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

Malak El-Kaassamani,[1] Miaoshan Yen,[2,3] Soha Talih ,[3,4] Ahmad El-Hellani [3,5,6]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/tobaccocontrol-2021-056986).

[1]Department of Chemistry, American University of Beirut Faculty of Arts and Sciences, Beirut, Lebanon
[2]Department of Biostatistics, Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA
[3]Center for the Study of Tobacco Products, Virginia Commonwealth University, Richmond, Virginia, USA
[4]Department of Mechanical Engineering, American University of Beirut Faculty of Engineering and Architecture, Beirut, Lebanon
[5]Division of Environmental Health Sciences, The Ohio State University College of Public Health, Columbus, Ohio, USA
[6]Center for Tobacco Research, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA

Correspondence to
Dr Ahmad El-Hellani, Division of Environmental Health Sciences, The Ohio State University College of Public Health, Columbus, OH 43210, USA; elhellani.1@osu.edu

Received 13 August 2021
Accepted 5 May 2022
Published Online First 13 May 2022

To cite: El-Kaassamani M, Yen M, Talih S, *et al*. *Tob Control* 2024;**33**:93–102.

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

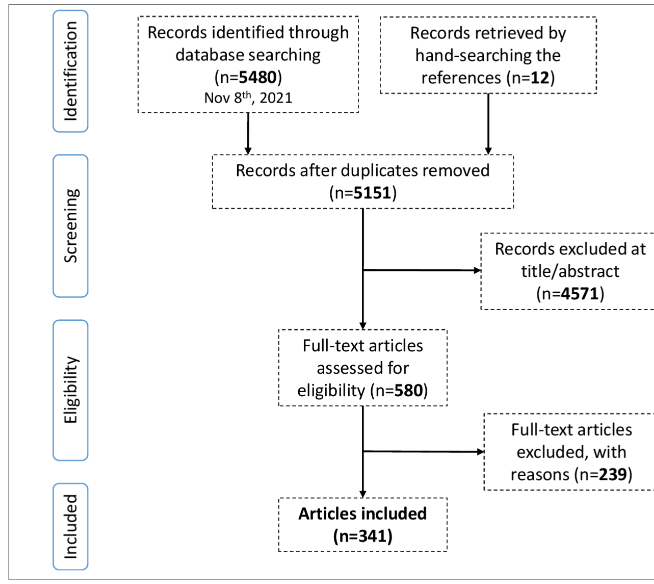

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the systematic review. Reasons for exclusion of a publication: not peer reviewed, not related to heated tobacco products (HTPs), discusses HTP in general or focuses on HTPs other than IQOS (eg, Glo, Ploom) 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%).

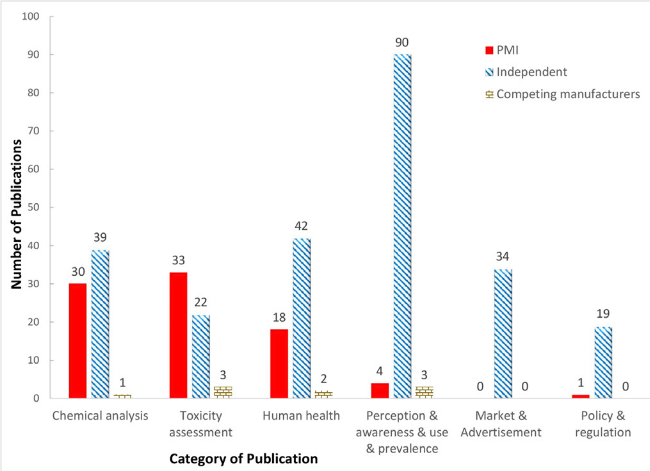

Figure 2 Categorisation of publications on IQOS according to the main topic covered. This includes publications by Philip Morris International (PMI)-affiliated or sponsored researchers, independent researchers and researchers affiliated with or supported by competing manufacturers of heated tobacco products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

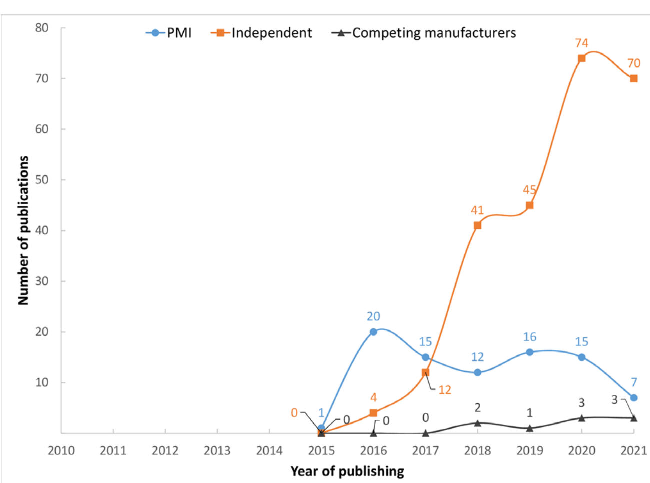

Figure 3 The temporal distribution of publications on IQOS starts from its introduction into the global market in 2014 and extends to 2021. PMI, Philip Morris International.

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

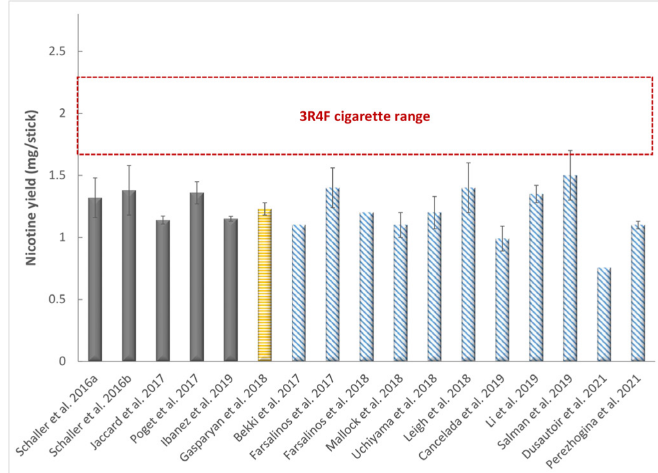

Figure 4 Nicotine yield in IQOS-R (regular tobacco flavour) aerosols generated under Health Canada Intense (HCI) regime. The dashed box represents the range of 3R4F cigarette smoke (1.70–2.26 mg/cigarette) obtained from data presented by five independent and five Philip Morris International (PMI)-sponsored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

Acknowledgements The authors thank the anonymous reviewers and the editor for their constructive comments and suggestions that made this manuscript more concise and informative.

Contributors AE-H conceived the study idea. AE-H and ME-K designed and conducted the literature search. ME-K and AE-H extracted and synthesised the data. AE-H wrote the first and final version of the manuscript. ST and MY performed the statistical analysis. All authors revised the manuscript and have approved its final version.

Funding This study was supported by a Rapid Response Project subaward under grant number U54DA036105 from the National Institute on Drug Abuse of the National Institutes of Health and the Center for Tobacco Products of the US Food and Drug Administration.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Soha Talih http://orcid.org/0000-0002-3520-675X
Ahmad El-Hellani http://orcid.org/0000-0002-1047-0597

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.