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Benzopyrene, smoke and money

The perfect Philip Morris International recipe for toxic scientific research

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In 2023, a concerning case reminiscent of classic tactics employed by the tobacco industry has come to light, exposing Philip Morris International's (PMI) continued influence on scientific research. The focus of PMI's efforts appears to be the promotion of their 'new' and 'innovative' tobacco products, casting a shadow over the credibility of these claims. Our investigation aims to unveil the extent of PMI's financial sway over select Swiss researchers, revealing that the targeted involvement of PMI employees in research is not an isolated incident. We conducted in-depth research to expose the meaning and ramifications of this new case of tobacco industry manipulated research.

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Living research: This paper is conceived as a living and dynamic research. We published a first version of this paper on February 8th, 2024, before receiving a full answer from ETHZ and the contracts that ETHZ signed with PMI. This new version is a revision of the initial paper and particularly add a full analysis of the PMI contracts. We strive for quality, and we are open to criticism and improvements. Our aim with this research is to promote full transparency, accountability and quality in scientific research.

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Abstract

In 2023, a concerning case reminiscent of classic tactics employed by the tobacco industry has come to light, exposing Philip Morris International's (PMI) continued influence on scientific research. The focus of PMI's efforts appears to be the promotion of their 'new' and 'innovative' tobacco products, casting a shadow over the credibility of these claims. Our investigation aims to unveil the extent of PMI's financial sway over select Swiss researchers, revealing that the targeted involvement of PMI employees in research is not an isolated incident. We conducted in-depth research to expose the meaning and ramifications of this new case of tobacco industry manipulated research.

An obscure title : a new example of a smoke screen!

The study in question, titled “Quantification and Mapping of Alkylation in the Human Genome,” conducted by the ETHZ Department of Health Sciences and Technology, initially appears unrelated to tobacco. However, a closer examination reveals PMI’s influence. The publication focuses on benzopyrene, a known carcinogen in tobacco smoke, and its impact on DNA modification. ETHZ, one of the top world technology universities, acknowledged collaboration with PMI scientists and financial support from the tobacco company for this study. The study was co-financed by the Swiss National Science Foundation (SNSF), but the SNSF was never informed that PMI was co-funding the research, therefore the ETHZ research team violated explicit SNSF rules. PMI signed a contract with the ETHZ research team for over one million Swiss francs in July 2017, well before requesting grants to the SNSF.

Language and Claims in Tobacco Industry

PMI has shifted its narrative, claiming to aim for a “smoke-free world” by promoting new tobacco products like IQOS. These products are marketed as “reduced risk” and “smoke-free,” but independent scientific evidence to support these claims is lacking. PMI's dual narrative – harm reduction for public health policy and continuing as a leading cigarette manufacturer for investors – is contradictory and brings PMI’s intentions into question. The ETHZ study allows PMI to reinforce their biased claims about their “innovative” heated tobacco products.

The Research’s Ethical Quandaries

The involvement of PMI employees in designing and supervising the study raises doubts about its independence. The extent of PMI's financial contribution remains undisclosed, further obscuring the research's impartiality. The lack of clarity on the necessity of PMI's involvement in this study adds to the ethical dilemmas. At the same moment of this publication, another almost identical article was publish by the same mix of authors from ETHZ and PMI, adding to the ethical confusion.

This ETHZ/PMI collaboration raises significant ethical concerns regarding transparency, conflicts of interest, and the true intent behind the research.

Previous Collaborations and Implications

From our research, it also appears that there have been previous collaborations between the lead researcher and PMI, including publications co-financed by PMI and prominently displayed on their website. This enduring relationship also contribute brings the researcher's impartiality into question, especially considering PMI's history of manipulating scientific findings.

The Need for Transparency and Independence in Research

The case at ETHZ underscores the crucial need for scientific research to be transparent and independent, criteria that cannot be fulfilled when research is under the influence of industries with vested interests. This situation highlights the ethical responsibility of researchers and institutions in upholding scientific integrity. It also emphasizes the importance of scrutinizing industry-funded research to safeguard public health and maintain the integrity of scientific discourse.

Benzopyrene, smoke and money

The perfect Philip Morris International recipe for toxic scientific research

In 2023, a concerning case came to light, reminiscent of tactics traditionally employed by the tobacco industry, exposing Philip Morris International's (PMI) continued influence on scientific research. The focus of PMI's efforts appears to have been the promotion of their 'new' and 'innovative' tobacco products, casting a shadow over the credibility of PMI's claims over the real toxicity of those products. Our investigation aimed to unveil the extent of PMI's financial influence over selected Swiss researchers. We discovered that PMI employees' targeted involvement in research at ETHZ was not isolated. A significant portion of the funding for this research came directly from PMI, though the exact amounts were not publicly disclosed. We obtained this data from ETHZ under the Swiss Federal Act on Public Transparency. PMI employees were also deeply involved in the research team and its publications at ETHZ. This close association between ETHZ's scientific research and a major tobacco industry player, whose primary objective is the profit-driven sale of harmful and deadly products, raises critical ethical questions about transparency, independence, conflicts of interest, scientific integrity, and the overall trustworthiness of the findings.

A first read: smoke or no smoke?

In February 2023, we stumbled upon a scientific article that appeared to be scientifically serious, extremely technical, and not even directly linked to the issue of smoking. The title itself promised a less than inviting read: "Quantification and Mapping of Alkylation in the Human Genome Reveal Single Nucleotide Resolution Precursors of Mutational Signatures" (we will call it for later clarity the "Quantification" article).[1] Who would wish to read an article with such an unsexy title, apart a very small circle of specialised toxicologists? Furthermore, nothing in the keywords associated with this article was suggesting a link with tobacco or smoke.[2]

When we began reading it, initially with very little interest, the article seemed to bear all the hallmarks of a serious and reputable scientific publication. However, quite quickly, we started to detect a hint of something amiss: we smelled smoke, and more specifically PMI smoke! Typically, especially in the case

of technical publications like this, few readers delve beyond the abstract. Yet, the figurative 'smoke' we started to discern compelled us to read on.

The study was conducted by a team of researchers of the Department of Health Sciences and Technology of the ETHZ. Before going further, we should stress that ETHZ, also known as Eidgenössische Technische Hochschule Zürich in German, is one of the world's leading universities in the fields of science, technology, engineering, and mathematics (STEM).

Image 1: On its web page PMI Science stress proudly its transparency and scientific rigor. Of course, those are only empty words (the black bubbles are from us).

The object of the study

The study investigated how certain chemical substances can cause DNA modifications leading to the development of some cancers, focusing on benzopyrene. According to the study's abstract, benzopyrene is *'a ubiquitous environmental carcinogen'* found in high concentrations in tobacco smoke.[3] Benzopyrene is a polycyclic aromatic hydrocarbon, which forms through the incomplete combustion of organic matter at temperatures between 300 °C (572 °F) and 600 °C (1,112 °F). The role of benzopyrene as a major cause of lung cancer is well-established in the scientific literature.[4] The WHO classifies benzopyrene as a Group 1 carcinogen, indicating its significant impact on DNA modification and cancer, which has been extensively studied.[5]

From "smelling smoke" to "finding the money"

On 23 February 2023, ETH Zürich announced on its "News & Events" web page under the headline "Where do toxins from tobacco attack DNA?", the publication of the "Quantification" study which was led by Mrs Shana J. Sturla (*Department of Health Sciences and Technology, ETHZ).*[6] This ETH News clearly indicates that *"For this study, the ETHZ scientists collaborated with scientists from the Philip Morris tobacco company. The company also helped finance the research. Additional funding for this study came from the Swiss National Science Foundation*."

Nowhere it is ever explained why this collaboration was necessary. It is only on January 25th, 2024, after a direct intervention by the Swiss National Science Foundation (SNSF), that this passage was corrected online: "*For this study, the ETHZ scientists collaborated with scientists from the Philip Morris tobacco company. The company also helped finance the research. Additional funding for aspects of the published work performed independently from Philip Morris* came from the Swiss National Science Foundation. * This passage was adjusted for precision on 25 January 2024.*" What aspects of the published work were performed "*independently*" from Philip Morris? Given that PMI employees were among the principal authors who designed and conducted the study, and also wrote the publication, how does the ETH define the concept of "*independence*"? It is interesting to note that in the ETH publication database, on the page presenting the publication, the PMI founding is not recognized even after the correction of January 25th.[7]

On January 25th, 2024, a correction was also published for the article itself in the journal ACS Central Science. This correction reformulated the funding acknowledgment in a somewhat strange way. The initial article stated, "*We acknowledge funding from Philip Morris International and the Swiss National Science Foundation (185020, 186332).*" The correction was published with this statement "*The funding statement is amended to clarify the independent nature of projects from which results are reported in the article*" and the correction read: "*We acknowledge funding from Philip Morris International and funding from the Swiss National Science Foundation (185020, 186332), which funded independent research projects*." [8] Can anyone grasp the significance of this difference? The publication discusses a single research project (the article consistently uses the wording "*this study*" and never "*those studies*"), and "*this study*" was conducted in very close collaboration by ETH researchers and PMI employees, with funding from PMI and the SNSF. However, the correction states that the SNSF funded "*independent research projects*." Independent from whom? Then why not publish two clearly separate studies? Should we stress again that some PMI employees are among the main authors of this study? Where is the clear line of differentiation between what PMI financed and what the SNSF financed?

Obviously, this correction was published in response to the pressure and criticism received, yet it fails to clarify any specifics about the funding—who used which funds and for what purposes? The authors do not seem willing to fully disclose the funding details, and in our opinion, this correction was a poor attempt to placate the criticism that such a publication provoked. This correction not only fails to address our criticism but also adds confusion to the entire issue of scientific manipulation by PMI.

Implications of language

As is generally the case in the public health domain, public health stakeholders in tobacco control are frequently confront the far-reaching impact of the tobacco industry's language and word choice. Recently, the tobacco marketplace has become increasingly diversified, with the tobacco industry marketing and claiming that their "*new products*" are "*smoke-free*" and less harmful than cigarettes. Big tobacco companies, like Philip Morris

International (PMI) and Japan Tobacco International (JTI), use terms like "*reduced risk products*", "*emerging and novel*", and "*smoke-free*" in their communications, thereby implying substantive improvements over older products (cigarettes) associated with disease and mortality.[9] This language is intentionally used to shape the thinking of consumers, but also the attitude of the wider public and policy makers towards the actions of those companies. We should not forget that PMI uses those arguments to very actively lobby for weak regulation and lower taxation of their pretended less risky products.

The PMI narrative

PMI has changed its narrative for some years now, claiming to aim for a "*smoke-free world*" with the goal of ending cigarette sales and shifting to new "*smokeless*" tobacco products that, they contend, pose reduced risks.[10] But PMI is running two parallel and very different narratives. On the one hand, they claim "*harm reduction*" in order to market their new products and influence public health policies; on the other hand, they continue to present themselves to their investors as a leading cigarette manufacturing company, with no sign of ditching their main lethal product.[11] A very good example of the double language of PMI is that, while they pretend to aim at a "*smoke free world*", at the same time the continue to invest and increase their production capacity in countries where they continue to see a potential to increase their cigarette production, as in the case in Egypt.[12] In its 2024 Report, PMI was eager to report that combustible products (i.e. cigarettes) generated a full-year net revenue growth of 4% (5,9% organically).[13] Clearly their real goal is to diversify and to introduce new deadly products, without getting rid of the old ones, in order to maintain and even increase their profits.

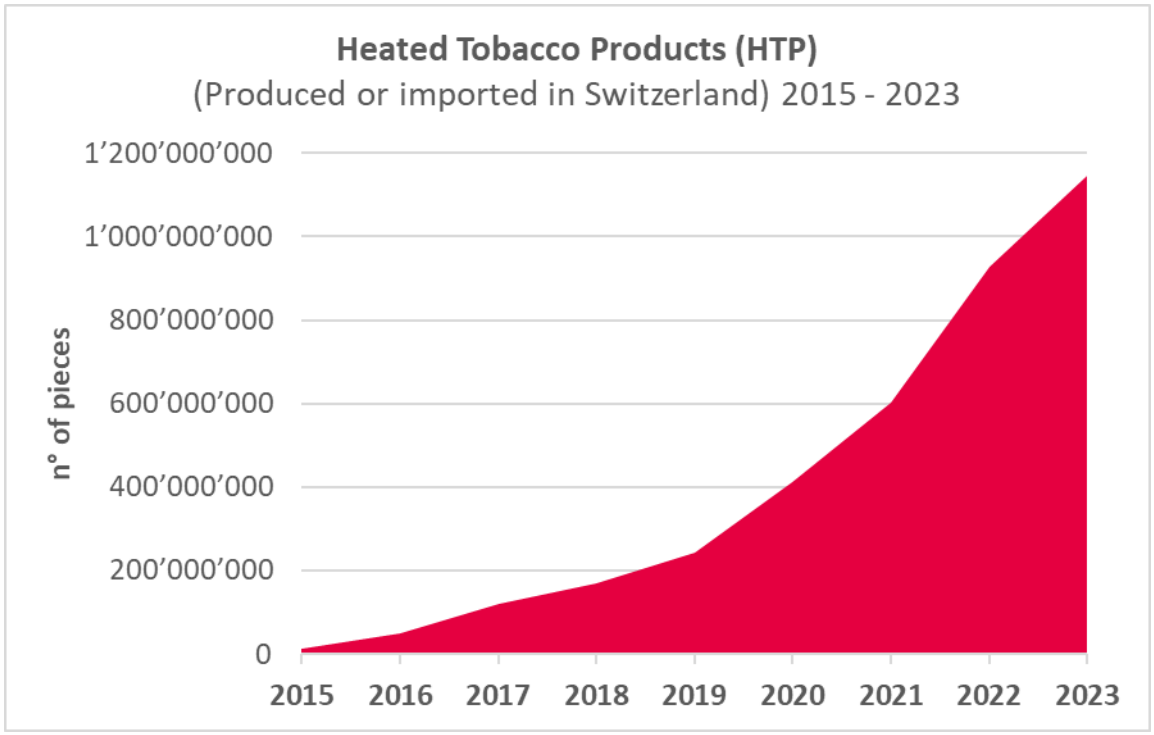

Image 2 : Evolution of heated tobacco products (HTP) sticks sold in Switzerland, 2015-2023, Source: Federal Office for Custom and Border Security (FOCBS)

The tobacco industry's reduced-risk claim is not supported by independent scientific evidence.[14] IQOS, produced by PMI, has the largest share of the heated tobacco product (HTP) market, especially in Switzerland. In 2023, in Switzerland, the sale of HTP products surpassed the sale of over 1 billion sticks, fully compensating the small decline since 2018 of the number of cigarettes sold. In their marketing and communication, PMI continuously insists that IQOS reduces one's exposure to harmful substances found in traditional cigarettes; for example, they claim a 95,9% reduction of benzopyrene emissions.[15] This figure of about 95-96% is regularly used by PMI in their advertisement, talking sometime about reduction of "*components*" and sometime about reduction of "*risks*". We want to stress that those claims have no valid independent (i.e. non-PMI paid) scientific base. We, like other public health experts, abundantly demonstrated that this "95%" claim is a lie and a manipulation.[16]

In March 2022, the American Food and Drug Administration (FDA) declared that, even if a particular heated tobacco product under consideration significantly reduces the production of harmful and potentially harmful chemicals (without endorsing any specific figure), it cannot be considered any safer than traditional cigarettes. The FDA, while authorizing the device under consideration to be marketed as a modified risk tobacco product (MRTP), also stressed that "*Importantly, this action does not mean this product is safe or 'FDA-approved.' There are no safe tobacco products."* [17] However, recent studies, fully independent from the tobacco industry, have highlighted several problematic issues concerning the yields of harmful and potentially harmful constituents generated by the heated tobacco products of PMI. Among those, research has clearly shown that the PMI's HTP are producing tar in significant amounts.[18] Although we still lack long term studies on the health impact of the use of HTP, growing evidence is pointing to a problematic impact, including on cardiovascular health. Another recent study highlighted the fact that even a brief HTP use in healthy young adults had immediate adverse effects on vascular function resulting in increased arterial stiffness and platelet thrombus formation, known risk factors for the development of atherosclerosis.[19]

Image 3: example of an advertisement by PMI for its IQOS product, November 2023, or of an online IQOS advertisement stating that IQOS does not produce TAR.

All marketing and advertisements for IQOS cleverly manipulate the concept of truth, as shown in image 2, leading consumers to believe their products are safer without always explicitly stating so. In certain countries, such as Dubai, the marketing for IQOS explicitly claims that their products are safer than cigarettes.

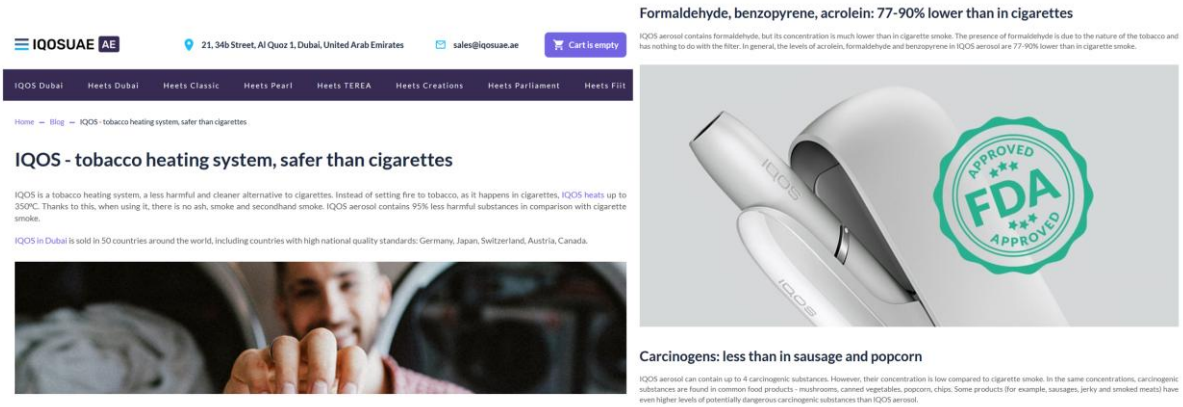

Image 4: the IQOSUAE website claiming IQOS is safer than cigarettes, using an image using a "FDA approved seal" as a marketing tool, and stating than IQOS has less carcinogens than sausages and popcorn.[20]

PMI's financing of research is part of their persistent effort to support such disputable claims, as other examples of PMI-funded research clearly show.[21] A common rhetorical tactic used by PMI is to assert that IQOS does not burn tobacco but merely heats it. Instead of using the term 'heated tobacco product (HTP)', the commonly preferred term in the scientific and tobacco control community, PMI uses "heat-not-burn" to emphasize the supposed absence of combustion compared to traditional cigarettes. However, it's important to note that benzopyrene is also generated by the pyrolysis that occurs in HTPs and that "*IQOS emissions contain carbon particles with most of the compounds released being formed by chemical reactions provides further evidence that IQOS emissions fit the definition of being both an aerosol and a smoke*.".[22]

Furthermore, TEREA tobacco sticks, used in the newest IQOS model called ILUMA, contain a tiny metal blade that is heated by induction to a temperature not disclosed by the manufacturer. This could potentially be much higher than in previous models, raising concerns about the release of heavy metals and other toxic volatile components. Additionally, the diversity of HTP systems makes toxicological measurements and comparisons across products very difficult.

Image 5: ETH tweet dated 23.02.2023 referring to the "Quantification" article.

An ETH tweet dated 23 February 2023 clearly highlights that the cause of lung cancer is tobacco smoke. Again, we wish to point out that, in our opinion, such a statement contributes to the instrumentalization by PMI of "*scientific*" statements that appears to support their claim that their smoke-free products (like IQOS) are less dangerous. The content of this tweet translates as follows *""Chemical compounds from tobacco smoke alter the DNA in lung cells, potentially leading to long-term cancer development. Researchers at ETHZ have now been able to precisely localize such changes for the first time."* This suggests that where there is no smoke, there is no DNA alteration, which perfectly suits the propaganda of PMI.

The general independent scientific consensus is that HTP users are still exposed to high levels of harmful substances, with the long-term consequences still unknown; thus, precaution is crucial in view of any promotion of these products as "*reducing harm*".[23] By promoting or tolerating non-independent and clearly biased research that allows PMI to further support their claims that HTPs present almost no danger compared to cigarettes, a prestigious scientific institution like ETH is in fact allowing PMI's efforts to manipulate scientific information and to increase the sale of their deadly products.

Directing the research

Two fundamental issues with the "Quantification" study are evident. The most concerning problem is that three of the article's main authors are employees of Philip Morris, all of whom were involved in designing and supervising the study. [24] All three are among the six that "*designed and supervised the study*." This raises significant concerns about the extent to which they have influenced the narrative to support the interests of PMI. The production of evidence is a social construction, influenced heavily by the framing of research, the definition of problems, and the choice of language, all of which directly affect the results.[25] Scientific knowledge is produced within a social context and is influenced by the norms, values, interests, and power structures of the society in

which it is generated. The tobacco industry has a clear and well-established strategy of funding research that directly supports their views and interests.[26]

The second problem is the financing of the research by PMI, particularly the extent and proportion of it relative to the funding from the Swiss National Science Foundation (185020[27], 186332[28]), according to a news article on the ETH web page stating that "*The company also helped finance the research. Additional funding for this study came from the Swiss National Science Foundation*." The significance of this PMI financial contribution was not initially disclosed, yet the ETH news implied that PMI was the primary funder. For full transparency, we believe that the amounts should be fully disclosed from the very beginning of a scientific research project. Specifically, how much was provided by PMI, under what terms, and if the research was already supported by two SNSF grants, why did ETH need additional funds from PMI? What were these funds used for? These are some of the questions we posed to ETH based on the Federal Act on Transparency.

In addition, another central question arises: Who exactly initiated this research? Was it PMI that approached the ETH team requesting such research? Or was it the ETH team that initiated the research and requested funding from PMI? What was the exact timeline of the research development and funding requests between the parties involved (ETH, PMI, SNSF)?

The Sturla/PMI publication is presented by PMI as one of their own studies. The PMI Publications webpage states that "*PMI Publications: We believe scientific results are meant to be shared. More than 1,180 scientists, engineers, technicians, and support staff are working on our smoke-free products. Transparency and open sharing of results and methods promote the use of best practices in scientific research, and the resulting scientific publications and presentations are the base upon which science-based discussions are built. As of 2022, we have published 511 scientific publications since 2008. We welcome you to browse our publications library and see the details of our research for yourself*."[29] When PMI openly refers to "*our*" publication library and "*our*" research, it suggests that the Sturla study can in no way be considered independent if PMI openly promotes it as one of their own products. This situation raises critical questions: Was the Sturla article an ETH/SNSF study or was a PMI study? What is the ETH position on this confusing situation?

Image 6: PMI webpage screenshot (21.12.2023)[30]

And a second "research" ….

A few days apart from the "Quantification" study, a second study was published by almost the same authors on almost the same topic under the title "*Dissection of Cancer Mutational Signatures with Individual Components of Cigarette Smoking*" (we will call it for later clarity the "Dissection" article)[31] This parallel study was entirely financed by PMI and 3 authors from PMI are also among those of the "Quantification" article.

The "Dissection" article, of which Mrs. Sturla is corresponding author, was published in the journal Chemical Research in Toxicology, for which Mrs. Sturla is also Editor-in-chief since early 2018.[32] This last element raises itself serious questions of compliance with peer reviews procedures and independence.

What is the exact connection between the "Quantification" and the "Dissection" articles? The "Quantification" was published on the 22 February 2023 and the "Dissection" was published online first on 28 February 2023. What a perfect timing! As one might expect the "Dissection" study cites the "Quantification" study (reference 52) indicating therefore a close connection between the 2 studies.

The "Dissection" study is reported as being fully and uniquely financed by PMI (but the exact amount again was not disclosed). The Conflict-of-interest statement of this article is formulated as it follows "*The authors declare no competing financial interest*.", by which we suppose we should understand that no interest competing with the PMI financial interests were involved in this study. It is also interesting to notice that in the ETH database webpage referring to this publication the PMI funding is not mentioned at all.[33]

Not only are several authors of the two studies the same, but the content of the two articles is very similar and closely interrelated. In fact, the content appears so close that it seems to be difficult to assert any real distinction

and state that the two research projects were independent of each other. This close connection of topic, financing, authors and publication timing raises significant ethical questions about the transparency and independence of the research. It also strengthens the impression that both studies were conducted on behalf and for the direct interest of PMI.

The objective of the "Dissection" study was, as explicitly stated, "*to characterize mutational signatures arising from individual constituents of tobacco smoke and evaluate how they relate to tobacco-associated cancer mutational signatures.*" The "Quantification" study does not openly state what its objective was but says "*In this study, we defined a first single-nucleotide resolution genome-wide map of N2-BPDE-dG in human lung cells and elucidated relationships between DNA adducts and local sequence contexts, genomic features, and mutational signatures associated with smoking-related lung cancers, as well as how these relationships may be modulated by increasing chemical exposure concentrations.*" The "Quantification" article appears to be lacking in necessary structural elements (we would expect a good scientific article to be written with traditional sections, like a research question and hypothesis, a clear description of the methodology, how data was collected and analysed, what the results were, a discussion and a conclusion) and we qualify its writing quality as not up to expected standards of clarity and organization, or, in other words, as rather "sloppy".

Many methodological criticisms could be found in both publications, but a detailed deconstruction is not necessary for our purposes. However, one important question could be raised: Why did the authors never address the relationship between the two articles? Both articles appeared in publications of the American Chemical Society (ACS) but was the ACS aware of the closeness in scope of the articles during the submission process? Who conducted the peer review for these articles?? Did the peer reviewers have any links to the tobacco industry?

Previous collaboration between Mrs. Sturla and PMI

Faced with these two very problematic publications, we could not help but wonder if there was a history behind these issues. Delving deeper into our research, we uncovered further unsettling findings. A search for 'Sturla' on the PMI science page reveals some other past collaborations, with those articles also prominently displayed on the PMI's website. These past collaborations demand scrutiny, particularly because they help to illuminate the real nature and depth of the relationship between Ms. Sturla and PMI.

We found a **first** problematic connection between Ms. Sturla and PMI ten years ago, in 2014, when Ms. Sturla published an article on systems toxicology. Systems toxicology represents a dynamic and interdisciplinary field that has emerged in response to the need for a more comprehensive understanding of the effects of toxicants on biological systems.[34]

This publication, prominently listed in the PMI Science database, lists Ms. Sturla as the first author, with Mr. Peitsch, the Chief Scientific Officer of PMI, as the corresponding author. This publication was co-financed by PMI and the SNSF. The funding for this study was disclosed as follows: "*The authors are funded by their respective institutions. S. Sturla acknowledges support by the Swiss National Science Foundation (grant no. 136247)".* However, we doubt that the fact that this grant was used to support this publication was ever declared to the SNSF.[35]

If Mr. Peitsch was the corresponding author, we should consider this publication to have been initiated and primarily funded by PMI. In the absence of precise data on funding and the roles of each author, it is difficult to consider it otherwise.

Regarding the funding declared by Ms Sturla, in the database of the SNSF grant n° 136247 correspond to a project for "Systems-wide responses of colon cells to food components and impact on cancer drug action". We searched for the word "colon" in the text of the article, and we were not able to find it. It is unclear how this SNSF grant relates to this PMI publication. Was the SNSF informed that part of its grant was used to write a publication with PMI that does not appear to be directly related to the aim of the grant?

We question again the actual composition of the funding. In this study one of the authors is Julia Hoeng of PMI, another is the chief scientific officer of PMI Manuel Peitsch, which, we need to stress this again, was the lead author of this publication and is also indicated as corresponding author. We find Ms Hoeng again in the 2023 publication of Mrs Sturla. This proves that Ms. Sturla's collaboration with PMI dates back at least 10 years.. How many grants has Ms. Sturla received over the years from PMI, including funding for conference participation and other non-research-related activities?)?

Secondly, we discovered a chapter authored by Ms. Sturla and her team in a book edited by Manuel Peitsch and Julia Hoeng of PMI in 2015.[36] Of the 16 chapters in this book, 6 are directly authored by PMI's employees, and

another 6 by private commercial laboratories or consultancies, where financial interests linked to PMI cannot be ruled out. This leaves only 4 chapters authored by seemingly independent academics.

The book is published by Springer, a commercial publisher, and its contents are not open access but must be purchased. Mrs. Sturla's chapter is priced at CHF 39.95. However, the chapter acknowledges that "*This work was financially supported by the Swiss National Science Foundation (Sinergia Project 136247)*." Therefore, this chapter was funded under the same grants as the previously mentioned article on systems toxicology. This situation raises an important question: Is it acceptable for work financed by the SNSF to be published in such a commercial manner? Interestingly, in the ETH publication database, on the page presenting this publication, the SNSF funding is not acknowledged. [37]

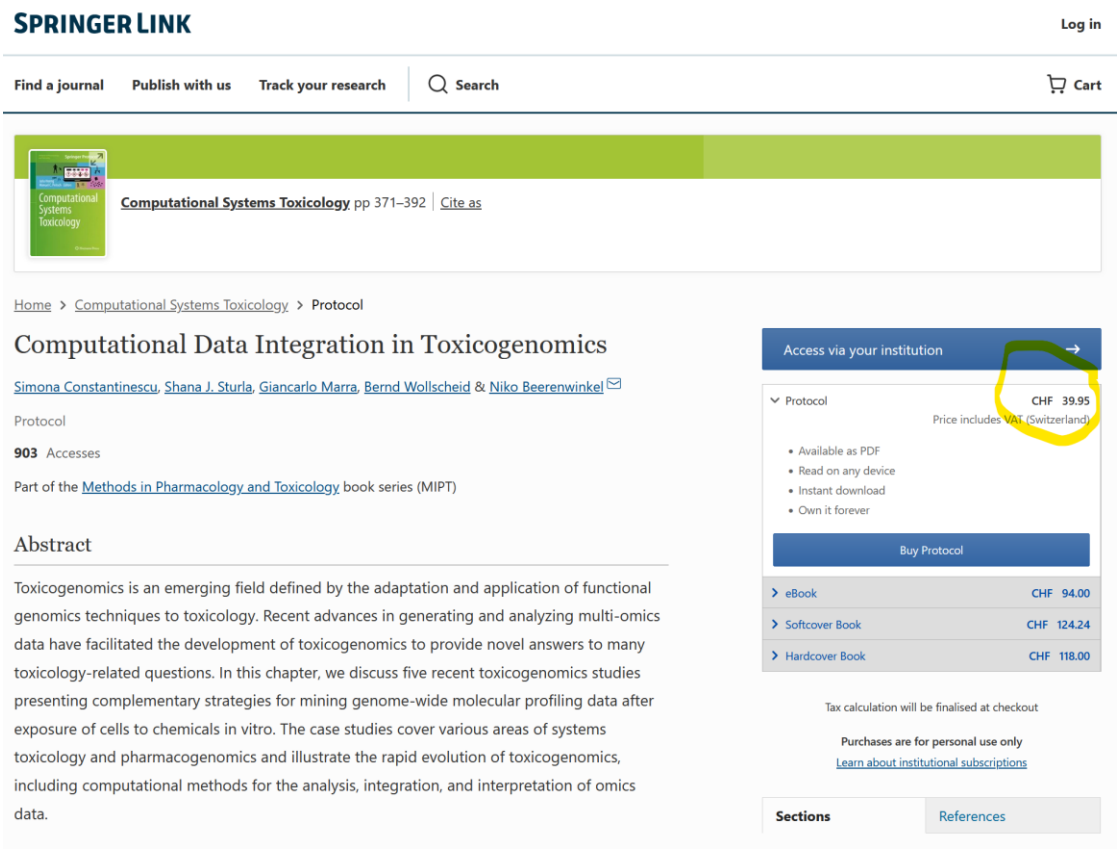

Image 7: Screenshot of the Spinger website, where is it possible to buy the Computational Data chapter (29.01.2024)

Ms Sturla was the corresponding author of yet another study, also listed in the PMI Science page. n 2017, Chemical Research in Toxicology published an important article on systems toxicology.[38] This study reports several funding (including the SNSF) but none openly by PMI. However, among the authors, we find another time the main PMI research officer Manuel Peitsch, which raises again serious ethical questions. The article underscores the importance of Mr Peitsch's role by stressing "*At PMI he leads the department responsible for*

the assessment of candidate Reduced Risk Tobacco Products through pre-clinical toxicology, systems toxicology, and clinical studies, as well as for their regulatory submissions." Was the research truly devoid of funding from PMI? If an author, employed by a commercial entity like PMI, contributes to a study in their capacity as a PMI employee, this involvement constitutes indirect funding from PMI, which should have been appropriately disclosed.

Moreover, there's an inherent risk associated with the tobacco industry's involvement in systems toxicology. Although systems toxicology offers a promising and innovative method for exploring the intricate interactions between toxicants and biological systems, it is not without its challenges and limitations. The field of systems toxicology, like any scientific discipline, is subject to ethical considerations and potential conflicts of interest. It is possible for industries, including the tobacco industry or any other, to try to manipulate or selectively interpret research findings to promote their products. Concerns such as funding bias, selective reporting, conflicts of interest, and transparency are particularly relevant when the tobacco industry is involved in research on reduced-risk products. Interestingly, the same year that Ms. Sturla's article on systems toxicology was published, a team of PMI scientists, led by Mr. Peitsch, used this approach to attempt to demonstrate that PMI's new heated tobacco products are better to traditional cigarettes.[39]

It's evident that the collaboration between Ms. Sturla and PMI isn't recent but rather stems from an enduring financial relationship and close personal ties. Such connections raise significant concerns about the integrity and independence of her research. Given these findings, we find it challenging to trust Ms. Sturla's impartiality, especially considering PMI's monetary influence and interests and how the tobacco industry is known for decades of distorting scientific findings and misleading the public about tobacco's adverse effects.

By aligning with PMI in this manner, researchers and scientific publications run the risk of becoming instruments for the company's promotional efforts. Currently, as we demonstrated earlier, PMI is promoting their heated tobacco devices, IQOS, championing the notion that the absence of combustion nearly nullifies health risks. Several of the studies that we mentioned here are cited in numerous PMI publications with a clear motive: to validate PMI's claims about the reduced risk associated with their IQOS product.

For instance, PMI has released a document titled: "The Science behind the Tobacco Heating System: A Summary of Published Scientific Articles 2017," where Ms. Sturla's work is notably acknowledged.[40] It would not be surprising if the 2023 Sturla/PMI publications were quoted and used by PMI in their 'scientific summaries' or conference presentations to further argue that smoking causes cancer (but that IQOS does not).

Another ETH research getting PMI money: different researchers, same manipulation?

After uncovering various research projects of Ms. Sturla funded by Philip Morris International (PMI), we conducted further detailed investigations. Our research revealed additional ETH researchers who have also received funding from PMI.

In 2020, a different team at ETH published a study titled "*Tracing the composition of single e-cigarette aerosol droplets in situ by laser-trapping and Raman scattering*" (hereafter referred to as the "Tracing" article).[41] This study, which examines electronic cigarette aerosols, was co-financed by PMI. The acknowledgements in the published article state, « *This work was supported by the Swiss National Science Foundation (SNSF grant no. 200020_172472), ETHZ, and Philip Morris International*. » However, similar to the situation with Sturla's publications, only the SNSF grant is mentioned on the ETH website, omitting any mention of PMI's financial contribution. [42] The SNSF web page presenting the various results and publications generated by this grant, mention also various "collaborations", but the one with PMI is not included.[43] Again, it appears that the the SNSF was not informed about PMI's involvement, and the amount of PMI funding was not disclosed.

Image 8: The « Tracing" study promoted by the PMI science web page (last consulted on 28.01.2024)

Subsequently, the same authors published another article in Chimia, though under a different title.[44] This publication appears to be nothing more than a concise, one-page summary of the "Tracing" article. Notably, it omits any reference to the funding sources. The article concludes with the statement, "*The measured partitioning of the main e-cigarette compounds between the droplet and gas phase as a function of time will improve our understanding of their deposition in the respiratory tracts and hence of their impact on health*." However, this

conclusion raises a critical question: Is the primary focus of this research genuinely on understanding the health impacts, or is it more concerned with optimizing the aerosol delivery of nicotine to the lungs of users of Electronic Nicotine Delivery Systems (ENDS)? It may significantly understate the situation to suggest that the benefits of this research for consumer health improvement are unclear.

This research utilized a PMI product initially named Nicocig MESH, which was later rebranded as Veev. The current Veev version employs a hybrid nicotine mixture, combining free-base nicotine with nicotine salts. PMI claims that "*It emits on average 99 percent lower levels of harmful chemicals compared to cigarettes*" [45], a statement that lacks verification from independent scientific research. Moreover, the Veev product has undergone significant modifications since its initial release, meaning the version studied is substantially different from the one currently available on the market. This lack of representativeness is a significant issue, considering the study focused solely on a single PMI product, whereas the market features thousands of diverse ENDS and e-liquids with vastly varying compositions. Ideally, in line with standard academic practices, this should have been acknowledged as a limitation of the study, yet the study did not mention any limitations.

In the study, Nicocig MESH's e-liquids were tested with nicotine concentrations of 2%, 3.5%, and 5%. However, the study does not clarify whether the nicotine in these liquids was in the form of free-base, salts, or a mixture, as is the case with the current market version of Veev. Notably, e-liquids with nicotine concentrations above 2% in closed systems, akin to those tested in the study, are illegal in Europe and Switzerland.[46] This raises questions about the decision to test e-liquids with such high nicotine concentrations, particularly when consumer health should be a primary concern. Why test concentrations that are not only illegal but also potentially harmful? Again, we cannot but question the actual intent and rationale of the study.

The "Tracing" article's failure to specify whether the nicotine used was free-base or in salt form is a significant oversight, especially given the varying pH levels (ranging from 3.4 to 9.9) of the tested nicotine concentrations. This variation is crucial because it directly correlates with the type of nicotine, raising important questions the article does not address. Nicotine salts are produced by adding an acid, usually benzoic acid (but other acids are possible), to freebase nicotine, which typically has an alkaline pH around 9. Adding acid lowers the pH, resulting in a more neutral solution that is less harsh on the throat, making the consumption more appealing for young and new users. This modification allows for higher nicotine levels to be delivered more comfortably than the concentrations found in freebase nicotine. Nicotine salts are also known for their rapid absorption into the bloodstream, higher than the freebase nicotine of traditional cigarettes, and their enhanced molecular stability, allowing for longer storage without degradation.

The absence of a clear distinction between the types of nicotine in the "Tracing" article creates a significant gap in understanding the implications of the tested concentrations and pH levels. Given that nicotine solutions with a pH below 7 are acidic, it's plausible that some of the tested liquids contained nicotine salts. The omission of specific nicotine types raises concerns about the rigor of the article's peer-review process and the overall

credibility of the research. Such an omission, particularly in a study involving nicotine concentrations already deemed illegal in certain regions, casts doubt on the study's relevance and validity in the context of consumer health and scientific integrity.

In research funded by PMI, it is often more revealing to note what is omitted than what is explicitly studied. The study defines the composition of e-liquids as primarily consisting of propylene glycol (PG), vegetable glycerin (VG), nicotine, flavoring supplements, and water—although not all e-liquids contain water. However, this description potentially overlooks other common e-liquid components, such as diethylene glycol, acetaldehyde, formaldehyde, acrolein, benzene, diacetyl, and heavy metals like cadmium, nickel, tin, and lead. These omissions raise questions about whether such chemicals were present in the Nicocig MESH e-liquids and why they were not considered in the study. By neglecting to mention these substances, the article appears to align with PMI's objective of downplaying the potential risks of their products, thus promoting their commercial interests.

The research's focus, and PMI's motivation for funding it are highly questionable. The "Tracing" study itself emphasizes the importance of its results for "*advancing e-liquid research and manufacturing*" suggesting a commercial rather than a health-oriented objective. It appears that the SNSF Grant was potentially utilized to support PMI's commercial interests, rather than prioritizing consumer health. Discovering this PMI-funded study leads to further speculation about the extent of PMI's financial involvement in other studies at ETH.

Tobacco industry influencing science

The tobacco industry, and PMI in particular, have a long history of influencing and distorting science[47] and the tactics used have been researched extensively.[48] Among the main nine tactics used by the tobacco industry to undermine health policies, Vital Strategies has clearly identified one of them as: "*Produces and disseminates misleading research and information: As scientific evidence revealed more and more harmful effects of smoking, amounting to tens of thousands of research papers, the industry countered by funding its own scientific studies. While historically such efforts focused on disputing the harm from tobacco, more recently the industry has been funding and producing misleading "research" and information focused on countering effective public health policies.*"[49] As written by Briggs and Vallone (2022), "*The tobacco industry is once again infiltrating scientific spaces and presenting a direct threat to the vital work of unbiased tobacco control scientists. With the popular introduction of e-cigarettes and other new nicotine products, the tobacco industry has remade itself into a self-proclaimed concerned corporate entity—and one that will go to great lengths to prop up their new products while opposing credible scientific findings. Both JUUL and Philip Morris have injected their narrative into scientific circles by publishing sponsored research in scientific journals*."[50]

Tobacco industry attempts to manipulate scientific research to influence public health policies has been demonstrated in Germany.[51] More recently, in Switzerland, when Swiss independent researchers published a

study that went against PMI claims on heated tobacco products[52], PMI attacked those researchers and tried to force them to retract their paper by pressuring the University of Lausanne.[53]

The new cases we are highlighting brings back nasty memories of a previous case, dating back more than 20 years ago, at the University of Geneva. It was uncovered and demonstrated that a professor at the University of Geneva had a long-standing financial relationship with PMI. Prof. Rylander had secretly received funds for research from the tobacco industry, which amounted to as much as US $ 85'000 a year for 30 years. He was among the best paid consultants at Philip Morris. The public health experts that denounced the case, proved this money was used in INBIFO, a secret lab in Cologne, to produce findings which were subsequently distorted to underplay the dangers of passive smoking. In one of Rylander reports, published in 1997, the conclusion stated that "*diet and lifestyles ought to be taken into consideration when considering the health effects of passive smoking*".[54] Prof. Rylander attacked the public health experts for defamation in a well-known legal case and lost.

A recent and important article titled "The Science for Profit Model—How and why corporations influence science and the use of science in policy and practice" conducted an analysis on the strategies used by the industry to manipulate scientific research. This model shows "*how these strategies work to maximise the volume, credibility, reach, and use of industry-favourable science, while minimising these same aspects of industry-unfavourable science. This creates doubt about harms of industry products/practices or efficacy of policies affecting industry; promotes industry favoured policy responses and industry products as solutions; and legitimises industry's role as scientific stakeholder. These efforts ultimately serve to weaken policy, prevent litigation, and maximise use of industry products/practices—maximising corporate profitability. We provide an accessible way to understand how and why corporations influence science, demonstrate the need for collective solutions, and discuss changes needed to ensure science works in the public interest*."[55]

All these tactics have recently been employed to effectively promote heated tobacco products, with PMI leading the charge. However, serious independent researchers are increasingly challenging the claims made by the tobacco industry regarding these products. A recent publication underscored that PMI invested hundreds of millions of dollars to promote their 'smoke-free world' claim. This publication states very clearly that "*Among the researchers who choose to remain independent of the tobacco industry, we do not know anyone supporting HTPs as a harm reduction tools*."[56]

Rejecting research funded by the tobacco industry

Since 2013, all journals associated with the BMJ do not accept any research funded by the tobacco industry.[57] This stance is mirrored by other prominent journals; PLOS Medicine instituted a similar ban in 2010[58], and the journals published by the American Thoracic Society have rejected such research since 1995.[59] The American Journal of Public Health also has a strict policy banning the publication of any research funded by the tobacco

industry.[60] The Lancet has not yet implemented such a policy, but there has been a recent call to develop and implement one.[61]

Important international global health institutions, like the Union Internationale Contre le Cancer (UICC), also oppose the tobacco industry's manipulation of scientific research, or the "*smokescreen of the tobacco industry's use of science*".[62] As early as the late 1990s, some research funding agencies began to take a stand. The Cancer Research Campaign in the United Kingdom, the Norwegian Cancer Society, and members of the UICC, such as those within the European Cancer League, no longer fund research at institutions that accept tobacco industry funds.[63] Very recently the Worldwide Cancer Research published a very clear policy statement on tobacco industry funding.[64]

The UICC, consistent in its longstanding policy of opposing any tobacco industry influence, announced in September 2024 its decision to withdraw as a supporting organization from the 10th World Cancer Series (WCS) scheduled in Brussels and organized by Economist Impact, a division of The Economist. This decision was prompted by UICC's discovery that Economist Impact collaborates with Philip Morris International (PMI) and Japan Tobacco International (JTI).[65] Several prominent speakers slated to attend immediately followed UICC's lead and withdrew upon learning of these ties. In response to the growing concerns, Ian Hemming, Managing Director of Economist Impact events, confirmed the cancellation of the conference. This incident has sparked a broader conversation about the appropriateness of tobacco industry sponsorships in healthcare-related events, particularly those aimed at combating illnesses directly linked to tobacco use. Additionally, this situation highlighted how Economist Impact's website hosts content that appears to conflict with public health advocacy, including pieces that portray PMI and JTI sympathetically and argue against high taxation on cigarettes, claiming it encourages illegal tobacco.[66]

In 2004, Switzerland signed the Framework Convention on Tobacco Control (WHO-FCTC) but has yet to ratify the convention due to inadequate national policies. This 20-year delay is largely attributed to the powerful tobacco industry lobby in the Swiss Parliament, which has been blocking progress on tobacco control. Consequently, Switzerland remains one of the few European countries without fundamental tobacco control policies.[67] One of the key provisions of the FCTC is art. 5.3, states: "*In setting and implementing their public health policies with respect to tobacco control, Parties shall act to protect these policies from commercial and other vested interests of the tobacco industry in accordance with national law*."[68] Switzerland had planned to ratify the FCTC as soon as the new law on tobacco products was set to enter to force on October 1st, 2024, however, as of now, no discussions in this direction have been initiated. In the meantime, all public health actors consider that a correct interpretation of international public law already requires Switzerland and all its public agencies and official bodies to act in accordance with the FCTC provision. We consider that the ETH, as a federal institution, should set an example, exhibiting the values of independence and transparency in support of public health and scientific research.

Did the SNSF know that it was co-financing research designed and supported by PMI?

The very clear, simple and direct answer is: no!

In early March 2023, we contacted the Swiss National Science Foundation (SNSF) to voice our concerns about its decision to fund research that was directed and co-financed by PMI. The SNSF demonstrated exemplary transparency and communication during our interactions. We met with SNSF representatives and learned that the principal investigators of the studies in question had not disclosed any planned collaboration with or co-financing from PMI, nor had they informed the SNSF of any PMI employees' involvement in the project. Given the strict regulations of the SNSF that safeguard research freedom and independence, the discovery of potential breaches led to an official investigation. This investigation resulted in the issuance of a corrigendum for the "Quantification" publication. We understand that the SNSF, as the major funder of scientific research in Switzerland, might be reluctant to initiate a full legal battle with ETHZ, one of the leading Swiss research universities. Such a conflict could potentially have led to the complete withdrawal of funding and might result in greater media exposure of the case. However, from our perspective, the correction issued was wholly insufficient to clarify the issues at hand and to establish responsibilities.

We hope this situation will prompt the SNSF to adopt more stringent policies that explicitly exclude the co-financing of research directed, designed, and/or co-sponsored by the tobacco industry. Given that the tobacco industry is among the most destructive industries globally, affecting all aspects of its activities, it is imperative that research funding bodies like the SNSF take a clear stand to prevent any association that might compromise the integrity of scientific research

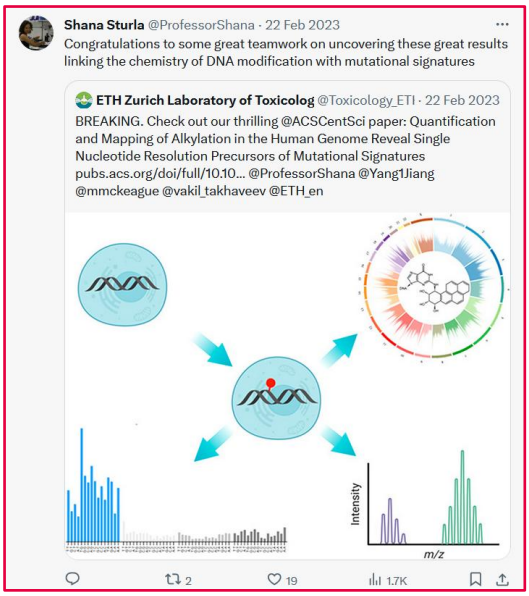

Image 9: A proud tweet by Mrs. Sturla about "some great teamwork": with the tobacco industry? (22.03.2023)

ETH and the PMI contracts

Before contacting the ETH directly, we wanted the Swiss National Science Foundation (SNSF) to clarify the issue first. Once that was done, in December 2023, we wrote to the president of the ETH seeking explanations and requested, based on the Swiss Federal Act on Transparency in Public Administration,[69] all contracts and documentation between ETH and any tobacco industries over the last 20 years, specifically including documents related to the highlighted collaborations with PMI. As a Swiss federal university, ETH is subject to the Act on Transparency like any other part of the federal administration.

This request led to a constructive initial meeting with some members of the ETH Presidency, during which we received the documents we had requested.

The contracts between PMI and the ETH

We obtained the contracts regarding 3 research agreements, that we summarize in the following table:

Project Title	Linked to the publication	Start-end date	Signed on	Amount
Evaluation of RRTP Prototypes	"Quantification" article	01.09.2017, duration 24 months	July 2017	CHF 1'026'610
Assessment of Raman spectroscopy for single droplet chemical characterization of e-cig aerosol	"Tracing" article	01.10-2018 – 31.03.2019	03.08.2018	CHF 120'000
Trial Cloud service agreement (online assessment tool that provides a task battery for employees to learn about cognitive strengths and weaknesses)	(no publication)	15.06.2018-01.10.2018	10.07.2018	CHF 45'000

Those are all the contracts we received, and ETHZ explicitly confirmed that no other contracts were passed with any other tobacco industry. As the documents can be obtained by anybody, based on the Federal Act on Transparency, we attach the 3 contracts to this study.

The «Evaluation of RRTP Prototypes» Agreement

This analysis reviews the key contractual agreements between PMI and ETHZ regarding the research program titled "Evaluation of RRTP Prototypes," signed in July 2017. The contract includes comprehensive details on research objectives, funding, confidentiality, and the management of research results, highlighting PMI's emphasis on controlling information and the commercial exploitation of research outcomes. This examination sheds light on the legal, ethical, and practical implications of the terms agreed upon, especially concerning transparency and intellectual freedom. This contract was signed in July 2017 and comprises the "Research Agreement" itself, an Appendix A "Research Programme Plan Project Title: DNA Adducts as Carcinogenesis Biomarkers", an Appendix B "Project Planning", and an Appendix C "Budget Estimation and Structure".

The copy we obtained has been redacted, mainly concerning the names of specific persons, but significant information in Appendix A has also been blackened out.

It is necessary to read this contract in detail to understand it properly. We can start by underscoring that the "Research Agreement" appears to have been drafted by PMI (referred to as the "Company") to extensively protect the commercial interests of PMI itself.

The preamble of the contract states very explicitly that: "A. The Company scientifically explores and develops novel tobacco products that reduce or eliminate harmful and potentially harmful constituents (Risk Reduced Tobacco Products, RRTP)." and "B. In order to scientifically examine and evaluate RRTP prototypes (or components thereof) developed by or under the control of the Company, the Company is interested in implementing a Research Programme with the ETHZ." This preamble clearly indicates that this research was initiated by PMI with the clear intent to develop something that would be profitable to their interests. With this research, they want to "scientifically examine and evaluate their RRTP prototypes," but they want to do this under their strictest control and supervision.

In Chapter 4 "Report" of the agreements, ETH is compelled to provide extensive and regular reports to PMI.

In Chapter 5 "Remuneration," the remuneration for ETH is planned, including salary costs, consumables, and equipment, other costs, and an infrastructure contribution of 10% of direct costs (this last amount is what is generally referred to as overhead). The exact amount is defined in Appendix C Budget, which gives a total amount of CHF 1'026'610 (out of which CHF 93'328 are overhead). We should stress that at no moment in this contract is it mentioned that additional funding should be provided by other sources, specifically the SNSF. This also indicates that the ETH team clearly omitted to inform the SNSF in their grant requests about the existence of this already signed agreement with PMI.

Chapter 6, aimed at "Project Results," focuses on the ownership of the results and appears to be drafted to grant as much control as possible to PMI over any "project inventions." What appears to be odd is that if this research aims to evaluate the danger of certain PMI products, what "invention" could be generated? This control of results and project inventions generated by the project is again stressed by Chapter 7 "Licences." Here, PMI is granted

“for any Project Results, including any Project Invention, solely owned by ETHZ […] at no additional costs a non-exclusive licence to use such patent rights in the Company Field.” We need to return to Chapter 1 of the Agreement to find under 1.3 the definition of “Company Field” which “means devices and accessories (or parts) for products that can be considered and/or consist, even partly, of tobacco, that are intended or not intended to be smoked, and that are likely to be present, or have the potential to present less risk of harm than conventional products.” This means that PMI can profit freely from any “inventions” resulting from the research for its own products and commercial interests.

What is left to ETH? After more than a page for Chapters 6 and 7, giving as much control as possible to PMI over any invention, license, or rights, Chapter 8 regulates the “Intellectual Freedom” of ETH in a bit less than two lines: “In any event, ETHZ has the right to use all Project results, protected or not, for basic scientific research and teaching purposes in any field.”

Almost two full pages are dedicated to Chapter 9 “Confidentiality.” In reading this chapter, it is again obvious that all is planned to protect the interests of the “Company,” i.e., PMI.

Chapter 10 on scientific publications is intended to give a strong control right to PMI to check any publication well in advance in order to object if there is any element in breach of PMI’s interests, like “patentable or other subject matter” or any “confidential information or company’s Background IP.” Additionally, ETH shall ensure to give, in any publication, appropriate recognition of the support received from the Company. This last provision ensures that PMI can in the future exploit the image of research conducted at ETH, under its strong control, for its own propaganda or marketing purposes.

In another example of the desire to control any information related to this agreement, some provisions of Chapter 15 "Miscellaneous" are striking. Under 15.2, neither party shall "without the respective other Party’s prior written approval advertise or otherwise publicize the existence or terms of this Agreement or the Research Programme or any other aspect of the relationship between the Parties." PMI wanted to keep this agreement as confidential as possible; only "general information concerning the existence of the Research Programme and the identity of the Parties can be made public" (15.3). Let’s translate this in clear terms: PMI wanted to keep secret the fact that this agreement was signed and that they paid ETH more than one million Swiss francs.

One last provision is imposed on ETH. Under 15.4 “If ETH is contacted by a third party, including any news organization, concerning ETH’s Zurich activities in relation to the Company, ETHZ shall: (i) make no comment; (ii) immediately notify Company of the third-party contact; and (iii) refer the third party to the Company.” Therefore, ETH should simply shut up and refer the request to PMI itself. When we sent our information request to the ETHZ under the Federal Act of Transparency, we were not referred to PMI nor we would have accepted it. We consider that some aspects of those provisions are in conflict with the Federal Act on Transparency and PMI has no right to block ETHZ to provide relevant information requested by a third party. But this showcases, PMI obsession with control any minimum detail that could go against its own image or interest. If anybody finances scientific research for the sake of progress and innovation, it should be more attached to transparency than to secrecy.

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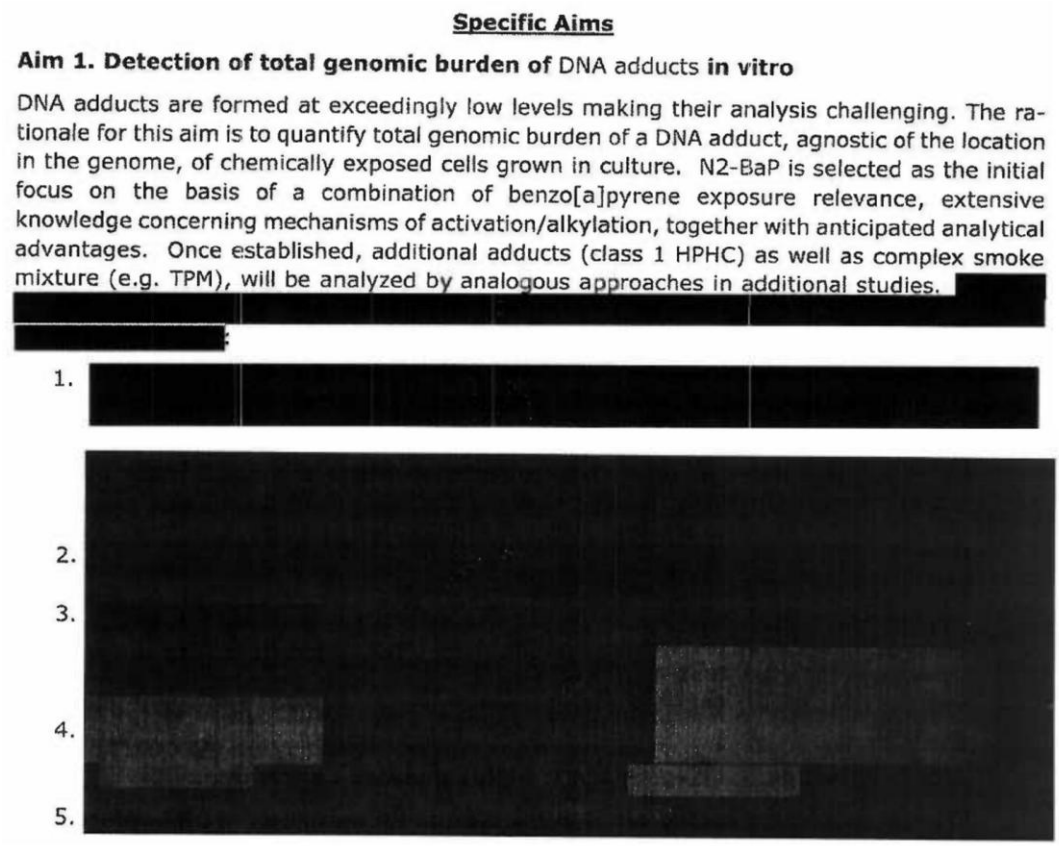


Specific Aims

Aim 1. Detection of total genomic burden of DNA adducts **in vitro**

DNA adducts are formed at exceedingly low levels making their analysis challenging. The rationale for this aim is to quantify total genomic burden of a DNA adduct, agnostic of the location in the genome, of chemically exposed cells grown in culture. N2-BaP is selected as the initial focus on the basis of a combination of benzo[a]pyrene exposure relevance, extensive knowledge concerning mechanisms of activation/alkylation, together with anticipated analytical advantages. Once established, additional adducts (class 1 HPHC) as well as complex smoke mixture (e.g. TPM), will be analyzed by analogous approaches in additional studies. [redacted]

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]

Image 10: Example of an heavily redacted part of Appendix A.

After the agreement, Appendix A regulates the Research Programme Plan under the Project Title: DNA Adducts as Carcinogenesis Biomarkers. This appendix specifies the aims of the research, but some parts of it have been heavily redacted. When a request is submitted to a federal authority, in this case, ETHZ, some information can be redacted, like names of specific persons, to protect their privacy. A request involving a third party, in this case, PMI, is submitted to this third party, which has the right to suggest that some information be redacted for confidentiality reasons. In this case, significant parts are redacted, and we can only speculate why. This is a research agreement, stating what is planned to be researched, not any results. The only conclusion we can draw

is that PMI does not wish any scientific transparency about its full and real research intentions, which is perfectly coherent with the long-standing PMI policy of scientific manipulation.

The PMI-ETHZ agreement was signed in July 2017, and it is obvious that it was initiated by PMI. It was only towards the end of 2018 that Ms. Sturla submitted two requests to the SNSF for grants that also supported this research. [70] Therefore, PMI was fully informed that those SNSF grants were submitted; Ms. Sturla should have informed the SNSF of the already signed agreement and the money received from PMI. Ms. Sturla did not inform the SNSF in accordance with the SNSF ethical requirements, and we can only speculate why. We can also consider that the grant requests to the SNSF were designed to additionally support the already PMI-initiated research.

This contractual agreement between PMI and ETHZ raises significant questions about the integrity and freedom of academic research when intertwined with corporate interests. The stipulations granting PMI extensive rights to control and censor information, and even influence public disclosures, set a concerning precedent for collaborations between academia and industry. Such control not only limits the dissemination of research findings but also contributes to shaping research agendas to favour corporate rather than public interests.

The "Assessment of Raman spectroscopy for single droplet chemical characterization of e-cig aerosol"

Another research agreement was signed between PMI and ETHZ in August 2018, which resulted in the second scientific publication we identified (the "Tracing" article). This research agreement covers a much more specific project directly commissioned by PMI, with the aim of assessing the use of Raman spectroscopy to quantify chemical compounds within individual aerosol droplets produced by an e-cigarette developed at PMI's R&D facility in Neuchâtel. To achieve this, the project employs optical trapping to analyse the droplets in their true aerosol phase.

The research aims to develop a new analytical method combining Raman spectroscopy and optical trapping to chemically characterize individual aerosol droplets, addressing a key limitation of current methods like gas chromatography-mass spectrometry (GC-MS), which only provides average chemical data across an entire aerosol sample. However, a critical limitation of this study is its exclusive focus on a single proprietary PMI product, significantly restricting the generalizability of the findings. The unique design, materials, and aerosol properties of PMI's device may not be representative of the broad range of e-cigarette products available on the market, making it difficult to apply these results to other devices, brands, or product categories.

Raman spectroscopy itself is a powerful analytical technique used to observe vibrational, rotational, and other low-frequency modes in molecules. It works by measuring the inelastic scattering of photons when light interacts with molecular bonds, with the resulting energy shifts providing detailed information about molecular structure and composition. Different types of molecules exhibit unique vibrational patterns, making Raman spectroscopy highly specific and widely used across chemistry, materials science, biotechnology, and physics for material

identification and characterization. It is likely that PMI commissioned the ETH team for this analysis because high-end Raman spectrometers are expensive, and PMI's R&D facilities in Neuchâtel may not have had the necessary equipment or expertise in-house.

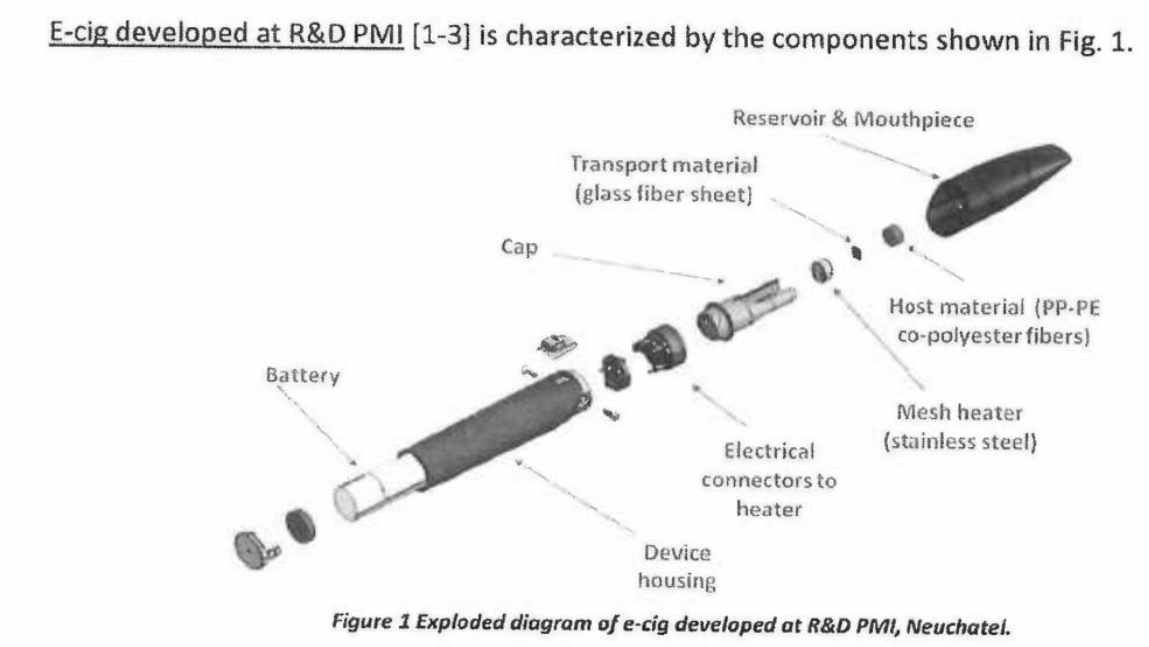


Image 11: Nicocig Mesh used during this study.

The product submitted to this research was an electronic cigarette of the brand Nicocig Mesh, but it seems to have disappeared from the market in 2019 or 2020. PMI acquired in 2014 the UK e-cigarette company Nicocig, however this appeared to be a failed investment. According to Euromonitor data, quoted by TobaccoTactics, PMI's share of the global e-cigarette market was 0.2% in 2019, indicating a continuing fall in market share from the 1.3% it held in 2014.[71]

The Research Agreement in this case is composed just of 2 pages, but in an annexe, we also find a document "Agreement Defining Special Provisions" which amends the standard General Terms and Conditions (GTC) Research ETHZ, in order to strengthen the rights of PMI.

The total amount received by ETHZ for this mandate was CHF 120'000 to cover "*a 50% postdoctoral scientist for laboratory work (equivalent to 3 months full time), use of existing highly specialized research equipment and infrastructure, consumables and replacement parts during operation, Data analysis, consulting and reporting*".

The "Trial Cloud Service" agreement

Following our request to the ETZH to receive all the contracts concluded with any tobacco industries over the last 20 years, we also received a third contract signed with PMI in 2018, for an amount of CHF 45'000.

This agreement outlines that ETHZ will provide Philip Morris International (PMI) with a cloud-based online assessment tool designed to evaluate employees' cognitive strengths and weaknesses through a series of

neuropsychological and personality tests. These include tasks such as the N-back test, the Tower of Hanoi, and time perspective measurements, with individualized reports generated for each employee and aggregated results shared with PMI to enable comparative analysis with past studies.

Critical Commentary

This type of service raises serious concerns about the scientific validity, ethical implications, and potential misuse of cognitive and personality assessments in a corporate setting — especially within a tobacco company like PMI. Tools developed for clinical or research purposes are often misapplied when transferred to workforce management, and the simplistic identification of "strengths and weaknesses" risks oversimplifying complex cognitive traits and reducing employees to numerical scores.

There is no indication in the agreement of how these results will be used by PMI, leaving the door open to problematic applications, such as using cognitive profiles for hiring, promotion, or even termination decisions. This creates a real risk of discrimination, especially when such assessments do not account for cultural, educational, or socio-economic differences that influence performance on these tasks. Moreover, conducting this kind of profiling under the guise of "employee development" — while data and control ultimately rest with a multinational tobacco corporation — raises fundamental ethical questions about employee autonomy, informed consent, and data exploitation.

It is particularly troubling that a leading academic institution like ETHZ lends its scientific credibility to a project with unclear boundaries between research and corporate surveillance. This type of collaboration risks normalizing invasive psychological monitoring in the workplace, with limited oversight on how the data might be combined with other employee information over time. Ultimately, this service appears to be less about employee development and more about gaining intrusive insight into employees' cognitive profiles, with significant potential for misuse in ways that could harm workers' rights and privacy.

The ETHZ ethical position on collaborations with the tobacco industry

ETHZ was founded in 1855 under the name “Polytechnikum” as a federal technical university with a clear purpose to serve and support the Swiss industrialization. Throughout its history, ETHZ always had close links and collaborations with various industrial branches. For a long time, those collaborations did not appear to be submitted to any ethical considerations.

Like any other research institution, ethical considerations are becoming increasingly important. For instance, ETHZ revised and implemented new rules of procedure to address scientific misconduct in June 2024.[72] During our discussion with ETHZ, we learned that further reflections on how to strengthen ethical standards in research are ongoing.

It became clear, during our discussions, that sensitivity towards collaboration with a very problematic industry like the tobacco industry is changing. If ETHZ is still currently refraining from naming a specific industry and banning any collaboration with it, the situation today is very different from the one of 2017/2018, when the

contracts we obtained were signed. From our understanding, signing such contracts today would probably be excluded.

An ethical reflection is ongoing and takes a certain time for a large and complex institution like ETHZ. From our point of view, we encourage ETHZ to totally ban any cooperation with the tobacco and nicotine industry.

Conclusion

Over the years, tobacco companies such as Philip Morris have employed a sophisticated strategy of funding biased research to influence scientific understanding and public perception regarding the health effects of smoking. Central to this strategy is the selective funding of research projects. These companies strategically cherry-pick topics, often favoring studies that would likely yield results minimizing the role of smoking, and today of heated tobacco products, in lung cancer, such as those focusing on genetic factors. This is coupled with supporting studies that produced contradictory or inconclusive results about the harms of smoking, and now concentrate on minimizing the impact of new tobacco and nicotine products, thereby creating a cloud of doubt and confusion both in the scientific community and among the public.

Philip Morris exert significant control over the outcomes of the research they fund. This control extend to influencing the design of research studies, including the selection of specific variables and methodologies. Even the interpretation of data is not immune to their influence, as these companies often play a role in how results are reported and presented, consistently in a way that downplayed the risks associated with tobacco and nicotine products.

The selective publishing of research findings is another tactic. Tobacco companies like Philip Morris would often publish only those findings that are favourable to them while withholding or downplaying harmful results. They even go as far as sponsoring scientific journals or specific articles that would publish research supporting their narrative.

These strategies effectively contribute to a significant misrepresentation of the scientific consensus on smoking and health. Tobacco companies amplify their funded research to propagate a false narrative of significant scientific disagreement about the harms of smoking. They champion the rhetoric of "sound science," calling for unreasonable levels of proof about the harms of smoking and setting an almost impossibly high bar for evidence.

The impact of these strategies is profound. They successfully undermine public health messages, making it difficult for clear and unequivocal health warnings to reach the public. This obfuscation delay regulatory actions and litigation against tobacco companies. Moreover, such practices raise significant ethical concerns about the integrity of scientific research when influenced by corporate interests with a vested agenda.

In recent years, as the overwhelming evidence about the dangers of smoking has become indisputable, these tactics have been increasingly scrutinized and criticized. Regulatory measures, legal actions, and a more informed

public have constrained the ability of tobacco companies to blatantly fund biased research. However, the “new normal” of the tobacco industry is to admit the harm of smoking tobacco and to pretend they want now to help smokers to quit with the help of their new commercial products. The way they continue to manipulate scientific research is thus moving away from denying the harm of cigarettes. Now they try to demonstrate that heated tobacco products (which provide an increasing source of benefits for those companies) are almost with no harm in comparison to cigarettes.

Therefore, their manipulative practices continue to influence current debates on corporate-funded research, underscoring the critical need for transparency and integrity in the scientific field. This narrative outlines the strategic approach taken by tobacco companies in manipulating scientific research, highlighting the ethical implications and long-term impact on public health and policy.

Luciano Ruggia, AT Director

[1] Jiang Y, Mingard C, Huber SM, et al. Quantification and Mapping of Alkylation in the Human Genome Reveal Single Nucleotide Resolution Precursors of Mutational Signatures. ACS Cent. Sci. 2023.
[2] The listed keywords were "Adducts, Cancer, Genetics, Genomics, Peptides and Proteins". When some keywords are missing (in this case smoking, tobacco, etc.) makes the article difficult to find and can contribute to hide it from scrutiny.
[3] Jiang, Yang; Mingard, Cécile; Huber, Sabrina M.; Takhaveev, Vakil; McKeague, Maureen; Kizaki, Seiichiro et al. (2023): Quantification and Mapping of Alkylation in the Human Genome Reveal Single Nucleotide Resolution Precursors of Mutational Signatures. In ACS Cent. Sci., Article acscentsci.2c01100. DOI: 10.1021/acscentsci.2c01100.
[4] Li, Wentao; Hu, Jinchuan; Adebali, Ogun; Adar, Sheera; Yang, Yanyan; Chiou, Yi-Ying; Sancar, Aziz (2017): Human genome-wide repair map of DNA damage caused by the cigarette smoke carcinogen benzoapyrene. In Proceedings of the National Academy of Sciences of the United States of America 114 (26), pp. 6752–6757. DOI: 10.1073/pnas.1706021114.
[5] Wang H, Liu B, Chen H, et al. Dynamic changes of DNA methylation induced by benzo(a)pyrene in cancer. Genes Environ 2023;45(1):21. doi:10.1186/s41021-023-00278-1 [published Online First: 1 July 2023].
[6] https://ethz.ch/en/news-and-events/eth-news/news/2023/02/where-do-toxins-from-tobacco-attack-dna.html (last consulted on 21.12.2023)
[7] https://www.research-collection.ethz.ch/handle/20.500.11850/603875 (last consulted 03.02.2024)
[8] Jiang Y, Mingard C, Huber SM, et al. Correction to "Quantification and Mapping of Alkylation in the Human Genome Reveal Single Nucleotide Resolution Precursors of Mutational Signatures". ACS Cent. Sci. 2024.
[9] O'Connor R, Durkin SJ, Cohen JE*, et al,* Thoughts on neologisms and pleonasm in scientific discourse and tobacco control, *Tobacco Control* 2021;30:359-360. https://tobaccocontrol.bmj.com/content/30/4/359
[10] Davies, Madlen; Stockton, Ben; Chapman, Matthew; Cave, Tamasin (2020): The 'Unsmoke' screen: the truth behind PMI's cigarette-free future. In The Bureau of Investigative Journalism, 2/24/2020. Available online at https://www.thebureauinvestigates.com/stories/2020-02-24/the-unsmoke-screen-the-truth-behindpmis-cigarette-free-future.
[11] Fitzpatrick, Iona; Dance, Sarah; Silver, Karin; Violini, Marzia; Hird, Thomas R. (2022): Tobacco industry messaging around harm: Narrative framing in PMI and BAT press releases and annual reports 2011 to 2021. In Frontiers in public health 10, p. 958354. DOI: 10.3389/fpubh.2022.958354.
[12] https://tobaccoreporter.com/2022/09/01/utc-to-manufacture-philip-morris-products-for-egypt/
[13] Philip Morris International Reports 2024 Fourth-Quarter & Full-Year Results, February 6, 2025, https://www.pmi.com/investor-relations/press-releases-and-events/press-releases-overview/press-release-details/?newsId=28366 (last consulted 21.02.205)
[14] Tobacco Tactics page on Heated Tobacco Products: https://tobaccotactics.org/wiki/heated-tobacco-products/ (last consulted on 21.12.2023)
[15] https://www.pmiscience.com/en/research/product-assessment-approach/platform-development/ths-mainstream-aerosol-compared-to-reference-cigarette-smoke/ (last consulted on 21.12.2023)
[16] https://www.at-schweiz.ch/at-blog/95percent
[17] https://www.fda.gov/tobacco-products/ctp-newsroom/fda-authorizes-reduced-exposure-claim-iqos-3-system-holder-and-charger (last consulted 30.01.2024)
[18] Uguna CN, Snape CE. Should IQOS Emissions Be Considered as Smoke and Harmful to Health? A Review of the Chemical Evidence. ACS Omega 2022.
[19] Lyytinen, Gustaf; Melnikov, Georgy; Brynedal, Amelie; Anesäter, Erik; Antoniewicz, Lukasz; Blomberg, Anders et al. (2024) Use of heated tobacco products (IQOS) causes an acute increase in arterial stiffness and platelet thrombus formation. In : Atherosclerosis, vol. 390, p. 117335. DOI: 10.1016/j.atherosclerosis.2023.117335.
[20] https://iqosuae.ae/blog/iqos-heating-system-safer-than-cigarettes/ (last consulted 01.02.2024)

[21] Szostak, Justyna; Boué, Stéphanie; Talikka, Marja; Guedj, Emmanuel; Martin, Florian; Phillips, Blaine et al. (2017): Aerosol from Tobacco Heating System 2.2 has reduced impact on mouse heart gene expression compared with cigarette smoke. In Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 101, pp. 157–167. DOI: 10.1016/j.fct.2017.01.013.

[22] Uguna, Clement N.; Snape, Colin E. (2022): Should IQOS Emissions Be Considered as Smoke and Harmful to Health? A Review of the Chemical Evidence. In ACS Omega, Article acsomega.2c01527. DOI: 10.1021/acsomega.2c01527.

[23] Tattan-Birch, Harry; Hartmann-Boyce, Jamie; Kock, Loren; Simonavicius, Erikas; Brose, Leonie; Jackson, Sarah et al. (2022): Heated tobacco products for smoking cessation and reducing smoking prevalence. In Cochrane Database of Systematic Reviews 2022 (1). DOI: 10.1002/14651858.CD013790.pub2.

[24] Julia Hoeng, Nicolas Sierro, Nikolai V. Ivanov - Philip Morris Products SA, Quai Jeanrenaud 3, Neuchatel 2000, Switzerland.

[25] The assertion that "the production of evidence is a social construction" reflects a key tenet in the philosophy of science, suggesting that scientific knowledge is influenced by social, political, and cultural contexts. This perspective is supported by philosophers like Thomas Kuhn and Bruno Latour. Kuhn's notion of "paradigms" in "The Structure of Scientific Revolutions" argues that scientific progress is not purely objective but is deeply influenced by the prevailing scientific consensus, which is shaped by socio-cultural factors. Similarly, Latour, in works like "Science in Action," emphasizes that scientific facts are constructed through complex social processes involving negotiation, persuasion, and consensus among scientists. These frameworks suggest that how research questions are framed, how problems are defined, and the choice of language can all shape the outcomes of research, aligning with the idea that research does not exist in a vacuum but is part of broader societal narratives and power structures.

[26] Bero, Lisa A. (2005): Tobacco industry manipulation of research. In Public health reports (Washington, D.C. : 1974) 120 (2), pp. 200–208. DOI: 10.1177/003335490512000215.

[27] From the SNF Grants Database, Grant 185020: Status: Ongoing, Start: 01.01.2020, End: 31.12.2023, Approved amount: 588,000 CHF. See https://data.snf.ch/grants/grant/185020 .

[28] From the SNF Grants Database, Grant 186332: Status: Ongoing Start: 01.01.2020 End: 31.12.2023 Approved amount: 2,027,990 CHF. See https://data.snf.ch/grants/grant/186332 .

[29] https://www.pmiscience.com/en/research/publications-library/ (last consulted on 21.12.2023)

[30] https://www.pmiscience.com/en/research/publications-library/quantification-and-mapping-of-alkylation-in-the-human-genome-rev/ (last consulted on 21.12.2023)

[31] Mingard C, Battey JND, Takhaveev V, et al. Dissection of Cancer Mutational Signatures with Individual Components of Cigarette Smoking. *Chem. Res. Toxicol.* 2023;36(4):714–23. doi:10.1021/acs.chemrestox.3c00021 [published Online First: 28 March 2023].

[32] https://www.acs.org/pressroom/newsreleases/2017/november/shana-sturla-new-editor-in-chief-of-chemical-research-in-toxicology.html (last consulted on 31.12.2023)

[33] https://www.research-collection.ethz.ch/handle/20.500.11850/610051 (last consulted 02.01.2024)

[34] Sturla SJ, Boobis AR, FitzGerald RE, et al. Systems toxicology: from basic research to risk assessment. Chem. Res. Toxicol. 2014;27(3):314–29. doi:10.1021/tx400410s [published Online First: 21 January 2014].

[35] In the SNSF web page related to this grant, this publication is not mentioned: https://data.snf.ch/grants/grant/136247 (last consulted on 10.01.2024).

[36] Constantinescu S, Sturla SJ, Marra G, et al. Computational Data Integration in Toxicogenomics. In: Peitsch MC, Hoeng J, eds. Computational Systems Toxicology. New York, NY: Springer Verlag 2015:371–92.

[37] https://www.research-collection.ethz.ch/handle/20.500.11850/112846 (last consulted 29.01.2024)

[38] Hartung T, FitzGerald RE, Jennings P, et al. Systems Toxicology: Real World Applications and Opportunities. Chem. Res. Toxicol. 2017;30(4):870–82. doi:10.1021/acs.chemrestox.7b00003 [published Online First: 31 March 2017].

[39] Iskandar AR, Martinez Y, Martin F, et al. Comparative effects of a candidate modified-risk tobacco product Aerosol and cigarette smoke on human organotypic small airway cultures: a systems toxicology approach. Toxicol Res (Camb) 2017;6(6):930–46. doi:10.1039/c7tx00152e [published Online First: 28 September 2017].
[40] Smith M, Haziza C, Hoeng J, et al. The Science behind the Tobacco Heating System: A Summary of Published Scientific Articles 2017.
[41] David G, Parmentier EA, Taurino I, et al. Tracing the composition of single e-cigarette aerosol droplets in situ by laser-trapping and Raman scattering. *Sci Rep* 2020;10(1):7929. doi:10.1038/s41598-020-64886-5 [published Online First: 13 May 2020].
[42] https://www.research-collection.ethz.ch/handle/20.500.11850/414847 (last consulted on 25.01.2024)
[43] https://data.snf.ch/grants/grant/172472 (last consulted on 28.01.2024)
[44] David G, Parmentier EA, Taurino I, et al. Assessment of the Chemical Evolution of E-Cigarette Droplets. Chimia (Aarau) 2020;74(9):733.
[45] https://www.pmi.com/glossary-section/glossary/veev (last consulted on 25.01.2024)
[46] Since 2014 and the Directive 2014/40/UE du Parlement européen et du Conseil du 3 avril 2014 relative au rapprochement des dispositions législatives, réglementaires et administratives des États membres en matière de fabrication, de présentation et de vente des produits du tabac et des produits connexes, et abrogeant la directive 2001/37/CE, JO L 127 du 29.4.2014, p. 1. Article 20 (2023). En ligne : https://eur-lex.europa.eu/legal-content/FR/TXT/?uri=CELEX%3A02014L0040-20150106, consulté le 1 juin 2023.
[47] Tobacco Tactics page on Influencing Science: Commissioning Research and Reviews https://tobaccotactics.org/wiki/influencing-science-commissioning-research-and-reviews/ (last consulted on 13.12.2023)
[48] Freeman, B.; Vittiglia, A.; Winstanley, M. (2018): 10A.3 Mechanisms of influence—Industry-funded research. In M. M. Scollo, M. H. Winstanley (Eds.): Tobacco in Australia: Facts and issues. Melbourne. Available online at https://www.tobaccoinaustralia.org.au/chapter-10-tobacco-industry/indepth-10a-strategies-for-influence/10a-3-the-mechanisms-of-influence-industry-funded-.
[49] Vital Strategies (2019): Crooked Nine. Nine ways the tobacco industry undermines health policy. New York. Available online at https://exposetobacco.org/resources/crookednine/.
[50] Briggs, Jodie; Vallone, Donna (2022): The Tobacco Industry's Renewed Assault on Science: A Call for a United Public Health Response. In Am J Public Health 112 (3), pp. 388–390. DOI: 10.2105/AJPH.2021.306683.
[51] Grüning, Thilo; Gilmore, Anna B.; McKee, Martin (2006): Tobacco industry influence on science and scientists in Germany. In Am J Public Health 96 (1), pp. 20–32. DOI: 10.2105/AJPH.2004.061507.
[52] Auer, Reto; Concha-Lozano, Nicolas; Jacot-Sadowski, Isabelle; Cornuz, Jacques; Berthet, Aurélie (2017): Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. In JAMA internal medicine 177 (7), pp. 1050–1052. DOI: 10.1001/jamainternmed.2017.1419.
[53] Philip Morris attaque une étude. Un article de l'Université de Lausanne mis en cause. (2017). In Le Nouvelliste, 6/9/2017. Available online at https://www.lenouvelliste.ch/suisse/philip-morris-attaque-une-etude-677015.
[54] Neroth P. Tobacco ties. *Lancet* 2004;364(9438):925–26.
[55] Legg T, Hatchard J, Gilmore AB. The Science for Profit Model-How and why corporations influence science and the use of science in policy and practice. PLOS ONE 2021;16(6):e0253272. doi:10.1371/journal.pone.0253272 [published Online First: 23 June 2021].
[56] Gallus S, Garattini S. Heated tobacco products in Italy. Tabaccologia 2023;21(31.07.2023). https://www.tabaccologiaonline.it/article/view/80.
[57] Godlee, Fiona; Malone, Ruth; Timmis, Adam; Otto, Catherine; Bush, Andy; Pavord, Ian; Groves, Trish (2013): Journal policy on research funded by the tobacco industry. In BMJ (Clinical research ed.) 347, f5193. DOI: 10.1136/bmj.f5193.
[58] A new policy on tobacco papers (2010). In *PLOS Medicine* 7 (2), e1000237.

[59] Knight I, Rattan R (2013). Medical journals refuse to publish tobacco-funded research. The Conversation, 16 October 2013. Available at: https://theconversation.com/medical-journals-refuse-to-publish-tobacco-funded-research-19201.
[60] Morabia, Alfredo (2022): Scientific Publishing and the Tobacco Industry. In Am J Public Health 112 (7), p. 951. DOI: 10.2105/AJPH.2022.306916.
[61] Pattemore, Philip; Edwards, Richard (2022): Tobacco company funding and conflict of interest. In *The Lancet*. DOI: 10.1016/S0140-6736(22)01289-2.
[62] 1 UICC. The smokescreen of the tobacco industry's use of science 2021. Available at: https://www.uicc.org/news/smokescreen-tobacco-industrys-use-science. (last consulted on 21.12.2023)
[63] Cohen, J. E.; Ashley, M. J.; Ferrence, R.; Brewster, J. M.; Goldstein, A. O. (1999): Institutional addiction to tobacco. In Tob Control 8 (1), pp. 70–74. DOI: 10.1136/tc.8.1.70.
[64] https://www.worldwidecancerresearch.org/for-researchers/research-policies/our-tobacco-industry-funding-policy/
[65] https://www.uicc.org/news-and-updates/announcements/uicc-withdraws-world-cancer-series (last consulted on 24.02.2025)
[66] Sweney, Mark; Bawden, Anna (2024) Economist Group cancer conference cancelled due to links to tobacco firms. Exclusive: Speakers and attendees pull out of Economist Impact event over ties to Philip Morris and Japan Tobacco. In : The Guardian, 21 septembre 2024. En ligne : https://www.theguardian.com/media/2024/sep/21/economist-group-cancer-conference-cancelled-due-to-links-to-tobacco-firms.
[67] https://www.at-schweiz.ch/fr/news-media/news/20-ans-cclat/
[68] WHO (2003): WHO Framework Convention on Tobacco Control. Geneva: World Health Organization.
[69] Loi fédérale sur le principe de la transparence dans l'administration (Loi sur la transparence, LTrans, 152.3), Available at : https://www.fedlex.admin.ch/eli/cc/2006/355/fr
[70] https://data.snf.ch/grants/grant/185020 and https://data.snf.ch/grants/grant/186332 (consulted on 05.03.2025)
[71] https://www.tobaccotactics.org/article/e-cigarettes-philip-morris-international/ (consulted on 05.03.2025)
[72] https://ethz.ch/staffnet/en/news-and-events/internal-news/archive/2024/02/new-rules-of-procedure-to-address-scientific-misconduct-are-adopted.html (consulted on 05.03.2025)

Trial Cloud Services Agreement (the "Agreement")

This Agreement is made by (1) Philip Morris International Management SA of Avenue de Rhodanie 50, 1007 Lausanne, Switzerland (the "**Client**"), and (2) [redacted] ETH Zurich, Rämistrasse 101, 8092 Zurich, Switzerland (the "**Supplier**"), (each a "**Party**" and together the "**Parties**").

1. **Cloud Services:** The Supplier shall deliver an online assessment tool that provides a task battery for employees to learn about cognitive strengths and weaknesses (together the "**Cloud Services**").

2. **Term:** This Agreement commences on 15.06.2018 and automatically expires on 01.10.2018 (the "**Term**").

3. **Fees:** The fees for the Cloud Services are 45k CHF and will be invoiced in one instalment.

4. **Intellectual Property Rights**

4.1 The Supplier owns or licences all Intellectual Property Rights in and to the Cloud Services and grants the Client a worldwide, non-exclusive, right to access and use the Cloud Services during the Term.

4.2 The Client owns or licences all Intellectual Property Rights in Client Data and grants the Supplier a limited licence to use the Client Data for the purposes of providing the Cloud Services during the Term.

5. **Information Security:** The Supplier shall comply with the Client's information security requirements set out at [redacted]

6. **Data Protection**

6.1 *Particulars of the Processing:*

(a) Subject Matter of the processing: Neuropsychological battery of tests that features tasks such as the N-back, Tower of Hanoi, Time perspective measurement, Personality assessments, etc.
(b) Duration of the processing: Time to complete all tasks takes a maximum of 3 hours per candidate.
(c) Nature and purpose of the processing: The results will be compiled in an individualized report and sent back to the respective employee. The averages of all participants, compared to those of previous studies, will be used to produce comparison analyses.
(d) Type of personal data being processed: Business email, name, tenure, age, type of education and background (control variables).
(e) Categories of data subjects: The resulting report is being generated with the help of Supplier's researchers (a Senior Scientist and a Research Assistant) who will handle the data under confidentiality agreements and will only share individual results with each of the concerned individuals. Only averages of all participants will be communicated to the company.

6.2 *Relationship of the parties:* The Supplier shall process the Client Personal Data, as a processor, on behalf of the Client, as a controller, for the purposes described in this Agreement and strictly in accordance with the documented instructions of the controller (the "**Permitted Purpose**"), except where otherwise required by any EU (or any EU Member State) law applicable to the processor. In no event shall the Supplier process the Client Personal Data for its own purposes or those of any third party. Each party shall comply with the obligations that apply to it under Applicable Data Protection Law.

6.3 *International transfers:* The Supplier shall not transfer (or permit the transfer of) the Client Personal Data outside of the European Economic Area ("**EEA**") unless (i) it has first obtained the Client's prior written consent; and (ii) it has taken such measures as are necessary to ensure the transfer is in compliance with Applicable Data Protection Law.

6.4 *Confidentiality of processing:* Subject to the below paragraph, the Supplier shall ensure that any person that it authorises or permits to process the Client Personal Data shall: (i) be subject to a strict duty of confidentiality; and (ii) only process the Client Personal Data only as necessary for the Permitted Purpose.

6.5 *Subprocessing:* The Supplier shall not subcontract any processing of the Client Personal Data to a third party subprocessor without the prior written consent of the Client.

6.6 *Security:* The Supplier shall implement appropriate technical and organisational measures to protect the Client Personal Data (i) from accidental or unlawful destruction, and (ii) loss, alteration, unauthorised disclosure of, or access to, the Client Personal Data, (each a "**Security Incident**")

6.7 *Security incidents:* Upon becoming aware of a Security Incident, the Supplier shall inform the Client without undue delay and shall provide all such timely information and cooperation as the Client may require in order for the Client to fulfil its data breach reporting obligations under (and in accordance with the timescales required by) Applicable Data Protection Law. The Supplier shall further take all such measures and actions as are necessary to remedy or mitigate the effects of the Security Incident and shall keep the Client of all developments in connection with the Security Incident.

6.8 *Cooperation and data subjects' rights:* The Supplier shall provide all reasonable and timely assistance to the Client to enable the Client to respond to: (i) any request from a data subject to exercise any of its rights under Applicable Data Protection Law; and (ii) any other correspondence, enquiry or complaint received from a data subject, regulator or other third party in connection with the processing of the Client Personal Data. In the event that any such request, correspondence, enquiry or complaint is made directly to the processor, the Supplier shall promptly inform the Client providing full details of the same.

6.9 *Deletion or return of Data:* Upon termination or expiry of this Agreement, the Supplier shall (at the Client's election) destroy or return to the Client all Client Personal Data (including all copies) in its possession or control (including any Client Personal Data which is in the possession of a third party for subprocessing). This requirement shall not apply to the extent that the Supplier is required by any EU (or any EU Member State) law to retain some or all of the Client Personal Data, in which event the Supplier shall isolate and protect such Client Personal Data from any further processing except to the extent required by such law.

6.10 *Audit:* The Supplier shall permit the Client (or its appointed third party auditors) to audit the Supplier's compliance with this clause 6 (Data Protection), and shall make available to the controller all information, systems and staff necessary for the Client (or its third party auditors) to conduct such audit.

7. **Confidentiality**

7.1 From time to time during the term of this Agreement, either Party and its Affiliates (as the "**Disclosing Party**") may disclose or make available to the other Party (as the "**Receiving Party**") information about its business affairs, products or services, confidential Intellectual Property Rights, trade secrets, third-party confidential information and other sensitive or proprietary information (collectively, "**Confidential Information**"). Confidential Information shall not include information that, at the time of disclosure and as established by documentary evidence: (i) is or becomes generally available to and known by the public other than as a result of, directly or indirectly, any breach of this clause by the Receiving Party or any of its representatives, (ii) is or becomes available to the Receiving Party on a non-confidential basis from a third-party source, provided that such third party is not and was not prohibited from disclosing such Confidential Information, (iii) was known by or in the possession of the Receiving Party or its representatives prior to being disclosed by or on behalf of the Disclosing Party; (iv) was or is independently developed by the Receiving Party without reference to or

use, in whole or in part, of any of the Disclosing Party's Confidential Information; or (v) is required to be disclosed pursuant to applicable law, regulation or a valid order issued by a court or governmental agency of competent jurisdiction.

7.2 The Receiving Party shall: (A) protect and safeguard the confidentiality of the Disclosing Party's Confidential Information with at least the same degree of care as the Receiving Party would protect its own Confidential Information, but in no event with less than a commercially reasonable degree of care; (B) not use the Disclosing Party's Confidential Information, or permit it to be accessed or used, for any purpose other than to exercise its rights or perform its obligations under this Agreement; and (C) not disclose any such Confidential Information to any person or entity, except to the Receiving Party's representatives who need to know the Confidential Information to assist the Receiving Party, or act on its behalf, to exercise its rights or perform its obligations under the Agreement.

7.3 At the Disclosing Party's written request, the Receiving Party shall promptly return, and shall require its representatives to return to the Disclosing Party all copies, whether in written, electronic or other form or media, of the Disclosing Party's Confidential Information.

7.4 The obligations of confidentiality contained in this Agreement shall continue in force indefinitely.

7.5 The Parties acknowledge that either Party's breach of this clause would cause the other Party irreparable injury for which damages would not be an adequate remedy. Therefore, in the event of such breach, the non-breaching Party may seek injunctive relief in addition to any other remedies it may have.

8. Return of Client Data: At the Client's written request, the Supplier shall promptly return all copies, whether in written, electronic or other form or media, of the Client Data.

9. General Provisions

9.1 The Supplier is and shall remain an independent contractor and this Agreement shall not be construed to create an association, partnership or joint venture, relation of principal and agent or of employer and employee between the Client and the Supplier. The Supplier shall not be considered nor shall it hold itself out to be an agent, employee or partner of any member of the Client Group for any purpose. The Supplier is not authorised, nor shall it purport to be authorised, to create obligations binding on any member of the Client Group.

9.2 This Agreement shall not be amended except by an agreement in writing signed by both Parties.

9.3 This Agreement sets out the entire agreement between the Parties and supersedes all prior agreements, arrangements and understandings, oral or written, between the Parties relating to the subject matter of this Agreement. The standard terms and conditions of the Supplier or any member of the Client Group shall be without legal effect in transactions under this Agreement.

9.4 This Agreement shall be binding upon and shall inure to the benefit of the Parties, their respective successors and assigns. The Parties shall not, nor shall they purport to, assign or encumber all or any part of their obligations or rights under this Agreement without the other Party's prior written consent.

9.5 No delay, omission or failure by either Party to exercise any of its rights under this Agreement shall be deemed to be a waiver of such rights or an acquiescence in the event giving rise to such right, but every such right may be exercised from time to time and as often as may be deemed expedient by the Party exercising such right.

9.6 Notices under this Agreement shall be void unless in writing and may be given or made by personal delivery or by prepaid registered post or by fax addressed to the intended recipient at the address specified on the first page of this Agreement in respect of the relevant Party (or at such other address as such Party may last have specified to the other Party in writing) and if so served shall, in the case of a notice sent by post, be deemed to be served on the third day following the date of posting and, if by personal delivery or by fax, on the date of such delivery.

9.7 This Agreement may be executed in any number of counterparts, each of which shall be an original, but all of which shall constitute one instrument.

9.8 Should any of the provisions of this Agreement be ineffective due to being invalid, illegal or unenforceable (an "**Ineffective Provision**"), such Ineffective Provision shall be ineffective only to the extent of such invalidity, illegality or unenforceability, without invalidating the remainder of such provisions or the remaining provisions of this Agreement. The Parties agree to attempt to substitute for any Ineffective Provision a valid, legal and enforceable provision which achieves to the greatest extent possible the economic, legal and commercial objectives of the Ineffective Provision.

9.9 This Agreement shall be governed by the laws of England and Wales without regard to its conflict of laws provisions. The application of the Vienna Convention on the Sale of Goods is excluded. The Parties agree to the exclusive jurisdiction of the courts of England, for the adjudication of any disputes arising under this Agreement.

10. Definitions and interpretation

10.1 In this Agreement:

"**Affiliate**" means an entity that, either directly or indirectly, controls, is controlled by, or is under common control with, the relevant entity, where "control" means the ability to direct the affairs of another by ownership, contract or otherwise.

"**Applicable Data Protection Law**" shall mean: (i) prior to 25 May 2018, Directive 95/46/EC of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data; and (ii) on and after 25 May 2018, Regulation 2016/679 of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) and "**controller**", "**processor**", "**data subject**", "**personal data**" and "**processing**" (and "**process**") shall have the meanings given in Applicable Data Protection Law.

"**Client Data**" means data that either: (a) the Client, or a person acting on its behalf, provides to the Supplier, or permits the Supplier to access, in connection with this Agreement; or (b) the Supplier creates in providing the Cloud Services. "**Client Personal Data**" means Client Data that is personal data.

"**Client Group**" means the Client and all its Affiliates (and "member of the Client Group" shall be construed accordingly).

"**Intellectual Property Rights**" means copyrights and related rights, moral rights, database rights, patents, industrial designs, utility models, supplementary protection certificates, petty patents, design rights, trade marks, service marks, trade names, rights in internet addresses and domain names, rights to goodwill or to sue for passing off, rights in unfair competition, rights in undisclosed or confidential information (such as know-how, trade secrets, inventions and other rights in confidential or proprietary information), and other rights of a similar nature, in each case whether registered or unregistered and including all applications (or rights to apply) for (and for renewals and extensions of such rights) such rights, as may now or in the future subsist anywhere in the world and all goodwill associated with them throughout the world.

Client:	[redacted]		**Supplier:**		[redacted]
By:		By:	By:		By:
Name:		Name:	Name:		Name:
Title:	[redacted]	Title:	Title:		Title: PROF. DIR.
Date:	10.07.2018	Date: 10.07.2018	Date:		Date: 2.7.18

RESEARCH AGREEMENT

by and among

ETH Zurich (Eidgenössische Technische Hochschule Zürich)
[redacted]
Raemistrasse 101
8092 Zurich, Switzerland

("**ETH Zurich**")

and

Philip Morris Products S.A.
Quai Jeanrenaud 5,
2000 Neuchâtel, Switzerland

("**Company**")

concerning the research programme "Evaluation of RRTP Prototypes"

PREAMBLE

A The Company scientifically explores and develops novel tobacco products that reduce or eliminate harmful and potentially harmful constituents (Risk Reduced Tobacco Products, RRTPs).

B In order to scientifically examine and evaluate RRTP prototypes (or components thereof) developed by or under the control of the Company, the Company is interested in implementing a Research Programme (Section 1.11) with the ETH Zurich.

C The present Research Agreement provides the terms and condition which shall apply such Research Programme.

Now, therefore, ETH Zurich and the Company (each referred to herein individually as a "Party" and collectively as the "Parties") agree to the following provisions:

[redacted]

1. DEFINITIONS

1.1 "**Affiliate**" means an entity that, either directly or indirectly, controls, is controlled by, or is under common control with, the relevant Party, and "control" means the ability, directly or indirectly, to direct the affairs of another by means of ownership, contract or otherwise.

1.2 "**Agreement**" means this Research Agreement.

1.3 "**Company Field**" means devices and accessories (or parts thereof) for products that can be consumed and/or consist, even partly, of tobacco, that are intended or not indended to be smoked, and that are likely to present, or have the potential to present less risk of harm than conventional tobacco products.

1.4 "**Confidential Information**" shall include all business and/or technical information (i) concerning the terms and conditions of this Agreement and each Research Programme, (ii) concerning the respective products, operations, research and development efforts, inventions, trade secrets, computer software, plans, intentions, market opportunities, processes, recipes, formulae, vendor and customer relationships, finances and other business operations and affairs of the disclosing Party and its Affiliates, and (iii) of third parties that the disclosing Party maintains in confidence, disclosed to the receiving Party in written and/or other materials, through the receiving Party's access to the premises, equipment or facilities of the disclosing Party or any of its Affiliates or by oral communication with employees, consultants or agents of the disclosing Party or its Affiliates, and all tangible embodiments of such information. The Confidential Information of each Party shall include the Confidential Information of its Affiliates.

1.5 "**Effective Date**" means the date of the last signature to this Agreement.

1.6 "**Expiration Date**" means the date when the last Research Project under the Research Programme is fully accomplished.

1.7 "**Project Results**" means all intellectual and industrial property rights, including, in particular, but not limited to, patents, utility models, copyrights, domain names, know-how, diagrams, logos, plans, all types of data, technical notes, prototypes, processes, methods, algorithms, all technical documentation, software generated under a Research Project.

1.8 "**Project Inventions**" means patentable Project Results.

1.9 "**Research Programme**" means, collectively, the Research Projects concerning the "Evaluation of RRTP Prototypes" performed under the Agreement, in substantially the form set out in Appendix A.

2. SUBJECT OF THE AGREEMENT

2.1 The Agreement sets forth the terms and conditions applicable to the Research Programme carried out by the Parties.

2.2 The Research Programme shall be structured in the form set out by Appendix A and, *inter alia*, shall describe the following aspects:

(a) Title of the Research Project

(b) Description of the Research Project

(c) Research questions

(d) Methods and research design

(e) Reports

(f) Commencement date and project timeline

(g) Remuneration

(h) Expenses

(i) Payment terms and invoicing

(j) Supplemental Conditions (if any)

3. PROJECT ORGANISATION

3.1 The Parties hereby designate the following persons as managers for the Research Programme ("Project Managers"):

- from ETH Zurich: [redacted]
- from Company: [redacted]

3.2 All correspondence relating to this Agreement and the applicable Research Programme must be addressed to the Project Managers. Legal questions and matters relating to intellectual property should, in addition, be addressed to:

ETH transfer
Rämistrasse 101
CH-8092 Zurich
Tel +41 (0)44 632 23 82, Fax +41 (0)44 632 11 84
E-mail transfer@sl.ethz.ch.

3.3 The Parties will coordinate the performance of the Research Programme and will support each other to the best of their abilities.

3.4 They will provide each other with all documents, objects, technical aids and resources required to carry out a Research Programme.

3.5 Programme meetings will take place as provided in the applicable Research Programme or as required upon agreement of the Parties.

4. REPORTS

[redacted]

4.1 ETH Zurich shall submit to Company written interim progress reports on a schedule agreed in the Research programme but at least after completion of the applicable r (Section 4.2 below). Such reports shall describe the technical progress made and the Project Results and identify any problems as may have been encountered.

4.2 ETH Zurich shall submit to Company for the Research Programme a final report within two (2) months after completion or abandonment. The final reports shall provide a detailed description of the research activities which have been conducted and provide all Project Results in detail.

4.3 Upon Company's request, ETH Zurich shall answer or clarify any questions Company might have in connection with an interim report or a final report.

5. REMUNERATION

5.1 In consideration of ETH Zurich's services rendered in connection with the Research Programme the Company shall compensate ETH Zurich in accordance with this Agreement. The total amount of such compensation (plus VAT, if applicable) shall be provided in the Research Programme in Appendix A and C and in Swiss Francs [CHF] based on a budget that shall include:

(a) Salary costs

(b) Consumables and equipment

(c) Other costs related to the Research Project

(d) Infrastructure contribution (10% of direct costs; rate subject to change)

5.2 The Research Programme shall include a payment schedule which shall provide for installments. The first installment shall be 17% of the total compensation provided for the applicable Research Programme and be payable at the date of signature.

5.3 Payments shall be made by the Company within 60 days upon receipt of the respective invoice to the account specified by ETH Zurich.

6. RIGHTS TO PROJECT RESULTS

6.1 Project Results generated by one Party solely and its share in jointly generated Project Results belong to such generating Party. Ownership in jointly generated Project Results is determined in accordance with the respective share that each Party has contributed to such Project Results. ETH Zurich will inform the Company about Project Results via reports according to Section 4 and, as the case may be, via publication drafts according to Section 10.

6.2 Subject to each Party's ownership rights in Project Results (Section 6.1) and subject to the provisions on licenses (Section 7), confidentiality (Section 9) and scientific publications (Section 10), ETH Zurich and the Company shall be free to use the Project Results.

6.3 It is in each Party's sole discretion to file patent applications on Project Inventions solely owned by them according to Section 6.1 and to maintain and defend such patent rights. Any Party that intends to file a patent application covering Project Results shall inform, by providing a description of the subject matter, the respective other Party about such intention in writing.

6.4 In the event of jointly owned Project Inventions according to Section 6.1, the Parties will consult with each other before filing a patent application and will mutually agree in writing on their individual roles, rights and obligations in filing a patent application, strategy, commercializing and defending such patent rights. None of the Parties has an obligation to maintain any of its solely or jointly owned patent rights. Unless otherwise agreed:

(a) each of the joint owners shall be entitled to use their jointly owned Project Inventions and respective patent rights for non-commercial research activities on a royalty-free basis, and without requiring the prior consent of the other joint owner, and

(b) each of the joint owners shall be entitled to otherwise exploit the jointly owned Project Inventions and respective patent rights and to grant non-exclusive licenses to third parties, if the other joint owner is given:

(1) at least 45 calendar days advance notice; and

(2) fair and reasonable financial compensation.

ETH Zurich shall cooperate with Company, execute a certificate of acknowledgement of the foregoing assignment and such other instruments or documents as Company shall reasonably request in order to register, establish, maintain, perfect or defend its rights in or to such intellectual property rights.

6.5 The rights of the Parties to intellectual property rights that has been generated previously, after or outside of the Research Programme ("**Background IP**") shall not be affected by this Agreement.

7. LICENSES

7.1 For any Project Results, including any Project Invention, solely owned by ETH Zurich, ETH Zurich herewith grants to the Company at no additional costs a non-exclusive license to use such patent rights in the Company Field including the right to grant sublicenses to the Company's Affiliates.

8. FREEDOM OF RESEARCH

In any event ETH Zurich has the right to use all Project Results, protected or not, for basic scientific research and teaching purposes in any field.

[redacted]

9. CONFIDENTIALITY

9.1 Each receiving Party hereby agrees:

(a) to hold Confidential Information in strict confidence, to apply to such Confidential Information at least the same standard of care with which it treats its own proprietary and confidential information of similar importance (and in any case not less than a reasonable standard of care), and to maintain tangible Confidential Information in a secure location;

(b) not to use any Confidential Information for its own or any third party's benefit or for any purpose other than in accordance with this Agreement or the Research Programme;

(c) not to disclose Confidential Information to any person other than (i) those of its (or its Affiliates') officers and employees who have a need to know such Confidential Information for the purposes of this Agreement or the Research Programme, and (ii) its legal advisors and consultants who are engaged to advise it in connection with this Agreement or the Research Programme, provided that such officers, employees, advisors and consultants are subject to confidentiality obligations substantially similar to those contained herein;

(d) to notify the disclosing Party immediately upon learning of any breach of the confidentiality obligations imposed by this Agreement and to accept responsibility for any use or disclosure of Confidential Information in violation of the terms of this Agreement and to take all steps as may be necessary to remedy such a breach;

(e) upon request (at any time) from the disclosing Party, to return to the disclosing Party (or, at the disclosing Party's request, to destroy in such manner as not to allow its re-creation (to the extent possible) and confirm to the disclosing Party in writing the receiving Party's compliance with this obligation), within fifteen (15) days of receipt of such request, all written and/or other materials containing Confidential Information provided to it by the disclosing Party in connection with this Agreement or the Research Programme, including all copies, recordings, summaries or other reproductions thereof, and all notes and/or other works prepared or based thereon, save that the receiving Party may:

(f) retain one complete copy of the Confidential Information in its archives (a) for the purpose of determining its obligations under this Agreement; and/or (b) where such retention is required by law, by any court of competent jurisdiction, by any official regulatory body, or under a subpoena, court order or other request pursuant to legal process; and

(g) retain any computer files containing the Confidential Information that are created during automatic system back-ups that cannot reasonably be deleted,

(h) provided in each case that such retained copy shall not be generally accessible and shall be treated in accordance with the restrictions in this Section 9;

(i) to notify the disclosing Party immediately if the receiving Party is requested or required to disclose any Confidential Information to a third party in connection with any civil or criminal investigation or any judicial or administrative proceeding, and to cooperate fully with the disclosing Party so that the disclosing Party may if it chooses object before the authority seeking the information and/or seek an appropriate protective order; and

(j) not to copy Confidential Information, in whole or in part, unless reasonably necessary for the purposes of this Agreement or the Research Programme.

9.2 Each receiving Party agrees to accept responsibility for any use or disclosure of Confidential Information by its officers or employees in violation of the terms of this Agreement and to take such steps as may be required by applicable law to enforce this obligation. The Company may require that ETH Zurich limits the disclosure of certain Company's Confidential Information to named individuals (involved in the performance of the implementation of a Research Programme) specified by Company.

9.3 The obligations of confidentiality under this Section 9.1 shall not apply to any Confidential Information that

(a) comes into the public domain other than through breach of this Agreement by the receiving Party,

(b) was known by the receiving Party (as established by its own records or other competent proof) before disclosure by the disclosing Party to the receiving Party,

(c) comes lawfully into the possession of the receiving Party from a third party who is not under an obligation to keep such information confidential, or

(d) disclosure of which is required by law, by any court of competent jurisdiction, or by any official regulatory body, under a subpoena, court order or other request pursuant to legal process, provided, however, that (i) the receiving Party complies with 9.1 (i), (ii) the Receiving Party may disclose only the information specifically required to be disclosed, and (iii) such information shall otherwise be subject to all of the terms of this Agreement.

9.4 Nothing in this Agreement shall prevent the Receiving Party from disclosing the terms of this Agreement or the Research Programme, including the disclosing Party's identity and any agreed payment terms, if necessary, to any government agency or official that, in the receiving Party's judgement, has a legitimate need to know.

9.5 None of the Confidential Information disclosed by the disclosing Party shall be construed as a representation, warranty, assurance, inducement or guarantee of any kind.

10. SCIENTIFIC PUBLICATIONS

10.1 The Parties agree that ETH Zurich shall be entitled to publish all Project Results, subject to Sections 10.2 to 10.5 below.

[redacted]

10.2 For purposes of allowing the Parties to protect patentable subject matter in the case of Joint Inventions and to prevent disclosure of Confidential Information, ETH Zurich agrees to give the Company an opportunity to review the proposed publication or presentation by sending a full copy of any such proposed publication or presentation at least three (3) months prior to the intended date of publication or it being first submitted for publication or presentation (whichever occurs first), or the intended date of presentation. Company shall have thirty (30) days, after receipt of said copies, to approve such proposed presentation or publication (the "Response Period"). The Company may object only if (i) there is patentable or other subject matter which needs protection and/or (ii) there is Confidential Information or Company's Background IP contained in the proposed presentation or publication.

In case of a planned disclosure at scientific conferences, ETH Zurich shall submit to Company a written summary of the intended disclosure and the provisions of Section 10.2 shall apply, whereby the time indicated shall be reduced to one (1) month.

10.3 If Company objects to the proposed publication or presentation within the Response Period, then ETH Zurich shall refrain from making such presentation or publication (i) until the Parties have agreed to a version which protects the Confidential Information from public disclosure, or (ii) until Company has filed patent application(s) directed to the patentable subject matter or otherwise sought protection for the information contained in the proposed presentation or publication.

10.4 ETH Zurich shall ensure that all and any publication, paper and presentation (collectively a "Publication") shall give appropriate recognition of the support received from the Company.

10.5 ETH Zurich shall send the Company at least one reprint of all published articles relating to Research Projects funded by the Company upon availability.

11. NO WARRANTIES

11.1 The Parties shall perform the Project to the best of their scientific knowledge exercising due care and taking into account the current state-of-the-art. They will endeavour to achieve the goals of each Research Project.

11.2 By its nature research involves the risk of unforeseen consequences. The Parties therefore do not guarantee that the intended goals and results of the Research Project will be reached. The Parties make no warranties, neither express nor implied, regarding the Project Results, including but not limited to warranties of originality, accuracy, non-infringement of third party rights, merchantability, completeness or fitness for a particular purpose. There is no duty to conduct searches with regard to registered intellectual property rights.

12. LIMITATIONS OF LIABILITY

12.1 Subject to Section 13, and with the exception for injury and death, the Parties assume no liability for any damages, including but not limited to any indirect or consequential loss or similar damage (e.g. loss of profit, loss of revenue or loss of contracts inter alia due to a shutdown; other costs and expenses) suffered in connection with this Agreement, provided such damage was not caused by a wilful intent or act of gross negligence.

12.2 The limitations of liability in Section 12.1 shall also be applicable to all auxiliary persons (including but not limited to consultants and students), agents and subcontractors involved by the Parties, and to any kind of (Confidential) Information exchanged as well as to Background IP and all other deliverables supplied under this Agreement.

13. INDEMNIFICATION FOR USE OF THE PROJECT RESULTS

The Parties use the Project Results at their own risk. Notwithstanding Section 12, a Party using any of the Project Results shall, to the fullest extent permitted by the applicable law, defend, indemnify and hold the other Party harmless against third party claims (including but not limited to claims based on mandatory product liability law) which are based on the Party's use of the Project Results.

14. TERM AND TERMINATION

14.1 This Agreement shall be effective as of the Effective Date and, subject to Sections 14.2 to 14.5, shall continue in effect until the Expiration Date.

14.2 The Company may terminate this Agreement and the Research Programme at any time without cause upon thirty (30) days' prior written notice to ETH Zurich. If Company terminates without cause, Company shall be responsible for payment of any salaries until the end of the Research Programme. ETH Zurich shall mitigate such salaries and costs through the deployment on other research programmes and by other possible means. Each Party may terminate this Agreement and this Research Programme at any time for cause upon written notice to the other Party in the event that the other Party is in material breach of any provision of this Agreement which breach has not been cured to the satisfaction of the non-breaching Party within fifteen (15) days after written notice thereof from the non-breaching party. In the case that ETH Zurich terminates for cause, Company shall compensate ETH Zurich for all costs that were incurred until effective termination. This includes salaries that, based on this Agreement, still have to be paid beyond the effective premature termination of this Agreement. In this respect, ETH Zurich shall not make unnecessary commitments for employment for this Project.

14.3 Upon termination of this Agreement and the Research Programme, ETH Zurich shall:

(a) In cases that are the result of a breach by ETH Zurich, ETH Zurich shall incur no further fees or expenses in connection with the Research without Company's prior written approval, and provide Company with all Project Results in progress and/or completed through the date of termination; and

(b) provided that termination was not as the result of a breach by ETH Zurich, send Company itemized invoices reflecting:

(1) the proportional part of the Research satisfactorily rendered through the date of termination in connection with the Research Programme(s) (and which have not already been paid for by PMP), and

(2) any reimbursable expenses properly incurred in connection with the Research Programme(s) through the date of termination (and which have not already been paid for by Company),

(3) and Company shall pay all undisputed amounts due to ETH Zurich within sixty (60) days after Company's receipt of such invoices.

14.4 Upon termination or expiration of this Agreement, except where provided otherwise in this Agreement) neither Party, nor any other person, shall be entitled to any compensation, damages, indemnity, commissions, goodwill payment or any other amount for any cause arising directly or indirectly from such termination or expiration.

14.5 Termination or expiration of this Agreement and the Research Programme shall be without prejudice to (i) any of the Parties' obligations contained herein which, by their nature, shall survive the termination or expiration of this Agreement, and (ii) any prior rights which a Party has accrued prior to the termination or expiration of this Agreement and the Research Programme.

[redacted]

15. MISCELLANEOUS

15.1 Each Party is and shall remain an independent contractor.

15.2 Unless explicitly provided otherwise in this Agreement, neither Party nor any Party's personnel shall, without the respective other Party's prior written approval, (i) advertise or otherwise publicize the existence or terms of this Agreement or the Research Programme or any other aspect of the relationship between the Parties, or (ii) use the name of the respective other Party or that of any of its Affiliates or any trade name, trademark or service mark or brand imagery belonging to a Party or any of its Affiliates in any press release, any form of advertising, or any of its business communications (internal or external) except those necessary to provide the research under the Research Programme.

15.3 The Parties agree that general information concerning the existence of the Research Programme and the identity of the Parties can be made public.

15.4 If ETH Zurich is contacted by a third party, including any news organization, concerning ETH Zurich's activities in relation to the Company, ETH Zurich shall: (i) make no comment; (ii) immediately notify Company of the third party contact; and (iii) refer the third party to the Company.

15.5 No delay, omission or failure by either Party to exercise any of its rights or remedies shall be deemed to be a waiver thereof or an acquiescence in the event giving rise to such right or remedy, but every such right and remedy may be exercised from time to time and so often as may be deemed expedient by the Party exercising such right or remedy.

15.6 This Agreement, together with the Research Programme, sets forth the entire agreement concerning the Research Programme between the Parties and supersedes all prior agreements, arrangements and understandings, oral or written, between the Parties on the subject matter hereof.

15.7 This Agreement, together with the Research Programmes, shall not be amended, modified or superseded except by a written agreement, signed by authorized representatives of both Parties, that expressly refers to this Agreement and expressly amends or supersedes this Agreement.

15.8 This Agreement and the Research Programme shall be binding upon and shall inure to the benefit of the Parties, their respective successors and assigns. Neither Party shall, nor purport to, assign or encumber all or any part of its obligations or rights hereunder without the other Party's prior signed written consent, save that Company may in its sole discretion assign all or any part of its rights hereunder to any of its Affiliates without the prior written consent of or notice to ETH Zurich.

15.9 The Parties will provide each other promptly, to the extent possible, with any mutual assistance required to enable the Parties to exercise the rights which are conferred on them by this Agreement. In particular they will provide the signatures required to obtain rights in intellectual property.

15.10 The validity or unenforceability of any term of or any right arising pursuant to this Agreement and the Research Programme shall not adversely affect the validity or enforceability of the remaining terms or rights of this Agreement and the Research Programme. In particular, if any provision (or part of a provision) is found to be unlawful or unenforceable, but would be lawful or enforceable if some part or parts thereof were deleted or modified, the Parties shall make such modification as may be necessary to make the provision valid and effective.

15.11 This Agreement shall be construed and governed by the laws of Switzerland, without reference to its conflict of laws principles, and shall not be governed by the United Nations convention of International Contracts on the Sale of Goods (the Vienna Convention). Place of jurisdiction for any dispute arising from, or in connection with, this Agreement shall be exclusively the courts of the city of Zurich.

15.12 The Appendices form an integral part of this Agreement. In the case of deviations between the Appendices and the Agreement, the Agreement shall prevail.

[redacted]

Signatures

Place 31.07.2017

Date 24.07.2017

ETH Zurich

Signature [redacted]

Name [redacted]

Title Prof. Dr.

Signature [redacted]

Name [redacted]

Title Prof.

Place Neuchâtel

Date 19 July 2017

Philip Morris Products SA

Signature [redacted]

Name [redacted]

Title [redacted]

Signature [redacted]

Name [redacted]

Title [redacted]

[redacted]

Appendix A Form of Research Programme

Research Programme Plan

Project Title: DNA adducts as carcinogenesis biomarkers

Summary of the research plan

Exposure to DNA-reactive chemicals can lead to accumulation of mutations in critical cellular genes initiated by the formation of DNA adducts. DNA adducts involve the covalent binding of a reactive chemical to DNA. Their formation is one of the earliest events in a genotoxic mode of carcinogenesis. Levels of DNA adducts represent not only exposure, but account for differences in metabolic activation vs. detoxification as well as repair. Therefore, DNA adducts are candidate biomarkers for *bridging the gap between markers of exposure and markers for risk* of developing critical mutations and initiating carcinogenesis. Limitations in using DNA adducts as biomarkers for risk include the technical difficulty in measuring adducts, which occur at extremely low abundance, and the availability of predictive models for how adduct formation is associated with mutation frequency.

The broad objectives of this research are to establish a quantitative model linking DNA adduct patterns (levels and genomic location) with the formation of mutations in vitro. The goals of this project are to establish new analytical approaches for detecting DNA adducts in the genome of cells exposed to chemicals in vitro. The planned work will center on three specific aims:

1. Detection of total genomic burden of DNA damage in vitro
2. Detection of DNA damage in highly mutated cancer genes
3. Localization of DNA damage in Genomic Regions

The foundational approach laid out in these three aims with an initial focus on N2-BaP-G will be expanded to include [redacted], other harmful and potentially harmful compounds (HPHCs) and their mixtures (e.g. TPM). The expected outcome will be quantitative in vitro strategies for evaluating mutation risk associated with chemical exposures.

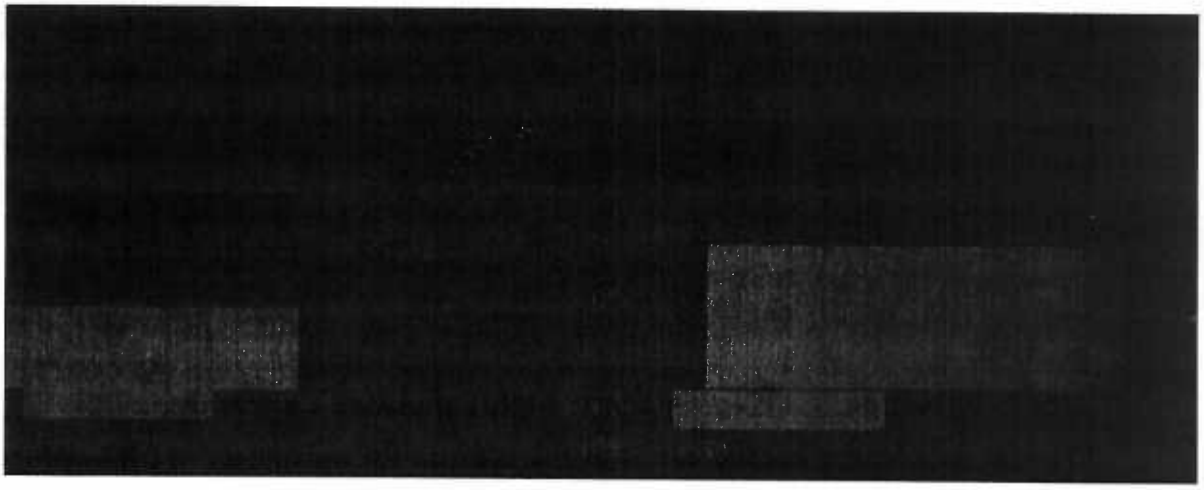
Specific Aims

Aim 1. Detection of total genomic burden of DNA adducts in vitro

DNA adducts are formed at exceedingly low levels making their analysis challenging. The rationale for this aim is to quantify total genomic burden of a DNA adduct, agnostic of the location in the genome, of chemically exposed cells grown in culture. N2-BaP is selected as the initial focus on the basis of a combination of benzo[a]pyrene exposure relevance, extensive knowledge concerning mechanisms of activation/alkylation, together with anticipated analytical advantages. Once established, additional adducts (class 1 HPHC) as well as complex smoke mixture (e.g. TPM), will be analyzed by analogous approaches in additional studies. [redacted]:

1. [redacted]

[redacted]



Study 1.1 - Dose-finding and metabolic competence study

We will establish dose-response relationship between benzo[a]pyrene exposure and altered cell viability by exposure of *BEAS-2B cells* to increasing concentrations of B[a]P. This study is needed to define dose ranges to be used in subsequent studies. Studies will be carried out to confirm the proficiency of BEAS-2B cells in metabolism of B[a]P to the trans-diol-bay region epoxide metabolite that is relevant for mutagenic DNA adduct formation. Similarly, dose-finding and metabolic competence of BEAS-2B cells will be studied for additional DNA adducts and smoke mixtures.

Study 1.2 - Adduct analysis

BEAS-2B cells will be exposed to B[a]P at 2-5 doses selected on the basis of dose-finding studies. Genomic DNA will be isolated and enzymatically hydrolyzed to the single nucleoside level. Digestion products will be separated and purified by HPLC and N2-BaP-G will be quantified by UPLC/MS-MS analysis by reference to calibration curves constructed during the same analysis.[1-3] Stable isotope labeled internal standards will be spiked into samples prior to analysis for absolute quantification of the adduct levels. The negative control will be vehicle-treated cells processed in the same way. Strategies such as the use of siRNA to silence nucleotide excision repair (NER) factors, co-treatment with an NER inhibitor such as UCN-01, or engineering of the cells to inactivate repair will be explored as a strategy to reduce repair-mediated elimination of the adduct and as a positive control.[4] After B[a]P, other suitable additional DNA adducts and smoke mixtures will be analyzed with a similar setup.

Study 1.3 - Establish rates of adduct formation and clearance

The study will be performed analogous to Study 1.2 (BEAS-2B cells), however, we will test the rates of adduct formation and clearance by treating cells for varying time periods prior to lysis and adduct analysis.

Study 1.4 – Establish an in vitro model for linking DNA alkylation and subsequent mutation

This work is needed to identify an in vitro test system that can be used for measuring DNA adducts and that will undergo mutations upon chemical exposure. Establishing a model to predict mutation frequency on the basis of DNA alkylation patterns is critical for linking DNA adduct patterns with mutation frequencies. Thus, it is necessary to define the relationship between alkylation in regions of the genome and their propensity to mutate all in a consistent in vitro system.

The most reliable model for initial studies is mouse embryonic fibroblasts (MEFs), and initial studies will therefore focus on the use of these cells.[5-8]

[redacted] However, researchers currently advancing this model report that it can take several months for mutant colonies to arrive and there is a high risk that their sensitivity to cytotoxicity is too acute and they simply die rather than give rise to mutant variants. [redacted] Finally, although to our knowledge it has not been attempted, such studies could be successful with [redacted]. These would be long-term goals after success using the MEFs. Another potentially interesting future model could be [redacted]. Thus, we will test the use of these MEFs for adduct analysis under conditions previously shown to lead to mutation accumulation.

Aim 2. Detection of DNA damage in highly mutated Cancer Genes

The rationale for the second aim is to characterize the prevalence of DNA adducts at genomic regions of interest on the basis of known mutational hot-spots in cancer genes In a 1996 study by Denissenko and co-workers, it was found that in human cells, evidence for preferential formation of adducts was observed at P53 hotspots.[9] The approach used involved modification of ligation-mediated PCR relying on the use of the UvrABC nuclease complex from Escherichia coli to cleave the adduct, whereby the 3' incision occurs four positions 3' to the adduct. The locations of breaks were visualized by amplification with gene-specific oligonucleotide primers and visualization of the locations of an incision by DNA sequencing gels. This work is a basis for a method to quantify levels of DNA damage in highly mutated cancer genes.

Study 2.1 Develop new amplification-free gene enrichment method

A variation of the UvrABC-LMPCR method will be created for interrogating a number of target sequences of interest (i.e., [redacted] negative control sequences will also be included). Using isolated genomic DNA as a test system, the DNA sequences will be evaluated by qPCR and the relative abundance of fragments will be evaluated in the context of mutation frequencies in human lung cells (data available in COSMIC database).

Study 2.2 In-gene quantification of DNA adducts with LC-MS/MS

BEAS-B2 cells will be treated with a concentration of individual chemical or smoke mixture for a time period established in Aim 1 studies to lead to detectable levels of adducts. Genomic sequences will be identified with the strategy established via Study 2.1. Isolated DNA samples will in parallel be hydrolyzed and analyzed as established in Aim 1 to quantify adduct levels in the enriched genomic regions. Bioinformatics expertise will be needed to evaluate the statistical significance of differences in levels of adducts in the amplified test sequences vs. negative control sequences vs. total genome burden levels, as well as statistically compared with distributions of mutations from cancer cells sequenced and recorded in the COSMIC database.

Aim 3. Localization of DNA damage in Genomic Regions

The rationale for this Aim is to determine the distribution of alkylation sites in the genome of in vitro exposed cells. The strategy established in Aim 2 involves targeting specific genes of pre-defined interest, whereas this approach does not require a priori knowledge of genes of interest. The enriched samples will be analyzed by mass spectrometry and DNA sequencing to evaluate the density of DNA damage in the captured strands and their location within the genome.

Study 3.1 Develop new antibody (Ab)-based method for gene agnostic DNA adduct sequencing

[redacted]

The enrichment of alkylated DNA will be performed by affinity purification. A monoclonal antibody that specifically recognizes BaP adducts is commercially available and will be used to immunoprecipitate alkylated DNA from BaP-exposed BEAS-2B cells. The cells will be treated with a concentration of BaP causing the formation of high levels of adducts (previously determined in Study 1.1). DNA will then be extracted and sheared by sonication to yield fragments 200-400 bp in length. The fragments will be denatured and immunoprecipitated with BPDE-DNA antibodies. The BPDE-enriched DNA fragments will be purified and prepared for Illumina sequencing. We will verify the presence of adducts in the captured DNA fragments and to quantify the amount of adducts. This information will be used to assess the density of DNA damage in the captured DNA sequences. A correlation between the levels of adduct in the captured genomic regions and the amount of cellular adduct in the whole genome scale (determined in Aim 1) will be performed. [redacted]

Study 3.2 Localization of DNA damage

This study involves the application of the method developed in Study 3.1 to BEAS-2B cells. Cells will be treated with BaP and subjected to Ab-based enrichment as described in Study 3.1. The immunoprecipitated DNA will then be subjected to DNA sequencing (Illumina HiSeq) to determine the identity of the captured DNA strands. Bioinformatics analysis of the pulled-down regions will allow the localization of the DNA damage in the human genome and evaluation of the statistical preference for particular regions. If sufficient levels of captured DNA are obtained for SMRT sequencing, this approach will be tested for localization of adducts at particular positions in the sequence, i.e. single-base resolution. [redacted]

Study 3.3 Model relationship of DNA alkylation with mutational profiles

This study is needed for the prediction of mutation risk on the basis of DNA alkylation patterns. The work will be carried out by methods optimized on the basis of all prior work, including use of the in vitro model validated in the course of Study 1.4. Following chemical treatment with non-cytotoxic concentrations of the alkylating agent, cell populations will be divided for analysis by the method developed in Study 3.2, or for re-growth period. Following re-growth, emerging colonies will be picked, further expanded and sequenced at PMI. Data between the two arms of the experiment, i.e. genomic localization of DNA vs mutational patterns in mutant clones, will be integrated to establish a predictive model linking alkylation patterns with frequency of different types of mutations. It is expected that refining the model will also require the integration of gene expression data, such as related to carcinogen activation, DNA repair, or translesion DNA synthesis activities. The performance of the prediction model will be assessed using a variety of different methods and metrics. As an example, a model built around mutations to KRAS will be tested on TP53. [redacted]

References

[redacted]

1. Taghizadeh, K.; McFaline, J. L.; Pang, B.; Sullivan, M.; Dong, M.; Plummer, E.; Dedon, P. C., Quantification of DNA damage products resulting from deamination, oxidation and reaction with products of lipid peroxidation by liquid chromatography isotope dilution tandem mass spectrometry. *Nature protocols* **2008,** *3* (8), 1287-1298.
2. Pirinen, E.; Canto, C.; Jo, Y. S.; Morato, L.; Zhang, H.; Menzies, K. J.; Williams, E. G.; Mouchiroud, L.; Moullan, N.; Hagberg, C.; Li, W.; Timmers, S.; Imhof, R.; Verbeek, J.; Pujol, A.; van Loon, B.; Viscomi, C.; Zeviani, M.; Schrauwen, P.; Sauve, A. A.; Schoonjans, K.; Auwerx, J., Pharmacological Inhibition of poly(ADP-ribose) polymerases improves fitness and mitochondrial function in skeletal muscle. *Cell metabolism* **2014,** *19* (6), 1034-41.
3. Madureira, D. J.; Weiss, F. T.; Van Midwoud, P.; Helbling, D. E.; Sturla, S. J.; Schirmer, K., Systems toxicology approach to understand the kinetics of benzo(a)pyrene uptake, biotransformation, and DNA adduct formation in a liver cell model. *Chem Res Toxicol* **2014,** *27* (3), 443-53.
4. Otto, C.; Spivak, G.; Aloisi, C. M.; Menigatti, M.; Naegeli, H.; Hanawalt, P. C.; Tanasova, M.; Sturla, S. J., Modulation of Cytotoxicity by Transcription-Coupled Nucleotide Excision Repair Is Independent of the Requirement for Bioactivation of Acylfulvene. *Chem Res Toxicol* **2017**.
5. Besaratinia, A.; Pfeifer, G. P., Enhancement of the mutagenicity of benzo(a)pyrene diol epoxide by a nonmutagenic dose of ultraviolet A radiation. *Cancer Res* **2003,** *63* (24), 8708-16.
6. Hashimoto, K.; Cho, Y.; Yang, I. Y.; Akagi, J.; Ohashi, E.; Tateishi, S.; de Wind, N.; Hanaoka, F.; Ohmori, H.; Moriya, M., The vital role of polymerase zeta and REV1 in mutagenic, but not correct, DNA synthesis across benzo[a]pyrene-dG and recruitment of polymerase zeta by REV1 to replication-stalled site. *J Biol Chem* **2012,** *287* (12), 9613-22.
7. Kucab, J. E.; Phillips, D. H.; Arlt, V. M., Metabolic activation of diesel exhaust carcinogens in primary and immortalized human TP53 knock-in (Hupki) mouse embryo fibroblasts. *Environ Mol Mutagen* **2012,** *53* (3), 207-17.
8. Krais, A. M.; Muhlbauer, K. R.; Kucab, J. E.; Chinbuah, H.; Cornelius, M. G.; Wei, Q. X.; Hollstein, M.; Phillips, D. H.; Arlt, V. M.; Schmeiser, H. H., Comparison of the metabolic activation of environmental carcinogens in mouse embryonic stem cells and mouse embryonic fibroblasts. *Toxicol In Vitro* **2015,** *29* (1), 34-43.
9. Denissenko, M. F.; Pao, A.; Tang, M.; Pfeifer, G. P., Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in P53. *Science* **1996,** *274* (5286), 430-2.

Research Programme Information

1. Reports:

ETH Zurich shall perform the Research Programme described in the following table, aligned with their corresponding dates. The Milestones will be performed according to the Research Programme Plan described above.

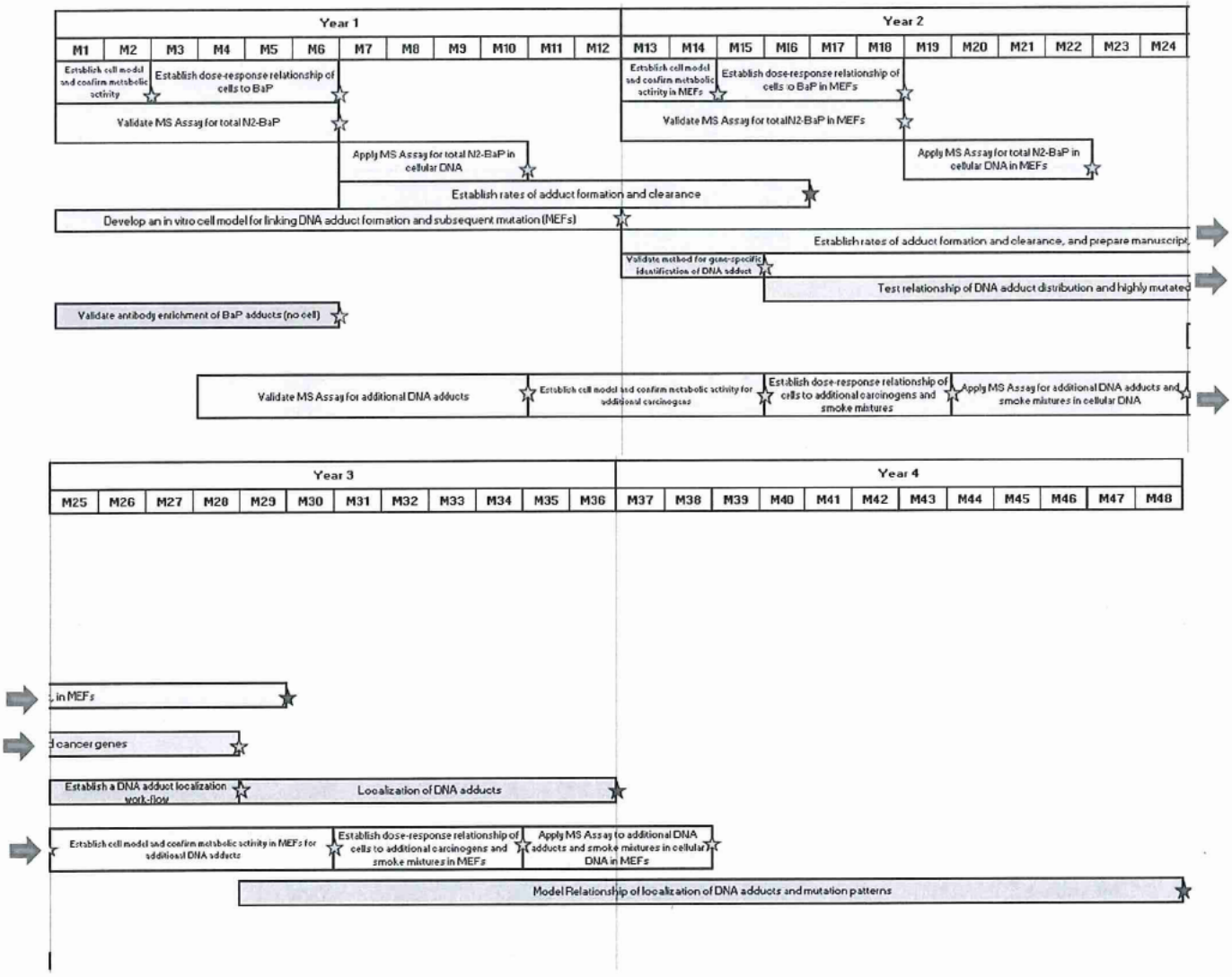
Study	Milestone	Deliverables	Delivery Dates
1.1	Establish cell model and confirm metabolic activity	Presentation report 1	Month 2
	Establish dose-response relationship of cells to BaP	Presentation report 2	Month 6
1.2	Validate MS Assay for total N2-BaP	Presentation report 3	Month 6
	Apply MS Assay for total N2-BaP in cellular DNA	Presentation report 4 Written experimental protocol + detailed SOP	Month 10
1.3	Establish rates of adduct formation and clearance	Presentation report 5	Month 16
1.4	Develop an in vitro cell model for linking DNA adduct formation and subsequent mutation (MEFs)	Presentation report 6	Month 12
	Establish rates of adduct formation and clearance in MEFs	Publication 1 (together with 1.3 results)	Month 29
2.1	Validate method for gene-specific identification of BaP adduct	Presentation report 7	Month 15
2.2	Test relationship of of BaP distribution and highly mutated cancer genes	Presentation report 8	Month 28
3.1	Validate antibody enrichment of BaP adducts	Presentation report 9	Month 6
	Establish a BaP localization work-flow	Written experimental protocol + detailed SOP	Month 28
3.2	Localization of BaP adducts	Publication 2	Month 36
4.1	Validate MS Assay for additional DNA adducts	Presentation report 10	Month 10
4.2	Establish cell model and confirm metabolic activity for additional carcinogens	Presentation report 11	Month 15
4.3	Establish dose-response relationship of cells to additional carcinogens and smoke mixtures	Presentation report 12	Month 19
4.4	Apply MS Assay for additional DNA adducts and smoke mixtures in cellular DNA	Presentation report 13	Month 24
4.5	Establish cell model and confirm metabolic activity in MEFs for additional DNA adducts	Presentation report 14	Month 30
4.6	Establish dose-response relationship of cells to additional carcinogens and smoke mixtures in MEFs	Presentation report 15	Month 34
4.7	Apply MS Assay to additional DNA adducts and smoke mixtures in cellular DNA in MEFs	Presentation report 16	Month 38
4.8	Model Relationship of localization of DNA adducts and mutation patterns	Publication 3	Month 48

The performance of points 4.2 to 4.7 will be subjected to the success of their predecessors, and Go/No Go decisions will be taken jointly with the ETH Zurich and Company for each step.

[redacted]

2. Commencement date and project timeline:	Project commencement date is 1st September 2017. Timelines are described in the above Section 1. and in the Project Planning in Appendix B.
3. Payment terms and invoicing:	As full consideration for the Research Programme fully performed during the term of this Project Agreement, PMP shall pay ETH Zurich a total Fixed Fee not to exceed CHF **1'026'610** (the "Fee"). Estimated budget is described in Appendix C. PROVIDED THAT payment of the Fee is: (a) subject to performance of the Research Programme in accordance with the terms of the Agreement including the project requirements; . Without prejudice to the provisions set forth above, the Parties agree that ETH Zurich shall invoice PMP the Fees in 5 instalments as set out below: • **CHF 177'330** to be invoiced at contract signature to cover the costs of Project initiation as well as material and reagents purchase, • **CHF 369'526** to be invoiced upon performance of all the Research Programme up to Month 12 (Section 1 of Research Programme Information), • **CHF 296'526** to be invoiced upon performance of the Research Programme up to Month 24 (Section 1 of Research Programme Information), • **CHF 143'779** to be invoiced upon performance of the Research Programme up to Month 36 (Section 1 of Research Programme Information), • **CHF 39'449** to be invoiced upon delivery of final report. Each invoice submitted by ETH Zurich in accordance with the above shall be in writing . Each such invoice shall be payable by PMP in accordance with Section 5 of the Agreement. No Fees shall exceed the itemized amounts specified above. Each invoice to be sent by the Institution hereunder shall be sent to PMP either: (1) via post to Krakow at the address specified in row 1 of this Project Agreement; or (2) via email as a PDF file to the e-mail address mentioned in Declaration of PDF Invoicing, provided that Institution has sent a signed, completed Declaration of PDF Invoicing to PMI Service Center Europe Sp. z o.o. ("PMISCE") and PMISCE has provided a confirmation of its acceptance of the signed document (including via electronic mail). In either case, each invoice should contain the following information: • The Purchase Order number • The WBS number, if received • The Project name • The name of PMP Responsible • The following billing company details: Philip Morris Products S.A. Quai Jeanrenaud 3 2000 Neuchâtel Switzerland

APPENDIX B PROJECT PLANNING



[redacted]

APPENDIX C BUDGET ESTIMATION AND STRUCTURE

ETHZ-PMI Project: DNA adducts as carcinogenesis biomarkers
Budget

Variable Rate: 10%

	salary/cost	% effort	salary-prorated	social costs	total direct	overhead	TOTAL
Year 1							
Technician	100000	1.0	100000	14000	114000	11400	125400
PhD student	47040	1.0	47040	6586	53626	5363	58988
Oberassistant	108000	0.5	54000	7560	61560	6156	67716
Postdoc	86300	0.5	43150	6041	49191	4919	54110
Reagents and supplies study 1.1	5124				5124	512	5637
Reagents and supplies study 1.2	3917				3917	392	4309
Reagents and supplies study 1.3	15373				15373	1537	16911
Reagents and supplies study 1.4	17079				17079	1708	18787
Reagents and supplies study 3.1	2548				2548	255	2803
sub-total					322418	32242	354660
Year 2							
Technician	100000	1.0	100000	14000	114000	11400	125400
PhD student	48540	1.0	48540	6796	55336	5534	60869
Postdoc	86300	1.3	115067	16109	131176	13118	144294
Reagents and supplies	48935				48935	4894	53829
sub-total					349447	34945	384391
Year 3							
PhD student	50040	1.0	50040	7006	57046	5705	62750
Postdoc	90600	1.0	90600	12684	103284	10328	113612
Reagents and supplies	29361				29361	2936	32297
sub-total					189691	18969	208660
Year 4							
PhD student	50040	1.0	50040	7006	57046	5705	62750
reagents and supplies	14681				14681	1468	16149
sub-total					71726	7173	78899

Direct	Overhead	TOTAL
933'282	93'328	1'026'610

[redacted]

Research Agreement

between

ETH Zurich (Eidgenössische Technische Hochschule Zürich)
Rämistrasse 101, 8092 Zurich, [redacted]

- hereinafter referred to as "**ETH Zurich**" -

and

Philip Morris Products S.A.
Quai Jeanrenaud 5, 2000 Neuchâtel

- hereinafter referred to as "**Partner**" -

1. Project Title and/or Project Number

Assessment of Raman spectroscopy for single droplet chemical characterization of e-cig aerosol

2. Background of the Project

The aim of the present project is to assess the use of Raman spectroscopy for the quantification of chemical compounds characterizing single aerosol droplets generated by a type of e-cig developed at R&D PMI, Neuchatel. To this end, optical trapping will be employed to probe the true aerosol phase.

3. Project managers

ETH Zurich: [redacted]

Partner: [redacted]

4. Description of research project

As detailed in Appendix A

5. Project start date and end date

Start date: October 1st, 2018

End date: March 31st, 2019

6. Milestones

1. Preparation of set-up for sampling aerosol from exhaust of smoking machine
2. Tests to trap aerosol droplets with different size both from test samples and from the exhaust of the smoking machine
3. Tests to acquire Raman spectra of single aerosol droplets from test samples and from the exhaust of the smoking machine

[redacted] [redacted]

4. A report will be provided at the end of the project by April 15th 2019.

7. Tangible Project Results

None

8. Remuneration

8.1 Budget

A total of CHF 120'000 (plus Swiss VAT, if applicable) for 50% of a postdoctoral scientist for laboratory work (equivalent to 3 months full time), use of existing highly-specialized research equipment and infrastructure, consumables and replacement parts during operation, Data analysis, consulting and reporting

8.2 Payment schedule

- CHF 60'000 (plus VAT if applicable) at the date of last signature
- CHF 60'000 (plus VAT if applicable) after delivery of final report

9. Appendices

Appendix A (Project Description), the GTC Research ETHZ (Version March, 2018) and the Special Provisions (Appendix B) form an integral part of this contract.

Signed by the duly authorized representatives of the Parties:

ETH Zurich

Zurich, dated 24.09.2018

Prof. Dr. [redacted]

Prof. Dr. [redacted] VP Research

Partner

Neuchâtel, dated September 11, 2018

[redacted]

Appendices:

- Appendix A: Project Description
- Appendix B: Special Provisions
- GTC Research ETHZ (Version March, 2018)

Appendix A – Description of Research Project

Title
Assessment of Raman spectroscopy for single droplet chemical characterization of e-cig aerosol

Summary
The aim of the present project is to assess the use of Raman spectroscopy for the quantification of chemical compounds characterizing single aerosol droplets generated by a type of e-cig developed at R&D PMI, Neuchatel. To this end, optical trapping will be employed to probe the true aerosol phase.

Background
Currently chemical analysis for determination of e-cig aerosol constituents and of thermal degradation products (e.g. carbonyls) is performed by *gas chromatography-mass spectrometry* (GC-MS). GC-MS provides an average quantification of the main constituents of aerosol/volatile compounds generated by e-cig.

E-cig developed at R&D PMI [1-3] is characterized by the components shown in Fig. 1.

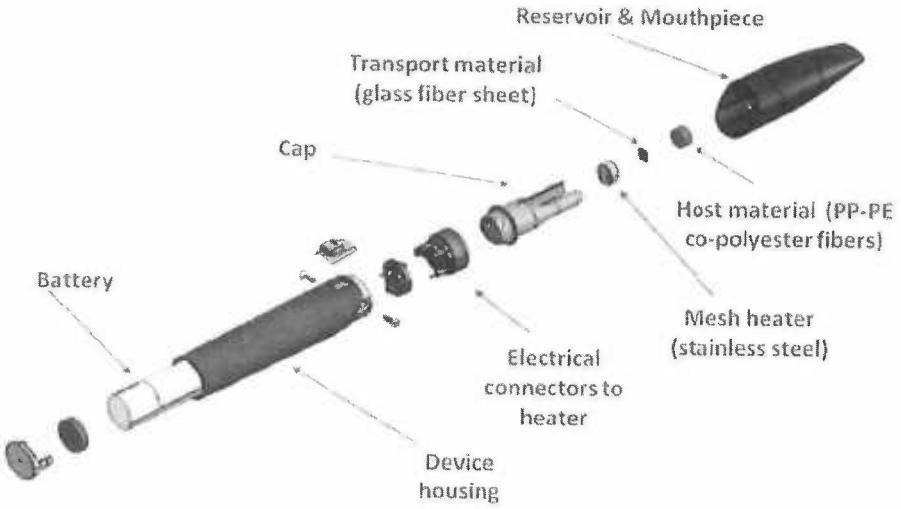


Figure 1 Exploded diagram of e-cig developed at R&D PMI, Neuchatel.

For characterization purposes, e-cigs are smoked with a smoking machine by a CORESTA smoking regime (55 mL within 3 s; rectangular profile; 30 s between puffs). For chemical analysis, the collection apparatus of aerosol and other volatile components consists of Cambridge filters. Then, GC-MS is performed.

Nowadays, no methods to precisely assess the chemical composition of a single aerosol droplet generated by e-cigs have been fully explored and validated. Such a techniques would allow us to check the uniformity in droplet composition and would enable us to recognize a correlation between droplet-size and relative percentage of chemical constituents. Such information would be helpful for tuning device characteristics during the development process of e-cigs.

Raman spectroscopy is a very well-known technique for the chemical characterization of aerosol [4]. At the same time, optical tweezers successfully enabled researchers to trap single aerosol droplets [5]. The two techniques have been already coupled [6-7] to determine chemical and physical characteristics of single aerosol droplets generated by a pressurized metered-dose inhaler (pMDI). Currently known single aerosol droplet Raman spectroscopy is limited to droplet sizes of several microns and above. The reason is twofold: submicron single droplets have been difficult to trap and with their sample volume several orders of magnitude smaller than for micron-sized droplets the sensitivity of Raman detection poses a major challenge.

In the present project, the possibility to quantify chemical constituents of single aerosol droplets generated by e-cigs by optical trapping and Raman spectroscopy will be investigated with the emphasis on submicron droplet sizes. To this end, test samples with well-defined compositions and droplet sizes will have to be studied in addition to e-cig aerosols. The final goal is to develop an additional tool, complementary to GC-MS, for aerosol characterization of e-cigs.

Deliverables

1. Definition of settings to trap e-cig aerosol droplets with different size
2. Evaluation of the possibility to characterize the aging of trapped aerosol droplets
3. Definition of settings to acquire Raman spectra
4. Identification of Raman peaks of Water, Vegetable Glycerol and Propylene Glycol and their quantification
5. Identification of Raman peaks of Nicotine. Evaluation of the limit of detection (LOD) for Nicotine by Raman spectroscopy when the maximum concentration of Nicotine in e-liquid is 10% in volume. -Evaluation of the possibility to quantify Nicotine by Raman spectroscopy when the maximum concentration of Nicotine in e-liquid is 10% in volume. - Evaluation of the possibility to quantify Nicotine by Raman spectroscopy when the maximum concentration of Nicotine in e-liquid is 2% in volume.

References

[1] https://www.nicocig.co.uk/mesh/

[2] https://www.pmi.com/smoke-free-products/mesh-taking-e-cigarettes-further

[3] https://www.pmiscience.com/platform-development/platform-portfolio/e-vapor-platforms/platform-4

[4] Fung, K. H., D. G. Imre, and I. N. Tang. "Detection limits for sulfates and nitrates in aerosol particles by Raman spectroscopy." Journal of aerosol science 25.3 (1994): 479-485.

[5] Hopkins, Rebecca J., et al. "Control and characterization of a single aerosol droplet in a single-beam gradient-force optical trap." Physical Chemistry Chemical Physics 6.21 (2004): 4924-4927

[6] Davidson, N., et al. "Measurement of the Raman spectra and hygroscopicity of four pharmaceutical aerosols as they travel from pressurised metered dose inhalers (pMDI) to a model lung." International journal of pharmaceutics 520.1 (2017): 59-69.

[7] Tong, H-J., et al. "Rapid interrogation of the physical and chemical characteristics of salbutamol sulphate aerosol from a pressurised metered-dose inhaler (pMDI)." Chemical Communications 50.98 (2014): 15499-15502.

Agreement Defining Special Provisions

By and among

ETH Zurich
[redacted]
Raemistrasse 101
8092 Zurich, Switzerland
("**ETH Zurich**")

and

Philip Morris Products S.A.
Quai Jeanrenaud 5
2000 Neuchatel, Switzerland
("**Partner**"),

Concerning the research program "Assessment of Raman spectroscopy for single droplet chemical characterization of e-cig aerosol" (the "**Project**").

Background:

A. Partner desires ETH Zurich to perform certain research for Partner and ETH Zurich desires to perform such research.
B. ETH Zurich and Partner agree that ETH Zurich will provide such research under the General Terms and Conditions for Research Projects of ETH Zurich ("**GTC Research ETHZ**", version March 2018) as modified pursuant to this Agreement Defining Special Provisions.

Now, therefore, ETH Zurich and the Company (each referred to herein individually as a "Party" and collectively as the "Parties") agree to the following Special Provisions modifying the GTC Research ETHZ as applicable to the Project:

1. Terms defined in this document (including in the introduction and Background) shall have the meanings given herein. Capitalized terms that are defined in the GTC Research ETHZ shall have the meanings given in the GTC Research ETHZ.

2. Section 3.3 of the GTC Research ETHZ is amended as follows:
"3.3 The installments are due as set forth in the agreement. In the absence of an installment schedule, the total remuneration for the Project is due upon termination of the agreement. ETH Zurich shall invoice the fee in accordance with the agreement and Section 3.4 of these GTC Research ETHZ. The Partner shall pay invoices within sixty (60) days upon receipt to an account nominated by ETH Zurich. No payments shall be made in cash or bearer instruments, nor shall any payments owed to the Supplier be made to a third party instead."

3. The following Section 3.4 shall be added to the GTC Research ETHZ following Section 3.3:
"3.4 ETH Zurich shall invoice Partner for all amounts due. Each invoice to be sent by the ETH Zurich hereunder shall be sent to Partner either: (1) via post to PMI Service Center Europe Sp. z o.o., Partner, PO Box 52, 30-969 Krakow 28, Poland; or (2) via email as a PDF file to the e-mail address mentioned in Declaration of PDF Invoicing as described in Appendix A, provided that ETH Zurich has sent a signed, completed Declaration of PDF Invoicing to PMI Service Center Europe Sp. z o.o. ("**PMISCE**") and PMISCE has provided a confirmation of its acceptance of the signed document (including via electronic mail), or (3) for ETH Zurich using

[redacted]

Coupa, the use of "web invoicing" wherever applicable in its respective country (based on legal and tax practices). In any case, each invoice should contain the following information:

- The Purchase Order number
- The WBS number, if received
- The Project name, including a reference to the applicable Project Agreement
- The name of Partner Contact, [redacted]
- The following billing company details:
  Philip Morris Products S.A.
  Quai Jeanrenaud 3
  2000 Neuchâtel, Switzerland.

In addition, a copy of each invoice should be sent to the Partner Contact via post at the above Philip Morris Products S.A. address or electronically as a PDF file (provided that the Partner responsible has provided ETH Zurich with his/her email address)."

4. The following Section 4.8 is added to the GTC Research ETHZ following Section 4.7:
"Partner shall own any deliverables (e.g., reports) provided by ETH Zurich under this agreement and shall be free to use them within its organization, including its Affiliates, subject to the restrictions set out in this agreement (including Section 6) and ownership of the underlying Project Results."

5. The following Section 6 shall replace the existing Section 6:
"6.1 ETH Zurich shall be entitled to publish all Project Results subject to the provisions of this Section 6.

6.2 To prevent disclosure of Confidential Information ETH Zurich shall give the Partner an opportunity to review the proposed publication or presentation by sending a draft copy of any such proposed publication or presentation with all relevant information at least three (3) weeks prior to the intended date of publication or presentation (whichever occurs first), or the intended date of presentation. The Partner shall then have thirty (30) days after receipt of said copies to approve such proposed presentation or publication (the "**Response Period**"). Failure to respond within the Response Period is considered as approval of the publication by the Partner. The Partner may object only if there is Confidential Information or Partner's background intellectual property contained in the proposed presentation or publication.

In case of a planned presentation at scientific conferences, ETH Zurich shall submit to Partner a written summary of the intended disclosure and the provisions of Section 6.2 shall apply, whereby the three (3) months period indicated shall be reduced to one (1) month.

6.3 If Partner objects to the proposed publication or presentation within the Response Period, then ETH Zurich shall refrain from making such presentation or publication until the Parties have agreed to a version which protects the Confidential Information from public disclosure.

6.4 ETH Zurich shall ensure that all and any publication, paper, and presentation (collectively a "**Publication**") shall give appropriate recognition of the financial and other support received from Partner, including by identifying Partner by name.

6.5 ETH Zurich shall send Partner at least one reprint of any published articles relating to the Project upon availability."

6. The following Section shall be added to the GTC Research ETHZ following Section 12.6:

[redacted]

"12.7 The Partner shall not use the names, logos or trademarks of ETH Zurich or its institutes, laboratories, researchers etc. in the context of advertisement without the prior written consent of ETH Zurich."

ETH Zurich

Zurich, dated 24.09.2018

[redacted]

Prof. Dr. [redacted]

[redacted]

Prof. Dr. [redacted], VP Research

Philip Morris Products, S.A.

[redacted]

Name: [redacted]

Neuchâtel, dated 03.Aug.2018

[redacted]

Name: [redacted]

Neuchâtel, dated 03 Aug 2018

ETH zürich

GENERAL TERMS AND CONDITIONS FOR RESEARCH PROJECTS OF ETH ZURICH („GTC Research ETHZ")

1. Scope

These GTC Research ETHZ govern the performance of a research project of ETH Zurich for/with the Partner as defined in the agreement ("Partner").

2. Performance and Organization

2.1 ETH Zurich will conduct the project as described in the agreement ("Project"). The parties will coordinate the performance of the Project and will, to the extent needed, support each other to the best of their abilities. Project meetings will take place as required. ETH Zurich will report to the Partner on the progress of the Project.

2.2 All correspondence relating to this agreement must be addressed to the Project managers. Legal and intellectual property matters shall be addressed to ETH transfer, Rämistrasse 101, CH-8092 Zurich. Changes in the person of Project manager will be notified to the other party (email sufficient).

3. Remuneration

3.1 The Partner shall pay ETH Zurich the remuneration as stipulated in the agreement, plus Swiss VAT, where applicable.

3.2 The Partner is aware that the Project might cause travel costs, additional hardware and/or consumables on ETH Zurich's part. Such expenses shall be remunerated by the Partner if approved, whereas such approval shall not be unreasonably withheld.

3.3 The installments are due as set forth in the agreement. In the absence of an installment schedule, the total remuneration for the Project is due upon termination of the agreement. The Partner shall pay the invoices within thirty (30) days upon receipt to an account nominated by ETH Zurich.

4. Project Results

4.1 The rights of the parties to any intellectual property that has been generated previously, after or outside of the Project ("Background IP") shall not be affected by the agreement.

4.2 All results generated in performance of the Project ("Project Results") by one party solely shall belong to such generating party. Project Results that are generated by both parties jointly and that are inseparable from each other shall be jointly owned by such parties. Entitlement to such joint ownership in Project Results is determined in accordance with applicable law and each parties ownership share is determined in accordance with its respective contribution to such Project Results.

4.3 For tangible Project Results to be provided by ETH Zurich pursuant to the agreement (e.g. prototypes and reports), ownership is assigned to Partner upon delivery. The Partner agrees that the tangible Project Results are neither intended to be sold nor to be applied in vivo. The Partner shall remove any reference to ETH Zurich attached or contained in the tangible Project Results before using or furnishing any tangible Project Results to third parties.

4.4 With the exception of Project Results consisting of statutory intellectual property rights ("Foreground IPR") and subject to the provisions on confidentiality in Section 5, on publications in Section 6, and on Data Protection & Export Control in Section 10, the Parties shall be free to use the Project Results without accounting or reporting to each other.

4.5 Subject to any contradicting open source license which might apply to certain Foreground IPR and subject to copyrights in publications, ETH Zurich grants to the Partner a non-exclusive, royalty-free, fully paid-up, worldwide license to use Foreground IPR solely owned by ETH Zurich including the right to sublicense to its Affiliates. "Affiliates" shall mean any legal entity which is controlled by, has control over or is under common control with Partner whereby "control" shall mean the holding of more than fifty (50) percent of the capital stock or participating shares entitled to vote for the election of directors.

4.6 To the extent the parties decide to protect joint Foreground IPR by filing a patent application, the parties shall keep such joint Foreground IPR confidential until filing but not longer than six (6) months from the creation of such joint Foreground IPR. In such case, the parties shall agree in writing on patent prosecution, defense and costs prior to filing. If no patent application is filed within this six (6) month period, ETH Zurich shall be free to publish such joint Foreground IPR subject to Section 6.

4.7 Except as provided otherwise in writing between the parties and subject to any contradicting open source license which might apply to certain joint Foreground IPR and subject to copyrights in publications, each party is entitled to use and grant non-exclusive license in its own name including the right to grant sublicenses for jointly owned Foreground IPR without reporting to the other party or remunerating each other.

5. Confidentiality

5.1 "Confidential Information" is to be understood as any information of any kind irrespective of whether it is provided in writing, orally, electronically, or in the form of samples, models, products or equipment etc., which is labeled as confidential and exchanged in any form and to which access is given by the disclosing party to the receiving party for the purpose of the Project. Receiving party will maintain secrecy with respect to Confidential Information and will use it solely for the performance of the Project. If Confidential Information is communicated in a non-written form, the disclosing party must provide to receiving party within ten (10) days from disclosure a written reproduction of the information that needs to be treated as confidential. The obligation of confidentiality ends five (5) years after the termination of the agreement.

5.2 Confidentiality obligations shall not apply to such information for which the receiving party can prove that such information (i) was already in the public domain before its disclosure by the disclosing party or is afterwards made public through no fault of the receiving party, (ii) was disclosed to the receiving party by a third party free of any obligation of confidentiality (iii) was already known to the receiving party before its disclosure or (iv) was developed by the receiving party independently. In the event that a party is required by law or a regulatory body to disclose Confidential Information, such party shall, wherever practicable, give to the other party reasonable advance notice of the intended disclosure.

5.3 Except for copies on routine information technology backups, copies for the purpose of monitoring compliance with its obligations hereunder and copies for the scientific verification of Project Results and subject to mandatory laws, the receiving party will destroy and/or delete any Confidential Information of the disclosing party upon termination of the Project.

6. Scientific Publication

6.1 ETH Zurich shall be entitled to publish all Project Results. Prior to publication, ETH Zurich shall submit a substantive draft (or in case of a planned presentation at scientific conferences a written summary of the intended disclosure) to the Partner for review. The Partner shall then have one (1) month to a) notify ETH Zurich of any objection concerning its Confidential Information whereas the parties shall find acceptable modification within one month to allow publication, and/or b) request the postpone-

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ment, for no more than three (3) months to file patents for joint Foreground IPR. Failure to respond within the abovementioned notification period is considered as approval of the publication.
6.2 In the event that the Partner wants to publish Project Results, he needs the prior written consent of ETH Zurich. Such consent shall not be unreasonably denied.

7. Warranty

7.1 ETH Zurich shall perform the Project to the best of its scientific knowledge exercising due care and taking into account recognized scientific standards. ETH Zurich will endeavor to achieve the goals of the Project.
7.2 By its nature research involves the risk of unforeseen consequences. ETH Zurich therefore does not guarantee that the intended goals and Project Results will be reached. ETH Zurich makes no warranties, neither express nor implied, regarding the Project Results, Background IP and other information and items exchanged under this agreement, including but not limited to warranties of non-infringement of third party rights. There is no duty to conduct searches with regard to existing intellectual property rights.

8. Liability

Subject to a breach of Section 5 and subject to Section 9 and to the extent permitted by the applicable law, ETH Zurich excludes any liability for any damages, including but not limited to any indirect damages or consequential loss or similar damage (e.g. loss of profit) suffered by Partner in connection with the agreement, provided such damage was not caused by ETH Zurich's willful intent or act of gross negligence.

9. Indemnification

The parties use the Project Results at their own risk. Notwithstanding Section 8, a party using any of the Project Results shall, to the fullest extent permitted by the applicable law, indemnify the other party against third party claims which are based on the party's use of the Project Results.

10. Data Protection and Export Control

10.1 The parties agree to comply with all applicable data protection laws and regulations. For personal data provided by ETH Zurich, the Partner shall (i) use such data only for research purposes not related to specific persons; (ii) protect such data by suitable technical and organizational measures, in particular against unauthorized processing; (iii) render such data anonymous as soon as the purpose of the processing permits; (iv) only disclose such data to a third party with the prior written consent of ETH Zurich (Email sufficient) and in compliance with any requirements imposed by ETH Zurich; and (v) publish such data only in a manner that the data subjects may not be identified.
10.2 Any export-controlled items such as goods, technology or software shall be provided solely to ETH Zurich's Project manager and only i) after the Partner informed ETH Zurich's Project manager in writing of any export-relevant restrictions pursuant to the applicable laws (including but not limited to U.S. export laws for items with U.S. origin) and of the respective export control classification, and ii) after the receipt of ETH Zurich's written consent, which may be provided at ETH Zurich's sole discretion.

11. Term and Termination

11.1 The agreement enters into force upon signature by both parties.
11.2 Subject to 11.3, the agreement shall terminate upon the completion of the Project. The provisions which, by their nature are intended to survive the expiry or termination of the agreement shall continue to apply.
11.3 Each party may prematurely terminate this agreement only in the event of a fundamental contractual breach by the other party but shall first give the other party thirty (30) days to remedy the breach.
11.4 In the event of premature termination, the Partner shall compensate ETH Zurich for all costs that were incurred until effective termination.

12 Miscellaneous

12.1 The agreement governs the contractual relationship of the parties in relation to the Project solely and exclusively. Any earlier agreements between the parties governing the same subject matter, including previously signed confidentiality agreements referring thereto, are hereby terminated and replaced by this agreement. Any changes to the agreement shall be agreed upon in writing. Any general terms and conditions of the Partner are excluded. Nullity of individual provisions shall not affect the validity of the agreement.
12.2 The parties do not, through this contractual relationship, acquire any rights from the other party apart from those which are explicitly conferred by the agreement. Nothing in this agreement shall imply any simple partnership between the parties. No party shall be entitled to commit the other party or the parties to any obligation in connection with this agreement, without the prior written consent of the other party.
12.3 Rights and obligations arising from the agreement may not be transferred to third parties without the written permission of the other party. In the event of an assignment of joint Foreground IPR by one party to a third party, the assigning party shall inform the other party beforehand. In any event, the assigning party shall ensure that the rights of the other party to assigned Foreground IPR, such as the licenses granted under this agreement, will not be affected by the assignment.
12.4 Deviations and amendments to the GTC Research ETHZ become valid and integral part of the agreement if stipulated in a separate document and signed by the parties ("Special Provisions").
12.5 In the event of inconsistencies between the main body of the agreement and the GTC Research ETHZ or the Special Provisions, the GTC Research ETHZ and the Special Provisions shall take precedence over the main body of the agreement. In the event of inconsistencies between the GTC Research ETHZ and the Special Provisions, the Special Provisions shall take precedence over the GTC Research ETHZ.
12.6 The agreement shall be construed and governed by the laws of Switzerland, without reference to its conflict of laws principles, and shall not be governed by the United Nations Convention on Agreements for International Sale of Goods (the Vienna Convention). The sole place of jurisdiction for any dispute arising from, or in connection with, the agreement shall be exclusively the courts of the city of Zurich.

GTC Research ETHZ (version March, 2018)

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Appendix A

DECLARATION OF PDF INVOICING

Lausanne 3-Aug-18

By signing the present Declaration, the Supplier accepts the Agreed Terms as defined on the next page.

Please fill in the below **Declaration of PDF Invoicing** and send it signed by decisive person in one of below ways:

- via e-mail (scanned hard copy) to: [redacted]
- to the address:

PMI Service Center Europe Sp. z o.o.
Al. Jana Pawla II 196
31-982 Krakow, Poland

Client 1092	*PMI Entity* **Philip Morris Products S.A. (Manufacturing)** Quai Jeanrenaud 3 2000 Neuchatel, Switzerland VAT No CHE116276488TVA	*PMI e-mail address only for .pdf invoices:* [redacted]
Supplier	*Supplier full name:* Your company full name *Supplier address:* Your company address *Supplier VAT number:* VAT No Your company VAT number.	*Supplier e-mail address only for .pdf invoices:* **Mandatory field. Indicate your company e-mail address/es from which you will send to PMI all PDF invoices.** *Supplier e-mail address only for contact purposes:* Indicate your company e-mail address to which PMI can confirm PDF Invoicing implementation.
	Your full name :Fill in.	*Date and your Signature:* Fill in.

Please note:

- After receiving your approval, we will send you a confirmation of the Effective Date from which you can start sending PDF invoices
- Your .pdf invoices can be sent **only from the mentioned Supplier Agreed e-mail Address**
- The above Declaration of PDF Invoicing refers **only to the Philip Morris Products S.A. (Manufacturing)**
- Your .pdf invoices issued for the above PMI Entity must be sent to **PhilipMorrisProductsSA-Manufacturing@pmi.com**

Yours faithfully,

Philip Morris International

DECLARATION OF PDF INVOICING: the Agreed Terms

(a) The Client and the Supplier are together referred to as the Parties.

(b) Relevant Invoices: invoices in respect of all relations between the Parties (contractual or otherwise).

(c) Working Day: a day on which PMI Service Center Europe Sp. z o.o. is open for business.

(d) This Declaration is effective as from the Effective Date.

(e) The Supplier shall send all Relevant Invoices to the Client in electronic form:

(i) in PDF format; and

(ii) via e-mail from the Supplier Agreed e-mail Address, to the Client Agreed e-mail Address.

(f) The Parties shall each implement appropriate procedures to ensure the authenticity of the origin, and integrity of the content, of the Relevant Invoices including the following:

(i) the title of the e-mail containing the invoice shall contain the Supplier's name, the number of the invoice, and the date of the invoice;

(ii) the title of the e-mail shall not include special characters and shall not be longer than 200 characters;

(iii) the e-mail shall contain only one PDF file;

(iv) each PDF file shall contain only one invoice; and

(v) the Supplier shall not send the Client the same invoice (i.e., relating to the same economic event) in both paper and in electronic form.

(g) Should any invoice fail to comply with the above requirements, it shall be invalid.

(h) The Client shall be deemed to receive invoices sent in accordance with the above:

(i) if the invoice reaches the Client's server on a Working Day between 0800 and 1600 hours (CET/CEST): at the time the invoice reaches the Client's server; and

(ii) if the invoice reaches the Client's server outside the above times: at 0800 on the first Working Day following.

(i) Each Party may terminate this Electronic Invoicing Procedure, for any reason, with immediate effect by notifying the other Party.

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