CONTENT OF HARMFUL AND POTENTIALLY HARMFUL SUBSTANCES IN CONVENTIONAL CIGARETTE SMOKE AND IN TOBACCO HEATING SYSTEM TSH 2.2. COMPARISON OF THE SCIENTIFIC RESULTS OF INDEPENDENT RESEARCH AND PHILIP MORRIS INTERNATIONAL

CONȚINUT DE SUBSTANȚE NOCIVE ȘI POTENCIAL NOCIVE ÎN FUMUL DE ȚIGĂRĂ CONVENȚIONALĂ ȘI ÎN SISTEMUL DE ÎNCĂLZIRE A TUUNULUI TSH 2.2. COMPARAȚIA REZULTATELOR ȘTIINȚIFICE ALE CERCETĂRII INDEPENDENTE ȘI PHILIP MORRIS INTERNATIONAL

Maria GONȚA, ORCID: 0000-0003-3476-0967
Viorica GLADCHI, ORCID: 0000-0002-5847-4466
Elena BUNDUCHI, ORCID: 0000-0003-2275-9918
Universitatea de Stat din Moldova, Chișinău

CZU: 613.84

e-mail maria.gonta@usm.md
e-mail viorica.gladchi@usm.md
e-mail elena.bunduchi@usm.md

In this paper, the content of harmful and potentially harmful constituents (HPHCs) in conventional cigarette smoke and in the Tobacco Heating System 2.2 (THS 2.2) product, developed by Philip Morris International (PMI) and marketed under the brand name IQOS (I Quit Ordinary Smoking), as well as for conventional 3R4F cigarettes, was examined using statistical data obtained from studies of scientific papers published between 2015 and 2022. Based on the analysis of the results presented by independent and industry-sponsored studies, it was found that the harmful and potentially harmful constituents (HPHC) are not entirely eliminated from the HTP aerosol, so these products are still not without risks for the population. The data obtained for all analyzed chemicals, with the exception of the substance with order number 30, N-nitrosoanabasine, support the theory put out in this study, according to at least one group or multiple groups of independent experts. In other words, in each individual case, at least one group of independent experts attests that the information provided by the company's experts about the concentrations of the analyzed compounds (at least for the maximum values obtained) in the aerosol stream emitted by an IQOS device is not diminished.

Keywords: *harmful and potentially harmful constituents, tobacco heating system*

INTRODUCTION

Heated tobacco products (HTP) are a relatively new category of tobacco products that were developed, as their manufacturers declare, as alternatives to conventional cigarettes because they would reduce the consumer's risk of illness as a result of inhaling fewer and smaller amounts of harmful substances.

There are extensive published reviews of heated tobacco products [1-7] that summarize studies on the health risks and composition of these products compared to conventional cigarettes.

The goal of this review was to evaluate the scientific evidence that is currently available regarding the qualitative and quantitative composition of THS aerosol (Philip Morris International (PMI) product) and cigarette smoke. Moreover, the study examined the levels of HPHCs from the PMI-58 list emitted by THS 2.2 devices, as measured by expert groups within the company, to ensure they are not lower than the levels established by independent expert groups (independent laboratories).

RESEARCH METHODOLOGY

In order to perform the meta-analysis of data on the content of HPHCs eliminated as a result of smoking regular cigarettes and those of the THS 2.2, a critical review of scientific publications in this field was carried out. The selection of scientific publications from open sources was carried out from the databases Scopus, Web of Science, Google Scholar, PubMed, MedLine, Embase, PsycINFO, ProQuest, CORE, Index Copernicus, SJR, and others.

Primarily, in the selection process, the titles and summaries of the papers that linked to the research theme were used. In cases where the material supplied was pertinent, whole scientific publications were printed and examined. Special attention was also paid to the bibliographic references cited in these papers, which served as an additional source of information. Likewise, information already available on the websites of PMI, Elsevier, Springer, and other sources that provide information on the use of THS 2.2 was analyzed. After the information was analyzed, only those scientific publications that are presented in English, are present in the pertinent international databases, have a DOI identification (Digital Object Identifier) and were published between January 1, 2015, and May 31, 2022, were chosen. There were removed duplicate papers, presentations at various conferences, brief summaries without analysis of primary data, collections of papers at various scientific events, papers presenting the findings of studies on the composition of the air in spaces where THS devices were used, papers analyzing the toxicological effects and dynamics of toxicological parameters over time, various particularities affecting health and various human organs as a result of smoking or using THS systems, pharmacokinetic studies and other studies related to the field of medicine. The meta-analysis did not use papers related to methodological peculiarities or in which imperfect research methods were applied. The search for bibliographic sources, analysis, and selection of scientific papers was carried out independently by three researchers. After analyzing the results, in cases of ambiguity or unclear expression, the final decision about accepting or rejecting scientific papers in future studies was taken collectively after discussions with arguments of particular opinions.

During the search of bibliographic sources, 261 papers were identified. After the primary screening of titles and abstracts, 43 of these papers were removed, and a further

25 papers or communications were subsequently removed during the second review. From the 193 eligible papers, 178 studies had been excluded for a variety of reasons. After analyzing the contents of the remaining papers for the meta-analysis, there remained 15 scientific papers analyzing the content of HPHCs in cigarette smoke and THS devices; this represents about 6% of the initial sources. Of these, 10 papers represent the results of independent studies, and 5 papers were published by members of research teams within PMI's scientific laboratories.

Independent studies were conducted in professional scientific labs in Japan (3 papers), China (2 papers), Germany, Finland, the USA, France, and Switzerland (each with one publication). The research initiated by PMI was carried out by scientists in Switzerland (5 papers).

RESULTS AND DISCUSSION

During the investigated period, 10 articles containing pertinent, independent experimental data were published regarding the HPHCs content of THS products, which represent the heat-not-burn (HNB) tobacco product that has been introduced to global markets. These data are compared with the values of harmful and potentially harmful substances provided by conventional 3R4F cigarettes (tab. 1).

Table 1

Analysis of data on the content of HPHCs presented by independent sources, compared to the PMI-58 list

Source	*Gideon St. Helen et al, 2018 [8]*	*Xiangyu Li et al, 2018 [18]*	*Mallock Nadja et al, 2018 [2]*	*Auer Reto et al, 2017 [9]*	*BekkiKanae et al, 2017 [12]*	*Shigehisa Uchiyama et al, 2018 [19]*	*Wang Liyun et al, 2020 [20]*	*Romain Dusautoir et al, 2020 [2020]*	*Bekki Kanae et al, 2021 [11]*	*Teemu Karkela et al, 2021 [10]*
Totally measured components	58	35	14	26	9	31	30	42	20	16
Detected components from the PMI-58 list	58	26	12	12	7	12	28	11	3	7
% of the PMI-58 list	100	45	21	21	12	21	48	19	5	12

The results presented in scientific articles are published in specialized journals – Tobacco Control (6.953 IF), Nicotine & Tobacco Research (5.825 IF), Archives of To-

xicology (5.153 IF), JAMA Intern. Medicine (44.424 IF), Journal of UOEH (0.90 IS), Chemical Research in Toxicology (3.973 IF), Toxicology Letters (4.271 IF), Journal of Hazardous Materials (14.224 IF), Environmental Science and Pollution Research (5.19 IF), and Environmental Health and Preventive Medicine.

All publications used Tobacco Heating System (THS2.2) products, marked under the brand IQOS and produced by Philip Morris International Inc., and reference cigarette 3R4F purchased from the University of Kentucky (USA). Both products were tested with the Health Canada Intense (HCI) puff regime. Chemical analysis of the aerosol emitted by THS2.2. and of the reference cigarette smoke 3R4F was carried out by applying methods using Comprehensive gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography coupled to a fluorescence detector, Gas chromatography (GC) coupled with a flame ionization detector (FID), Liquid chromatography-tandem mass spectrometry (LCMS/MS), FTIR spectroscopy and others. The concentrations of detected substances are expressed in mg/stick, µg/stick, or ng/stick.

The perfect analysis of the data found in these papers is challenging for a number of reasons, the most notable of which are as follows:

- the uneven distribution of the determined components. The number of determined components in general and the number of determined components included in the PMI-58 list vary significantly depending on the goals of each research project (tabs. 1, 2). The most complete compilation of information is presented in the source [8], which indicates the concentrations of 100% and 95% HPHCs, respectively, in the aerosol produced by THS2.2 and conventional cigarette smoke 3R4F, included in the PMI-58 list. Other studies analyze a much smaller number of substances from this list, which makes it difficult to compare the data and perform statistical analysis on them;
- the number of replicates of the analyses is different from one article to another, from one parameter to another within the same article [2, 9], or is not indicated [9, 10].

As a result, these factors degrade statistical processing quality and decrease the veracity of result comparisons.

Another peculiarity is the fact that in several independent scientific publications, several determined parameters are not included in the PMI-58 list. For example, in the source [11] only 5% of the detected components are found in the PMI-58 list, in the sources [10, 12] the share of these substances is 12%, and in the source [13] only 19% of detected substances are included in the list of PMI-58 components (tab. 1).

The analysis of the results presented in the five scientific papers published by scientists from PMI shows that all of the research presented was carried out by scientists at PMI's Center for Research & Development (R&D) located in Switzerland, and the data were obtained as part of that research related to the comparison of levels of hazardous and potentially harmful constituents (HPHC) found in PMI's THS aerosol with levels found in smoke from a reference cigarette, based on analyses by Labstat International ULC, an independent contract research organization [21]; chemical composition, genotoxicity, cytotoxicity, and physical properties of the THS aerosol [14]; comparative assessment

of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes [15]; an experimental investigation into the operation of an electrically THS [16]; comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening [17]. The analysis of data on the content of HPHCs presented by PMI scientists is presented in the tab. 2.

Table 2

Analysis of data on the content of HPHCs presented by PMI

Source	*ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories, Switzerland, 2017 [21]*	*Jean-Pierre Schaller et al., 2016 [22]*	*G. Jaccard, et al., 2017 [15]*	*V. Cozzani, et al., 2020 [16]*	*Mark C. Bentley, et al., 2020 []*
Detected components from the PMI-58 list	58	58	46	34	10
% of the PMI-58 list	100	100	79	59	17

The publications were published in prestigious specialized journals - Analytical and Bioanalytical Chemistry (3.286 IF, Springer Publishing), Regulatory Toxicology and Pharmacology (3.271 IF), Thermochimica Acta (3.378 IF) (Elsevier Publishing), and Frontiers in Pharmacology (5.988 IF, indexed in the Web of Science database).

CONCLUSIONS

The research supporting the review provides evidence demonstrating heated tobacco products' potential as a qualitatively and quantitatively less dangerous substitute for traditional cigarettes. In comparison to the 4800 compounds found in cigarette smoke, 529 chemical elements were found in THS2 aerosol, excluding water, glycerin, and nicotine, at concentrations higher than 100 ng per item. Decreased yields for particular substances, which were the objects of study in the research reviewed, start at over 50% and can reach over 90%. The statistical processing showed that at least one group of independent experts, in each separate case, confirmed that the data provided by the company's experts for the concentrations of the analyzed substances (at least for the maximum levels obtained) in the aerosol stream emitted by a THS device are not diminished.

However, we think that information about HNB products should be treated carefully and with reserve for the time being, for several reasons.

Between independent and industry investigations, there is a discrepancy in the number of compounds tested (priority-regulated toxicants). For the HCI and International Organization for Standardization (ISO) smoking regimes, HnB product emission monitoring is carried out; however, different puffing situations based on human puffing behavior must be considered in the evaluations. There were chemicals found in THS 2.2 aerosol that were not found in cigarette smoke.

Regulatory authorities face challenges in overseeing so-called heated tobacco products (HTP). To effectively monitor and assess HTPs, relevant global oversight mechanisms are necessary.

Funding

Philip Morris Sales and Marketing SRL is the sole source of funding and sponsor of this research publication.

References:

1. Jankowski, M. et al. New ideas, old problems? Heated tobacco products – a systematic review. International Journal of Occupational Medicine and Environmental Health 2019;32(5):595–634 https://doi.org/10.13075/ijomeh.1896.01433
2. Mallock N, Pieper E, Hutzler C, Henkler-Stephani F, Luch A. Heated tobacco products: a review of current knowledge and initial assessments. *Front Public Health*. 2019;7:287. DOI: 10.3389/fpubh.2019.00287
3. Simonavicius Erikas et al. Heat-not-burn tobacco products: a systematic literature review. *Tob Control* 2019;28:582-594, doi:10.1136/tobaccocontrol-2018-054419
4. Drovandi, A. et al. Human Biomarker Exposure From Cigarettes Versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis. *Nicotine & Tobacco Research*, Volume 22, Issue 7, July 2020, Pages 1077-1085, https://doi.org/10.1093/ntr/ntz200
5. Znyk, M et al. Exposure to Heated Tobacco Products and Adverse Health Effects, a Systematic Review. *Int. J. Environ. Res. Public Health* 2021, *18*(12), 6651, https://doi.org/10.3390/ijerph18126651
6. Ratajczak, A 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(2):409. DOI: 10.3390/ijerph17020409
7. Akiyama, Y. and Sherwood, N. Systematic review of biomarker findings from clinical studies of electronic cigarettes and heated tobacco products. *Toxicology Reports* 8 (2021) 282-294, https://doi.org/10.1016/j.toxrep.2021.01.014
8. Gideon St. Helen,1,2 Peyton Jacob III,1,2 Natalie Nardone,1 Neal L Benowitz1,2,3*, IQOS: examination of Philip Morris International's claim of reduced exposure,* Tob Control, 2018; 27: s30–s36. doi:10.1136/tobaccocontrol-2018-054321

9. Auer, Reto et al. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. In: JAMA Internal Medicine July 2017 Volume 177, Number 7, pp. 1050-1051. doi: 10.1001/jamainternmed.2017.1419.
10. Teemu, K. et al. Comparison of 3R4F cigarette smoke and IQOS heated tobacco product aerosol emissions. *In: Environmental Science and Pollution Research (2022) 29:27051–27069* https://doi.org/10.1007/s11356-021-18032-x
11. Bekki, K. et al. Analysis of furans and pyridines from new generation heated tobacco product in Japan. *In: Environmental Health and Preventive Medicine* (**2021**) 26:89, https://doi.org/10.1186/s12199-021-01008-1
12. Bekki Kanae et al. Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes. In: *J UOEH 39*(3), pp. 201-207(2017)doi.org/10.7888/juoeh.39.201
13. Dusautoir, R. 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. *In: Journal of Hazardous Materials* (2020), doi: https://doi.org/10.1016/j.jhazmat.2020.123417S
14. Jean-Pierre Schaller, Daniela Keller, Laurent Poget, Pascal Pratte, Etienne Kaelin,Damian McHugh, Gianluca Cudazzo, Daniel Smart, Anthony R. Tricker, Lydia Gautier,Michel Yerly, Roger Reis Pires, Soazig Le Bouhellec, David Ghosh, Iris Hofer, Eva Garcia,Patrick Vanscheeuwijck, Serge Maeder. Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regulatory Toxicology and Pharmacology 81 (2016) S27-S47. http://dx.doi.org/10.1016/j.yrtph.2016.10.001
15. G. Jaccard , D. Tafin Djoko, O. Moennikes, C. Jeannet, A. Kondylis, M. Belushkin, *Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes,* Regulatory Toxicology and Pharmacology, 90 (2017) p.1-8. https://doi.org/10.1016/j.yrtph.2017.08.006.
16. Cozzani, V et al. An experimental investigation into the operation of an electrically heated tobacco system. In: *Thermochim Acta, 2020* https://doi.org/10.1016/j.tca.2019.178475
17. Mark C. Bentley et al. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. In: *Analytical and Bioanalytical Chemistry* (2020) 412:2675-2685. https://doi.org/10.1007/s00216-020-02502-1
18. Xiangyu Li et al. Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes. *Nicotine & Tobacco Research*. January 2018. https://doi.org/10.1093/ntr/nty005
19. Uchiyama, S et al. Simple Determination of Gaseous and Particulate Compo-

unds Generated from Heated Tobacco Products. Chemical Research in Toxicology. June 2018. https://doi.org/10.1021/acs.chemrestox.8b00024

20. Wang, 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. In: Toxicology Letters 331 (2020) 200–207 https://doi.org/10.1016/j.toxlet.2020.06.017
21. ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories, Switzerland, 2017*(*https://www.pmiscience.com/en/research/product-assessment-approach/platform-development/ths-mainstream-aerosol-compared-to-reference-cigarette-smoke/)
22. Schaller JP, Keller D, Poget L, Pratte P, Kaelin E, McHugh D et al. *Evaluation of the tobacco heating system 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol*. Regulatory Toxicology and Pharmacology, Volume 81, Supplement 2, 30 November 2016, Pages S27-S47.