Section A

Institution: University of St Andrews

Unit of Assessment: UoA 07: Earth Systems and Environmental Sciences

Title of case study: Alternatives to combustible tobacco: Changing UK health policy and international corporate strategy

Period when the underpinning research was undertaken: 2010 - 31 December 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Ed Stephens	Principal Research Fellow	01 October 1972 - present

Period when the claimed impact occurred: 2015 - 31 December 2020

Is this case study continued from a case study submitted in 2014? N

Section B

1. Summary of the impact (indicative maximum 100 words)

Vaping and smoking simulator at the University of St Andrews

Globally some 1,300,000,000 people smoke tobacco and about half will die from inhaling its combusted products (about 7,000,000 people per year). Though not risk free, vaping is considered a much less harmful means of acquiring nicotine and vaper numbers worldwide are estimated at about 50,000,000. A few countries, including the UK, have actively encouraged vaping as an aid to smoking cessation and the majority of the UK's 3,200,000 people (vapers) are ex-smokers. Public misperception of the health risks of vaping is a significant obstacle on the pathway to smoking cessation. Dr Ed Stephens' disease potency toxicological modelling has investigated the long-term implications of vaping for cancer with results that address two contrasting areas: (1) in public health, where the research has contributed to shaping policy and informing regulators, practitioners and users on the cancer risks; and (2) by providing key evidence which has led to radical shifts in "Big Tobacco" strategies that phase out cigarettes entirely and replace them with smoke-free products. Four of these companies, Philip Morris, British American Tobacco, Japan Tobacco and Imperial Tobacco, exceeded USD120,000,000,000 in combined sales in 2019.

2. Underpinning research (indicative maximum 500 words)

In 2010, Dr Ed Stephens established a laboratory, with EU support, in the School of Earth and Environmental Sciences to investigate the role that tobacco plays in transferring environmental toxicants, notably "heavy metals", from the cultivation environment to the smoke aerosol created

when tobacco is combusted. Evidence was found that variations in geology, soils and atmospheric pollution are reflected in the tobacco crop and, subsequently, the smoke emissions to which users are exposed (**R1**). For example, combustion creates conditions to ensure that the oxidised form of arsenic, As(V), that is typical of fresh tobacco leaf, is reduced during combustion to As(III), a much more toxic valence state (**R2**).

By 2014, electronic nicotine delivery systems (ENDS), including e-cigarettes, had gained wide acceptance with users of combustible cigarettes (CC) in some economically developed countries for their perceived health benefits. Stephens modified his lab to facilitate the analysis of ENDS products and provided evidence that the burden of several toxicants and carcinogens is lower than in CC smoke for the same volume of emissions (**R3**).

While this relationship mostly held for individual toxicants, there was no clarity on how health risks compared between smoking, vaping and abstinence. To address this knowledge gap, the chemical compositions of emissions from CC and ENDS under standard laboratory conditions were collated in a database from all known peer-reviewed publications that met a particular standard. Because CC and ENDS emissions data were not directly comparable, a parameterisation was devised to enable like-with-like comparison. The cancer potency of the emission from each experiment was then computed from the emissions concentrations and carcinogenic (unit) risks for each compound. The aggregate potency results provided a useful proxy for cancer risk (**R4**) which was further refined for a subset of products using the more complete benchmark dose toxicological model (**R5**).

This synthesis led Stephens to create a *cancer potency spectrum* reflecting relative risks (Figure 1, reproduced from **R4**), the only published example to compare quantitatively the risks of disease due to various forms of inhaling nicotine (i.e. smoking, vaping, etc.). It shows that relative risk spans nearly six orders of magnitude from the extremely low cancer risk of ambient air to the very high risk of tobacco smoke. Stephens also identified the individual compounds that contribute most to carcinogenicity (**R4**) thereby providing guidance and focus for future research on further reduction of risk. The unexpected finding was that, unlike combustible tobacco, e-cigarettes do not occupy a narrow, well-defined region of the risk spectrum but span almost the whole range: from a risk equivalent to that of a medically-prescribed nicotine inhaler up to the risk of tobacco smoke, although most values fall below 1% of smoking risks. Further research indicated that high-risk e-cigarette emissions were associated with experiments in which the heating coil was run at unusually high power (**R6**). Devices that deliver nicotine aerosols from heating tobacco without combustion (HTP, see below) have risks of 1-10% those of aerosols from combusting tobacco (**R4, R5**).

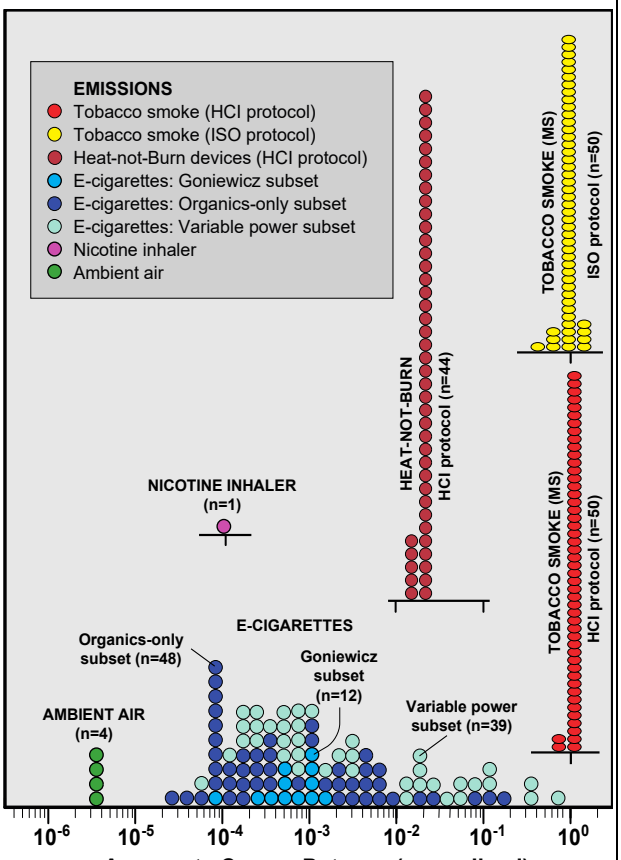


Figure 1. Normalised relative cancer potencies of uncontaminated air and emissions from various forms of nicotine delivery compared with average tobacco smoke (set to 1). Each circle/ellipse is an individual experiment. (from R4).

3. References to the research (indicative maximum of six references)

The research was supported by Cancer Research UK and The Carnegie Trust and has been published in highly regarded peer-reviewed journals.

R1 O'Connor, RJ, Li, Q, **Stephens, WE**, Hammond, D, Elton-Marshall, T, Cummings, T, Giovino, GA, Fong, GT. Cigarettes sold in China: design, emissions and metals (2010) *Tobacco Control* **19**, 47-53. DOI: 10.1136/tc.2009.030163 [Stephens provided the data and text on

metals, other authors contributed on design and emissions.]

R2 Campbell, RCJ, **Stephens, WE,** Finch, AA, Geraki, K. Controls on the valence species of arsenic in tobacco smoke: XANES investigation with implications for health and regulation. (2014) *Environmental Science & Technology* **48**, 3449-3456. DOI: 10.1021/es4039243

R3 Visser, W.; Geraets, L.; Klerx, W.; Hernandez, L.; **Stephens, W.E**.; Croes, E.; Schwillens, P.; Cremers, H.; Bos, P.; Talhout , R. (2015) The health risks of using e-cigarettes. *RIVM Letters* 2015-0144, 47pp. (https://www.rivm.nl/bibliotheek/rapporten/2015-0144.html, consulted 26.11.2020)

R4 Stephens, W.E. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with tobacco smoke. *Tobacco Control* **27**, 10-18. DOI: 10.1136/tobaccocontrol-2017-053808.

R5 Slob, W., Soeteman-Hernández, L., Bil, W., Staal, Y.C.M., **Stephens, W.E.**, Talhout, R. (2020). A method for comparing the impact on carcinogenicity of tobacco products: a case study on heated tobacco versus cigarettes. Risk Analysis 40 (7), 1355-1366 DOI: 10.1111/risa.13482.

R6 Stephens, W.E., de Falco, B., Fiore, A. (2019) A Strategy for Efficiently Collecting Aerosol Condensate Using Silica Fibers: Application to Carbonyl Emissions from E-Cigarettes. Chemical Research in Toxicology 32, 2053-2062. DOI: 10.1021/acs.chemrestox.9b00214.

4. Details of the impact (indicative maximum 750 words).

On current trends 12,000,000,000 avoidable deaths will be attributable to smoking-related causes over this century and the emissions from combusting tobacco leaf are identified as the main culprits. Current consensus, supported by the underpinning research in section 2, is that ENDS help users to quit combustibles while protecting both users and bystanders from the highly toxic emissions of combusted tobacco. Population-scale modelling for the US estimates that replacing combustibles with ENDS would prevent up to 6,600,000 premature deaths over a 10-year period.

Stephens' research (exemplified by **R1**-**R3**) as described in section 2 culminated with **R4**, where he was sole contributor of the data compilation and its interpretation. **R5** was based on **R4** and was a collaboration on further methodological development while other authors provided new toxicological analyses. This research comparing the cancer potencies of emissions from ENDS with tobacco smoke led to proxies for the relative risks of cancer from a range of devices used to aerosolise nicotine (cigarettes, heated tobacco products (HTP), e-cigarettes, nicotine inhalators etc.). The scientific evidence has helped bring about necessary strategic changes on several fronts in the ongoing battle to prevent deaths as a result of inhaling the highly toxic aerosols of combustible tobacco products. His research has:

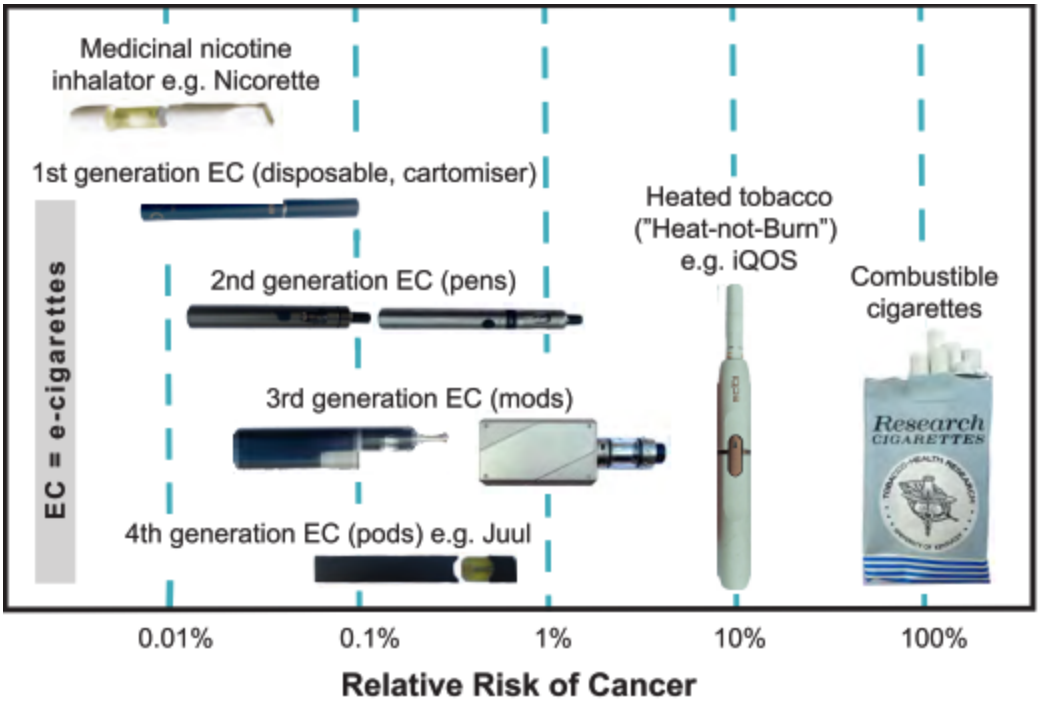
(1) provided key corroborative evidence on relative risks for Public Health England (PHE) to implement UK Government policy in radically revising its tobacco control policy to promote ENDS as aids in smoking cessation; informed the WHO expert panel on the relative risks of ENDS; and widely informed people (users) via social media routes on the relative risks of the various methods of nicotine delivery;

(2) contributed to profound changes in the long-term business strategies of the leading tobacco companies Philip Morris International (PMI), Japan Tobacco International (JTI) and Imperial to replace their combustible cigarette product ranges with smoke-free, non-combustible products. This follows the 2020 formal approval of PMI's flagship HTP by US regulators (FDA) for which **R4** was cited among the key evidence for reducing health risks.

(1) Influencing Public Health Policy for Smoking Cessation through government, WHO, NGOs and the public.

The UK Government's Tobacco Control Plan addressed ENDS in 2017 and in the associated Parliamentary debate the research at the University of St Andrews regarding the relative risks of cancer was explicitly cited (**S1, p. 29**). In the report commissioned from PHE to implement the associated legislation, 'Evidence review of e-cigarettes and heated tobacco products 2018' (**S2**), the harm-reduction potential of e-cigarettes was adopted as its centrepiece policy for

smoking cessation, citing directly data from **R4,** "*EC cancer potencies were largely found to be only a small fraction of those of smoking (0.4%)*" (**S2, p. 155**), and emphasising as the first Key Finding that "*cancer potencies of e-cigarettes were largely under 0.5% of the risk of smoking*" (**S2, p. 174**). PHE has led the world (often controversially) in its proactive adoption of e-cigarettes as the most effective means of reducing the considerable health burden of smoking combustibles. The Tobacco Control lead within PHE with responsibility for grounding UK tobacco policy in scientific evidence has stated, "*While the data on the role of non tobacco nicotine products in cardiovascular and respiratory disease remains highly contested, the work of Dr Stephens has, to a very great degree, helped to settle the issue on the risk of cancer. … (his) work helped to establish that risk, not simply in the context of recreational nicotine products, such as cigarettes but also pharmaceutical products for the treatment of tobacco dependency. … In short, I consider that the work [of Dr Stephens] has had a material impact on UK tobacco control policy and greatly improved the international policy debate*" (**S3, p. 1**). When addressing the health risks of ENDS PHE's Tobacco Control Lead summarises **R4** in his regular presentation (**S3, p. 19, slide 17**) and *"[he] always spend[s] some time explaining the paper's significance"* (**S3, p. 1**). UK policy was derived from The WHO's 2003 Framework Convention on Tobacco Control (FCTC), signed by 168 nations, that recognises tobacco as an epidemic requiring global action. Since ENDS became popular in the 2010s, the WHO has sought to provide authoritative advice on the safety of these products through TobReg, its expert science advisory panel. TobReg's report in 2017 highlighted Stephens' research on risk by reproducing text and a diagram from **R4** verbatim (**S4, pp. 58 & 59).** Nicotine users were directly engaged through the NGO, Cancer Research UK, which hosted a Science blog interview with Dr Stephens on heat-not-burn products to explain the concept and relative risks of HTPs (**S5, pp. 1-4**). In the US, a complementary story covered by the Tobacco Control blog which directly references Stephens' research (**R4**) received over 21,000 site visits (**S5, p. 9**). The findings on risk were also reported in newspapers including The Guardian (monthly average multiplatform readership: 24,165,000 (**S5, p. 14**)) and Irish Times (average daily readership: 390,000 (**S5, p. 19**) that led to far wider engagement with the research, **R4**, than solely through an academic audience, ultimately resulting in over 40,000 downloads of **R4** from the BMJ website and more than 100,000 downloads of the abstract placing it 24th in 2,684 outputs in this BMJ journal (**S6**). Altmetric (score 463) indicates that 91% of social media content occurred through members of the public (**S6**).



Cancer risk from vaping compared with smoking (arbitrarily set at 100%) using cancer potency as a proxy and commercial devices to reflect risk ranges. Note the risk scale is logarithmic – at the low risk end a medically prescribed nicotine inhaler poses about 0.01% the risk of smoking.

(2) Impact on Big Tobacco's long-term business strategies.

Pressure from changing public attitudes, international public health policies and the growing popularity of ENDS as means for acquiring nicotine, collectively, pose an existential threat to "Big Tobacco". The four largest international tobacco companies, namely Philip Morris, British American Tobacco, Japan Tobacco and Imperial Tobacco (PMI, BAT, JTI and Imperial), whose collective annual revenues in 2019 exceeded USD120,000,000,000, responded to public pressure and government policies (section 4.1), in part as a result of the Stephens' research (**R4**), now accept that business as usual cannot continue and have changed their business development direction from combustible cigarettes to smoke-free products. As well as entering the e-cigarette market, they have consolidated their reliance on tobacco by creating HTP devices that release nicotine and flavours when tobacco is heated below combustion temperatures. Since the launch in Japan in 2014 of iQOS, PMI's flagship "smoke-free" HTP product, the company has pursued, for global commercial reasons, regulatory approval in the US in order to market iQOS formally as a "reduced risk" product. PMI's request submitted to the US Food & Drug Administration (FDA) in 2017 was eventually approved in July 2020 after three years of detailed scrutiny. FDA's scientific reviewers found seven peer-reviewed publications on the chemical toxicology of the iQOS aerosol, with **R4** being the only one to quantify the health risks compared with combustible cigarettes (**S7, p. 22)**. This study was thus an important factor in the FDA's approval of iQOS as a "*modified risk tobacco product".* This was the first time that tobacco products received this approval, which permits the marketing of a product where the issuance of the order "*is expected to benefit the health of the [US] population as a whole*" (**S8**). In a press release welcoming the FDA's approval of iQOS, PMI announced a stunning change to their strategic vision, stating, "*To date, we have invested USD 7.2 billion [USD7,200,000,000] in the research and development of our smoke-free products. Furthermore, we have committed to stop selling cigarettes as soon as possible. Our ambition is to secure a smoke-free future for all*" (**S9**). BAT, JTI and Imperial are currently on similar journeys to replace their combustible products and the methodology of Stephens (**R4**) is playing a similar role (being directly quoted) in demonstrating the risk differential with combustibles (**S10**).

5. Sources to corroborate the impact (indicative maximum of ten references)

S1. Parliamentary debate statement by Mary Glindon MP (Labour, North Tyneside). Hansard for 19th October 2017, p. 29.

S2. Public Health England report, "Evidence review of e-cigarettes and heated tobacco products 2018", chapter on "Health Risks of EC (electronic cigarettes)", pp. 155 & 174.

S3. Supporting letter from the Tobacco Control Lead, Public Health England and presentation by the Tobacco Control Lead, Public Health England (slide 17).

S4. WHO Study Group on Tobacco Product Regulation, WHO Technical Report Series 1015, section 3.7.2, pg 58. ISBN 978-92-4-121024-9, pp. 58-59.

S5. Blogs and newspaper readership data

S6. Altmetric data for article R4, downloaded 07/12/2020.

S7. FDA Technical Review (2018) (Stephens cited in evidence base, pp. 21-22).

S8. PMI's strategy statement July 2020 (see final section "The vision of a smoke-free future").

S9. FDA Press Release approving PMI's iQOS as a modified risk product (highlighted sections)

S10. Peer-reviewed paper by JTI employees on risk comparison citing **R4** and **R5** (p. 1511) and Presentation by Imperial employees linking **R4** to industry directions (section 4).