*. IQOS debut in the USA: Philip Morris international's heated tobacco device introduced in Atlanta, Georgia. *Tob Control* 2020;29:e152–4.
108 Ratajczak A, Jankowski P, Strus P, *et al*. Heat not burn tobacco Product—A new global trend: impact of Heat-Not-Burn tobacco products on public health, a systematic review. *Int J Environ Res Public Health* 2020;17:409.
109 Gale N, McEwan M, Eldridge AC, *et al*. Changes in biomarkers of exposure on switching from a conventional cigarette to tobacco heating products: a randomized, controlled study in healthy Japanese subjects. *Nicotine Tob Res* 2019;21:1220–7.
110 Gasparyan H, Mariner D, Wright C, *et al*. Accurate measurement of main aerosol constituents from heated tobacco products (HTPs): implications for a fundamentally different aerosol. *Regul Toxicol Pharmacol* 2018;99:131–41.
111 CORESTA. Reference products used in tobacco and smoke analyses, 2013. Available: https://www.coresta.org/sites/default/files/pages/tji0213-p150-154-refproducts.pdf
112 McAdam K, Davis P, Ashmore L, *et al*. Influence of machine-based puffing parameters on aerosol and smoke emissions from next generation nicotine inhalation products. *Regul Toxicol Pharmacol* 2019;101:156–65.
113 Institute of Medicine. *Governance and conduct of studies. scientific standards for studies on modified risk tobacco products*. Washington, DC: The National Academies Press, 2012.
114 Mallock N, Pieper E, Hutzler C, *et al*. Heated tobacco products: a review of current knowledge and initial assessments. *Front Public Health* 2019;7:287.
115 Slob W, Soeteman-Hernández LG, Bil W, *et al*. A method for comparing the impact on carcinogenicity of tobacco products: a case study on heated tobacco versus cigarettes. *Risk Anal* 2020;40:1355–66.
116 Max WB, Sung H-Y, Lightwood J, *et al*. Modelling the impact of a new tobacco product: review of Philip Morris international's population health impact model as applied to the IQOS heated tobacco product. *Tob Control* 2018;27:s82–6.
117 Roulet S, Chrea C, Kanitscheider C, *et al*. Potential predictors of adoption of the tobacco heating system by U.S. adult smokers: an actual use study. *F1000Res* 2019;8:214.
118 Lachenmeier DW, Anderson P, Rehm J. Heat-Not-Burn tobacco products: the devil in disguise or a considerable risk reduction? *Int J Alcohol Drug Res* 2018;7:8–11.
119 McKelvey K, Popova L, Kim M, *et al*. Heated tobacco products likely appeal to adolescents and young adults. *Tob Control* 2018;27:s41–7.
120 Lüdicke F, Picavet P, Baker G, *et al*. Effects of switching to the tobacco heating system 2.2 menthol, smoking abstinence, or continued cigarette smoking on biomarkers of exposure: a randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (Part 1). *Nicotine Tob Res* 2018;20:161–72.
121 Haziza C, de La Bourdonnaye G, Donelli A, *et al*. Reduction in exposure to selected harmful and potentially harmful constituents approaching those observed upon smoking abstinence in smokers switching to the menthol tobacco heating system 2.2 for 3 months (Part 1). *Nicotine Tob Res* 2020;22:539–48.
122 McKelvey K, Popova L, Kim M, *et al*. IQOS labelling will mislead consumers. *Tob Control* 2018;27:s48–54.
123 Kang H, Cho S-I, S-i C. Heated tobacco product use among Korean adolescents. *Tob Control* 2020;29:466–8.
124 Hwang JH, Ryu DH, Park S-W. Heated tobacco products: cigarette complements, not substitutes. *Drug Alcohol Depend* 2019;204:107576.
125 TobaccoTactics. IQOS Use, "Switching" and "Quitting": The Evidence, 2020. Available: https://tobaccotactics.org/wiki/iqos-use-evidence/
126 Cook DM, Bero LA. Identifying carcinogens: the tobacco industry and regulatory politics in the United States. *Int J Health Serv* 2006;36:747–66.
127 Leone FT, Carlsen K-H, Chooljian D, *et al*. Recommendations for the appropriate structure, communication, and investigation of tobacco harm reduction claims. An official American thoracic Society policy statement. *Am J Respir Crit Care Med* 2018;198:e90–105.
128 Lindblom EN. How might manufacturers of e-cigarettes get new product and MRTP orders from FDA more quickly and easily? *Food and Drug Law Journal* 2018;73:624–41.
129 Sarles SE, Hensel EC, Robinson RJ. Surveillance of U.S. corporate filings provides a proactive approach to inform tobacco regulatory research strategy. *Int J Environ Res Public Health* 2021;18:3067.

Supporting Information

A Systematic Review on IQOS: Highlights on Literature Features and Chemical Analysis

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Table S1. Search strategies and outcomes for all databases (**first search on Nov 1st, 2020**, *updated search on Nov 8th, 2021*).

Database	Search Strategy	Outcome
Scopus	(ALL (“iqos”) OR ALL (“Heat-not-burn AND tobacco”) OR ALL (“tobacco” AND “heating” AND “system”) OR ALL (“heated” AND “tobacco” AND “product”)) AND NOT INDEX (medline) AND (LIMIT - TO (PUBYEAR, 2020) OR LIMIT-TO (PUBYEAR, 2019) OR LIMIT - TO (PUBYEAR, 2018) OR LIMIT - TO (PUBYEAR, 2017) OR LIMIT- TO (PUBYEAR, 2016) OR LIMIT - TO (PUBYEAR, 2015) OR LIMIT - TO (PUBYEAR, 2014) OR LIMIT- TO (PUBYEAR, 2013) OR LIMIT - TO (PUBYEAR, 2012) OR LIMIT - TO (PUBYEAR, 2011) OR LIMIT- TO (PUBYEAR, 2010)) AND (LIMIT- TO (LANGUAGE, “English”))	**2534 references exported** *1156 references exported*
PubMed	(((IQOS) OR (Heat-not-burn tobacco)) OR (Tobacco Heating System)) OR (Heated tobacco product) Limit: 2010-2020. Language filter: English.	**505 references exported** *216 references exported*
Web of Science	((ALL = (“IQOS” OR “Heat-not-Burn tobacco” OR “Tobacco Heating System” OR “Heated tobacco product”)) AND Language: (“English”) Period: 2010-2020.	**847 references exported** *222 references exported*

Table S2. Categorization of the collected literature according to study funding or author affiliation, the main topic covered, type of publication, and year of publication. The order was sorted according to funding/affiliation. The inserted table summarizes the codes we used for the different categories.

	Variables	Codes
F/A	Other manufacturers of HTP (BAT, JTI)	Other
	Philip Morris International	PMI
	Independent research	Ind
Topic	Chemical analysis	Chem
	Toxicity assessment	Tox
	Human health (Clinical/case report)	Health
	Perceptions & Awareness & Use & Prevalence	PAUP
	Marketing	Market
	Policy & regulation	Policy
Type of paper	Original Research article	Original
	Brief report/Research letter/case report	Brief
	Review	Rev
	Letter/Commentary/protocols/opinion/Industry watch	LCPOI

Title	DOI/PMID/URL	Funding/Affiliation	Topic	Type	Year
A comparative study on changes in the use of heat-not-burn tobacco products based on whether apartment buildings have designated non-smoking areas	10.18332/TPC/136028	Ind	PAUP	Original	2021
Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name	10.1001/jamainternmed.2017.1419	Ind	Chem	LCPOI	2017

A Newly Developed Aerosol Exposure Apparatus for Heated Tobacco Products for In Vivo Experiments Can Deliver Both Particles and Gas Phase With High Recovery and Depicts the Time-Dependent Variation in Nicotine Metabolites in Mouse Urine	10.1093/ntr/ntab123	Ind	Tox	Original	2021
Heat-not-burn tobacco products are about to reach their boiling point	10.1136/tobaccocontrol-2016-053264	Ind	PAUP	LCPOI	2017
A sensitive method for the determination of tobacco-specific nitrosamines in mainstream and sidestream smokes of combustion cigarettes and heated tobacco products by online in-tube solid-phase microextraction coupled with liquid chromatography-tandem mass spectrometry	10.1016/j.aca.2019.04.073	Ind	Chem	Original	2019
A Simple Method to Simultaneously Determine the Level of Nicotine, Glycerol, Propylene Glycol, and Triacetin in Heated Tobacco Products by Gas Chromatography Flame Ionization Detection	10.1093/jaoacint/qsab140	Ind	Chem	Original	2021
A survey of users of the IQOS tobacco vaporizer: perceived dependence and perceived effects on cigarette withdrawal symptoms	10.1080/10550887.2020.1847994	Ind	PAUP	Original	2020
Acute effect of heat-not-burn versus standard cigarette smoking on arterial stiffness and wave reflections in young smokers	10.1177/2047487320918365	Ind	Health	Original	2021
Acute Effects of a Heat-Not-Burn Tobacco Product on Pulmonary Function	10.3390/medicina56060292	Ind	Health	Original	2020

Acute effects of a heat-not-burn tobacco product on pulmonary function of healthy non smokers	10.1183/13993003.congress-2019.OA3311	Ind	Health	Original	2019
Acute Effects of Heated Tobacco Product (IQOS) Aerosol Inhalation on Lung Tissue Damage and Inflammatory Changes in the Lungs	10.1093/ntr/ntaa267	Ind	Tox	Original	2021
Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 2 Randomized Trial	10.1161/jaha.118.010455	Ind	Health	Original	2019
Acute effects of JUUL and IQOS in cigarette smokers	10.1136/tobaccocontrol-2019-055475	Ind	Health	Brief	2020
Acute eosinophilic pneumonia following heat-not-burn cigarette smoking	10.1002/rcr2.190	Ind	Health	Brief	2016
Adolescent Use of and Susceptibility to Heated Tobacco Products	10.1542/peds.2020-049597	Ind	PAUP	Original	2021
Adult Smokers' Awareness and Interest in Trying Heated Tobacco Products: Perspectives from Mexico, where HTPs and E-Cigarettes are Banned	10.3390/ijerph17072173	Ind	PAUP	Original	2020
Age restriction and warnings for minor viewing and health risk in heated tobacco product videos on YouTube	10.1080/14659891.2020.1779832	Ind	Market	Original	2021
New Zealand's legal action against IQOS postponed, consultation with Big Tobacco follows	29121631	Ind	Policy	LCPOI	2017

An overview of iQOS® as a new heat-not-burn tobacco product and its potential effects on human health and the environment	10.4274/tjps.galenos.2018.79095	Ind	Health	Rev	2019
Analysis of FDA's IQOS marketing authorisation and its policy impacts	10.1136/tobaccocontrol-2019-055585	Ind	Policy	Original	2020
Analysis of furans and pyridines from new generation heated tobacco product in Japan	10.1186/s12199-021-01008-1	Ind	Chem	Original	2021
Analysis of presumed iqos influencer marketing on instagram in the Czech republic in 2018–2019	https://www.scopus.com/inward/record.uri?eid=2-s2.0-85073752127&partnerID=40&md5=114d21719b9f07133df47e928c43229b	Ind	Market	Original	2019
Are Heated Tobacco Product Users Less Likely to Quit than Cigarette Smokers? Findings from THINK (Tobacco and Health IN Korea) Study	10.3390/ijerph17228622	Ind	PAUP	Original	2020
Assessment of industry data on pulmonary and immunosuppressive effects of IQOS	10.1136/tobaccocontrol-2018-054296	Ind	Health	Original	2018

Assessment of IQOS Marketing Strategies at Points-of-Sale in Israel at a Time of Regulatory Transition	10.1093/ntr/ntab142	Ind	Market	Original	2021
Assessment of tobacco heating system 2.4 on osteogenic differentiation of mesenchymal stem cells and primary human osteoblasts compared to conventional cigarettes	10.4252/WJSC.V12.I8.841	Ind	Tox	Original	2020
Association of alcohol and drug use with use of electronic cigarettes and heat-not-burn tobacco products among Korean adolescents	10.1371/journal.pone.0220241	Ind	PAUP	Original	2019
Association of heated tobacco product use with smoking cessation in Chinese cigarette smokers in Hong Kong: a prospective study	10.1136/tobaccocontrol-2020-055857	Ind	PAUP	Original	2020
Awareness and Ever Use of "Heat-Not-Burn" Tobacco Products Among US Adults, 2017	10.1016/j.amepre.2018.04.031	Ind	PAUP	Brief	2018
Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA	10.1136/tobaccocontrol-2018-054654	Ind	PAUP	Original	2020
Awareness and perceived risk of heated tobacco products	10.18001/trs.6.1.2	Ind	PAUP	Original	2020
Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan	10.1111/add.13231	Ind	PAUP	Original	2016
Awareness and use of heated tobacco products among US adults, 2016-2017	10.1136/tobaccocontrol-2018-054323	Ind	PAUP	Original	2018

Awareness and Use of Heated Tobacco Products among Youth Smokers in Hong Kong: A Cross-Sectional Study	10.3390/ijerph17228575	Ind	PAUP	Original	2020
Awareness and Use of 'Heat-not-burn' Tobacco Products in Great Britain	10.18001/trs.4.2.4	Ind	PAUP	Original	2018
Awareness of Marketing of Heated Tobacco Products and Cigarettes and Support for Tobacco Marketing Restrictions in Japan: Findings from the 2018 International Tobacco Control (ITC) Japan Survey	10.3390/ijerph17228418	Ind	Market	Original	2020
Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults	10.1136/tobaccocontrol-2018-054390	Ind	PAUP	Brief	2018
Awareness, trial and use of heated tobacco products among adult cigarette smokers and e-cigarette users: findings from the 2018 ITC Four Country Smoking and Vaping Survey	10.1136/tobaccocontrol-2020-055985	Ind	PAUP	Original	2020
Beliefs about the Harmfulness of Heated Tobacco Products Compared with Combustible Cigarettes and Their Effectiveness for Smoking Cessation among Korean Adults	10.3390/ijerph17155591	Ind	PAUP	Original	2020
New Zealand's legal action against IQOS postponed, consultation with Big Tobacco follows: a response from the Ministry of Health	29240751	Ind	Policy	LCPOI	2017
Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette	10.1111/add.14365	Ind	Chem	Original	2018
Categorizing IQOS-Related Twitter Discussions	10.3390/ijerph18094836	Ind	Market	Original	2021

Changes in smoking habits and behaviors following the introduction and spread of heated tobacco products in Japan and its effect on FEV(1) decline: a longitudinal cohort study	10.2188/jea.JE20210075	Ind	PAUP	Original	2021
Characterization of airborne particles emitted by an electrically heated tobacco smoking system	10.1016/j.envpol.2018.04.137	Ind	Chem	Original	2018
Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes	10.1093/ntr/nty005	Ind	Chem	Original	2019
Cigarette smoke extract and heated tobacco products promote ferritin cleavage and iron accumulation in human corneal epithelial cells	10.1038/s41598-021-97956-3	Ind	Tox	Original	2021
Combustible cigarettes, heated tobacco products, combined product use, and periodontal disease: A cross-sectional JASTIS study	10.1371/journal.pone.0248989	Ind	PAUP	Original	2021
No Smoke-Just Cancer-Causing Chemicals	10.1001/jamainternmed.2017.1425	Ind	Chem	LCPOI	2017
Perplexing Conclusions Concerning Heat-Not-Burn Tobacco Cigarettes	10.1001/jamainternmed.2017.5843	Ind	Chem	LCPOI	2017
Comparative Indoor Pollution from Glo, Iqos, and Juul, Using Traditional Combustion Cigarettes as Benchmark: Evidence from the Randomized SUR-VAPES AIR Trial	10.3390/ijerph17176029	Ind	Chem	Original	2020

Comparing Factors Related to Any Conventional Cigarette Smokers, Exclusive New Alternative Product Users, and Non-Users among Japanese Youth: A Nationwide Survey	10.3390/ijerph17093128	Ind	PAUP	Original	2020
Comparing the Characteristics of Cigarette Smoking and e-Cigarette and IQOS Use among Adolescents in Taiwan	10.1155/2020/7391587	Ind	PAUP	Original	2020
Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes	10.7888/juoeh.39.201	Ind	Chem	Original	2017
Comparison of cytotoxicity of cigarette smoke extract derived from heat-not-burn and combustion cigarettes in human vascular endothelial cells	10.1016/j.jphs.2021.07.005	Ind	Tox	Original	2021
Comparison of cytotoxicity of IQOS aerosols to smoke from Marlboro Red and 3R4F reference cigarettes	10.1016/j.tiv.2019.104652	Ind	Tox	Original	2019
Comparison of End Tidal Carbon Monoxide Levels between Conventional Cigarette, Electronic Cigarette and Heated Tobacco Product among Asiatic Smokers	10.1080/10826084.2020.1781180	Ind	Health	Original	2020
Comparison of Free Radical Levels in the Aerosol from Conventional Cigarettes, Electronic Cigarettes, and Heat-Not-Burn Tobacco Products	10.1021/acs.chemrestox.9b00085	Ind	Chem	Original	2019
Comparison of IQOS (heated tobacco) and cigarette smoking on cardiac functions by two-dimensional speckle tracking echocardiography	10.1016/j.taap.2021.115575	Ind	Health	Original	2021

Comparison of the chemical composition of aerosols from heated tobacco products, electronic cigarettes and tobacco cigarettes and their toxic impacts on the human bronchial epithelial BEAS-2B cells	10.1016/j.jhazmat.2020.123417	Ind	Chem	Original	2021
Concurrent Daily and Non-Daily Use of Heated Tobacco Products with Combustible Cigarettes: Findings from the 2018 ITC Japan Survey	10.3390/ijerph17062098	Ind	PAUP	Original	2020
Correlates of Awareness and Use of Heated Tobacco Products in a Sample of US Young Adults in 2018-2019	10.1093/ntr/ntaa007	Ind	PAUP	Original	2020
Creating a market for IQOS: analysis of Philip Morris' strategy to introduce heated tobacco products to the Australian consumer market	10.1136/tobaccocontrol-2020-056057	Ind	Market	Original	2020
Criminal mercury vapor poisoning using heated tobacco product	10.1007/s00414-018-1923-4	Ind	Health	Brief	2019
Cross-sectional study on the awareness, susceptibility and use of heated tobacco products among adolescents in Guatemala City, Guatemala	10.1136/bmjopen-2020-039792	Ind	PAUP	Original	2020
Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells	10.1136/tobaccocontrol-2018-054317	Ind	Tox	Brief	2018
Development of a standardized new cigarette smoke generating (SNCSG) system for the assessment of chemicals in the smoke of new cigarette types (heat-not-burn (HNB) tobacco and electronic cigarettes (E-Cigs))	10.1016/j.envres.2020.109413	Ind	Chem	Original	2020

Differential effects of heat-not-burn and conventional cigarettes on coronary flow, myocardial and vascular function	10.1038/s41598-021-91245-9	Ind	Health	Original	2021
DNA methylation abnormalities and altered whole transcriptome profiles after switching from combustible tobacco smoking to heated tobacco products	10.1158/1055-9965.Epi-21-0444	Ind	Health	Original	2021
Do Young Adults Attend to Health Warnings in the First IQOS Advertisement in the US? An Eye-Tracking Approach	10.1093/ntr/ntaa243	Ind	Market	Original	2021
Early adoption of heated tobacco products resembles that of e-cigarettes	10.1136/tobaccocontrol-2020-056089	Ind	PAUP	Original	2021
E-cigarettes or heat-not-burn tobacco products - advantages or disadvantages for the lungs of smokers	10.5603/arm.2019.0020	Ind	Health	Rev	2019
Educational gradients in the use of electronic cigarettes and heat-not-burn tobacco products in Japan	10.1371/journal.pone.0191008	Ind	PAUP	Original	2018
Effect of a hypothetical modified risk tobacco product claim on heated tobacco product use intention and perceptions in young adults	10.1136/tobaccocontrol-2021-056479	Ind	PAUP	Original	2021
Effect of IQOS introduction on cigarette sales: evidence of decline and replacement	10.1136/tobaccocontrol-2019-054998	Ind	Market	Original	2020

Perplexing Conclusions Concerning Heat-Not-Burn Tobacco Cigarettes-Reply	10.1001/jamainternmed.2017.5861	Ind	Chem	LCPOI	2017
Effects of conventional and heated tobacco product smoking on discoloration of artificial denture teeth	10.1016/j.prosdent.2020.05.031	Ind	Tox	Original	2021
Effects of Exposure to Tobacco Cigarette, Electronic Cigarette and Heated Tobacco Product on Adipocyte Survival and Differentiation In Vitro	10.3390/toxics8010009	Ind	Tox	Original	2020
Effects of Fetal Exposure to Heat-Not-Burn Tobacco on Testicular Function in Male Offspring	10.1248/bpb.b20-00390	Ind	Tox	Original	2020
Effects of IQOS health warnings and modified risk claims among young adult cigarette smokers and non-smokers	10.1136/tobaccocontrol-2021-056810	Ind	PAUP	Brief	2021
Effects of modified risk tobacco product claims on consumer comprehension and risk perceptions of IQOS	10.1136/tobaccocontrol-2020-056191	Ind	PAUP	Original	2021
Effects of tobacco product type and characteristics on appeal and perceived harm: Results from a discrete choice experiment among Guatemalan adolescents	10.1016/j.ypmed.2021.106590	Ind	PAUP	Original	2021
Effects of visual exposure to iqos use on smoking urge and behavior	10.18001/TRS.7.1.3	Ind	PAUP	Original	2021
E-learning course improves knowledge in tobacco dependence, electronic nicotine delivery systems and heat-not-burn products in Medical School students	10.7417/ct.2021.2353	Ind	PAUP	Original	2021

Electronic, heat-not-burn, and combustible cigarette use among chronic disease patients in Japan: A cross-sectional study	10.18332/tid/94455	Ind	PAUP	Original	2018
Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products, and conventional cigarettes	10.1080/02786826.2017.1300231	Ind	Chem	Original	2017
Estimating the Carcinogenic Potency of Second-Hand Smoke and Aerosol from Cigarettes and Heated Tobacco Products	10.3390/ijerph17228319	Ind	Health	Original	2020
Evaluation of the Opinions of Family Physicians on Some Tobacco Products	10.1007/s10900-020-00872-2	Ind	PAUP	Original	2020
Evaluation of Tobacco Product-Selling Websites Accessed Using Search Engines	10.5152/TurkThoracJ.2019.190124	Ind	Market	Original	2020
Evolving IQOS packaging designs change perceptions of product appeal, uniqueness, quality and safety: a randomised experiment, 2018, USA	10.1136/tobaccocontrol-2018-054910	Ind	PAUP	Brief	2019
Examining perceptions about IQOS heated tobacco product: consumer studies in Japan and Switzerland	10.1136/tobaccocontrol-2018-054322	Ind	PAUP	Original	2018
Exhaled Carbon Monoxide Levels in Forty Resistant to Cessation Male Smokers after Six Months of Full Switch to Electronic Cigarettes (e-Cigs) or to A Tobacco Heating Systems (THS)	10.3390/ijerph16203916	Ind	Health	Original	2019

Exposure Assessment of Environmental Tobacco Aerosol from Heated Tobacco Products: Nicotine and PM Exposures under Two Limited Conditions	10.3390/ijerph17228536	Ind	Chem	Original	2020
Exposure of heat-not-burn tobacco effect on the quality of air and expiratory plume	10.1016/j.microc.2021.106733	Ind	Chem	Original	2021
Health consequences of smoking - focusing on alternative smoking methods	10.5114/pja.2019.88291	Ind	Health	Rev	2019
Factors that influence smokers' and ex-smokers' use of IQOS: a qualitative study of IQOS users and ex-users in the UK	10.1136/tobaccocontrol-2019-055306	Ind	PAUP	Original	2021
FDA's reduced exposure marketing order for IQOS: Why it is not a reliable global model	10.1136/tobaccocontrol-2020-056316	Ind	Policy	Original	2021
Free Radical Production and Characterization of Heat-Not-Burn Cigarettes in Comparison to Conventional and Electronic Cigarettes	10.1021/acs.chemrestox.0c00088	Ind	Chem	Original	2020
Free-Base and Total Nicotine, Reactive Oxygen Species, and Carbonyl Emissions From IQOS, a Heated Tobacco Product	10.1093/ntr/nty235	Ind	Chem	Original	2019
Free-Base Nicotine Is Nearly Absent in Aerosol from IQOS Heat-Not-Burn Devices, As Determined by H-1 NMR Spectroscopy	10.1021/acs.chemrestox.9b00076	Ind	Chem	Original	2019
Gendered factors for heated tobacco product use: Focus group interviews with Korean adults	10.18332/TID/120103	Ind	PAUP	Original	2020

Google shopping queries for vaping products, JUUL and IQOS during the E-cigarette, or Vaping, product use Associated Lung Injury (EVALI) outbreak	10.1136/tobaccocontrol-2021-056481	Ind	PAUP	Brief	2021
Harm Perceptions and Beliefs about Potential Modified Risk Tobacco Products	10.3390/ijerph18020576	Ind	PAUP	Original	2021
Harmful chemicals of heat not burn product and its induced oxidative stress of macrophages at air-liquid interface: Comparison with ultra-light cigarette	10.1016/j.toxlet.2020.06.017	Ind	Chem	Original	2020
Heated Tobacco Products: A Review of Current Knowledge and Initial Assessments	10.3389/fpubh.2019.00287	Ind	Health	Rev	2019
Health outcomes in COPD smokers using heated tobacco products: a 3-year follow-up	10.1007/s11739-021-02674-3	Ind	Health	Original	2021
Heat-not-burn tobacco products: a systematic literature review	10.1136/tobaccocontrol-2018-054419	Ind	Chem	Rev	2019
Heat not burn tobacco promotion on instagram	10.1016/j.addbeh.2018.09.003	Ind	Market	Original	2019
Heated debates on regulations of heated tobacco products in South Korea: the news valence, source and framing of relative risk/benefit	10.1136/tobaccocontrol-2020-056131	Ind	Policy	Original	2021

Heated Tobacco Product Awareness, Use, and Perceptions in a Sample of Young Adults in the United States	10.1093/ntr/ntab058	Ind	PAUP	Brief	2021
Heated tobacco product marketing: internet platforms undermine regulations	10.1183/13993003.congress-2019.PA1693	Ind	Market	Original	2019
Heated tobacco product regulation under US law and the FCTC	10.1136/tobaccocontrol-2018-054560	Ind	Policy	Original	2018
Heated tobacco product smokers in Japan identified by a population-based survey	10.2188/jea.JE20190199	Ind	PAUP	Original	2019
Heated tobacco product use among Korean adolescents	10.1136/tobaccocontrol-2019-054949	Ind	PAUP	Brief	2020
Heated tobacco product use among US adolescents in 2019: The new tobacco risk	10.18332/tpc/130502	Ind	PAUP	Original	2021
Heated tobacco product use and associated factors among U.S. youth, 2019	10.1016/j.drugalcdep.2020.108150	Ind	PAUP	Original	2020
Heated tobacco product use and its relationship to quitting combustible cigarettes in Korean adults	10.1371/journal.pone.0251243	Ind	PAUP	Original	2021
Heated tobacco products and combusted cigarettes: comparing global prices and taxes	10.1136/tobaccocontrol-2018-054602	Ind	Policy	Brief	2019

Heated Tobacco Products and Nicotine Pouches: A Survey of People with Experience of Smoking and/or Vaping in the UK	10.3390/ijerph18168852	Ind	Health	Original	2021
A critical appraisal of the harm reduction argument for heat-not-burn tobacco products	10.26633/rpsp.2018.161	Ind	Policy	LCPOI	2018
Heated Tobacco Products Have Reached Younger or More Affluent People in Japan	10.2188/jea.JE20190260	Ind	PAUP	Original	2021
Heated tobacco products likely appeal to adolescents and young adults	10.1136/tobaccocontrol-2018-054596	Ind	PAUP	Original	2018
Heated tobacco products use in Chinese adults in Hong Kong: a population-based cross-sectional study	10.1136/tobaccocontrol-2018-054719	Ind	PAUP	Original	2020
Human Biomarker Exposure From Cigarettes Versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis	10.1093/ntr/ntz200	Ind	Health	Rev	2019
Carbon monoxide levels after inhalation from new generation heated tobacco products	10.1186/s12931-018-0867-z	Ind	Health	LCPOI	2018
Heated Tobacco Products: Awareness and Ever Use Among U.S. Adults	10.1016/j.amepre.2020.11.011	Ind	PAUP	Original	2021

Heated tobacco products: Cigarette complements, not substitutes	10.1016/j.drugalcdep.2019.107576	Ind	PAUP	Original	2019
Commentary on 'This could change everything'	10.1136/tobaccocontrol-2018-054451	Ind	Policy	LCPOI	2018
Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control	10.1136/tobaccocontrol-2018-054340	Ind	Policy	LCPOI	2018
Heated Tobacco Products: Volatile Emissions and Their Predicted Impact on Indoor Air Quality	10.1021/acs.est.9b02544	Ind	Chem	Original	2019
Heat-Not-Burn cigarette induces oxidative stress response in primary rat alveolar epithelial cells	10.1371/journal.pone.0242789	Ind	Tox	Original	2020
Heat-not-burn cigarettes induce fulminant acute eosinophilic pneumonia requiring extracorporeal membrane oxygenation	10.1016/j.rmcr.2018.12.002	Ind	Health	Brief	2019
Heat-not-burn tobacco (IQOS), oral fibroblasts and keratinocytes: cytotoxicity, morphological analysis, apoptosis and cellular cycle. An in vitro study	10.1111/jre.12888	Ind	Tox	Original	2021
Heated tobacco products: the example of IQOS	10.1136/tobaccocontrol-2018-054601	Ind	Health	LCPOI	2018

Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol	10.1136/tobaccocontrol-2017-053947	Ind	PAUP	Original	2018
Heat-not-burn Tobacco Products and the Increased Risk for Poly-tobacco Use	10.5993/ajhb.45.1.16	Ind	PAUP	Original	2021
Heated tobacco products: things we do and do not know	10.1136/tobaccocontrol-2018-054774	Ind	Health	LCPOI	2018
Heat-Not-Burn Tobacco Products Are Getting Hot in Italy	10.2188/jea.JE20180040	Ind	PAUP	LCPOI	2018
New ideas, old problems? Heated tobacco products - a systematic review	10.13075/ijomeh.1896.01433	Ind	Health	Rev	2019
Heat Not Burn Tobacco Product-A New Global Trend: Impact of Heat-Not-Burn Tobacco Products on Public Health, a Systematic Review	10.3390/ijerph17020409	Ind	PAUP	Rev	2020
Heat-not-burn tobacco products: concerns from the Italian experience	10.1136/tobaccocontrol-2017-054054	Ind	PAUP	Brief	2019
Heat-Not-Burn Tobacco Products: The Devil in Disguise or a Considerable Risk Reduction?	10.7895/ijadr.250	Ind	Tox	Original	2018
Heat-not-Burn Tobacco Products: Tobacco Industry Claims No Substitute for Science	10.1542/peds.2017-2383	Ind	Policy	LCPOI	2018

Heat-not-burn tobacco, electronic cigarettes, and combustible cigarette use among Japanese adolescents: a nationwide population survey 2017	10.1186/s12889-020-08916-x	Ind	PAUP	Original	2020
Heat-Not-Burn Tobacco Products: An Emerging Threat to Cardiovascular Health	10.1152/ajpheart.00708.2020	Ind	Health	Rev	2020
'I perceive it to be less harmful, I have no idea if it is or not:' a qualitative exploration of the harm perceptions of IQOS among adult users	10.1186/s12954-021-00490-8	Ind	PAUP	Original	2021
Immunotoxic mechanisms of cigarette smoke and heat-not-burn tobacco vapor on Jurkat T cell functions	10.1016/j.envpol.2020.115863	Ind	Tox	Original	2021
Impact of Electronic Alternatives to Tobacco Cigarettes on Indoor Air Particular Matter Levels	10.3390/ijerph17082947	Ind	Chem	Original	2020
Impact of exclusive e-cigarettes and heated tobacco products use on muco-ciliary clearance	10.1177/20406223211035267	Ind	Health	Original	2021
Impact of modified risk tobacco product claims on beliefs of US adults and adolescents	10.1136/tobaccocontrol-2018-054315	Ind	PAUP	Original	2018
Inferences beyond a claim: A typology of potential halo effects related to modified risk tobacco product claims	10.1136/tobaccocontrol-2019-055560	Ind	Market	Original	2021

Informing iQOS Regulations in the United States: A Synthesis of What We Know	10.1177/2158244019898823	Ind	Policy	Rev	2020
Investigation of Volatile Organic Compounds and Benzo a pyrene Contents in the Aerosols of Cigarettes and IQOS Tobacco Heating System Using High-Performance Gas Chromatography/Mass Spectrometry	10.1007/s12668-021-00898-3	Ind	Chem	Original	2021
IQOS ? a heat-not-burn (HnB) tobacco product ? chemical composition and possible impact on oxidative stress and inflammatory response. A systematic review	10.1080/15376516.2019.1669245	Ind	Chem	Rev	2020
IQOS campaign in Israel	10.1136/tobaccocontrol-2018-054619	Ind	Market	LCPOI	2018
Lest We Forget: Harm-Reduction Research is Important and Increasing, but Other Facets of Tobacco Control Research Remain a High Priority	10.1093/ntr/ntx260	Ind	Policy	LCPOI	2018
NEW ZEALAND COURT DISMISSES MINISTRY OF HEALTH CASE AGAINST 'HEAT-NOT-BURN' TOBACCO PRODUCTS, HIGHLIGHTING THE NEED TO FUTURE-PROOF TOBACCO CONTROL LAWS	10.1111/add.14376	Ind	Policy	LCPOI	2018
Philip Morris International introduces new heat-not-burn product, IQOS, in South Korea	10.1136/tobaccocontrol-2017-053965	Ind	Market	LCPOI	2018
IQOS labelling will mislead consumers	10.1136/tobaccocontrol-2018-054333	Ind	Market	Original	2018

Possible hepatotoxicity of IQOS	10.1136/tobaccocontrol-2018-054320	Ind	Tox	LCPOI	2018
IQOS marketing strategies in the USA before and after US FDA modified risk tobacco product authorisation	10.1136/tobaccocontrol-2021-056819	Ind	Market	Original	2021
IQOS point-of-sale marketing strategies in Israel: a pilot study	10.1186/s13584-018-0277-1	Ind	Market	Brief	2019
IQOS(TM) vs. e-Cigarette vs. Tobacco Cigarette: A Direct Comparison of Short-Term Effects after Overnight-Abstinence	10.3390/ijerph15122902	Ind	Health	Original	2018
iQOS: evidence of pyrolysis and release of a toxicant from plastic	10.1136/tobaccocontrol-2017-054104	Ind	Chem	Original	2019
IQOS: examination of Philip Morris International's claim of reduced exposure	10.1136/tobaccocontrol-2018-054321	Ind	Chem	Original	2018
Commentary on Gravely et al (2019): Beginning a new era of nicotine products-beyond the four national-level determinants of nicotine vaping products (NVPs) use	10.1111/add.14611	Ind	PAUP	LCPOI	2019
Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks	10.1007/s00204-018-2215-y	Ind	Chem	Original	2018

Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims	10.26633/rpsp.2018.161	Ind	Market	Original	2018
Marketing IQOS in a dark market	10.1136/tobaccocontrol-2017-054216	Ind	Market	Brief	2019
Mechanisms of toxicity and biomarkers of flavoring and flavor enhancing chemicals in emerging tobacco and non-tobacco products	10.1016/j.toxlet.2018.02.025	Ind	Tox	Original	2018
Modelling the impact of a new tobacco product: review of Philip Morris International's Population Health Impact Model as applied to the IQOS heated tobacco product	10.1136/tobaccocontrol-2018-054572	Ind	Health	Original	2018
Recent findings in the pharmacology of inhaled nicotine: Preclinical and clinical in vivo studies	10.1016/j.neuropharm.2020.108218	Ind	Tox	Rev	2020
New Tobacco and Tobacco-Related Products: Early Detection of Product Development, Marketing Strategies, and Consumer Interest	10.2196/publichealth.7359	Ind	Market	Original	2018
New tobacco products, old advertising strategies: point-of-sale advertising in Guatemala	10.1136/tobaccocontrol-2020-055681	Ind	Market	Brief	2020
IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette	10.1183/23120541.00159-2018	Ind	Tox	LCPOI	2019

Official statement of the Spanish society of pulmonology and thoracic surgery (SEPAR) on electronic cigarettes and IQOS®	10.1016/j.arbr.2019.04.007	Ind	Health	LCPOI	2019
PMI reduced-risk claims and upselling of IQOS via Reviti life insurance	10.1136/tobaccocontrol-2019-055145	Ind	Market	LCPOI	2019
News Media Presentations of Heated Tobacco Products (HTPs): A Content Analysis of Newspaper and Television News Coverage in South Korea	10.1080/10810730.2021.1931988	Ind	Market	Original	2021
Nicotine Delivery and User Ratings of IQOS Heated Tobacco System Compared With Cigarettes, Juul, and Refillable E-Cigarettes	10.1093/ntr/ntab094	Ind	PAUP	Original	2021
Nicotine Delivery to the Aerosol of a Heat-Not-Burn Tobacco Product: Comparison With a Tobacco Cigarette and E-Cigarettes	10.1093/ntr/ntx138	Ind	Chem	Original	2018
Point-of-sale marketing of heated tobacco products in Israel: cause for concern	10.1186/s13584-019-0316-6	Ind	Market	LCPOI	2019
Novel tobacco products including electronic cigarette and heated tobacco products increase risk of allergic rhinitis and asthma in adolescents: Analysis of Korean youth survey	10.1111/all.14212	Ind	Health	Original	2019
Occupational difference in use of heated tobacco products: a cross-sectional analysis of retail workers in Japan	10.1136/bmjopen-2021-049395	Ind	PAUP	Original	2021

There can be smoke without fire: warranted caution in promoting electronic cigarettes and heat not burn devices as a safer alternative to cigarette smoking	10.1183/23120541.00114-2019	Ind	Market	LCPOI	2019
Passive Exposure to Pollutants from a New Generation of Cigarettes in Real Life Scenarios	10.3390/ijerph17103455	Ind	Chem	Original	2020
Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (IQOS, e-cigarette) in passenger cars	10.1016/j.ijheh.2019.01.003	Ind	Chem	Original	2019
Perceived relative harm of heated tobacco products (IQOS), e-cigarettes, and cigarettes among adults in Canada: Findings from the ITC Project	10.18332/TID/127233	Ind	PAUP	Brief	2020
Perceptions of Harmfulness of Heated Tobacco Products Compared to Combustible Cigarettes among Adult Smokers in Japan: Findings from the 2018 ITC Japan Survey	10.3390/ijerph17072394	Ind	PAUP	Original	2020
Perceptions of heated tobacco products (HTPs) and intention to quit among adult tobacco users in Korea	10.2188/jea.JE20200213	Ind	PAUP	Original	2021
Perceptions of the IQOS Heated Tobacco Product on Twitter in the United States	10.3389/fcomm.2021.728604	Ind	PAUP	Original	2021
This should change everything: using the toxic profile of heat-not-burn products as a performance standard to phase out combustible cigarettes	10.1136/tobaccocontrol-2017-054219	Ind	Policy	LCPOI	2019

A Philip Morris advertisement for its heated tobacco product IQOS sets a troubling precedent	10.1136/tobaccocontrol-2019-055363	Ind	Market	LCPOI	2020
Effects of combustible tobacco smoking and novel tobacco products on oxidative stress: Different sides of the same coin?	10.1016/j.cotox.2020.05.001	Ind	Health	LCPOI	2020
Heated tobacco products for smoking cessation and reducing smoking prevalence	10.1002/14651858.CD013790	Ind	Health	LCPOI	2020
IQOS debut in the USA: Philip Morris International's heated tobacco device introduced in Atlanta, Georgia	10.1136/tobaccocontrol-2019-055488	Ind	Market	LCPOI	2020
IQOS is not an acronym: A call to researchers and journals	10.1136/tobaccocontrol-2019-055571	Ind	Market	LCPOI	2020
PMI's heated tobacco products marketing claims of reduced risk and reduced exposure may entice youth to try and continue using these products	10.1136/tobaccocontrol-2019-055318	Ind	PAUP	Original	2020
PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes	10.1136/tobaccocontrol-2018-054413	Ind	Health	Original	2018
Rapid increase in heated tobacco product (HTP) use from 2015 to 2019: from the Japan 'Society and New Tobacco' Internet Survey (JASTIS)	10.1136/tobaccocontrol-2020-055652	Ind	PAUP	LCPOI	2020

Study Profile: The Japan "Society and New Tobacco" Internet Survey (JASTIS): A Longitudinal Internet Cohort Study of Heat-Not-Burn Tobacco Products, Electronic Cigarettes, and Conventional Tobacco Products in Japan	10.2188/jea.JE20190317	Ind	PAUP	LCPOI	2020
Prevalence and predictors of heated tobacco product use and its relationship with attempts to quit cigarette smoking among Korean adolescents	10.1136/tobaccocontrol-2019-055114	Ind	PAUP	Original	2020
Prevalence and predictors of heated tobacco products use among male ever smokers: results from a Korean longitudinal study	10.1186/s12889-021-10344-4	Ind	PAUP	Original	2021
Prevalence of heated tobacco product use among adolescents in Taiwan	10.1371/journal.pone.0244218	Ind	PAUP	Original	2020
Prevalence, Use Behaviors, and Preferences among Users of Heated Tobacco Products: Findings from the 2018 ITC Japan Survey	10.3390/ijerph16234630	Ind	PAUP	Original	2019
Profiling the Acute Effects of Modified Risk Products: Evidence from the SUR-VAPES (Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking) Cluster Study	10.1007/s11883-020-0824-4	Ind	Health	Original	2020
Proximity of IQOS and JUUL points of sale to schools in Israel: a geospatial analysis	10.1136/tobaccocontrol-2021-056718	Ind	Market	Original	2021
The Ill Effects of IQOS on Airway Cells: Let's Not Get Burned All Over Again	10.1165/rcmb.2020-0094LE	Ind	Health	LCPOI	2020

Reasons for Regularly Using Heated Tobacco Products among Adult Current and Former Smokers in Japan: Finding from 2018 ITC Japan Survey	10.3390/ijerph17218030	Ind	PAUP	Original	2020
The Impact of Heated Tobacco Products on Smoking Cessation, Tobacco Use, and Tobacco Sales in South Korea	10.4082/kjfm.20.0140	Ind	PAUP	Rev	2020
Revolution or redux? Assessing IQOS through a precursor product	10.1136/tobaccocontrol-2018-054327	Ind	Market	Original	2018
Role of diabetes in lung injury from acute exposure to electronic cigarette, heated tobacco product, and combustible cigarette aerosols in an animal model	10.1371/journal.pone.0255876	Ind	Tox	Original	2021
Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system	10.7416/ai.2016.2089	Ind	Chem	Brief	2016
Second-hand smoke generated by combustion and electronic smoking devices used in real scenarios: Ultrafine particle pollution and age-related dose assessment	10.1016/j.envint.2017.07.014	Ind	Chem	Original	2017
Simple Determination of Gaseous and Particulate Compounds Generated from Heated Tobacco Products	10.1021/acs.chemrestox.8b00024	Ind	Chem	Original	2018
Smoking E-CigaRette and HEat-noT-burn products: validation of the SECRHET questionnaire	10.7417/ct.2019.2142	Ind	PAUP	Original	2019
Social Response to the FDA Authorization of Heated Tobacco Products (HTPs)	10.18001/trs.6.1.3	Ind	PAUP	Original	2020

The Public Health Standard in Action-Analysis of the US Food and Drug Administration's IQOS Review	10.1001/jamaoncol.2020.3316	Ind	Policy	LCPOI	2020
Subacute lung injury associated with heated tobacco products	10.18678/dtfd.896093	Ind	Health	Brief	2021
Targeted characterization of the chemical composition of juul systems aerosol and comparison with 3r4f reference cigarettes and iqos heat sticks	10.3390/separations8100168	Ind	Chem	Original	2021
The FCTC dilemma on heated tobacco products	10.1186/s12992-020-00596-x	Ind	Policy	Original	2020
The Frequency of Use and Harm Perception of Heated Tobacco Products (HTPs): The 2019 Cross-Sectional Survey among Medical Students from Poland	10.3390/ijerph18073381	Ind	PAUP	Original	2021
US regulator adds to confusion around heated tobacco products	10.1136/bmj.m3528	Ind	Policy	LCPOI	2020
The impact of heated tobacco products on arterial stiffness	10.1177/1358863x20943292	Ind	Health	Brief	2020
Exposure to Heated Tobacco Products and Adverse Health Effects, a Systematic Review	10.3390/ijerph18126651	Ind	Health	Rev	2021
Alternative tobacco products use and its impact on urologic health - will the lesser evil still be evil? A commentary and review of literature	10.5173/ceju.2021.0110	Ind	Health	LCPOI	2021

The Role of Novel (Tobacco) Products on Tobacco Control in Italy	10.3390/ijerph18041895	Ind	Policy	Original	2021
The trace of airborne particulate matter from smoking e-cigarette, tobacco heating system, conventional and hand-rolled cigarettes in a residential environment	10.1007/s11869-019-00760-2	Ind	Chem	Original	2019
The Use of Heated Tobacco Products is Associated with Asthma, Allergic Rhinitis, and Atopic Dermatitis in Korean Adolescents	10.1038/s41598-019-54102-4	Ind	Health	Original	2019
IQOS marketing in the US: The need to study the impact of FDA modified exposure authorization, marketing distribution channels, and potential targeting of consumers	10.3390/ijerph181910551	Ind	Market	LCPOI	2021
They're heating up: Internet search query trends reveal significant public interest in heat-not-burn tobacco products	10.1371/journal.pone.0185735	Ind	PAUP	Original	2017
Philip Morris International used the e-cigarette, or vaping, product use associated lung injury (EVALI) outbreak to market IQOS heated tobacco	10.1136/tobaccocontrol-2021-056661	Ind	Market	LCPOI	2021
Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS	10.1136/tobaccocontrol-2018-054318	Ind	Chem	Brief	2018
Toxic mechanisms of cigarette smoke and heat-not-burn tobacco vapor inhalation on rheumatoid arthritis	10.1016/j.scitotenv.2021.151097	Ind	Tox	Original	2021

Trends and Patterns of Tobacco and Nicotine Product Use Among Youth in Canada, England, and the United States From 2017 to 2019	10.1016/j.jadohealth.2021.02.011	Ind	PAUP	Original	2021
Trends in use of e-cigarette device types and heated tobacco products from 2016 to 2020 in England	10.1038/s41598-021-92617-x	Ind	PAUP	Original	2021
Unboxed: US Young Adult Tobacco Users' Responses to a New Heated Tobacco Product	10.3390/ijerph17218108	Ind	PAUP	Original	2020
Unburned Tobacco Cigarette Smoke Alters Rat Ultrastructural Lung Airways and DNA	10.1093/ntr/ntab108	Ind	Tox	Original	2021
PMI New Zealand conflates IQOS heated tobacco products with electronic nicotine delivery systems	10.1136/tobaccocontrol-2021-056964	Ind	Market	LCPOI	2021
USE AND AWARENESS OF HEATED TOBACCO PRODUCTS IN EUROPE	10.2188/jea.JE20200248	Ind	PAUP	Brief	2021
Use of heated tobacco products in smoke-free locations in Japan: The JASTIS 2019 study	10.1136/tobaccocontrol-2020-055951	Ind	PAUP	Original	2020
Use of heated tobacco products where their use is prohibited	10.1136/tobaccocontrol-2020-056398	Ind	PAUP	Original	2021
Use of Heated Tobacco Products within Indoor Spaces: Findings from the 2018 ITC Japan Survey	10.3390/ijerph16234862	Ind	PAUP	Original	2019

Use of Multiple Tobacco and Tobacco-Like Products Including Heated Tobacco and E-Cigarettes in Japan: A Cross-Sectional Assessment of the 2017 JASTIS Study	10.3390/ijerph17062161	Ind	PAUP	Original	2020
Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke	10.1136/tobaccocontrol-2018-054325	Ind	Tox	Original	2018
What Is Accounting for the Rapid Decline in Cigarette Sales in Japan?	10.3390/ijerph17103570	Ind	Market	Original	2020
Workplace smoke-free policies that allow heated tobacco products and electronic cigarettes use are associated with use of both these products and conventional tobacco smoking: the 2018 JASTIS study	10.1136/tobaccocontrol-2019-055465	Ind	PAUP	Original	2020
Young Adult Correlates of IQOS Curiosity, Interest, and Likelihood of Use	10.18001/trs.6.2.1	Ind	PAUP	Original	2020
A cross-category puffing topography, mouth level exposure and consumption study among Italian users of tobacco and nicotine products	10.1038/s41598-019-55410-5	Other	PAUP	Original	2020
Accurate measurement of main aerosol constituents from heated tobacco products (HTPs): Implications for a fundamentally different aerosol	10.1016/j.yrtph.2018.09.016	Other	Chem	Original	2018
Changes in Biomarkers of Exposure on Switching From a Conventional Cigarette to Tobacco Heating Products: A Randomized, Controlled Study in Healthy Japanese Subjects	10.1093/ntr/nty104	Other	Health	Original	2019
Comparative study of the effects of cigarette smoke versus next generation tobacco and nicotine product extracts on endothelial function	10.1016/j.redox.2021.102150	Other	Tox	Original	2021

Cross-sectional survey to assess tobacco and nicotine product use since the introduction of tobacco heating products in japan: Wave 1	10.18001/TRS.7.3.6	Other	PAUP	Original	2021
In vitro RNA-seq-based toxicogenomics assessment shows reduced biological efect of tobacco heating products when compared to cigarette smoke	10.1038/s41598-018-19627-0	Other	Tox	Original	2018
Results from a 2018 cross-sectional survey in Tokyo, Osaka and Sendai to assess tobacco and nicotine product usage after the introduction of heated tobacco products (HTPs) in Japan	10.1186/s12954-020-00374-3	Other	PAUP	Original	2020
Systematic review of biomarker findings from clinical studies of electronic cigarettes and heated tobacco products	10.1016/j.toxrep.2021.01.014	Other	Health	Rev	2021
The use of human induced pluripotent stem cells to screen for developmental toxicity potential indicates reduced potential for non-combusted products, when compared to cigarettes	10.1016/j.crtox.2020.11.001	Other	Tox	Original	2020
3-D Nasal Cultures: Systems Toxicological Assessment of a Candidate Modified-Risk Tobacco Product	10.14573/altex.1605041	PMI	Tox	Original	2017
A Comparative Study of Non-Volatile Compounds Present in 3R4F Cigarettes and iQOS Heatsticks Utilizing GC-MS	https://doi.org/10.4236/ajac.2019.103007	PMI	Chem	Original	2019
A comprehensive study on the leaching of metals from heated tobacco sticks and cigarettes in water and natural waters	10.1016/j.scitotenv.2020.136700	PMI	Chem	Original	2020

A Meta-Analysis of the Performance of a Blood-Based Exposure Response Gene Signature Across Clinical Studies on the Tobacco Heating System 2.2 (THS 2.2)	10.3389/fphar.2019.00198	PMI	Health	Original	2019
A review of the impacts of tobacco heating system on indoor air quality versus conventional pollution sources	10.1016/j.chemosphere.2018.05.039	PMI	Chem	Rev	2018
A Screening Method by Gas Chromatography-Mass Spectrometry for the Quantification of 24 Aerosol Constituents from Heat-Not-Burn Tobacco Products	10.2478/cttr-2019-0013	PMI	Chem	Original	2019
A six-month systems toxicology inhalation/cessation study in ApoE(- / -) mice to investigate cardiovascular and respiratory exposure effects of modified risk tobacco products, CHTP 1.2 and THS 2.2, compared with conventional cigarettes	10.1016/j.fct.2019.02.008	PMI	Tox	Original	2019
A systems toxicology approach for comparative assessment: Biological impact of an aerosol from a candidate modified-risk tobacco product and cigarette smoke on human organotypic bronchial epithelial cultures	10.1016/j.tiv.2016.11.009	PMI	Tox	Original	2017
Aerosol from a candidate modified risk tobacco product has reduced effects on chemotaxis and transendothelial migration compared to combustion of conventional cigarettes	10.1016/j.fct.2015.09.016	PMI	Tox	Original	2015
Aerosol from Tobacco Heating System 2.2 has reduced impact on mouse heart gene expression compared with cigarette smoke	10.1016/j.fct.2017.01.013	PMI	Tox	Original	2017
Air quality assessment of the Tobacco Heating System 2.2 under simulated residential conditions	10.1007/s11869-019-00697-6	PMI	Chem	Original	2019

An 8-Month Systems Toxicology Inhalation/Cessation Study in Apoe-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared With Conventional Cigarettes	10.1093/toxsci/kfv243	PMI	Tox	Original	2016
An experimental investigation into the operation of an electrically heated tobacco system	10.1016/j.tca.2019.178475	PMI	Chem	Original	2020
Analysis of chemical deposits on tooth enamel exposed to total particulate matter from cigarette smoke and tobacco heating system 2.2 aerosol by novel GC-MS deconvolution procedures	10.1016/j.jchromb.2020.122228	PMI	Chem	Original	2020
Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: A randomized controlled study in confinement	10.1016/j.yrtph.2016.09.014	PMI	Health	Original	2016
Biomarker of exposure level data set in smokers switching from conventional cigarettes to Tobacco Heating System 2.2, continuing smoking or abstaining from smoking for 5 days	10.1016/j.dib.2016.11.047	PMI	Health	Original	2017
Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes	10.1016/j.yrtph.2017.08.006	PMI	Chem	Original	2017
Comparative effects of a candidate modified-risk tobacco product Aerosol and cigarette smoke on human organotypic small airway cultures: a systems toxicology approach	10.1039/c7tx00152e	PMI	Tox	Original	2017

Comparative systems toxicology analysis of cigarette smoke and aerosol from a candidate modified risk tobacco product in organotypic human gingival epithelial cultures: A 3-day repeated exposure study	10.1016/j.fct.2016.12.027	PMI	Tox	Original	2017
Comparative systems toxicology assessment of the Tobacco Heating System 2.2 and reference cigarettes (3R4F), on human organotypic respiratory tissue cultures	10.1016/j.toxlet.2016.06.1588	PMI	Tox	Original	2016
Comparing the preclinical risk profile of inhalable candidate and potential candidate modified risk tobacco products: A bridging use case	10.1016/j.toxrep.2020.09.004	PMI	Health	Original	2020
Comparison of monoamine oxidase inhibition by cigarettes and modified risk tobacco products	10.1016/j.toxrep.2019.11.008	PMI	Tox	Original	2019
Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality	10.1016/j.yrtph.2016.06.005	PMI	Chem	Original	2016
Comparison of the Pharmacokinetics of Nicotine Following Single and Ad Libitum Use of a Tobacco Heating System or Combustible Cigarettes	10.1093/ntr/ntv220	PMI	Health	Original	2016
Comprehensive air quality assessment of the tobacco heating system 2.2 under simulated indoor environments	10.3390/atmos12080989	PMI	Chem	Original	2021
Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening	10.1007/s00216-020-02502-1	PMI	Chem	Original	2020

Crowd-Sourced Verification of Computational Methods and Data in Systems Toxicology: A Case Study with a Heat-Not-Burn Candidate Modified Risk Tobacco Product	10.1021/acs.chemrestox.6b00345	PMI	Tox	Original	2017
Determination of eight carbonyl compounds in aerosols trapped in phosphate buffer saline solutions to support in vitro assessment studies	10.1016/j.talanta.2018.02.048	PMI	Chem	Original	2018
Development and validation of a method for quantification of two tobacco-specific nitrosamines in indoor air	10.1016/j.chroma.2018.10.037	PMI	Chem	Original	2018
Development of Models for the Estimation of Mouth Level Exposure to Aerosol Constituents from a Heat-Not-Burn Tobacco Product Using Mouthpiece Analysis	10.1515/cttr-2017-0005	PMI	Chem	Original	2017
Effect of Switching to the Tobacco Heating System Versus Continued Cigarette Smoking on Chronic Generalized Periodontitis Treatment Outcome: Protocol for a Randomized Controlled Multicenter Study	10.2196/15350	PMI	Health	Original	2021
Effects of cigarette smoke and tobacco heating aerosol on color stability of dental enamel, dentin, and composite resin restorations	10.3290/j.qi.a41601	PMI	Health	Original	2019
Effects of cigarette smoke, cessation and switching to a candidate modified risk tobacco product on the liver in Apoe(-/-) mice - a systems toxicology analysis	10.3109/08958378.2016.1150368	PMI	Tox	Original	2016
Effects of Cigarette Smoke, Cessation, and Switching to Two Heat-Not-Burn Tobacco Products on Lung Lipid Metabolism in C57BL/6 and Apoe-/- Mice-An Integrative Systems Toxicology Analysis	10.1093/toxsci/kfv244	PMI	Tox	Original	2016

Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically Relevant Biomarkers to Assess a Candidate Modified Risk Tobacco Product: A Randomized Trial	10.1158/1055-9965.epi-18-0915	PMI	Health	Original	2019
Effects of Switching to the Menthol Tobacco Heating System 2.2, Smoking Abstinence, or Continued Cigarette Smoking on Clinically Relevant Risk Markers: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 2)	10.1093/ntr/ntx028	PMI	Health	Original	2018
Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 1)	10.1093/ntr/ntw287	PMI	Health	Original	2018
Estimating the population health impact of introducing a reduced-risk tobacco product into Japan. The effect of differing assumptions, and some comparisons with the U.S	10.1016/j.yrtph.2018.10.010	PMI	PAUP	Original	2018
Evaluation of Biological and Functional Changes in Healthy Smokers Switching to the Tobacco Heating System 2.2 Versus Continued Tobacco Smoking: Protocol for a Randomized, Controlled, Multicenter Study	10.2196/11294	PMI	Health	LCPOI	2018
Evaluation of the Tobacco Heating System 2.2 (THS2.2). Part 5: microRNA expression from a 90-day rat inhalation study indicates that exposure to THS2.2 aerosol causes reduced effects on lung tissue compared with cigarette smoke	10.1016/j.yrtph.2016.11.018	PMI	Tox	Original	2016
Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program	10.1016/j.yrtph.2016.07.006	PMI	Policy	Original	2016

Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol	10.1016/j.yrtph.2016.10.001	PMI	Chem	Original	2016
Evaluation of the Tobacco Heating System 2.2. Part 3: Influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the Tobacco Heating System 2.2 aerosol	10.1016/j.yrtph.2016.10.016	PMI	Chem	Original	2016
Evaluation of the Tobacco Heating System 2.2. Part 4: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects compared with cigarette smoke	10.1016/j.yrtph.2016.10.015	PMI	Tox	Original	2016
Evaluation of the Tobacco Heating System 2.2. Part 6: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of a mentholated version compared with mentholated and non-mentholated cigarette smoke	10.1016/j.yrtph.2016.11.004	PMI	Tox	Original	2016
Evaluation of the Tobacco Heating System 2.2. Part 7: Systems toxicological assessment of a mentholated version revealed reduced cellular and molecular exposure effects compared with mentholated and non-mentholated cigarette smoke	10.1016/j.yrtph.2016.11.001	PMI	Tox	Original	2016
Evaluation of the Tobacco Heating System 2.2. Part 8: 5-Day randomized reduced exposure clinical study in Poland	10.1016/j.yrtph.2016.11.003	PMI	Health	Original	2016
Evaluation of the tobacco heating system 2.2. Part 9: Application of systems pharmacology to identify exposure response markers in peripheral blood of smokers switching to THS2.2	10.1016/j.yrtph.2016.11.011	PMI	Health	Original	2016

Favorable Changes in Biomarkers of Potential Harm to Reduce the Adverse Health Effects of Smoking in Smokers Switching to the Menthol Tobacco Heating System 2.2 for 3 Months (Part 2)	10.1093/ntr/ntz084	PMI	Health	Original	2020
Household Surveys in the General Population and Web-Based Surveys in IQOS Users Registered at the Philip Morris International IQOS User Database: Protocols on the Use of Tobacco- and Nicotine-Containing Products in Germany, Italy, and the United Kingdom (Greater London), 2018-2020	10.2196/12061	PMI	PAUP	LCPOI	2019
Impact of switching to a heat-not-burn tobacco product on CYP1A2 activity	10.1016/j.toxrep.2020.10.017	PMI	Tox	Original	2020
Impact of using a tobacco heating system (THS) on indoor air quality in a nightclub	10.4209/aaqr.2019.04.0211	PMI	Chem	Original	2019
Impacts of exhaled aerosol from the usage of the tobacco heating system to indoor air quality: A chamber study	10.1016/j.chemosphere.2019.02.095	PMI	Chem	Original	2019
In Vitro Systems Toxicology Assessment of a Candidate Modified Risk Tobacco Product Shows Reduced Toxicity Compared to That of a Conventional Cigarette	10.1021/acs.chemrestox.5b00321	PMI	Tox	Original	2016
Innovative methodology based on the thermo-denuder principle for the detection of combustion-related solid particles or high boiling point droplets: Application to 3R4F cigarette and the Tobacco Heating System THS 2.2	10.1016/j.jaerosci.2017.12.011	PMI	Chem	Original	2018

Investigating a toxic risk (self-inflicted) the example of conventional and advanced studies of a novel Tobacco Heating System	10.1016/j.yrtph.2016.07.020	PMI	Tox	LCPOI	2016
Investigation and comparison of the transfer of TSNA from tobacco to cigarette mainstream smoke and to the aerosol of a heated tobacco product, THS2.2	10.1016/j.yrtph.2018.06.011	PMI	Chem	Original	2018
Investigation into the presence or absence of solid particles generated from thermal processes in the aerosol from an electrically heated tobacco product with and without filter elements	10.4209/AAQR.200667	PMI	Chem	Original	2021
Investigation of menthol content and transfer rates in cigarettes and Tobacco Heating System 2.2	10.1016/j.yrtph.2018.11.004	PMI	Chem	Original	2019
Investigation of solid particles in the mainstream aerosol of the Tobacco Heating System THS2.2 and mainstream smoke of a 3R4F reference cigarette	10.1177/0960327116681653	PMI	Chem	Original	2017
Lung Function in Users of a Smoke-Free Electronic Device With HeatSticks (iQOS) Versus Smokers of Conventional Cigarettes: Protocol for a Longitudinal Cohort Observational Study	10.2196/10006	PMI	Health	LCPOI	2018
Mainstream smoke constituents and in vitro toxicity comparative analysis of 3R4F and 1R6F reference cigarettes	10.1016/j.toxrep.2019.02.009	PMI	Chem	Original	2019
Mitochondrial Network and Biogenesis in Response to Short and Long-Term Exposure of Human BEAS-2B Cells to Aerosol Extracts from the Tobacco Heating System 2.2	10.33594/000000216	PMI	Tox	Original	2020

Impact of 6-Month Exposure to Aerosols From Potential Modified Risk Tobacco Products Relative to Cigarette Smoke on the Rodent Gastrointestinal Tract	10.3389/fmicb.2021.587745	PMI	Tox	Original	2021
Multi-omics systems toxicology study of mouse lung assessing the effects of aerosols from two heat-not-burn tobacco products and cigarette smoke	10.1016/j.csbj.2020.04.011	PMI	Tox	Original	2020
Nicotine pharmacokinetic profiles of the Tobacco Heating System 2.2, cigarettes and nicotine gum in Japanese smokers	10.1016/j.yrtph.2017.07.032	PMI	Health	Original	2017
Non-inferiority trial comparing cigarette consumption, adoption rates, acceptability, tolerability, and tobacco harm reduction potential in smokers switching to Heated Tobacco Products or electronic cigarettes: Study protocol for a randomized controlled trial	10.1016/j.conctc.2020.100518	PMI	PAUP	Original	2020
Perplexing Conclusions Concerning Heat-Not-Burn Tobacco Cigarettes	10.1001/jamainternmed.2017.5840	PMI	Chem	LCPOI	2017
Potential predictors of adoption of the Tobacco Heating System by U.S. adult smokers: An actual use study	10.12688/f1000research.17606.1	PMI	PAUP	Original	2019
Reduced Chronic Toxicity and Carcinogenicity in A/J Mice in Response to Life-Time Exposure to Aerosol from a Heated Tobacco Product Compared with Cigarette Smoke	10.1093/toxsci/kfaa131	PMI	Tox	Original	2020
Reduced Exposure to Harmful and Potentially Harmful Smoke Constituents With the Tobacco Heating System 2.1	10.1093/ntr/ntw164	PMI	Health	Original	2017

Reduction in Exposure to Selected Harmful and Potentially Harmful Constituents Approaching Those Observed Upon Smoking Abstinence in Smokers Switching to the Menthol Tobacco Heating System 2.2 for 3 Months (Part 1)	10.1093/ntr/ntz013	PMI	Health	Original	2020
Respiratory effects of exposure to aerosol from the candidate modified-risk tobacco product THS 2.2 in an 18-month systems toxicology study with A/J mice	10.1093/toxsci/kfaa132	PMI	Tox	Original	2020
Robustness of HPHC reduction for THS 2.2 aerosol compared with 3R4f reference cigarette smoke under high intensity puffing conditions	10.2478/cttr-2020-0008	PMI	Chem	Original	2020
Robustness of HPHC Reduction in THS 2.2 Aerosol Relative to 3R4F Reference Cigarette Smoke under Extreme Climatic Conditions	10.2478/cttr-2021-0008	PMI	Chem	Original	2021
Role of testing standards in smoke-free product assessments	10.1016/j.yrtph.2018.06.021	PMI	Chem	Original	2018
Structural, functional, and molecular impact on the cardiovascular system in ApoE(-/-) mice exposed to aerosol from candidate modified risk tobacco products, Carbon Heated Tobacco Product 1.2 and Tobacco Heating System 2.2, compared with cigarette smoke	10.1016/j.cbi.2019.108887	PMI	Tox	Original	2020
Systems Toxicology Assessment of the Biological Impact of a Candidate Modified Risk Tobacco Product on Human Organotypic Oral Epithelial Cultures	10.1021/acs.chemrestox.6b00174	PMI	Tox	Original	2016
Systems toxicology meta-analysis of in vitro assessment studies: biological impact of a candidate modified-risk tobacco product aerosol compared with cigarette smoke on human organotypic cultures of the aerodigestive tract	10.1039/c7tx00047b	PMI	Tox	Original	2017

Systems toxicology study reveals reduced impact of heated tobacco product aerosol extract relative to cigarette smoke on premature aging and exacerbation effects in aged aortic cells in vitro	10.1007/s00204-021-03123-y	PMI	Tox	Original	2021
Systems toxicology-based assessment of the candidate modified risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells	10.1016/j.tox.2015.11.007	PMI	Tox	Original	2016
The biological effects of long-term exposure of human bronchial epithelial cells to total particulate matter from a candidate modified-risk tobacco product	10.1016/j.tiv.2018.02.019	PMI	Tox	Original	2018
Tobacco Heating System 2.2 has a limited impact on DNA methylation of candidate enhancers in mouse lung compared with cigarette smoke	10.1016/j.fct.2018.11.020	PMI	Tox	Original	2019
Toxicological assessment of Tobacco Heating System 2.2: Findings from an independent peer review	10.1016/j.yrtph.2019.03.007	PMI	Tox	Original	2019
UV-254 degradation of nicotine in natural waters and leachates produced from cigarette butts and heat-not-burn tobacco products	10.1016/j.envres.2020.110695	PMI	Chem	Original	2021
Validation of selected analytical methods using accuracy profiles to assess the impact of a Tobacco Heating System on indoor air quality	10.1016/j.talanta.2016.05.022	PMI	Chem	Original	2016

Table S3. Yields of nicotine, formaldehyde, acetaldehyde, and acrolein in the aerosols of IQOS with different flavored sticks compared to smoke of tobacco cigarettes under a variety of puffing regimes.

Reference	Affiliation /funding	Puff Duration (sec)	Inter-Puff-Interval (sec)	Puff Volume (mL)	Item	Nicotine (mg/item)	Formaldehyde (ug/item)	Acetaldehyde (ug/item)	Acrolein (ug/item)
Schaller et al. 2016a	PMI		HCI		IQOS-R	1.32 ± 0.16	5.53 ± 0.69	219.00 ± 31.00	11.30 ± 2.36
			HCI		IQOS-M	1.21 ± 0.09	4.55 ± 0.25	205.00 ± 12.00	9.15 ± 0.43
			HCI		3R4F	1.89 ± 0.16	56.5 ± 12.1	1555.00 ± 184.00	154.00 ± 20.00
			ISO		IQOS-R	0.49 ± 0.08	1.85 ± 0.24	149.00 ± 10.00	4.89 ± 0.74
		2.4	25	60	IQOS-R	1.64 ± 0.22	4.62 ± 0.45	205.00 ± 10.00	10.63 ± 0.74
		2.4	25	80	IQOS-R	1.80 ± 0.41	5.34 ± 0.53	203.00 ± 12.00	10.74 ± 0.56
		4.5	22	110	IQOS-R	2.19 ± 0.43	7.73 ± 1.02	185.00 ± 20.00	12.90 ± 2.09
		2.4	30	40	IQOS-R	0.76 ± 0.19	2.07 ± 0.53	145.00 ± 11.00	5.18 ± 0.43
		2.4	30	80	IQOS-R	1.13 ± 0.11	3.12 ± 0.34	148.00 ± 14.00	5.07 ± 0.32
Schaller et al. 2016b	PMI		HCI		IQOS-R	1.38 ± 0.20	10.16 ± 10.08	211.00 ± 60.00	10.96 ± 5.16
			HCI		3R4F	1.88	88.90	1694.00	161.00
Jaccard et al. 2017	PMI		HCI		IQOS-R	1.14 ± 0.03	7.98 ± 0.50	217.00 ± 7.85	9.63 ± 0.70
			HCI		3R4F	1.86 ± 0.17	85.20 ± 16.70	1641.00 ±258.00	156.00 ± 25.40

Poget et al. 2017	PMI		HCI		IQOS-R	1.36 ± 0.09			
			ISO		IQOS-R	0.49 ± 0.04			
		2.4	25	60	IQOS-R	1.64 ± 0.10			
		2.4	25	80	IQOS-R	1.80 ± 0.19			
		4.5	22	110	IQOS-R	2.19 ± 0.20			
		2.4	30	40	IQOS-R	0.76 ± 0.09			
		2.4	30	80	IQOS-R	1.13 ± 0.05			
Ibanez et al. 2019	PMI		HCI		IQOS-R	1.15 ± 0.02			
			HCI		3R4F	2.26 ± 0.06			
Bentley et al. 2020	PMI		HCI		IQOS-R			313.00	5.20
			HCI		3R4F			1253.00	463.00
Gasparyan et al. 2018	BAT		HCI		IQOS-R	1.23 ± 0.05			
Auer et al. 2017	Ind		ISO		IQOS-R	0.30 ± 0.21	3.20 ± 2.70	133.00 ± 35.00	0.90 ± 0.60
			ISO		LSBL	0.36	4.30 ± 0.40	610.00	1.10
Bekki et al. 2017	Ind		HCI		IQOS-R	1.10			
			HCI		IQOS-M	1.20			
			HCI		1R5F	1.00			
			HCI		3R4F	1.70			
Farsalinos et al. 2018	Ind		HCI		IQOS-R	1.40 ± 0.16			
			HCI		IQOS-M	1.38 ± 0.11			
			HCI		Marlb	1.99 ± 0.20			
		4	30	55	IQOS-R	1.41 ± 0.08			
		4	30	55	IQOS-M	1.43 ± 0.13			
Farsalinos et al. 2018	Ind		HCI		IQOS-R	1.20	6.40 ± 1.80	144.10 ± 23.30	10.80 ± 4.00
			HCI		IQOS-M	1.20	5.00 ± 1.40	176.70 ± 32.60	10.40 ± 1.90

			HCI		Marlb	1.80	67.20 ± 14.00	1062.20 ± 161.40	112.70 ± 14.20
		3	30	80	IQOS-R	1.30	9.10 ± 3.70	146.80 ± 22.30	8.10 ± 2.00
		3	30	80	IQOS-M	1.30	13.60 ± 5.30	187.80 ± 61.80	10.60 ± 6.10
		3	30	80	Marlb	2.10	74.40 ± 24.20	1372.90 ± 191.20	156.80 ± 32.10
		3	25	90	IQOS-R	1.60	17.10 ± 2.40	165.10 ± 10.50	10.40 ± 1.80
		3	25	90	IQOS-M	1.70	22.60 ± 4.80	187.10 ± 13.40	13.10 ± 1.20
		3	25	90	Marlb	2.40	71.40 ± 15.40	1212.60 ± 144.20	160.90 ± 19.30
Leigh et al. 2018	Ind		HCI		IQOS-R	1.40 ± 0.20			
			HCI		Marlb	2.10 ± 0.10			
Mallock et al. 2018	Ind		HCI		IQOS-R	1.10 ± 0.10	5.30 ± 0.40	179.40 ± 10.50	9.90 ± 1.20
			HCI		Min-Cig	1.07 ± 0.06	29.30 ± 3.80	930.00 ± 85.00	89.20 ± 7.30
			HCI		Max-Cig	2.70 ± 0.14	130.30 ± 10.80	1540.00 ± 153.00	154.10 ± 13.60
Uchiyama et al. 2018	Ind		HCI		IQOS-R	1.20 ± 0.13	4.80 ± 1.00	190.00 ± 16.00	7.30 ± 1.10
			HCI		IQOS-M	1.20 ± 0.03	6.20 ± 0.63	210.00 ± 5.10	8.20 ± 0.83
			HCI		IQOS-Mn	1.20 ± 0.17	6.00 ± 0.86	230.00 ± 9.90	8.30 ± 0.86
			HCI		1R5F	1.10 ± 0.17	25.00 ± 0.75	1300.00 ± 88.00	110.00 ± 6.80
			HCI		3R4F	2.1 ± 0.12	41.00 ± 2.70	1500.00 ± 19.00	130.00 ± 6.50

			HCI		CM6	2.60 ± 0.26	42.00 ± 4.00	1200.00 ± 12.00	100.00 ± 4.50
			ISO		IQOS-R	0.40 ± 0.07	3.40 ± 0.23	150.00 ± 7.00	4.00 ± 0.62
			ISO		IQOS-M	0.43 ± 0.08	2.60 ± 0.34	150.00 ± 8.30	3.90 ± 0.61
			ISO		IQOS-Mn	0.32 ± 0.11	3.00 ± 0.27	160.00 ± 7.90	3.70 ± 0.54
			ISO		1R5F	0.12 ± 0.04	5.10 ± 0.64	160.00 ± 15.00	11.00 ± 0.74
			ISO		3R4F	0.76 ± 0.01	16.00 ± 0.38	590.00 ± 29.00	45.00 ± 1.50
			ISO		CM6	1.20 ± 0.13	29.00 ± 2.40	680.00 ± 14.00	55.00 ± 0.69
Cancelada et al. 2019	Ind		HCI		IQOS-R	0.99 ± 0.10	2.52 ± 0.08	181.00 ± 31.00	5.40 ± 0.70
			HCI		IQOS-M	0.60 ± 0.14	2.33 ± 0.07	151.00 ± 26.00	4.90 ± 0.60
			HCI		IQOS-L	0.70 ± 0.06	2.31± 0.07	151.00 ± 26.00	5.30 ± 0.70
Li et al. 2019	Ind		HCI		IQOS-R	1.35 ± 0.07	8.84 ± 0.43	128.50 ± 9.96	4.01 ± 0.15
			HCI		3R4F	1.90	20.00	567.00	56.70
			ISO		IQOS-R	0.50 ± 0.03	21.87 ± 0.81	210.00 ± 21.71	6.37 ± 0.32
			ISO		3R4F	0.71	68.10	1534.00	155.00
Meehan-Atrash et al. 2019	Ind		HCI		IQOS-L	1.23 ± 0.24			
			HCI		Marlb	1.21 ± 0.15			
		55	30	3	IQOS-R	1.22 ± 0.12			
		55	30	3	Marlb	1.11 ± 0.08			
Salman et al. 2019	Ind		HCI		IQOS-R	1.50 ± 0.20	0.85 ± 0.28	301.46 ± 15.80	
			HCI		Marlb	1.80 ± 0.11	3.17 ± 0.33	1059.00 ± 9.03	

			ISO		IQOS-R	0.77 ± 0.06			
			ISO		Marlb	0.80 ± 0.05			
Bitzer et al. 2020	Ind	2.5	30	75	IQOS-R	1.47 ± 0.012			
		2.5	30	75	1R6F	2.08 ± 0.09			
Wang et al. 2020	Ind		ISO		IQOS-R	0.55 ± 0.01	8.80 ± 0.30	130.20 ± 4.60	4.30 ± 0.20
			ISO		Ultra-Lit	0.12 ± 0.01	4.20 ± 0.10	100.60 ± 4.50	8.50 ± 0.30
			ISO		3R4F	0.71 ± 0.01	20.00 ± 0.70	567.00 ± 10.00	56.70 ± 1.40
Dusautoir et al. 2021	Ind		HCI		IQOS-R	0.76	1.88 ± 0.11	320.25 ± 6.57	
			HCI		3R4F	0.95	2.55 ± 0.61	1663.45 ± 595.40	
Perezhogina et al. 2021	Ind		HCI		IQOS-R	1.1 ± 0.03			
			HCI		IQOS-M	0.99 ± 0.08			
			HCI		3R4F	1.66 ± 0.11			

PMI: Philip Morris International; Ind: independent research; HCI: Health Canada Intense puffing regime; ISO: International Organization for Standardization puffing regime; IQOS-R: regular tobacco flavor sticks; IQOS-M: menthol flavored sticks; IQOS-Mn: mint flavored sticks; IQOS-L: light or yellow sticks; LSBL: Lucky Strike blue light cigarette; Marlb: Marlboro regular cigarettes; Max-cig and Min-cig: the maximum and minimum yields of tobacco cigarettes as reported by Counts et al. (2005); Ultra-Lit: Ultra-light cigarette.

To: Editor in Chief

Re: A Systematic Review on IQOS that Accounts for Data Source: Analysis of Mainstream Emissions, Secondhand Emissions, and the Environmental Impact of IQOS waste

Dear Dr. Barnoya,

Kindly find below the "answers to comments" related to the revision of the manuscript entitled: "**A Systematic Review on IQOS that Accounts for Data Source: Analysis of Mainstream Emissions, Secondhand Emissions, and the Environmental Impact of IQOS waste**" (tobaccocontrol-2021-056986.R4) submitted on Mar 30, 2022.

Formatting Amendments (where applicable):

Reviewer(s)' Comments to Author (if any):

Editor(s)' Comments to Author (if any):

In the abstract and methods section, they need to revise the search date with the search years as they do not match. Search date was Nov 2021, but the years range from 2020 to 2022.

We thank the editor for this comment. The years range was changed in the Abstract and the Methods section to 2010-2021.