# 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 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.

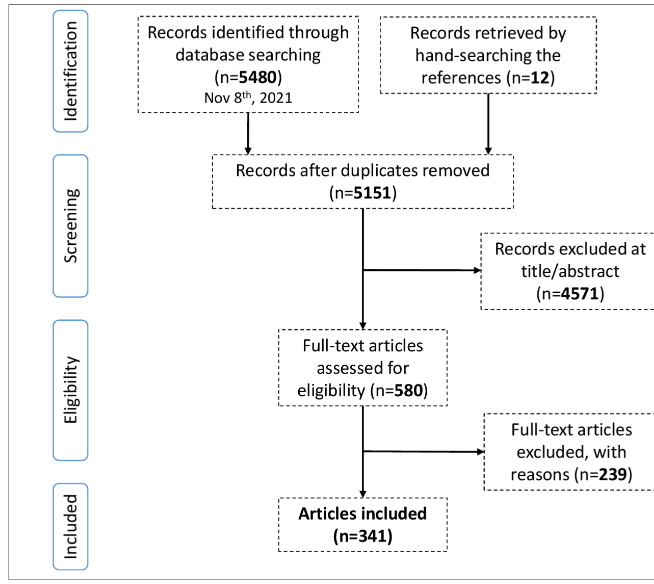


**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the systematic review. Reasons for exclusion of a publication: not peer reviewed, not related to heated tobacco products (HTPs), discusses HTP in general or focuses on HTPs other than IQOS (eg, Glo, Ploom) without testing IQOS for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

## 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%).

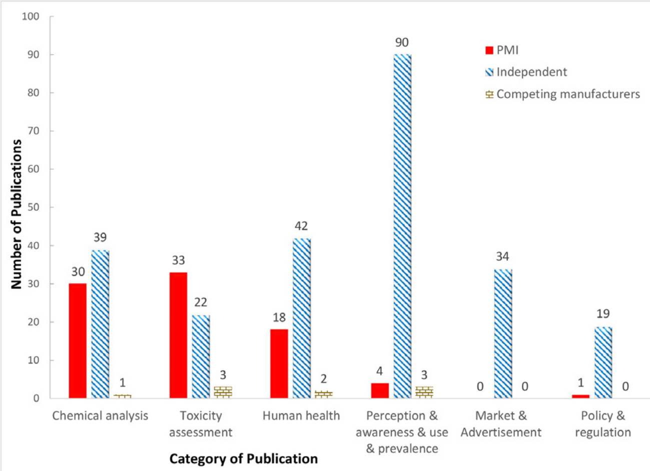


**Figure 2** Categorisation of publications on IQOS according to the main topic covered. This includes publications by Philip Morris International (PMI)-affiliated or sponsored researchers, independent researchers and researchers affiliated with or supported by competing manufacturers of heated tobacco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

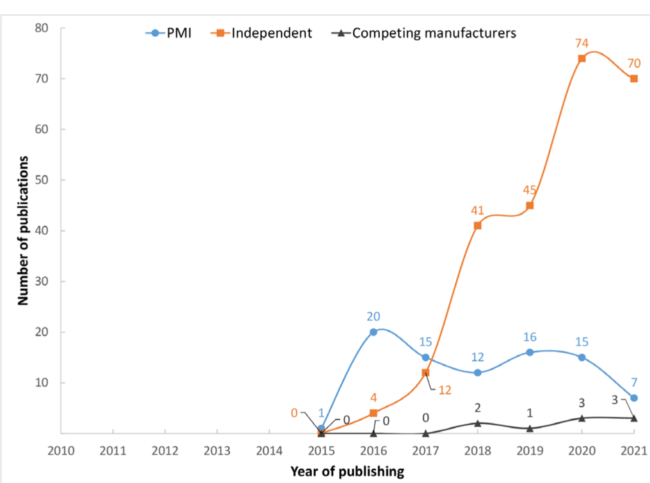


**Figure 3** The temporal distribution of publications on IQOS starts from its introduction into the global market in 2014 and extends to 2021. PMI, Philip Morris International.

**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

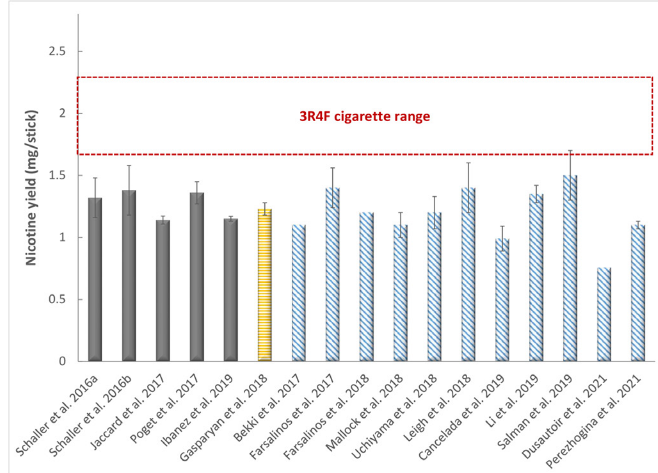


**Figure 4** Nicotine yield in IQOS-R (regular tobacco flavour) aerosols generated under Health Canada Intense (HCI) regime. The dashed box represents the range of 3R4F cigarette smoke (1.70–2.26 mg/cigarette) obtained from data presented by five independent and five Philip Morris International (PMI)-sponsored 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.

individual and public health,[104] so they reported comprehensively on IQOS emissions, toxicity assessment, health impact, and marketing and regulation.

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 $\chi^2$ 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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