

Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 1 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

Annex 2-1: Significant Findings on Scientific Publications

Product	<i>Marlboro Amber HeatSticks</i> <i>Marlboro Green Menthol HeatSticks</i> <i>Marlboro Blue Menthol HeatSticks</i> <i>IQOS System Holder and Charger</i> <i>IQOS 3 System Holder and Charger</i>
FDA STN	PM0000424-PM0000426, PM0000479 and PM0000634
Reporting Period	March 1, 2021 to February 28, 2022

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 2 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

TABLE OF CONTENTS

1	Overview	3
2	Significant Findings by Scientific Area.....	3
2.1	Aerosol Chemistry and Physics & Indoor Air Quality.....	4
2.1.1	Aerosol Chemistry and Physics.....	4
2.1.2	Indoor Air Quality	7
2.2	Standards and Systems Toxicology.....	10
2.3	Clinical	21
2.4	Perception & Behavioral Studies and Post-Market Studies	35
2.4.1	Use Behavior	36
2.4.2	Youth Usage	43
2.4.3	Quitting.....	46
2.4.4	Claims, Messages, Consumer perception.....	48
2.4.5	Social media	52
2.5	Population Health Impact Modeling	53
3	Summary and Conclusion.....	54

LIST OF TABLES

Table 1	Description of Study Population by Study	43
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Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 3 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

1 OVERVIEW

Significant findings from scientific publications are presented in an integrated manner by scientific area in this section for the period from March 1, 2021, to February 29, 2022.

Throughout this Annex, we reference publications that are related to the *IQOS* THS generally. PMP S.A. sells modified versions of the *IQOS* System Holder and Charger and additional variants of *HeatSticks* in markets outside of the U.S. The publications in this section may be related to versions of the *IQOS* System Holder and Charger and *HeatSticks* other than the Authorized Products, as PMP S.A. believes it is important to provide this information because those other versions are designed to have the same principles of operation and performance as the Authorized Products.

2 SIGNIFICANT FINDINGS BY SCIENTIFIC AREA

A systematic literature search and review of retrieved articles was conducted and originally identified 226 publications that reported information related to Heated Tobacco Products (HTPs).

94 publications have been excluded from reporting here as they a) did not represent original research in a scientific discipline, b) did not represent a systematic review, c) were not available in English, d) mentioned HTPs, but upon review, did not include HTP-related data or e) presented obvious bias and spread misinformation.¹

The remaining 132 publications are listed in [Annex 2-2](#). Of those, 27 report results from studies conducted or sponsored by PMP S.A.² or other tobacco and nicotine containing product manufacturers, and 105 report data from studies conducted by independent researchers.

The literature summary provided below gives an overview of the 82 publications presenting significant findings that were not previously reported.

The publications included in our literature summary encompass various scientific fields including:

- Aerosol chemistry and physics, including data on product properties related to non-combustion, emissions of harmful and potentially harmful constituent (HPHCs),

¹ We report as an example Bravo-Gutierrez, O. A.; Falfan-Valencia, R.; Ramirez-Venegas, A. et al. “Lung Damage Caused by Heated Tobacco Products and Electronic Nicotine Delivery Systems: A Systematic Review”, *Int J Environ Res Public Health*, 2021; moreover, this study concludes that HTPs should be regulated, which is the case in the U.S.

² PMP S.A would like to emphasize that, when sponsoring a study, we only participate in financing, but have no influence on the design of the study, nor participate on the interpretation of the ensuing results.

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 4 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

non-targeted analysis of the emissions from the product, indoor air quality and secondhand exposure;

- Standard and systems toxicology including *in-vitro* toxicology testing, *in-vivo* inhalation studies, and animal models of disease;
- Clinical studies on exposure reduction to HPHCs, effect on biomarkers of potential harm (BoPH) and early marker of disease risk;
- Observational studies on trends related to the potential impact of the product on smoking-related diseases;
- Both perception/behavioral and post-market studies, primarily outside the U.S., to assess the impact of the *IQOS* Tobacco Heating System on product use trajectories, impact on former and never smokers, impact on cessation, product acceptability and the impact of marketing approaches;
- Population health impact modeling.

2.1 Aerosol Chemistry and Physics & Indoor Air Quality

2.1.1 Aerosol Chemistry and Physics

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 5 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 6 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 7 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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2.1.2 Indoor Air Quality

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 8 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 9 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 10 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



2.2 Standards and Systems Toxicology

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 11 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 12 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 13 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 14 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 15 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



(b) (4)

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 16 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 17 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 18 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 19 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 20 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

inflammatory markers of rats exposed to *IQOS* aerosol were determined. Reactive oxygen
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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 21 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 22 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 23 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 24 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 25 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 26 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 27 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 28 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 29 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 30 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 31 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 32 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 33 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 34 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 35 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 36 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.4.1 Use Behavior

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2.4.1.1 Cross-Sectional Studies – General Population

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 37 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 38 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 39 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 40 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 41 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 42 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 43 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 44 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 45 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 46 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



2.4.3 Quitting

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¹⁵ Funded by the Korean Ministry of Health and Welfare

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Philip Morris Products S.A.	Confidential
2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 47 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)



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2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 48 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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2.4.4 Claims, Messages, Consumer perception

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2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 49 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 50 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 51 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 52 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

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2.4.5 Social media

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2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 53 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.5 Population Health Impact Modeling

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[Redacted]

[Redacted]

[Redacted]

[Redacted]

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2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 54 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

(b) (4)

3 SUMMARY AND CONCLUSION

When discussing the harms and benefits of switching to e-cigarettes, Begh and Aveyard¹⁸ stated that *“it is possible from appropriately conducted toxicological studies and emerging epidemiological data to conclude that e-cigarettes are substantially less risky than smoking, even if the precise risks remain uncertain.”* As more evidence continues to be gathered for HTPs, including IQOS Tobacco Heating System, then it is reasonable to believe that the same argument should apply but it is crucial that the emerging science is critically evaluated by experts taking careful account of experimental design to determine that realistic exposure conditions were used, and the results are of human relevance.

Many experts and authorities agree that a risk continuum for tobacco and nicotine containing products exists, and that not all tobacco and nicotine-containing products are equally harmful. Such products range from very low-harm (e.g., Nicotine Replacement Therapy) to very high-harm (e.g., cigarettes, cigars, hookah pipe), with HTPs being distinctly lower in their risk profile compared to cigarettes.¹⁹ Switching completely to HTPs such as IQOS Tobacco Heating System would significantly reduce smokers’ exposure to HPHCs present in cigarette smoke, which are the main cause of smoking-related diseases.

While the scientific evidence continues to develop, regulators must consider the evidence of the risks associated with *both* the existing product and the novel product designed as an alternative. And, while HTPs are not risk-free, the available evidence supports that the risks are significantly reduced for both users and non-users against the well-proven risks of continued smoking.

¹⁸ Begh, R. and Aveyard, P. 2020 CrossTalk proposal: The benefits of e-cigarettes outweigh the harms. J. Physiol.

¹⁹ Abrams D. et al., (2018) Harm minimization and tobacco control: Reframing societal views of nicotine use to rapidly save lives, 39 Ann. Rev. Pub. Health. 193-213

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2022 Annual Report PM0000424-PM0000426, PM0000479 and PM0000634	Page 55 of 55
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

This thesis is confirmed by our literature review, which covers a wide range of studies in various scientific disciplines, including publications raising concerns that have been carefully considered. In conclusion, the extensive data reviewed do not provide any significant findings impacting the APPH status of *IQOS* Tobacco Heating System.

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