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Vaping flavoured e-cigarettes 'leads to heart disease, strokes and heart attacks', scientists warn

mirror.co.uk/science/beware-flavoured-e-cig-scientists-12703518

June 14, 2018

By
Shivali Best

- 10:00, 14 JUN 2018
- Updated11:42, 15 JUN 2018

Science

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They're often portrayed as 'healthier' alternatives to cigarettes, but scientists have warned about the dangers of e-cigarettes.

A new study by researchers from Boston University has revealed that the flavour additives using in e-cigarettes can impair blood vessel function, and inhaling them can lead to heart damage .

Dr Jessica Fetterman, who led the study, said: "Increased inflammation and a loss of nitric oxide are some of the first changes to occur leading up to cardiovascular disease and events like heart attacks and stroke, so they are considered early predictors of heart

disease.

“Our findings suggest that these flavoring additives may have serious health consequences."

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The flavour additives using in e-cigarettes can impair blood vessel function, and inhaling them can lead to heart damage (Image: Getty)

In the study, the researchers looked at the effects of nine chemical flavourings often used in e-cigarettes on endothelial cells - the cells that line the blood vessels and the inside of the heart.

Flavours tested included menthol, burnt flavour, vanilla, cinnamon, clove, butter, strawberry, banana and spicy cool.

Their analysis revealed that all nine flavours had detrimental effects on endothelial cells.

Dr Fetterman said: “Our work and prior research have provided evidence that flavorings induce toxicity in the lung and cardiovascular systems.

“Flavorings are also a driver of youth tobacco use and sustained tobacco use among smokers.”

The researchers hope their findings will lead to new regulations to prevent access, sales and marketing of e-cigarettes to youth.

Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction

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Arteriosclerosis, Thrombosis, and Vascular Biology

Original Research

Jessica L. Fetterman, Robert M. Weisbrod, Bihua Feng, Reena Bastin, Shawn T. Tuttle, Monica Holbrook, Gregory Baker, Rose Marie Robertson, Daniel J. Conklin, Aruni Bhatnagar, Naomi M. Hamburg

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Abstract

Objective—Use of alternative tobacco products including electronic cigarettes is rapidly rising. The wide variety of flavored tobacco products available is of great appeal to smokers and youth. The flavorings added to tobacco products have been deemed safe for ingestion, but the cardiovascular health effects are unknown. The purpose of this study was to examine the effect of 9 flavors on vascular endothelial cell function.

Approach and Results—Freshly isolated endothelial cells from participants who use nonmenthol- or menthol-flavored tobacco cigarettes showed impaired A23187-stimulated nitric oxide production compared with endothelial cells from nonsmoking participants. Treatment of endothelial cells isolated from nonsmoking participants with either menthol (0.01 mmol/L) or eugenol (0.01 mmol/L) decreased A23187-stimulated nitric oxide production. To further evaluate the effects of flavoring compounds on endothelial cell phenotype, commercially available human aortic endothelial cells were incubated with vanillin, menthol, cinnamaldehyde, eugenol, dimethylpyrazine, diacetyl, isoamyl acetate, eucalyptol, and acetylpyrazine (0.1–100 mmol/L) for 90 minutes. Cell death, reactive oxygen species production, expression of the proinflammatory marker IL-6 (interleukin-6), and nitric oxide production were measured. Cell death and reactive oxygen species production were induced only at high concentrations unlikely to be achieved in vivo. Lower concentrations of selected flavors (vanillin, menthol, cinnamaldehyde, eugenol, and acetylpyridine) induced both inflammation and impaired A23187-stimulated nitric oxide production consistent with endothelial dysfunction.

Conclusions—Our data suggest that short-term exposure of endothelial cells to flavoring compounds used in tobacco products have adverse effects on endothelial cell phenotype that may have relevance to cardiovascular toxicity.

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Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction

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Conclusions—Our data suggest that short-term exposure of endothelial cells to flavoring compounds used in tobacco products have adverse effects on endothelial cell phenotype that may have relevance to cardiovascular toxicity. **(*Arterioscler Thromb Vasc Biol*. 2018;38:00-00. DOI: 10.1161/ATVBAHA.118.311156.)**

Key Words: endothelial cells ■ eugenol ■ inflammation ■ nitric oxide ■ tobacco

Electronic cigarettes (e-cigarettes) came on the market in 2003, and since that time, their popularity has increased dramatically. The majority of adult e-cigarette users are current or former combustible cigarette smokers, which has garnered interest on whether e-cigarettes may aid in smoking cessation or be a harm-reduction tool in smokers.[1–3] In addition, e-cigarette use by youth is rising rapidly with ≈16% of high school students having used an e-cigarette in the past 30 days, whereas 37% of high schoolers reported ever use of an e-cigarette in 2015.[4–7] Importantly, studies have shown that youth who try e-cigarettes are at a 3- to 5-fold greater risk for combustible cigarette smoking, suggesting that e-cigarettes are serving as a gateway to other tobacco product use.[6,8] Further, e-cigarettes are marketed and perceived as being safer than combustible cigarettes because of the limited number of ingredients in the electronic liquid (primarily nicotine, propylene glycol/glycerin, and often contain flavorings).

Although combustible cigarettes are prohibited from containing characterizing flavors, with the exception of menthol, other tobacco products including e-cigarettes, cigars, little cigars, cigarillos, smokeless tobacco, and hookah are unrestricted regarding flavoring addition. Electronic liquids are available in a wide variety of flavorings with ≈7000 on the market with menthol, sweet, and fruity electronic liquids being the most popular.[9] The flavorings used in tobacco products, including electronic liquids, greatly increase the appeal of tobacco products and mask the harshness associated with use.[9–13] In 2014, of the high school students who reported use of a tobacco product, an estimated 73% reported using a flavored tobacco product,[10] and among youth, flavorings are cited as a primary reason for use of alternative tobacco products, including e-cigarettes, hookah, and cigars.[10,14,15] Although the majority of the morbidity and mortality burden of combustible cigarette smoking is attributable to cardiovascular disease, the

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Nonstandard Abbreviations and Acronyms	
DHE	dihydroethidium
e-cigarettes	electronic cigarettes
eNOS	endothelial NO synthase
HAEC	human aortic endothelial cell
ICAM-1	intercellular adhesion molecule-1
IL-6	interleukin-6

effects of tobacco product flavorings on the cardiovascular system are largely unknown.

The cardiovascular system is exposed to circulating toxins, and measures of vascular function are rapidly altered in response to environmental exposures. The endothelium plays a key role in maintaining vascular homeostasis, which has been shown to be disrupted by several cardiovascular risk factors, including combustible cigarette smoking.[16–18] Endothelial dysfunction not only precedes the development of atherosclerosis but also predictive of worse outcomes, including myocardial infarction and cardiac death.[19,20] Combustible cigarette smoking has been shown to induce endothelial dysfunction characterized by increased oxidative stress, a loss of nitric oxide signaling, inflammation, oxidative stress, and a prothrombotic phenotype.[16–18] Several studies in endothelial cells suggest that acrolein, an aldehyde found in combustible cigarette smoke and e-cigarette aerosol, induces inflammation and oxidative stress.[21–23] A recent study showed that flow-mediated vasodilation was impaired in young, healthy tobacco naïve individuals and combustible cigarette smokers 30 minutes after the use of an e-cigarette, suggesting that acute e-cigarette use impairs endothelial function.[24] However, the mechanisms underlying e-cigarette–induced vascular injury are largely unknown, and whether tobacco product flavorings induce endothelial dysfunction is unclear.

In this study, we developed an in vitro screening panel to identify whether flavorings added to tobacco products are toxic to endothelial cells and, if so, what levels induce toxicity. We selected a panel of measures of endothelial function, including measures of cell death, oxidative stress, inflammation, and nitric oxide bioavailability. Under pathological conditions, endothelial cells undergo cell death, have increased oxidative stress, decrease production or lose bioavailable nitric oxide, and become proinflammatory. We tested the vascular endothelial cell toxicity of common flavoring compounds in tobacco products across many different chemical classes. The flavorings vanillin, cinnamaldehyde, eugenol, acetylpyridine, and menthol impaired A23187-induced nitric oxide production and increased expression of the proinflammatory mediator, IL-6 (interleukin-6), suggesting that these flavors are harmful to the endothelium (Table 1).

Materials and Methods

Data available upon request from the authors.

Study Participants

We enrolled age- and sex-matched nonsmokers who do not use any tobacco products, nonmenthol cigarette smokers, and menthol cigarette smokers. All participants enrolled had no risk factors (diabetes mellitus, smoking, hypertension, dyslipidemia) or known cardiovascular disease. All participants provided written consent, and all study protocols were approved by the Boston Medical Center Institutional Review Board.

Flow-Mediated Vasodilation

Endothelial function was evaluated using flow-mediated vasodilation in which hyperemic flow stimulates endothelial nitric oxide production and subsequent vasodilation. As previously described, hyperemic flow was induced by proximal forearm cuff occlusion of the upper arm for 5 minutes, and a Toshiba SSH-140A ultrasound system was used to measure brachial artery diameter at baseline and 1 minute after the 5-minute occlusion.[25] The commercially available software, Brachial Analyzer version 3.2.3 (Medical Imaging Applications), was used to assess flow-mediated dilation data. Flow-mediated vasodilation is expressed as percent dilation.

Venous Endothelial Cell Biopsy

Venous endothelial cells were freshly isolated from nonsmokers, nonmenthol cigarette smokers, and menthol cigarette smokers without cardiovascular disease, as previously described.[26–28] A 0.018-inch J-wire (Arrow International, Reading, PA) was inserted through a 20 or 22 gauge catheter in a vein of the forearm and used to gently rub the inside of the vessel. After removal, the J-wire was rinsed several times with red blood cell lysis and dissociation buffer. The sample was then centrifuged and cells applied to poly-L-lysine–coated slides (Sigma, St Louis, MO). Nitric oxide production and bioavailability were then assessed immediately after isolation as outlined below.

Cell Culture Conditions and Tobacco Flavorings Exposures

Commercially available (Lonza Inc, Walkersville, MD) human aortic endothelial cells (HAECs) were cultured from passage 4 to 7 (EGM-2 [endothelial cell growth medium] complete media, Lonza). When the cells were near confluent, serum was withdrawn for 4 hours, and the cells were exposed to a flavoring compound diluted in media (phenol red–free EGM-2, Lonza) for 90 minutes at 37°C before measurement of apoptosis, oxidative stress, inflammation, and nitric oxide production as outlined below. Controls were vehicle matched to flavoring. All flavors are food safe grade, production lot consistent, and obtained from Sigma-Aldrich (St Louis, MO; Table I in the online-only Data Supplement for catalog numbers).

The flavoring compounds were heated at temperatures achieved using e-cigarette tank devices to test the potential toxicity of thermal degradation productions. A drop-tube furnace consisting of a quartz tube was configured in a vertical position and set to temperatures 200°C±50°C or 700°C±50°C. Vanillin, menthol, or eugenol were added dropwise into the heated area of the furnace where the flavoring compound was quickly aerosolized. The aerosol then moved through a glass impinge for collection in an ethanol solution (55% in PBS). Test concentrations of thermal product solutions were determined from the volume of flavoring compound initially added to the furnace before heating and collection. All cell exposures to the aerosolized flavoring compounds were compared with ethanol vehicle control.

Measurement of Nitric Oxide Bioavailability

HAECs were grown on 8-well slides, and after a 90-minute flavoring exposure, the cells were incubated with 3 µmol/L 4,5-diaminofluorescein diacetate (Calbiochem) for 30 minutes. After 2 washes with Hanks' balanced salt solution, cells were stimulated with 1 µmol/L A23187 (Sigma) for 15 minutes and fixed with 2% paraformaldehyde. Mean fluorescence intensity (excitation of 498 nm) of individual cells (20 cells per condition) was measured on a fluorescence microscope (Nikon Eclipse TE2000). Data are expressed as percent increase in 4,5-diaminofluorescein diacetate fluorescence stimulated by A23187 compared with unstimulated cells.

Quantification of Cell Death

HAECs were grown on 8-well slides, incubated with flavoring compounds for 90 minutes, fixed with 2% paraformaldehyde, and stored at −80°C. A commercially available TUNEL assay (terminal deoxynucleotidyl transferase dUTP nick-end labeling; Roche) was performed,

Table 1. Tobacco Product Flavorings Tested

Tobacco Product Flavoring	Class	Subgroup	Characterizing Flavor
Eugenol	Alcohols, phenols	Phenol	Clove
Vanillin	Aldehyde	Aromatic aldehyde	Vanilla
Cinnamaldehyde	Aldehyde	Aromatic aldehyde	Cinnamon
Menthol	Alcohols, phenols	Cyclic terpene	Mint, cooling effect
2,5-dimethylpyrazine	Pyrazine	Alkyl pyrazine	Strawberry
Diacetyl	Ketone	Diketone	Butter
Isoamyl acetate	Ester	Aliphatic esters	Banana
Eucalyptol	Ether	Ether	Spicy, cooling effect
Acetylpyridine	Pyridine	Pyridine	Burnt

and cells were imaged on a fluorescence microscope (Nikon Eclipse TE2000) for fluorescein and DAPI (4',6-diamidino-2-phenylindole; Vector Laboratories). DNAse 1 (Sigma) was used as a positive control for apoptosis. A minimum of 50 cells were quantitated for each condition. Data are presented as % TUNEL-positive cells.

Assessment of Oxidative Stress

HAECs were grown on 96-well plates and, after flavoring exposure, were incubated with dihydroethidium (DHE, 10 µmol/L, Thermo Fisher) for 30 minutes. Cells were washed 3× to remove DHE with Hanks' balanced salt solution. Fluorescence was measured on a plate reader with an excitation of 518 nm and emission of 606 nm (Molecular Devices). Antimycin A (50 µmol/L; Sigma) treatment for 30 minutes was used as a positive control. Data are presented as fold change in DHE fluorescence compared with vehicle control.

Quantification of IL-6 and ICAM-1 (Inflammatory) Activation

HAECs were grown on 6-well plates and were incubated an additional 90 minutes in media after flavoring exposure, allowing for a total time of 180 minutes for changes in RNA expression. Cells were scraped into Qiazol (Qiagen), frozen, thawed, chloroform (1/5 of the Qiazol volume) extracted, and shaken for 15 seconds. After a 5-minute incubation at room temperature, the samples were centrifuged at 12 000*g* for 15 minutes at 4°C. The aqueous phase was collected and RNA was extracted with a kit (miRNeasy Micro Kit, Qiagen) according to the manufacturer's instructions. RNA was eluted in 14 µL of water and quantified with a Nanodrop spectrophotometer (Thermo Fisher, average of 200 ng RNA/µL). cDNA synthesis of mRNA was performed with a cDNA reverse transcription kit (Quanta Bio, Beverly, MA). Reverse transcription-quantitative polymerase chain reaction was performed with a Viia7 (Applied Biosystems) thermal cycler using TaqMan Master Mix and TaqMan primers for IL-6 and ICAM-1 (intercellular adhesion molecule-1; Thermo Fisher). The $2^{-\Delta Ct}$ was calculated from threshold Ct values using GAPDH as a reference gene. Data are expressed as relative quantification to matched control.

Statistical Analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY). Data are expressed as mean±SD, unless otherwise indicated. We evaluated each measure for normality using the Shapiro–Wilk test. For between group comparisons, variables with normal distribution were compared using a 1-way ANOVA using post hoc Dunnett 2-sided tests with contrasts to control (vehicle alone) or χ^2 testing for continuous or categorical data, respectively. For variables that were not normally distributed, we used Kruskal–Wallis tests. For 2-group comparisons before and after treatment, we used paired *t* tests, and for variables not normally distributed, we used Wilcoxon signed-rank tests. A $P<0.05$ was considered to be statistically significant.

Results

In a healthy endothelium, stimulation with eNOS (endothelial NO synthase) agonists, such as A23187, induces an increase in nitric oxide which in vivo results in vasodilation and is indicative of cardiovascular health.[19,29] Venous endothelial cells were freshly isolated by venous biopsy from nonsmokers (n=9), nonmenthol cigarette smokers (n=6), and menthol cigarette

Table 2. Clinical Characteristics

	Nonsmokers (n=9)	Nonmenthol Cigarette Smokers (n=6)	Menthol Cigarette Smokers (n=6)
Age, y	29±4	40±10	39±14
Female sex, n (%)	5 (55)	2 (33)	2 (33)
Black race, n (%)	6 (66)	5 (83)	5 (83)
Body mass index, kg/m^2	26.3±2.9	28.9±7.3	26.9±4.4
Systolic blood pressure, mm Hg	115±11	123±6	128±23
Diastolic blood pressure, mm Hg	65±6	73±9	77±10
Heart rate, bpm	59±6	64±9	57±8
Packs per day, n		0.7±0.2	1.4±0.7
Pack years		21±10	27±22

Data are expressed as mean±SD.

smokers (n=6) of similar age and sex (Table 2). Nonmenthol and menthol cigarette smokers had a similar number of packs smoked per day (0.7±0.2 versus 1.4±0.7; *P*=0.4) and pack years (21±10 versus 27±22; *P*=0.7). As part of larger, on-going study of vascular function and smoking, we evaluated flow-mediated vasodilation in the patients recruited for endothelial cell biopsy. We found a trend for lower flow-mediated vasodilation between the smoking groups and nonsmokers (Figure I in the online-only Data Supplement; *P*=0.12 between groups).

Freshly isolated endothelial cells collected from nonmenthol and menthol cigarette smokers had lower nitric oxide production in response to A23187 stimulation compared with cells from nonsmokers (*P*=0.003 nonsmokers versus nonmenthol cigarette smokers; *P*=0.012 nonsmokers versus menthol cigarette smokers; Figure 1A). The impairment in A23187-stimulated nitric oxide production was similar between nonmenthol cigarette smokers and menthol cigarette smokers (*P*=0.86; Figure 1A). The absence of a difference in A23187-stimulated nitric oxide production is likely because of the overwhelming toxicity of the many components of tobacco smoke that are already maximally impairing nitric oxide bioavailability. Consistent with this, we observed that the treatment of endothelial cells from nonmenthol cigarette smokers with 0.01 mmol/L menthol did not further impair nitric oxide production in response to A23187 (2.1±2.4 versus −2.6±5.1; *P*=0.5). Treatment of freshly isolated endothelial cells from healthy participants with 0.01 mmol/L menthol (Figure 1B) or 0.01 mmol/L eugenol (Figure 1C) impaired nitric oxide production in response to A23187 stimulation. These findings suggest that flavoring compounds induce endothelial cell dysfunction in human cells similarly to the abnormal function in active cigarette smokers.

To further characterize the acute effects of several flavoring compounds on a broad set of endothelial phenotypes, we studied commercially available endothelial cells. Several tobacco product flavorings and doses induced cell death measured by TUNEL assay (Figure 2). Specifically, all flavorings tested induced cell death at the highest concentration tested (10–100 mmol/L). Cinnamaldehyde precipitated out of solution at concentrations >10 mmol/L; therefore, all experiments were performed at 10 mmol/L or lower concentrations. Cinnamaldehyde, eugenol, dimethylpyrazine, isoamyl acetate, and eucalyptol treatment at 10 mmol/L increased cell death compared with vehicle control. Treatment of HAECs with 1 mmol/L dimethylpyrazine also increased cell death, suggesting that endothelial cells are especially sensitive to dimethylpyrazine exposure.

Oxidative stress was assessed using the fluorescent dye DHE after treatment of HAECs with flavorings across several concentrations (Figure 3). As expected, the positive control, antimycin A, increased the levels of oxidants as measured by an increase in DHE fluorescence. Vanillin and eugenol increased oxidative stress at the highest concentration tested (10 mmol/L vanillin, 10 mmol/L eugenol), whereas all other flavorings tested had no effect on oxidative stress. The concentrations of vanillin and eugenol that increased oxidative stress were also the same concentrations that caused cell death, suggesting significant damage to endothelial cells at these levels. The concentrations of flavorings for all additional assays tested were performed at concentrations below the dose observed to induce cell death.

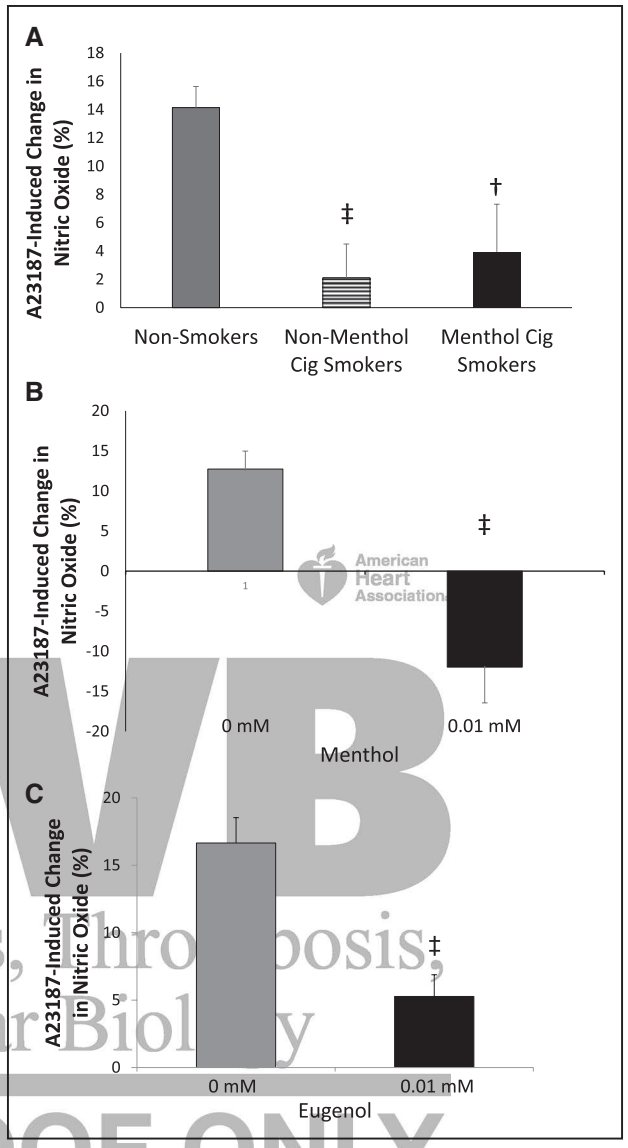

Figure 1. Menthol and eugenol impair nitric oxide production in freshly isolated endothelial cells from human participants. Endothelial cells from menthol (n=6) and nonmenthol cigarette smokers (n=6) had a lower change in nitric oxide measured by 4,5-diaminofluorescein diacetate (DAF-2DA) fluorescence in response to A23187 stimulation compared with endothelial cells from nonsmokers (n=9, ‡*P*<0.01, †*P*<0.05; **A**). Treatment of endothelial cells freshly isolated from healthy participants with 0.01 mmol/L menthol (**B**) or eugenol (**C**) decreased DAF-2DA fluorescence in response to A23187 stimulation (n=5, ‡*P*<0.01 for menthol; n=5, ‡*P*<0.01 for eugenol). Data are expressed as mean±SEM.

Expression of a proinflammatory mediator, IL-6, was quantified in HAECs 3 hours after exposure to flavoring compounds (Figure 4). Vanillin, cinnamaldehyde, eugenol, and acetylpyridine increased IL-6 expression at most concentrations tested, even in the 0.001 to 0.01 mmol/L range. Menthol increased IL-6 expression at 10 and 100 mmol/L but not at the lower concentrations (0.01–1 mmol/L). Dimethylpyrazine, diacetyl, isoamyl acetate, and eucalyptol had no effect on IL-6 expression in HAECs. Expression of the adhesion molecule, ICAM-1, was quantified in HAECs after a 3-hour exposure to flavoring compounds (Figure II in the online-only Data Supplement). Vanillin at a concentration of 10 mmol/L increased ICAM-1

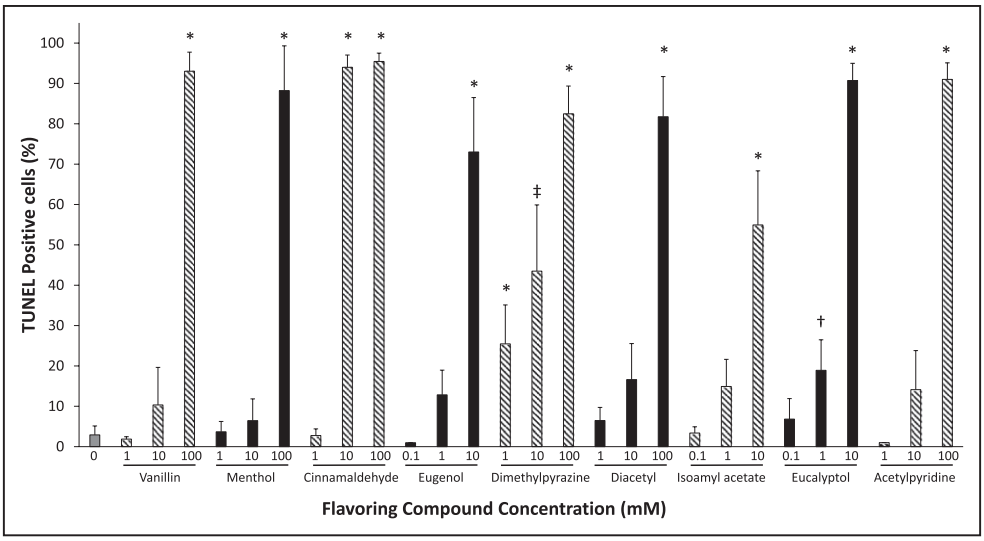

Figure 2. Tobacco flavoring compounds induce cell death. The percentage of cells staining positive for DNA strand breaks (TUNEL positive [terminal deoxynucleotidyl transferase dUTP nick-end labeling]) after a 90 min incubation with varying concentrations of flavor compounds were detected using immunofluorescence (n=3–4, *P<0.001, ‡P<0.01, †P<0.05 compared with vehicle control). Data are expressed as mean±SEM.

expression in HAECs whereas other concentrations and flavoring compounds had no effect on ICAM-1 expression.

HAECs treated with the selected flavorings vanillin, menthol, cinnamaldehyde, eugenol, or acetylpyridine displayed a loss of nitric oxide production in response to A23187 stimulation at all the tested concentrations of tobacco product flavoring (Figure 5). In HAECs exposed to varying concentrations of eugenol for 90 minutes, phosphorylation of eNOS at its activation site, Serine 1177, in response to A23187 was impaired (Figure III in the online-only Data Supplement), suggesting that eugenol-induced decrease in nitric oxide bioavailability is due, in part, to an impairment in eNOS activation. Further, HAECs were treated with vanillin, eugenol, and menthol that had been aerosolized at temperatures designed to simulate those achieved using e-cigarette devices (200°C and 700°C) for 90 minutes and then A23187-stimulated nitric oxide was assessed. Treatment of HAECs with vanillin aerosolized at 200°C but not 700°C decreased nitric oxide production in response to A23187 stimulation (Figure 6). HAECs treated with eugenol at 200°C and 700°C impaired nitric oxide production in response to A23187 stimulation while aerosolized menthol treatment had no effect (Figure 6). Collectively, these data suggest that heating of the flavoring compounds alters their toxicity.

Discussion

Our study provides evidence that flavoring additives in tobacco products induce acute alterations in endothelial function. Treatment of endothelial cells from nonsmokers with menthol and eugenol resulted in a loss of nitric oxide signaling, recapitulating the phenotype observed in endothelial cells

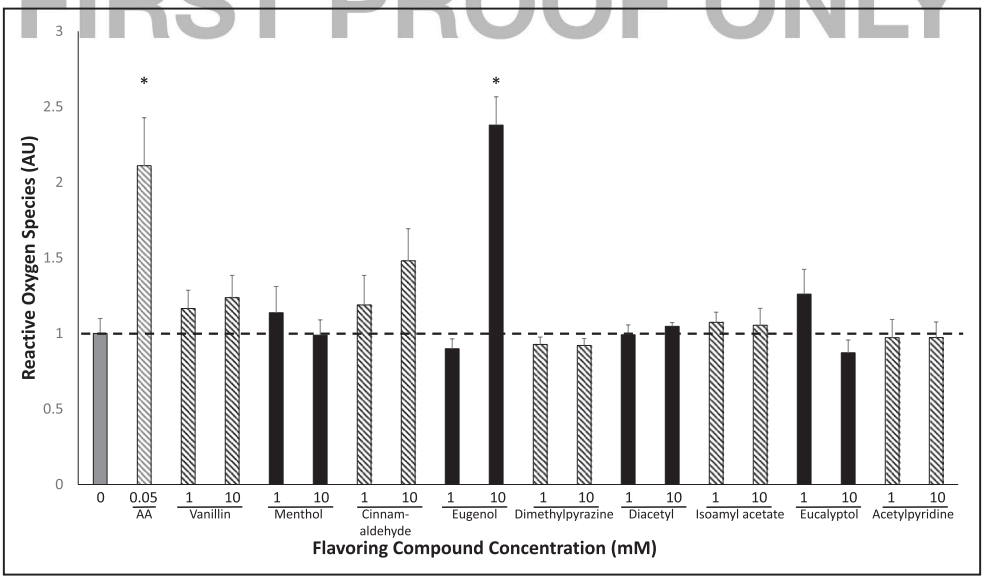

Figure 3. Tobacco flavoring compounds increase oxidative stress. Oxidative stress was measured by quantifying the fluorescent dye dihydroethidium after exposure of human aortic endothelial cells to flavoring compounds at varying concentrations (n=3, *P<0.001). Antimycin A (AA), a stimulus for mitochondrial oxidant generation, served as a positive control. Data are expressed as mean±SEM.

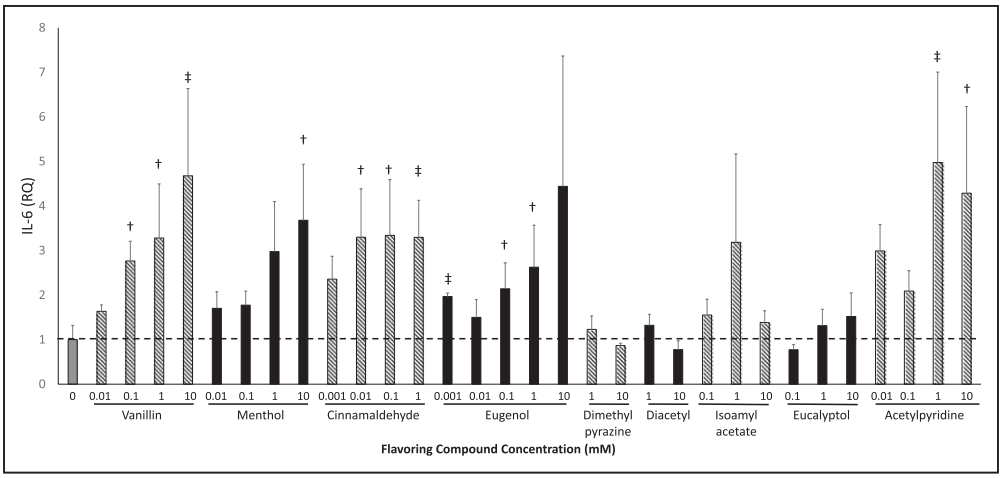

Figure 4. Tobacco flavoring compounds increase endothelial cell inflammation. IL-6 (interleukin-6) expression was quantified using reverse transcription-quantitative polymerase chain reaction 3 h after initial flavoring exposure in human aortic endothelial cells. All data are expressed as the relative quantification compared with vehicle alone treated cells (n=3–6, ‡*P*<0.01, †*P*<0.05). Data are expressed as mean±SEM.

from nonmenthol and menthol cigarette smokers. We found a similar degree of impairment in nitric oxide bioavailability in endothelial cells from nonmenthol and menthol cigarette smokers, which is consistent with prior literature showing that nonmenthol and menthol cigarette smokers have a similar degree of cardiovascular risk.[30–34] We then systematically assessed the impact of several flavoring compounds, in the absence of combustion products, on a panel of measures of endothelial function, including nitric oxide production, oxidative stress, inflammation, and cell death. The unique chemical characteristics of each flavoring compound led to variable changes in different outcomes whereas at some concentrations, all tobacco product flavoring compounds induced cell death. Oxidative stress was induced by the flavoring compounds but at concentrations that are likely supraphysiological. Notably, the flavorings vanillin, cinnamaldehyde, eugenol, and acetylpyridine impaired A23187-induced nitric oxide production and increased expression of the proinflammatory mediator, IL-6, across all concentrations tested, suggesting that the endothelium is particularly sensitive to these flavors. Menthol also increased IL-6 expression at the higher concentrations tested (10 and 100 mmol/L) and impaired nitric oxide production in response to A23187 at doses as low as 0.01 mmol/L. Treatment of HAECs with flavoring additives vanillin and eugenol aerosolized at temperatures achieved using e-cigarettes, impaired nitric oxide production in response to A23187 stimulation whereas aerosolized of menthol had no effect on nitric oxide production. The impairment in nitric oxide bioavailability observed after treatment with native and aerosolized flavoring additives suggests that the heating process alters the flavoring-induced endothelial

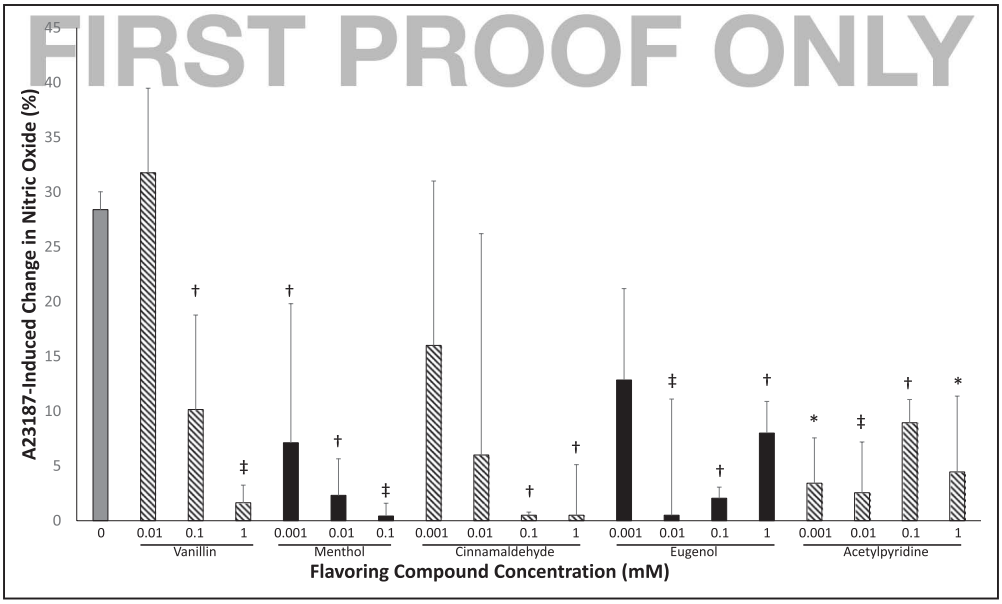

Figure 5. Tobacco flavoring compounds impair nitric oxide production in human aortic endothelial cells (HAECs). Nitric oxide production (4,5-diaminofluorescein diacetate [DAF-2DA] fluorescence) in response to A23187 stimulation was decreased in HAECs treated with flavoring compounds (n=3, **P*<0.001, ‡*P*<0.01, †*P*<0.05 compared with untreated control). Data are presented as percent change in DAF-2DA fluorescence in response to A23187 stimulation. Data are expressed as mean±SEM.

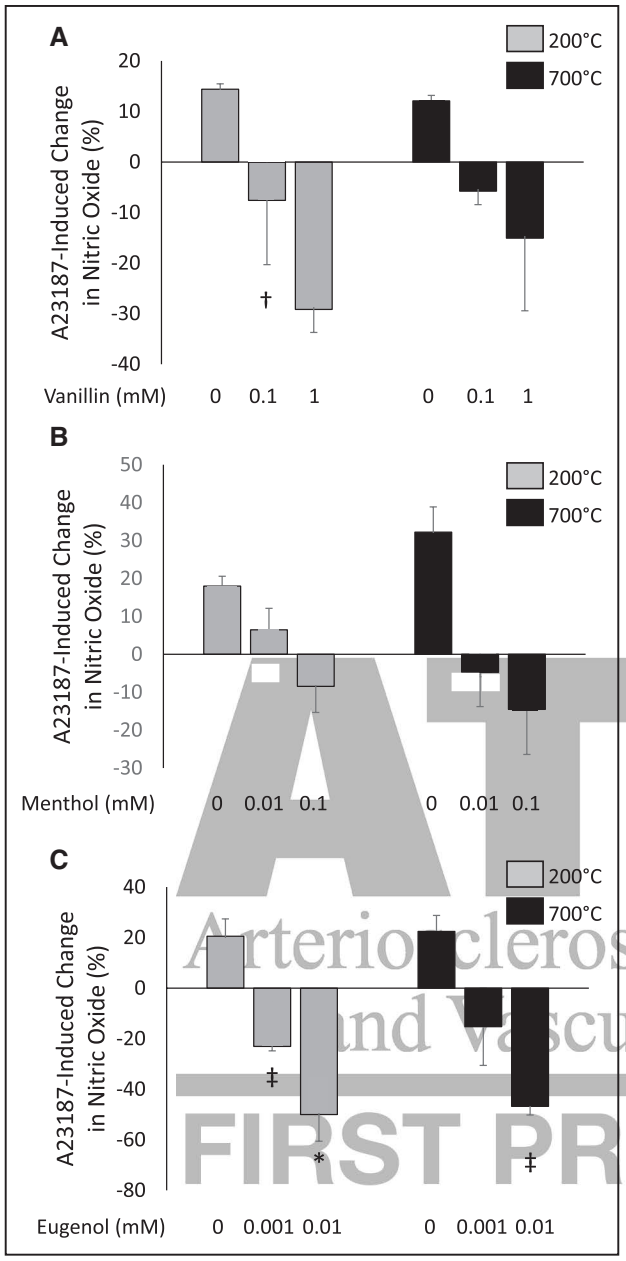

Figure 6. Differential effects of aerosolizing tobacco flavoring compounds on A23187-stimulated nitric oxide production in human aortic endothelial cells (HAECs). Treatment of HAECs with vanillin aerosolized at 200°C impaired A23187-stimulated nitric oxide production (4,5-diaminofluorescein diacetate [DAF-2DA] fluorescence), but this impairment was not observed with vanillin aerosolized at 700°C (n=3, †P<0.05 compared with untreated vehicle control, **A**). HAECs treated with menthol aerosolized at 200°C or 700°C had no effect on A23187-stimulated nitric oxide production (n=3, **B**). Treatment of HAECs with eugenol aerosolized at 200°C and 700°C impaired nitric oxide production in response to A23187 stimulation (n=3, *P<0.001, ‡P<0.01, compared with vehicle control, **C**). Data are presented as percent change in DAF-2DA fluorescence in response to A23187 stimulation. Data are expressed as mean±SEM.

dysfunction for some flavors but not others. Collectively, our data suggest that acute exposure to flavoring additives used in tobacco products induce characteristics of endothelial dysfunction at potentially physiologically relevant concentrations.

Although several studies have investigated the toxicity of tobacco product flavorings on pulmonary epithelial cells, few studies have assessed flavoring toxicity on the vascular endothelium. In human umbilical vein endothelial cells, treatment with vapor extract from different e-cigarette devices for 24 to 48 hours decreased endothelial cell viability and proliferation and altered endothelial cell morphology to varying degrees across the products, but to less of an extent that combustible cigarette smoke extract.[35] Among the e-cigarette products used to generate the vapor extracts, all contained flavorings, but the authors did not provide product information.[35] Thus, differentiating which flavored products were toxic on endothelial cells in this study was not possible.[35] In another study, e-cigarette condensate treatment of rodent pulmonary endothelial cell lines increased monolayer permeability, decreased cellular metabolic activity, and reduced cellular proliferation.[36] Interestingly, exposure to e-cigarette condensate without nicotine had a similar effect on endothelial barrier function as the e-cigarette condensate with nicotine, suggesting the effects of e-cigarette condensate are independent of nicotine.[36] In healthy nonsmokers and combustible cigarette smokers, use of an e-cigarette with unflavored electronic liquid impaired flow-mediated vasodilation, a measure of endothelial function and nitric oxide bioavailability, and increased measures of oxidative stress.[24] However, measures of oxidative stress (serum Nox2 [NADPH oxidase 2]-derived peptide and 8-isoPGF2α [8-iso-prostaglandin F2 alpha]) and nitric oxide bioavailability were less impacted by a single e-cigarette use compared with smoking a single combustible cigarette, suggesting that e-cigarettes could be a reduced harm tobacco product.[24] Hence, several studies have tested the toxicity of e-cigarette generated vapor on endothelial cell phenotype, but few have determined whether the flavor additives induce endothelial cell toxicity.

We measured the acute effects of flavoring compounds used in tobacco products on a select panel of measures of endothelial cell function in vitro to rapidly screen for flavor toxicity. Moreover, acute endothelium dysfunction is often observed immediately after smoking (cigarettes and e-cigarettes) and is recognized as a predictor of increased cardiovascular risk and disease.[19,20,24,37] We found differential effects of the flavoring compounds on nitric oxide bioavailability, cell death, oxidative stress, and IL-6 expression that may be related to their different chemical properties. All of the flavoring compounds tested impaired nitric oxide production, which may be the result of reactive oxygen species scavenging nitric oxide and reduced eNOS activation. Nitric oxide is a cardioprotective signaling molecule that inhibits vascular inflammation and thrombosis and plays a key role in regulating vascular tone.[19,29] The loss of nitric oxide signaling is known to promote a proinflammatory and prothrombotic endothelium, resulting in vascular dysfunction and atherosclerotic plaque formation.[19,38] The flavoring compounds that impaired nitric oxide production also upregulated IL-6 which is consistent with oxidative stress, a known stimulus of inflammatory signaling pathways. Treatment of freshly isolated endothelial cells from nonsmokers with menthol or eugenol recapitulated the loss of nitric oxide bioavailability observed in endothelial cells from nonmenthol and menthol cigarette smokers, suggesting an effect of menthol exposure separate from cigarette smoke. Our studies are strengthened

by the application of only the flavoring compounds to the cells, allowing us to isolate the effects of individual flavors on endothelial function. Other pathways may be impacted in endothelial cells by flavoring compound exposure, and the mechanisms are yet to be explored.

Our study has many limitations. We incubated endothelial cells with tobacco product flavoring compounds suspended in media without heating or addition of other typical electronic liquid constituents, such as the solvents propylene glycol and glycerol. Heating or combustion of the flavoring compounds likely alters the compounds, making them more or less toxic.[39] Consistent with this hypothesis, aerosolization of select flavoring compounds, vanillin and eugenol, did not alter their effects on nitric oxide bioavailability. However, aerosolization of menthol reduced menthol's inhibition of A23187-induced nitric oxide production. Similarly, we studied only the acute effects of flavoring compounds on endothelial cell function, and the effects associated with chronic use of flavored tobacco products need to be addressed. In addition, the in vitro effects may be different than the in vivo effects observed after flavored tobacco product use. The impairment in nitric oxide production in the endothelial cells from menthol cigarette smokers may not be directly attributable to the presence of menthol and is likely the result of the combined effects of multiple constituents in menthol cigarette smoke. This is consistent with the epidemiological evidence, showing that both menthol and nonmenthol cigarettes increase cardiovascular risk to a similar extent.[30–34] A study evaluating the pharmacokinetics of menthol estimated the daily exposure of menthol to be ≈80 µmol for an individual who smokes 20 mentholated cigarettes and estimated an absorption of ≈20% of the menthol in a combustible cigarette.[40] In our study, at a dose comparable to this estimated daily exposure, we found that treatment of endothelial cells from healthy, nonsmokers with 10 µmol/L menthol impaired A23187-stimulated nitric oxide production, suggesting that the concentrations evaluated in vitro are likely to be achieved in vivo. However, further work is needed to evaluate the levels of flavoring compounds and their metabolites in the circulation after use of flavored tobacco products.

We provide evidence that flavoring additives to tobacco products impair stimulated nitric oxide production and inflammation suggestive of endothelial dysfunction across a range of concentrations likely to be achieved in vivo. All flavorings tested impaired A23187-induced nitric oxide production, suggesting that measures of eNOS activation and nitric oxide production are sensitive measures of endothelial cell toxicity in vitro. The toxicity data generated herein, using a variety of common flavorings, provide quantitative support for the regulatory prohibition or the establishment of limitations on allowable levels of these flavorings in electronic liquids and other tobacco products. Future studies will focus on how the toxicity of the flavorings is altered with heating and characterization of the levels obtained in the circulation after use of an e-cigarette.

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Disclosures

None.

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Highlights

- The cardiovascular health effects of flavoring additives used in tobacco products, including electronic cigarettes, have not yet been studied.
- Our data suggest that short-term exposure of endothelial cells to flavoring compounds used in tobacco products have adverse effects on endothelial cell phenotype that may have relevance to cardiovascular toxicity.
- The toxicity data generated herein, using a variety of common flavorings, provide quantitative support for the regulatory prohibition or the establishment of limitations on allowable levels of these flavorings in electronic liquids and other tobacco products.
- Future studies will focus on how the toxicity of the flavorings is altered with heating and characterization of the levels obtained in the circulation after use of an electronic cigarette.

Arteriosclerosis, Thrombosis, and Vascular Biology

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Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction

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Supplemental Data for: Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction

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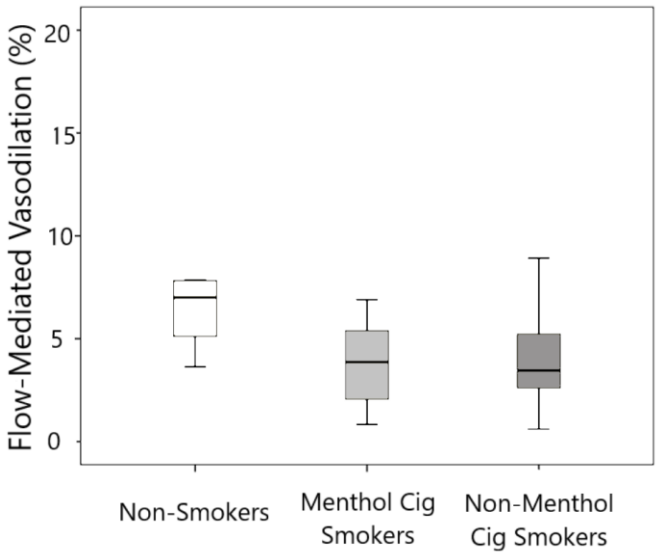
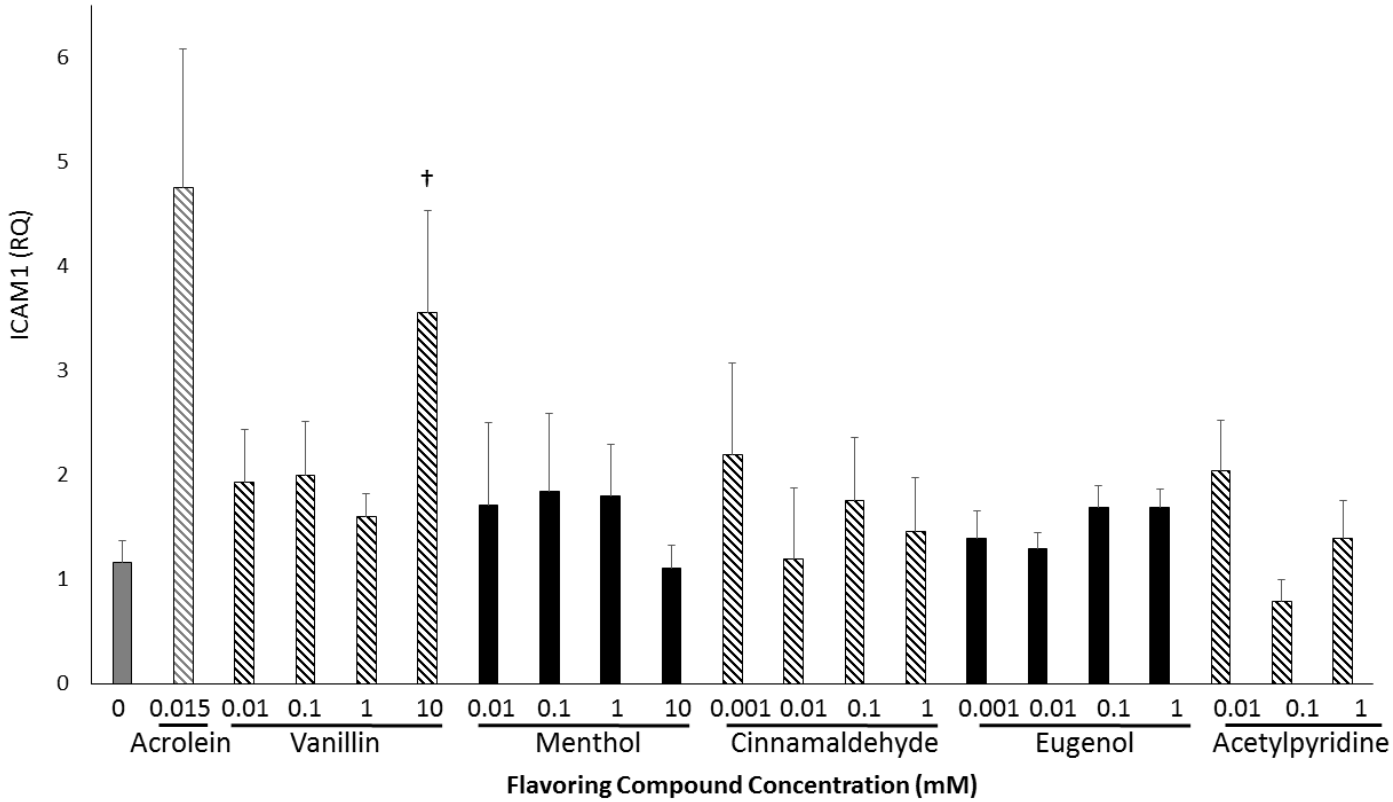
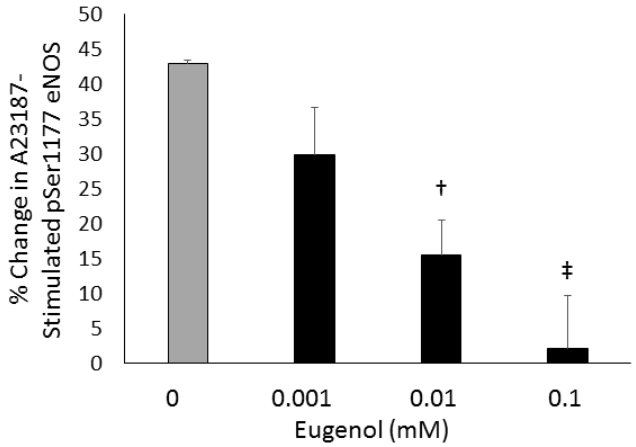


Supplemental Figure I: Flow-mediated vasodilation was numerically lower in menthol (n=5) and non-menthol (n=5) cigarette smokers compared to non-smokers (n = 8; *P*=0.12 between groups). Data are expressed as Mean ± standard deviation.



Supplemental Figure II: Flavoring compound treatment had no effect on ICAM1 expression. Treatment of HAECs with flavoring compounds for 90 minutes had no effect on ICAM1 expression with the exception of 10mM vanillin which, increased ICAM1 expression compared to untreated control (†P<0.05). Treatment of HAECs with the positive control acrolein trended towards an increase in ICAM1 expression compared to untreated cells (P=0.06). Data are expressed as relative quantification (RQ) compared to untreated control (N=3-4).



Supplemental Figure III: Eugenol treatment impairs eNOS activation. Treatment of HAECs with varying doses of eugenol for 90 minutes impaired eNOS phosphorylation at its activation site, Serine 1177 in response to A23187 stimulation (n = 3, ‡P<0.01, †P<0.05 compared to untreated control). Data are presented as percent change in phosphorylation of eNOS at its Serine 1177 site in response to A23187 stimulation and are expressed as the Mean ± SEM.

Supplemental Table I. Major Resources

Flavoring Compounds	**Vendor**	**Catalog #**
Vanillin	Sigma-Aldrich	V1104
Menthol	Sigma-Aldrich	63660
Eugenol	Sigma-Aldrich	E51791
Cinnamaldehyde	Sigma-Aldrich	W228613
2,5-dimethylpyrazine	Sigma-Aldrich	175420
Diacetyl (2,3-butanedione)	Sigma-Aldrich	B85307
Isoamyl acetate	Sigma-Aldrich	112674
Eucalyptol	Sigma-Aldrich	C80601
Acetylpyridine	Sigma-Aldrich	W325104
Endothelial Phenotype Measures		
0.018" J-wire for Endothelial Biopsy	Fisher Scientific	NC0147469
Human aortic endothelial cells	Lonza	CC-2535
DAF-2DA	Calbiochem	251505
A23187	Sigma-Aldrich	C7522
TUNEL	Sigma-Aldrich	11684809910
DAPI	Vector Laboratories	H-1200
Dihydroethidium (DHE)	ThermoFisher	D23107
IL-6 TaqMan Primers	ThermoFisher	Hs00985639_m1
ICAM TaqMan Primers	ThermoFisher	HS99999152_m1
GAPDH TaqMan Primer	ThermoFisher	4331182

Will San Francisco's Ban on Flavored Tobacco Spark a National Trend?

kqed.org/futureofyou/442372/will-san-franciscos-ban-on-flavored-tobacco-spark-a-national-trend

June 12, 2018

Lesley McClurg

Published on Jun 11

Rhiannon Griffith-Bowman smokes an e-cigarette at Digital Ciggz in San Rafael, California. *(Justin Sullivan/Getty Images)*

Despite a multimillion dollar campaign by tobacco giant R.J. Reynolds, San Francisco will soon implement the most comprehensive restrictions on e-cigarettes in the country. The move is already sparking other cities to follow.

> 'What California does, almost always spreads not only across the country, but globally.'*Matt Myers, Campaign for Tobacco-Free Kids*

This week's vote on San Francisco's Proposition E was expected to be close, but the measure is passing with nearly 70 percent of the vote. That's an insurmountable lead even though mail-in ballots are still being counted. The ban includes all flavored tobacco products from vaping liquids to menthol cigarettes to flavored hookah.

"You know, I probably would have voted for it too," said Brian Richardson a resident of Los Angeles who owns a Bay Area vaping store. "As much as I like to sell vape liquids at my store in San Francisco, I agree some type of regulation is necessary."

The law goes into effect 10 days after the election is certified, which will likely be sometime

in July. If a San Francisco store violates the ban, it could result in the suspension of their tobacco sales permit or further penalties as defined under the city's health code.

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Growing Momentum in California

The same week voters passed San Francisco's ban, the Board of Supervisors in San Mateo County unanimously passed a similar comprehensive ban that will also remove traditional tobacco products from pharmacies. Supervisor Carole Groom says the measure is about prevention, especially among young people.

"Every day, 2,500 kids try their first cigarette and that's what we're trying to stop," said Groom. "Eighty-one percent of the youth in a recent survey told us that their first cigarette was flavored. That's the kind of thing we're trying to stop with this ordinance."

Several other communities like Oakland, El Cerrito and Palo Alto have similar bans pending, though none are as comprehensive as the ones in San Francisco and San Mateo County.

City officials like Groom say local initiatives are necessary because there is very little regulation of e-products at the federal level, even though use is increasing. A 2016 report from the U.S. Surgeon General cited a 900 percent increase in the use of e-cigarettes by high school students from 2011 to 2015.

Brian Richardson vaping on a walk just north of Big Sur, California *(Andrea Cardenas Kline)*

Brian Richardson owns the Vapor Den, a hip, Lower Haight-neighborhood vape shop with low lighting, leather couches and row after row of top-shelf vape liquids. He says he opened his doors in 2012 to help smokers quit.

"We used to act as a center to essentially educate people on the alternatives to smoking," said Richardson, who smoked a pack a day for 25 years. "My customers used to be people trying to kick the habit. But over the years the demographic kept getting younger. Now people in their 20s are just looking for the latest and greatest devices with new flavors."

Manipulative Marketing Ploys to Attract Kids

When Richardson started vaping in 2009, there were only two flavors on the market; menthol and tobacco. Now there's more than 7,000, like cotton candy, apple crumb and watermelon, which are often packaged in brightly colored bottles with clowns and cartoon characters.

"Regulation is necessary today because of the abuse and marketing ploys some of these companies are using to attract kids who may have never smoked a cigarette in their life," said Richardson.

He says his best selling products are made by Juul, which makes liquids with significantly higher amounts of nicotine and which Richardson calls the most abusive company in the business.

"You take a couple of puffs and you actually feel like you're kind of high," said Richardson.

Colorful nicotine-filled pods, pictured on the right, are inserted into the Juul e-cigarette, which educators say looks deceptively like a flash drive, making it harder to identify. *(Juul Labs)*

He says that even though San Francisco's ban will likely crush sales at the Vapor Den, he plans to stay open. He thinks customers will buy their vaping liquids online but visit his shop when seeking advice on a device or to stock up on batteries and coil replacements.

But many other small shop owners are terrified about the aftermath of the ban.

“Prop E is going to have a huge impact on businesses like mine," said Miriam Zouzounis, a board member of the Arab American Grocers Association, which represents over 400 businesses in San Francisco. "I fear that many small businesses will close in the wake of its passage." She said the law would disproportionately affect Arab, Sikh and Asian store owners.

An Expensive Fight

The R.J. Reynolds Tobacco Company spent nearly $13 million blanketing the city in advertisements to stop the ban. The company sells the nation’s best-selling menthol cigarette and popular vaping products called Vuse. Jacob McConnico a spokesperson for R.J. Reynolds, called the vote a setback for tobacco harm-reduction efforts.

"History has shown regulations that go to extremes to limit consumer choice result in unintended consequences, including criminal activity," McConico wrote in an email. He did not respond when asked whether the company planned to sue.

The tobacco industry sued in both New York and Providence, Rhode Island, when those cities passed limited bans on flavored tobacco products, but the industry lost in both cases.

Tobacco Industry Pushes Back

San Francisco’s Board of Supervisors unanimously approved the ban last year. It was scheduled to go into effect last April, but then an opposition campaign raised enough signatures to put a referendum on the ballot, which is why the measure was put before voters on Tuesday.

The fight in favor of the ban was primarily funded by a personal $1.8 million donation from Michael R. Bloomberg, the former mayor of New York City. The American Cancer Society, the American Heart Association, the American Lung Association and Tobacco-Free Kids Action Fund contributed a combined total of $500,000.

Advocates Predict a Domino Effect

Matt Myers, the president of the Campaign for Tobacco-Free Kids, one of the primary advocacy organizations behind the San Francisco ban, predicts this is just the first of many bans across the country.

"California repeatedly has been the leader on innovation on tobacco control," said Myers. "And what California does almost always spreads not only across the country, but globally."

San Francisco especially has a history of taking on Big Tobacco. In 1983, the city passed a workplace smoking restriction. Several tobacco companies tried to stop the ordinance by forcing a referendum. But their expensive campaigning efforts failed, as voters upheld the restrictions. The industry lost many similar fights across the country as communities successfully removed smoking from offices.

"San Francisco's ban is really going to be a trendsetter for all over the country," said Stanton Glantz, who heads the Center for Tobacco Control Research and Education at UC San Francisco. "I just came back from an international meeting in South Africa and people were talking about the San Francisco ordinance."

E-Cigs Emit Higher Levels of Chromium and Nickel Than Traditional Cigarettes

viterbi.usc.edu/news/news/2014/e-cigarettes-emit-higher-levels-of-some-toxic-metals-than-traditional-cigarettes-chromium-nickel.htm

Constantinos Sioutas and team find e-cig second-hand smoke contains increased levels of toxic metals

Tweet

By: Robert Perkins
September 04, 2014 —

Getty Images

E-cigarettes are healthier for your neighbors than traditional cigarettes, but still release toxins into the air, according to a new study from USC.

Scientists studying secondhand smoke from e-cigarettes discovered an overall 10-fold decrease in exposure to harmful particles, with close-to-zero exposure to organic carcinogens. However, levels of exposure to some harmful metals in second-hand e-cigarette smoke were found to be significantly higher.

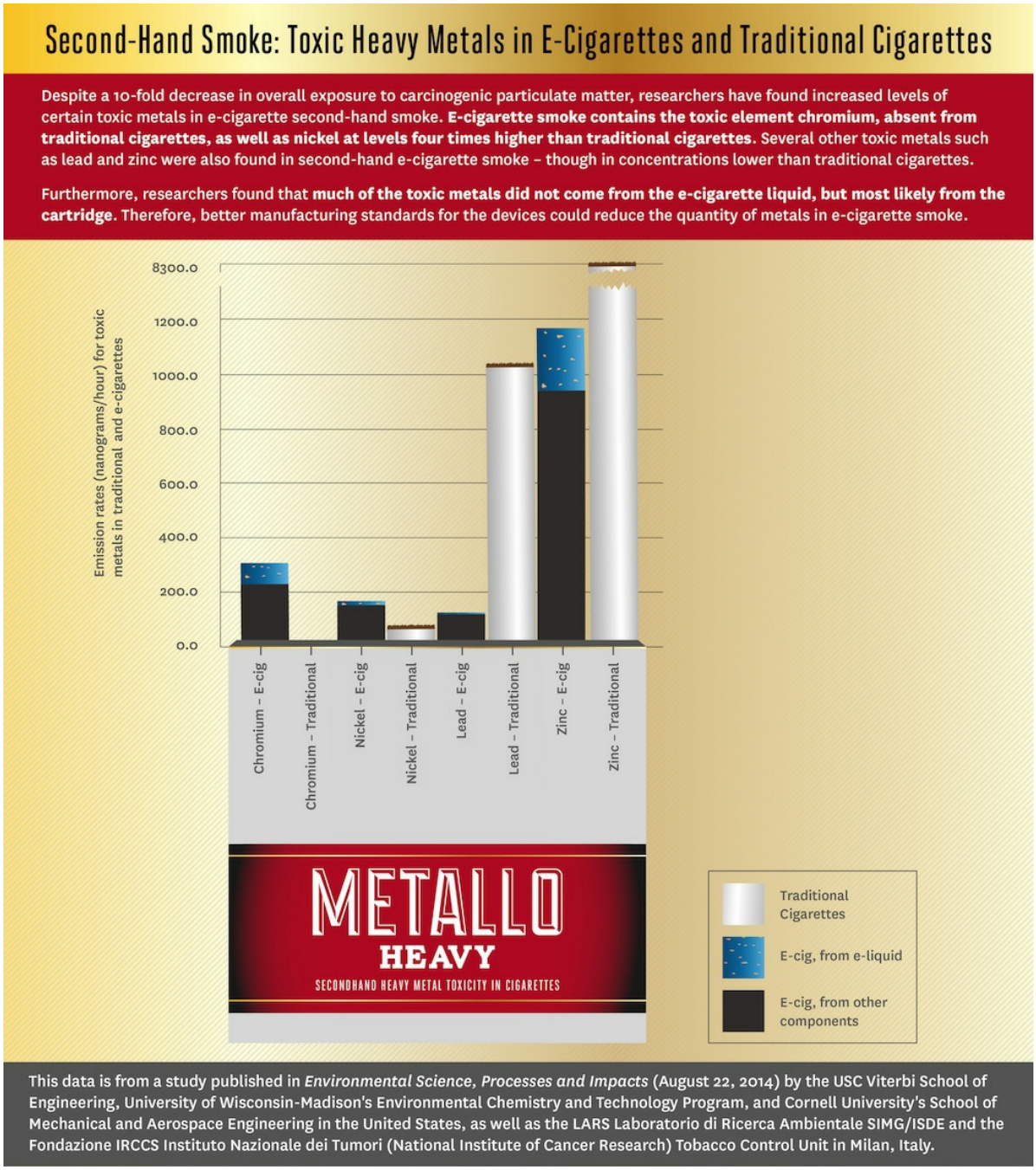
While tobacco smoke contains high levels of polycyclic aromatic hydrocarbons – cancer-causing organic compounds – the level of exposure to these substances was reduced to almost zero in second-hand e-cigarette smoke, due to the fact that they do not burn organic material the way old-fashioned cigarettes do.

However, despite the lack of harmful organic material and a decrease in the majority of toxic metals emissions, e-cigarette smoke contains the toxic element chromium, absent from traditional cigarettes, as well as nickel at levels four times higher than normal cigarettes. In addition, several other toxic metals such as lead and zinc were also found in second-hand e-cigarette smoke – though in concentrations lower than for normal cigarettes.

“Our results demonstrate that overall electronic cigarettes seem to be less harmful than regular cigarettes, but their elevated content of toxic metals such as nickel and chromium do raise concerns,” said Constantinos Sioutas, professor at the USC Viterbi School of Engineering, and corresponding author of the study, which was published online on August 22 by the Journal of Environmental Science, Processes and Impacts.

Sioutas and his colleagues at Fondazione IRCCS Instituto Nazionale dei Tumori (National Institute of Cancer Research) in Milan, Italy, began this study with the goal of quantifying the level of exposure to harmful organics and metals in second-hand e-cigarette smoke, in hopes of providing insight for the regulatory authorities.

“The metal particles likely come from the cartridge of the e-cigarette devices themselves – which opens up the possibility that better manufacturing standards for the devices could reduce the quantity of metals in the smoke,” said Arian Saffari, a PhD student at USC Viterbi and lead author of the paper. “Studies of this kind are necessary for implementing effective regulatory measures. E-cigarettes are so new, there just isn’t much research available on them yet.”



USC Viterbi

For this study, the researchers conducted all of the experiments in offices and rooms. While volunteer subjects were smoking regular cigarettes and e-cigarettes, the researchers collected particles in the indoor air and studied the chemical content and sources of the samples.

“Offices and rooms– not laboratories – are the environments where you’re likely to be exposed to second-hand e-cigarette smoke, so we did our testing there to better simulate real-life exposure conditions,” Saffari said.

Sioutas and Saffari compared the smoke from a common traditional cigarette brand with smoke from an Elips Serie C e-cigarette, one of the most popular European brands. The results could vary based on which type of cigarettes and e-cigarettes are tested, the researchers noted.

Sioutas and Saffari collaborated with researchers from LARS Laboratorio and the Fondazione IRCCS Instituto Nazionale dei Tumori in Milan, Italy, as well as University of Wisconsin-Madison and Cornell University in the United States.

Financial support for the study was provided by the Fondazione IRCCS Instituto Nazionale dei Tumori.

Is Vaping Really Any Better Than Smoking?

Care2 Healthy Living | Is Vaping Really Any Better Than Smoking?

I'm an ex-smoker. The pack-a-day kind who struggled to go longer than an hour without lighting up. I'm still amazed —and grateful—I was able to kick the habit.

I sometimes wonder if I would I have made the transition to vaping, if it had been an option when I still smoked. Probably not. I was too cool for school back then. For me, smoking was all about image, and vaping just looks silly to me.

I get the irony, obviously, but I still think vaping is even more pointless than smoking cigarettes. I mean, why bother, right? My jaded opinions aside, is vaping really any better than smoking? I decided to investigate.

Is vaping bad for your health?

While you're no longer permitted to smoke in public buildings, it's still considered acceptable to wander through the mall in a cloud of vapor. However, that will likely soon be a thing of the past.

With more and more studies being done, the health risks of vaping are becoming harder to ignore. Irfan Rahman —a toxicologist at the University of Rochester in New York— heard stories of bleeding mouths and throats and slow-healing sores from young vapers.

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Rahman and his team headed to the labs to find out what sort of damage the vapor inhaled from e-cigarettes was inflicting. Along with potentially promoting gum disease, vaping inhibits the repair of damaged cells and messes with your immunity.

Worryingly, teen vaping is on the rise. Because e-cigarettes don't contain tobacco, youth are under the misguided impression that vaping poses no health risks. The sale of vaping supplies to minors is banned in most U.S. states, however that unfortunately doesn't prevent kids from buying online.

There's also the issue of secondhand vaping to take into account. While most e-cig proponents firmly believe there's no risk associated with their habit, studies have shown that vaping does in fact impair indoor air quality. 'Nuff said.

What about vaping and the environment?

According to the Environmental Blog, vaping is a more eco-friendly alternative to smoking. Among other things, they say there's less air and land pollution, less chance of accidental fires and no litter in the form of cigarette butts, either.

Not everyone agrees, though. Some people are of the opinion that e-cigarettes put the environment at risk.

One study from USC Biterbi reported that secondhand vapor contains toxic metals. While another —this time from the European Commission— claimed that the disposable components of e-cigarettes also pose a risk to the environment.

How do Smoking and Vaping Impact Our Love Lives?

When it comes to finding your significant other, smoking is generally frowned upon in the dating world. But is it any better for people who vape? A recent study surveyed 1,000 nonsmokers, smokers and vapers to learn about dating preferences.

Not surprisingly, their findings revealed that over 85 percent of nonsmokers say smoking makes someone less attractive. What was interesting, however, was that 17 percent of those who wouldn't date a smoker said they would date someone who vaped.

Wait, what!?

When quizzed about why they were reluctant to date a smoker or a vaper, participants offered a variety of reasons. Some claimed the smell was off-putting, others cited health risks as the main issue. A fair number even said it was because they'd be embarrassed.

Admittedly, I've never kissed a vaper, so I can't comment on that front, but I only have to think about the plumes of vapour I've seen surrounding the e-cig brigade to know for sure I wouldn't want to date someone who vaped. I like to see the person I'm having a conversation with.

The jury might still be out regarding the health risks of vaping, but to my mind, if it looks like a duck and quacks like a duck, it's probably is a duck. Some people say it's possible to stay healthy even if you smoke. Maybe, but why would you want to do that to your body? If you're looking to quit the habit, these apps will help you stop smoking.

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Concerns explode over new health risks of vaping

sciencenewsforstudents.org/article/concerns-explode-over-new-health-risks-vaping

April 14, 2018

Vaping is not risk-free, especially for kids and teens. A host of new studies have now uncovered worrisome health concerns. For instance, the atomizer shown here can make vapors hotter and riskier to health.

Chaowalit466/iStockphoto

When Irfan Rahman talked to young vapers, some complained of bleeding mouths and throats. And these bloody sores seemed slow to heal. Such reports concerned this toxicologist at the University of Rochester in New York. So he decided to investigate what the vapors inhaled from electronic cigarettes might be doing to mouth cells.

Last October, his team showed those vapors inflame mouth cells in ways that could potentially promote gum disease. That gum damage can destroy the tissues that hold teeth in place. So severe gum disease could lead to tooth loss.

But that's hardly the end of it.

Vapers inhale those same gases and particles into their lungs. Rahman wondered what effects those vapors might have on cells there. One gauge would be to test how long any lung-cell damage took to heal. And his latest data confirm that e-cigarette vapors also make it hard for lung cells to repair damage.

Students as young as 12 or 13 are now more likely to vape than to smoke. Many are under the impression that because e-cigs don't contain tobacco, they pose little risk to health. Wrong.

Over the past few months, research has turned up evidence that vaping can pose many brand new risks. The vapors mess with immunity, some studies show. “Smoker’s cough” and bloody sores have begun showing up in teen vapers. The hotter a vaped liquid gets, the harsher its effects on human cells. And a relatively new vaping behavior called “dripping” ups the heat. This threatens to intensify a teen’s risks from those vapors.

Some new data even suggest that e-cig vapors may contain cancer-causing chemicals.

“There are a lot of potentially harmful substances in e-cigarettes. If you’re a teen with your whole life in front of you, why take that risk?” asks Rob McConnell. He’s an internal medicine specialist at the University of Southern California (USC) in Los Angeles.

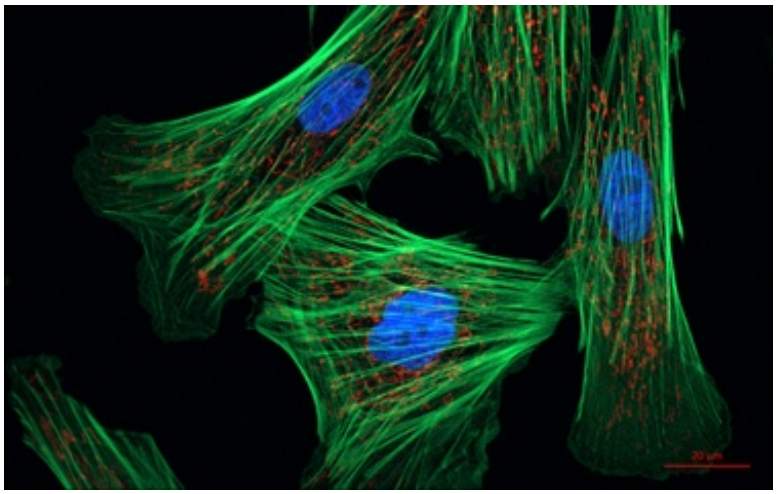
The newly emerging data suggest that adolescents ignore these risks at their peril.

Impaired wound healing

Cells in the body face constant damage from foreign substances, infections and injury. Most times, nothing bad happens to their host. That’s because the body has a system in place to heal itself. Most major organs have special cells — fibroblasts (FY-broh-blasts) — that repair damaged or injured tissue.

Fibroblasts make up the connective tissues that keep organs in place. But when injured, these cells morph into wound-healers. “If you cut your hand, fibroblasts are the guys that are going to come in and help heal it,” explains Rahman.

In their wound-healing form, fibroblasts at the edges of a cut will shrink. This causes the wound to close up. This squeezing or contraction of the skin takes a lot of energy. Fortunately, fibroblasts are powered by cellular engines. Called mitochondria (My-toh-KON-dree-uh), these tiny powerhouses turn food (sugar) into fuel.



Fibroblast cells (such as those seen here) repair damaged or injured tissues. The cells’ nuclei are colored blue. Their mitochondria are red. Filaments (green) help the fibroblast contract.

ZEISS Microscopy/Wikimedia Commons (CC-BY 2.0)

In the lab, Rahman and his colleagues grew lung fibroblasts in *Petri dishes*. Then they cut into the community of growing cells to mimic a wound. Afterward, they exposed the growing cells to e-cigarette vapors.

As expected, the fibroblasts morphed into wound-healing cells. But unexpectedly, they didn't close up the cut. Curious, Rahman looked more closely at the cellular machinery. Some mitochondria had been destroyed. The fibroblasts simply had run out of the energy they needed before they could successfully squeeze the wound closed.

Rahman's team described its findings March 3 in *Scientific Reports*.

It's not clear yet if the fibroblast damage that Rahman showed in the lab signals that wounds will heal more slowly in people who vape. After all, in the lab, scientists can manipulate one variable at a time while holding other factors constant. But in the body, many processes will be at work all at once. This can make it harder to tease out whether such lab tests mimic well what would happen to an otherwise healthy person.

And that's why Rahman now hopes to compare rates of wound healing in people who vape to rates in those who don't. For now, however, he's worried that what he saw in the lab may indeed mimic risks to people.

Smoker's cough becomes vaper's cough?

Inhaling pollution can irritate the lungs. And when the assaulting particles are breathed in regularly, the lungs tend to respond by triggering a cough that won't go away, explains McConnell at USC. He has been studying the effects of air pollution in kids. Inhaling irritating particles or gases may lead to bronchitis (Bron-KY-tis). That's when the airways that channel oxygen to the lungs become irritated and inflamed.

Researchers have found evidence that vaping can irritate the lungs and lead to chronic wheezing and coughs, a condition known as bronchitis.

AlexRaths/iStockphoto

Bronchitis may cause wheezing, too, and coughs that bring up thick mucus known as phlegm (FLEM). The germs that cause colds, flu and bacterial infections can sometimes trigger bronchitis. So can breathing in heavily polluted air, tobacco smoke or certain chemical fumes.

When these symptoms don't go away, the bronchitis is called *chronic* (KRON-ik). And cigarette smoking is its most common cause. That's why chronic bronchitis is typically referred to as "smoker's cough."

McConnell's team decided to look for signs of bronchitis in vaping teens. After all, he explains, "There are a lot of these irritants in e-cigarette vapor."

The researchers asked 2,000 students in the Los Angeles, Calif., area about their vaping habits. All were in their last two years of high school. The researchers also asked the teens about any respiratory symptoms. These could include coughs or phlegm.

Anyone who reported a daily cough for at least three straight months was judged to have chronic bronchitis. A student with persistent phlegm or congestion for three months or more that was *not* accompanied by a cold or flu also was suspected of having chronic bronchitis.

About 500 of the students said they had vaped at some point. And about 200 had vaped within the past 30 days. Those recent vapers were about twice as likely to have chronic bronchitis as were kids who had never vaped, the researchers report. Students who had vaped in the past, but *not* in the last month, also were about as likely as current vapers to have chronic bronchitis.

The researchers looked for other possible causes of the teens' persistent coughs and phlegm. One of these was local air pollution. They also looked at the teens' exposure to triggers for allergic *asthma*. Such triggers can include molds and pet dander. Yet even accounting for all of that did not erase the link between vaping and chronic bronchitis.

The findings, first announced in November, will appear in an upcoming issue of the *American Journal of Respiratory and Critical Care Medicine*.

These data also support what has been seen in studies conducted in human and animal cells, Rahman notes.

It worries McConnell that vapers show some of the same lung symptoms as cigarette smokers. It also worries him that more teens are taking up vaping. E-cigarette use grew an astounding 900 percent among high school students between 2011 and 2015.

Cigarette smokers with chronic bronchitis often develop permanent lung damage as they get older. Researchers don't know yet whether long-term vapers will too.

"People haven't been using e-cigarettes long enough to answer that question," observes McConnell. E-cigarettes have been available in the United States only since 2007.

Teens lured by fruity flavors

A third new study investigated the role of flavor in e-cig use, especially by teens.

E-cigarettes don't burn tobacco as true cigarettes do. Yet they still are considered tobacco products. That's because the liquids that are vaporized in e-cigarettes usually contain nicotine. It's the addictive substance found in tobacco leaves — one that also gives cigarettes their stimulant effect, or "buzz."

Vaping liquids can come in many pleasing flavors, which can make e-cigarettes more appealing to kids and teens, scientists warn.

Lindsay Fox/Wikimedia Commons (CC-BY 2.0)

A team of researchers led by Li-Ling Huang at the University of North Carolina (UNC) in Chapel Hill wanted to know whether the e-liquid's flavor affected how safe people thought vaping was. To do this, they reviewed 40 studies on flavored tobacco products. These included flavored e-cigs. Most of the studies had been conducted between 2010 and 2016.

Both tobacco users and non-users said tobacco products were more appealing when the products had pleasing flavors. Younger people were particularly interested in fruity and candy-flavored products. In fact, this is one reason the U.S. Food and Drug Administration in 2009 banned cigarettes flavored with anything but menthol. It was to limit their appeal to kids.

"It turns out that an interest in flavors is one of the main reasons that youth try e-cigarettes," says Adam Goldstein of UNC. An author of the new study, his past work had focused on tobacco use.

Teens also tended to perceive pleasantly flavored products as less harmful than tobacco-flavored ones, his team's data show. Their findings are due to appear in an upcoming issue of *Tobacco Control.*

Goldstein says it's important to note that just because something doesn't taste like tobacco doesn't mean it is safe. Studies have shown that some flavor compounds in e-liquids (such as cinnamon extract) appear to become harmful when heated in an e-cigarette.

Review studies like this one point to potentially important trends. Such studies may help shape new policies, Goldstein says. (Policies are actions taken by government, companies or other large groups.)

Goldstein believes that removing flavorings would be one way to discourage kids from experimenting with e-cigs. "Research suggests that if you remove the flavors, far fewer youth around the country would use any tobacco product," he says. And that would put fewer kids at risk for vaping-related damage to the mouth and lungs.

Toxic metals in e-liquids

At the heart of every e-cigarette is a metal coil used to heat up the flavored e-liquid that will become a vapor. Scientists have found a number of harmful chemicals in e-cigarette vapors. Some can cause cancer. Among these are formaldehyde (For-MAAL-de-hide) and

acetaldehyde (Ass-et-AAL-de-hide). Previous studies had shown that some e-liquids that were considered harmless could become toxic — but only after they were heated by an e-cig's especially hot coil.

Now Catherine Hess of the University of California, Berkeley, and her colleagues have turned up traces of toxic metals in the e-liquids used in five different brands of e-cigarettes. Those liquids came packaged from the manufacturer in non-refillable e-cigs. The scientists chose to look at these "first-generation" e-cigarettes because they are inexpensive, which can make them especially attractive to teens.

Scientists have found toxic chemicals in the vapors of some e-cigarettes and toxic metals in some liquids that would be vaped.

Alter_Photo/iStockphoto

The most concerning of these metals were nickel, chromium and manganese. The amounts of them varied between brands. All three metals occur naturally in rock formations all over the planet. Inside the body, though, they can cause trouble. Research suggests that nickel and certain forms of chromium may cause cancer. Manganese can harm the nervous system.

The researchers measured only the amount of toxic metals in the e-liquids, not how much ended up in the vapor. "More research is needed to see whether e-cigarette users are being exposed to these chemicals when they inhale — and what the long-term effects of those exposures might be," says Rahman, who was not involved in this study.

Hess's team published its results in the January *Environmental Research*.

Another new study turned up benzene in e-cig vapors. This chemical is known to pose a cancer risk to people. Chemist James Pankow and his team at Portland State University in Oregon don't know the chemical's source. Benzene is, however, a toxic component of cigarette smoke. The levels in e-cig vapors were not as high as in cigarette smoke. Still, Pankow argues, that does not mean that vaping poses little benzene risk.

"The fact that vaping can deliver benzene levels many times higher than those found in the ambient [air] — where it's already recognized as a cancer risk — should be of concern to anyone using e-cigarettes," he says. Higher-power e-cigs, which burn hotter, produced the most benzene in the Portland State tests. So, Pankow now urges, "Please stay away from high power if it's available on your device."

His team published its findings March 8 in the journal *PLOS ONE.*

Concerns about dripping

Newer-generation e-cigs allow users to choose — and change — what flavorings they heat up in their devices. Most vapers choose a liquid with nicotine (that addictive, stimulant found in tobacco). To get the biggest nicotine hit from each puff, some vapers take the outside cover off of their e-cigarette and use an eyedropper to “drip” the liquid directly onto the device’s coil.

This is an atomizer used for dripping. A couple drops of e-liquids are dripped directly onto the hot coils to create a vapor cloud.

librakv/iStockphoto

E-liquids reach higher temperatures when dripped directly onto the coil. This also creates a bigger vapor cloud and provides a bigger throat hit. A new study now raises special concerns for teens who drip.

Allowing the liquid to get superhot can transform harmless chemicals in the e-liquid into toxic ones. (Note: At least one recent study showed that the hotter the vaped liquid became, the more likely it was to undergo such a toxic transformation.) And dripping makes this super-heating likely. Some people even use attachments, called atomizers, to do this more effectively.

Vaping hobbyists that do smoke tricks may have popularized dripping, says Suchitra Krishnan-Sarin. A psychiatrist at Yale University in New Haven, Conn., she’s been studying vaping behaviors in teens. Many now drip, she and her colleagues report.

This team surveyed 1,080 Connecticut high schoolers who said they vaped. One in every four teen vapers said he or she had tried dripping.

This is the first time any study has reported on the popularity of dripping in teens. (Researchers don’t yet know how common dripping is among adults.) The new statistics appear in the February *Pediatrics.*

Most teens who dripped said they had hoped it would let them make thicker vapor clouds or give the vapor a stronger taste. At present, little is known about the health risks of this type of vaping, Krishnan-Sarin notes.

And that worries her. “There’s great concern,” she says, “that kids are being exposed to higher levels of known carcinogens this way.” Researchers don’t yet know if this is true. And that’s because no one has yet studied whether more of these compounds get into the body when people drip instead of vaping normally.

For now, Krishnan-Sarin says a bigger vapor cloud or more flavorful hit probably isn’t worth

the risk. “You don’t know what you’re exposing yourself to,” she points out, and no one should assume that the e-liquids and the vapors they generate are harmless.

Power Words

(for more about Power Words, click here)

acetaldehyde A colorless liquid that is in the cascade of breakdown products that develops when the body metabolizes alcohol. Manufacturers use the chemical to make a range of products, including vinegar, perfume and flavorings. According to the U.S. National Toxicology Program, this chemical is also “reasonably anticipated to be a human carcinogen.”

adolescent A transitional stage of physical and psychological development that begins at the onset of puberty, typically between the ages of 11 and 13, and ends with adulthood.

asthma A disease affecting the body’s airways, which are the tubes through which animals breathe. Asthma obstructs these airways through swelling, the production of too much mucus or a tightening of the tubes. As a result, the body can expand to breathe in air, but loses the ability to exhale appropriately. The most common cause of asthma is an allergy. Asthma is a leading cause of hospitalization and the top chronic disease responsible for kids missing school.

behavior The way a person or other organism acts towards others, or conducts itself.

cancer Any of more than 100 different diseases, each characterized by the rapid, uncontrolled growth of abnormal cells. The development and growth of cancers, also known as malignancies, can lead to tumors, pain and death.

carcinogen A substance, compound or other agent (such as radiation) that causes cancer.

cell The smallest structural and functional unit of an organism. Typically too small to see with the naked eye, it consists of watery fluid surrounded by a membrane or wall. Animals are made of anywhere from thousands to trillions of cells, depending on their size. Some organisms, such as yeasts, molds, bacteria and some algae, are composed of only one cell.

chemical A substance formed from two or more atoms that unite (become bonded together) in a fixed proportion and structure. For example, water is a chemical made of two hydrogen atoms bonded to one oxygen atom. Its chemical symbol is H_2O. Chemical can also be an adjective that describes properties of materials that are the result of various reactions between different compounds.

chronic A condition, such as an illness (or its symptoms, including pain), that lasts for a long time.

coil Concentric rings or spirals formed by winding wire or other fiber around and around a core.

colleague Someone who works with another; a co-worker or team member.

compound (often used as a synonym for chemical) A compound is a substance formed from two or more chemical elements united in fixed proportions. For example, water is a compound made of two hydrogen atoms bonded to one oxygen atom. Its chemical symbol is H_2O.

connective tissue Certain groups of cells that attach to form the boundaries for — and interfaces between — many structures throughout the body.

dander Flakes of skin in an animal's fur or hair.

e-cigarette (short for electronic cigarette) Battery-powered device that disperses nicotine and other chemicals as tiny airborne particles that users can inhale. These devices heat up a flavored liquid until it evaporates, producing vapors. People use these devices are known as vapers.

e-liquid A term for the solutions heated to the evaporation point in an electronic cigarette. These solutions are the basis of the vapors that will be inhaled. The liquid typically contains a solvent into which flavorings and nicotine have been dissolved.

factor Something that plays a role in a particular condition or event; a contributor.

fibroblast A type of cell found in connective tissue; it makes and releases proteins important in wound healing.

Food and Drug Administration (or FDA) A part of the U.S. Department of Health and Human Services, FDA is charged with overseeing the safety of many products. For instance, it is responsible for making sure drugs are properly labeled, safe and effective; that cosmetics and food supplements are safe and properly labeled; and that tobacco products are regulated.

formaldehyde A widely used and toxic chemical that manufacturers add to plastics, resins, some fertilizers, dyes, medicines and embalming fluids. It's even in the treatments used to keep fabrics from wrinkling.

generation A group of individuals born about the same time or that are regarded as a single group. Your parents belong to one generation of your family, for example, and your grandparents to another. Similarly, you and everyone within a few years of your age across the planet are referred to as belonging to a particular generation of humans. The term also is sometimes extended to year classes of other animals or to types of inanimate objects (such as electronics or automobiles).

germ Any one-celled microorganism, such as a bacterium, fungal species or virus particle. Some germs cause disease. Others can promote the health of higher-order organisms, including birds and mammals. The health effects of most germs, however, remain unknown.

high school A designation for grades nine through twelve in the U.S. system of compulsory public education. High-school graduates may apply to colleges for further, advanced education.

immunity The ability of an organism to resist a particular infection or poison by providing cells to remove, kill or disarm the dangerous substance.

infection A disease that can spread from one organism to another. It's usually caused by some sort of germ.

journal (in science) A publication in which scientists share their research findings with the public.

manganese Chemical element with the atomic number 25. It's a hard gray metal in the transition series. Manganese is an important component of special steels.

mitochondria (sing. mitochondrion) Structure in all cells (except bacteria and archaea) that break down nutrients and convert them into a form of energy known as ATP.

mucus A slimy substance produced in the lungs, nose, digestive system and other parts of the body to protect against infection. Mucus is made mainly of water but also includes salt and proteins such as mucins. Some animals use mucus for other purposes, such as to move across the ground or to defend themselves against predators.

nervous system The network of nerve cells and fibers that transmits signals between parts of the body.

nickel Number 28 on the periodic table of elements, this hard, silvery element resists oxidation and corrosion. That makes it a good coating for many other elements or for use in multi-metal alloys.

nicotine A colorless, oily chemical produced in tobacco and certain other plants. It creates the "buzz" associated with smoking. Highly addictive, nicotine is the substance that makes it hard for smokers to give up their use of cigarettes. The chemical is also a poison, sometimes used as a pesticide to kill insects and even some invasive snakes or frogs.

organ (in biology) Various parts of an organism that perform one or more particular functions. For instance, an ovary is an organ that makes eggs, the brain is an organ that interprets nerve signals and a plant's roots are organs that take in nutrients and moisture.

particle A minute amount of something.

pediatrics A field of medicine that has to do with children and especially child health. A doctor who works in this field is known as a pediatrician.

persistent An adjective for something that is long-lasting.

Petri dish A shallow, circular dish used to grow bacteria or other microorganisms.

pollutant A substance that taints something — such as the air, water, our bodies or products. Some pollutants are chemicals, such as pesticides. Others may be radiation, including excess heat or light. Even weeds and other invasive species can be considered a

type of biological pollution.

respiratory Of or referring to parts of the body involved in breathing (called the respiratory system). It includes the lungs, nose, sinuses, throat and other large airways.

risk The chance or mathematical likelihood that some bad thing might happen. Or the hazard — or peril — itself.

statistics The practice or science of collecting and analyzing numerical data in large quantities and interpreting their meaning. A professional who works in this field is called a statistician.

stimulant Something that triggers an action. (in medicine) Drugs that can stimulate the brain, triggering a feeling of more energy and alertness. Caffeine, for instance, is a mild stimulant that for a short while enhances alertness and helps fight drowsiness. Other stimulants, including some dangerous illegal drugs — such as cocaine — have stronger or longer-lasting effects.

tissue Made of cells, any of the distinct types of materials that make up animals, plants or fungi. Cells within a tissue work as a unit to perform a particular function in living organisms. Different organs of the human body, for instance, often are made from many different types of tissues.

tobacco A plant cultivated for its leaves, which many people burn in cigars, cigarettes, and pipes. Tobacco leaves also are sometimes chewed. The main active drug in tobacco leaves is nicotine, a powerful stimulant (and poison).

toxic Poisonous or able to harm or kill cells, tissues or whole organisms. The measure of risk posed by such a poison is its toxicity.

vaping (v. to vape) A slang term for the use of e-cigarettes because these devices emit vapor, not smoke. People who do this are referred to as vapers.

vapors Fumes released when a liquid transforms to a gas, usually as a result of heating.

variable (in mathematics) A letter used in a mathematical expression that may take on different values. (in experiments) A factor that can be changed, especially one allowed to change in a scientific experiment. For instance, when researchers measure how much insecticide it might take to kill a fly, they might change the dose or the age at which the insect is exposed. Both the dose and age would be variables in this experiment.

Readability Score:

7.6

Citation

Journal: J.F. Pankow et al. Benzene formation in electronic cigarettes. *PLOS ONE.* March 8, 2017. doi: 10.1371/journal.pone.0173055.

Journal: W. Lei et al. Myofibroblast differentiation and its functional properties are inhibited by nicotine and e-cigarette via mitochondrial OXPHOS complex III. *Scientific Reports.* Vol. 7, March 3, 2017. doi: 10.1038/srep43213.

Journal: S. Krishnan-Sarin. E-cigarettes and “dripping” among high-school youth. *Pediatrics*. Vol. 139, March 2017, p. e 20163224. doi: 10.1542/peds.2016-3224.

Journal: C.A. Hess et al. E-cigarettes as a source of toxic and potentially carcinogenic metals. *Environmental Research.* Vol. 152, January 28, 2017, p. 221. doi: 10.1016/j.envres.2016.09.026.

Journal: L.L. Huang et al. Impact of non-menthol flavours in tobacco products on perceptions and use among youth, young adults and adults: A systematic review. *Tobacco Control.* Published early online November 21, 2016. doi: 10.1136/tobaccocontrol-2016-053196.

Journal: R. McConnell et al. Electronic-cigarette use and respiratory symptoms in adolescents. *American Journal of Respiratory and Critical Care Medicine*. Early online November 2, 2016. doi: 10.1164/rccm.201604-0804OC.

Journal: S. Talih. “Direct dripping”: A high-temperature, high-formaldehyde emission electronic cigarette use method. *Nicotine & Tobacco Research*. Vol. 18, April 2016, p. 453. doi: 10.1093/ntr/ntv080.

Further Reading

Questions for ‘Concerns explode over new health risks of vaping’

Wordfind (click here)

From: [redacted]
To: [redacted] "'Kwong, Antonio'" [redacted] "'Vienna LAI'" <[redacted]>,
Cc: [redacted]

Date: Thursday, June 21, 2018 06:38AM
Subject: Canadian test method for tobacco - real life measurement

[redacted]

The ISO test method for tobacco products needs replacement by the Canadian method which more accurately shows the actual toxins ingested by smoking

Attachments:

RIVM-CanadianTestMethod.pdf

Focus

Study: EU test undervalued toxicity of cigarettes

The Dutch study found that in some cigarettes the levels of tar was up to 26 times higher simply by using a different measurement system (Photo: Stas Svechnikov)

By Peter Teffer

Brussels, 14. Jun, 17:13
The test method currently used in the EU to determine levels of carbon monoxide, nicotine, and tar in cigarettes structurally underestimates the presence of those harmful substances, according to a Dutch study out this week.

Measured levels of tar were at least twice as high when using a different testing method, and up to 26 times as high, said the Dutch National Institute for Public Health and the Environment (RIVM) on Tuesday (12 June).

Cigarettes have minuscule holes, which smokers sometimes cover when they hold the cigarette with their fingers or mouth. During the official test clean air enters through these holes (Photo: Cameron Kirby)

Nicotine levels were between two and 17 times as high, and carbon monoxide between two and 20 times as high.

The RIVM tested 100 cigarettes using the so-called Canadian Intense (CI) method. Only one cigarette had values below the EU legal limit.

The RIVM and the Dutch deputy minister for health, Paul Blokhuis, said that the CI test procedure was more realistic than the one that is currently used in the EU, by the International Standards Organisation (ISO).

Both tests are done by machines.

The main difference was that in the method used by the Dutch, minuscule holes in the cigarettes were covered, just like many smokers sometimes do when they hold the cigarette with their fingers or mouth.

These filter ventilation holes are not covered during the standard EU test, and allow additional clean air to enter, diluting the measured levels of carbon monoxide, nicotine, and tar.

Blokhuis said in a letter to parliament on Tuesday he would inform the European Commission and the 27 other EU member states of the "worrying results", and ask health commission Vytenis Andriukaitis about any follow-up.

Commission spokeswoman Anca Paduraru told EUobserver in an email on Thursday, however, that the Netherlands had presented the issue in an expert group on 6 June, "but there was limited interest from the other member states to take this discussion forward at this point."

She added the issue could be discussed at a next meeting of the EU's expert group on tobacco policy.

No 'gold standard'

Spokeswoman Paduraru noted that during the revision of the tobacco products directive, there was not enough evidence to switch measurement methods.

"The commission is aware of the limitations of currently available methods for the measurement of tar, nicotine and carbon monoxide in cigarettes," she said.

"Current measurements methods (including Canadian Intense method) do not correspond to actual human exposure as the methods use machines for measurements," Paduraru added.

She also stressed that because the machine-based results were not properly reflecting actual smoking behaviour, cigarette packs no longer have the tar, nicotine and carbon monoxide levels on the labels.

According to the 2014 directive, the commission has the authority to propose a new test method.

"But in the absence of a gold standard and for the purpose of regulatory continuity, the International Standards Organisation methodologies continue to be used for emission measurements," said the commission spokeswoman.

"By 2021, the commission will report on the application of the tobacco products directive. If appropriate and based on the findings of the report, proposals for amending the directive may be expected," she added.

Filter ventilation 'was known'

The Dutch ministry of health published emails from three of the four major tobacco companies, in which they respond to the results.

In its response, British American Tobacco (BAT) refuted Blokhuis' statement that the Canadian Incense method estimated smoking behaviour more accurately.

"Smoking habits vary per individual, making it impracticable to design a test that adequately reflects human smoking habits," said BAT.

Imperial Tobacco made similar points, and added that the existence of the minuscule holes in cigarettes was no secret.

"The application of filter ventilation has been known, understood and permitted by EU regulators under all current and past European Tobacco regulation, most recently in the revised TPD, 2014," it said.

Tobacco company Philip Morris was quoted in Dutch newspaper Volkskrant on Thursday saying that it would accept a different testing method – but that in that case the legal limits would also have to change.

According to an EU-funded survey published last year, 26 percent of EU citizens said they were smokers, while 20 percent said they had once been smokers but since quit.

In particular Greece (37 percent), Bulgaria (36 percent) and France (36 percent) have a high share of smokers.

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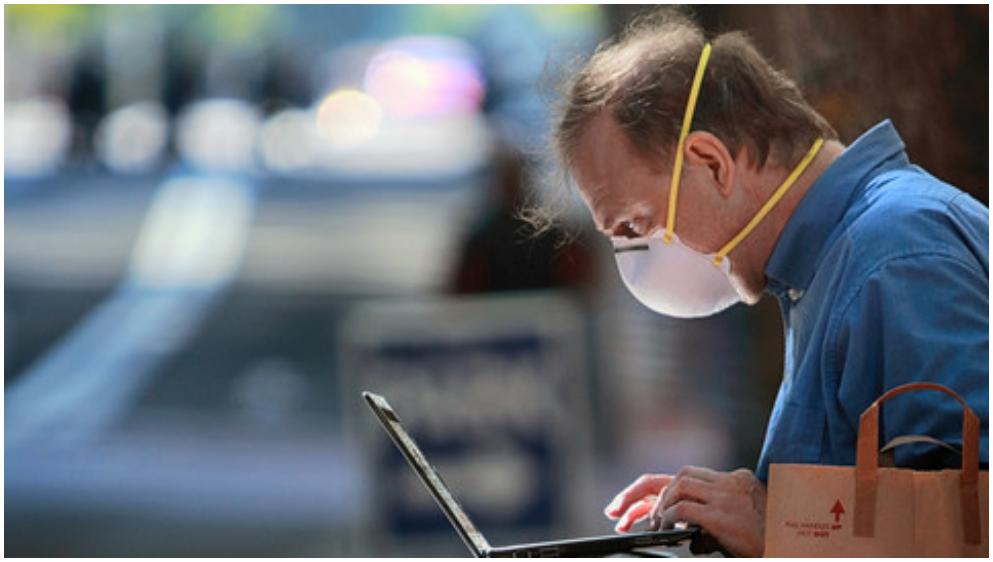

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18. May, 09:14

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Measurement methods for TNCO

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

How are TNCO values determined?

The tar, nicotine and carbon monoxide (TNCO) contents in cigarettes are determined using a smoking machine, which smokes a cigarette in accordance with an established method. In The Netherlands and the rest of the EU the so-called ISO (International Organization of Standardization) method is used, as set out by the European Commission. This makes it possible to check that products do not exceed the maximum permissible quantities of TNCO (Tar, Nicotine and Carbon monoxide) and to compare products. Cigarette smoke is permitted to contain a maximum of 10 mg (milligram) of tar, 1 mg (milligram) of nicotine and 10 mg (milligram) of carbon monoxide when smoked in accordance with the ISO (International Organization of Standardization) method.

Disadvantages of the ISO (International Organization of Standardization) method

However, the measurements taken using the ISO (International Organization of Standardization) method do not provide an accurate picture of the amount of TNCO (Tar, Nicotine and Carbon monoxide) that smokers actually inhale. The reasons for this include the fact that in the case of the ISO (International Organization of Standardization) method the ventilation holes are not covered, whereas smokers (partly) close these holes with their fingers or lips. The TNCO (Tar, Nicotine and Carbon monoxide) contents measured are therefore lower than the contents inhaled by smokers.

The alternative measuring method

There is an alternative method that gets closer to the TNCO (Tar, Nicotine and Carbon monoxide) contents inhaled by a smoker, namely the Canadian Intense (CI) method. Using this method the smoking machine takes puffs on the cigarette faster, with a greater volume, and the ventilation holes are taped over (see table). Measurements using the CI (Canadian Intense) method produce higher TNCO values in cigarettes than measurements using the ISO (International Organization of Standardization) method.

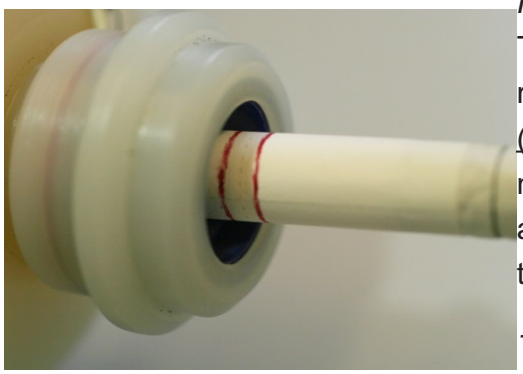

Figure. A test cigarette in the smoking machine. There is a series of ventilation holes between the red lines. In the test according to the ISO (International Organization of Standardization) method these holes remain open; in the test according to the CI (Canadian Intense) method the holes are taped up.

Table. Specific characteristics of the ISO (International Organization of Standardization) method and the Canadian Intense method, which are used to test cigarettes using a smoking machine. The bottom line provides an indication of the smoking behaviour of an average smoker.

	Duration of a puff	Time between puffs	Volume of a puff	Blocking of ventilation in filter
ISO (International Organization of Standardization) method	2 sec (second)	60 sec	35 ml (milliliter)	0 % (not taped)
Canadian Intense method	2 sec	30 sec	55 ml	100 % (fully taped)
Average smoker	1,4 sec	33 sec	53 ml	50 % (by fingers and lips)

Difference between TNCO (Tar, Nicotine and Carbon monoxide) values with and without holes in the filter

The presence of filter ventilation thins the smoke and thus the inhaled concentration of nicotine. In order to inhale the desired amount of nicotine smokers adapt their behaviour depending on the degree of filter ventilation, for example by inhaling more deeply, for longer or more often, or they even smoke more cigarettes.

In the case of a more intense smoking method or if the ventilation holes are closed off, greater quantities of harmful substances end up in the smoke. The increase is different for each substance as the combustion process is affected by the additional air drawn in. So for each mg of nicotine smokers are exposed to higher concentrations of, for example, tar, carbon monoxide, acetaldehyde and acrolein. These substances are harmful to health as they are toxic, carcinogenic and/or addictive.

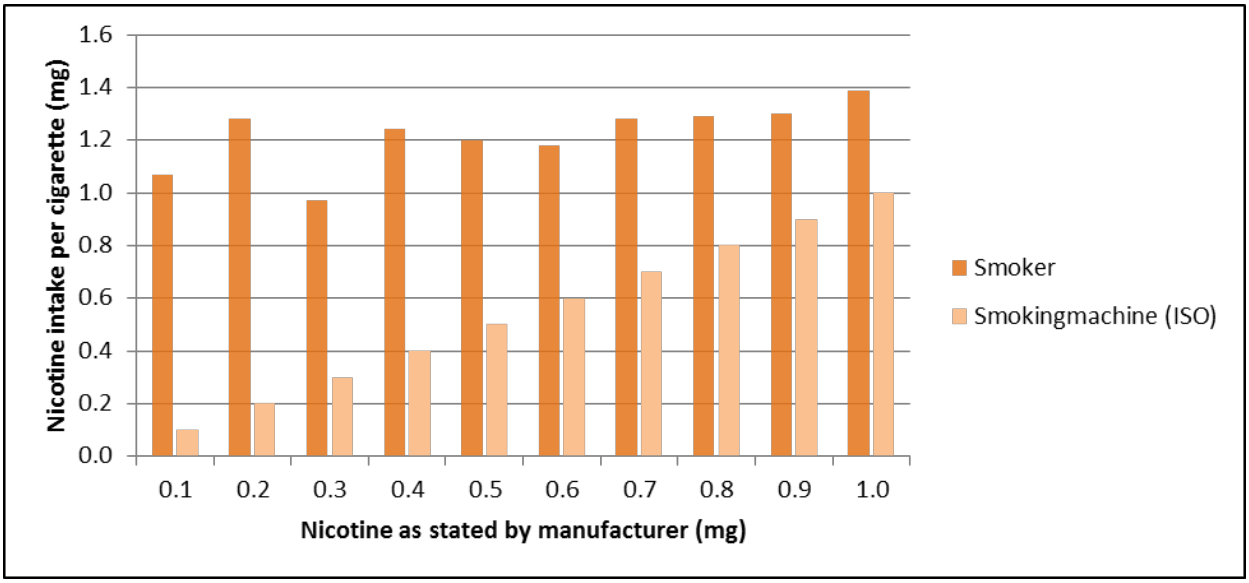

Figure. The amount of nicotine determined by a smoking machine using the ISO (International Organization of Standardization) method, compared with the amount of nicotine that a smoker actually inhales (based on Jarvis et al. 2001). The tobacco in all cigarettes contains the same amount of nicotine, but the amount of filter ventilation affects the values that the smoking machine measures. More filter ventilation results in lower values, whereas the amount of nicotine that a smoker inhales remains the same. Smokers thus get as much nicotine from a 'light' cigarette as from a 'heavy' cigarette by adapting their behaviour.

What does this mean for your cigarette?

The RIVM database includes the TNCO (Tar, Nicotine and Carbon monoxide) values, as provided by manufacturers, for cigarettes that were available on the Dutch market in 2015. Cigarettes with low TNCO values generally have more filter ventilation and are referred to by the media as 'cheating cigarettes'. The TNCO (Tar, Nicotine and Carbon monoxide) values give an indication of the amount of ventilation in the filters rather than the amount of harmful substances that smokers inhale.

Filter ventilation

See how RIVM measures TNCO in smoke

Download this video

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Datum 12 juni 2018
Betreft Resultaten RIVM-onderzoek 100 merkvarianten sigaretten met Canadian Intense methode

Geachte voorzitter,

Met deze brief wil ik uw Kamer informeren over de uitkomst van een onderzoek dat het RIVM heeft uitgevoerd naar de emissieniveaus van teer, nicotine en koolmonoxide (TNCO) van 100 merkvarianten sigaretten die in Nederland verkrijgbaar zijn.

Dit onderzoek is uitgevoerd in het kader van de discussie over de meetmethode die wordt gebruikt bij het meten van de TNCO-waarden. Zoals eerder aan uw Kamer aangegeven[1], worden voor verificatiedoeleinden deze TNCO-waarden gemeten met de voorgeschreven ISO-meetmethode, in overeenstemming met de Europese tabaksproductenrichtlijn 2014/40/EU (TPD). Deze ISO-methode geeft echter een onderschatting van de werkelijke hoeveelheden TNCO die rokers binnenkrijgen. Dit wordt onder andere veroorzaakt doordat de te meten rook wordt gemengd met lucht die wordt aangezogen door de ventilatiegaatjes die in het filter van de sigaret zijn aangebracht. Rokers dichten deze gaatjes veelal met hun vingers af wanneer zij roken. De ventilatiegaatjes worden niet afgedicht wanneer sigaretten met de ISO-methode worden onderzocht. Een meer reële meting is de Canadian Intense (CI)-methode, waarbij deze gaatjes worden afgeplakt zodat de resultaten beter overeenkomen met wat rokers daadwerkelijk binnenkrijgen.

Iedereen weet dat roken schadelijk is en het is daarbij van belang dat mensen kunnen nagaan wat de daadwerkelijke TNCO-waarden van sigaretten kunnen zijn. Met dit onderzoek zijn daarom van 100 merkvarianten sigaretten de TNCO-waarden met de CI-methode door het RIVM gemeten. Deze resultaten zijn vergeleken met de waarden die de producenten en importeurs hebben gerapporteerd waarbij de TNCO-waarden zijn gemeten met de voorgeschreven ISO-methode. De resultaten van het onderzoek zijn opgenomen in de bijgevoegde bijlage. Deze resultaten worden ook op de website van het RIVM gepubliceerd en nader toegelicht.

[1] Brief van de Staatssecretaris van Volksgezondheid, Welzijn en Sport van 6 mei 2018, Kamerstukken II, 2017/2018, 32011, nr. 63.

De gemeten teerwaarden zijn minimaal 2 – 26 keer hoger als de CI-methode wordt toegepast in plaats van de ISO-methode. De nicotine- en koolmonoxidewaarden liggen met de CI-methode respectievelijk 2 – 17 en 2 – 20 keer hoger dan de waarden die met de ISO-methode zijn verkregen. De grootste verschillen tussen metingen met deze twee methoden worden vooral gevonden bij sigaretten waar de ISO-methode relatief lage TNCO-waarden geeft. De lage TNCO-waarden die met de ISO-methode worden gevonden, worden vooral veroorzaakt door een hoge mate van filterventilatie. Met de ISO-methode worden er aanmerkelijke verschillen in TNCO-waarden tussen merkvarianten gevonden die grotendeels verdwijnen wanneer met de CI-methode wordt gemeten. Dit heeft er grotendeels mee te maken dat de filters en dus de filtergaatjes bij de CI-methode worden afgeplakt terwijl die gaatjes bij de ISO-methode openblijven. Daarnaast spelen verschillen in instellingen binnen de methoden voor de tijd tussen trekjes en het volume van de trekjes hierbij een rol. Bij de CI-methode neemt de rookmachine trekjes met een groter volume sneller achter elkaar. Op basis van de resultaten van de CI-metingen lijkt er geen reden te zijn om aan te nemen dat er verschillen in schadelijkheid bestaan tussen merken en merkvarianten.

Het is zeer zorgelijk als consumenten aan hogere TNCO-waarden worden blootgesteld dan de volgens de ISO-methode gemeten TNCO-waarden. Zoals ik eerder aan uw Kamer kenbaar heb gemaakt[1], heb ik dit ook besproken met de Eurocommissaris voor gezondheid en voedselveiligheid, dhr. V.P. Andriukaitis. De Eurocommissaris gaf aan dat het belangrijk is dit op Europees niveau te bespreken en dat hij bereid is ons hierin te steunen. Op 6 juni jl. heeft in Brussel een bijeenkomst met technische experts plaatsgevonden waar de problematiek en de verschillende alternatieve meetmethoden besproken is. Daar is geconcludeerd dat de testmethode ook onderwerp moet zijn van de rapportage van de Europese Commissie over de toepassing van de Europese tabaksproducten-richtlijn. Ik ben van mening dat de resultaten van het RIVM-onderzoek het belang hiervan alleen maar meer onderstrepen. Ik zal dan ook de Europese Commissie en andere Lidstaten op de hoogte stellen van de verontrustende resultaten uit het RIVM onderzoek. Tevens zal ik de Eurocommissaris dhr. V.P. Andriukaitis vragen, wat, tegen deze achtergrond, zijn vervolgstappen zullen zijn. Uiteraard zal ik uw Kamer hierover informeren.

Hoogachtend,

de staatssecretaris van Volksgezondheid,
Welzijn en Sport,

Paul Blokhuis

RIVM measures much higher levels of tar, nicotine and carbon monoxide in cigarettes

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Publication date: 12 June 2018
Modificationdate: 13 June 2018

Tar, nicotine and carbon monoxide (TNCO) levels measured in accordance with the Canadian Intense (CI) method are at least twice as high as the levels measured in accordance with the prescribed ISO (International Organization for Standardization) method. In some cases, the levels measured with the CI (Canadian Intense) method are even more than 20 times higher than those measured by the ISO (International Organization for Standardization) method. This is the result of research by RIVM (Dutch National Institute for Public Health and the Environment), examining 100 cigarettes using the Canadian Intense method.

This study was conducted because of the discussion about the measurement method used to measure the levels of tar, nicotine and carbon monoxide (TNCO) in cigarettes. Up to now, these levels were measured using the prescribed ISO (International Organization for Standardization) measurement method, in accordance with the European Tobacco Products Directive. However, this ISO (International Organization for Standardization) method underestimates the actual amounts of TNCO (Tar, nicotine and carbon monoxide) that smokers ingest. This is caused, among other things, by the fact that the measured smoke is mixed with air that is sucked in via the ventilation holes in the filter of the cigarette. A more realistic method is the Canadian Intense method; in this method these holes are taped closed.

In this study, RIVM (Dutch National Institute for Public Health and the Environment) measured the tar, nicotine and carbon monoxide levels of 100 brands of cigarettes using the Canadian Intense method. These results were compared with the TNCO (Tar, nicotine and carbon monoxide) levels reported by the manufacturers and importers, which were measured using the prescribed ISO (International Organization for Standardization) method.

The measured tar contents with the CI (Canadian Intense) method are 2 to 26 times higher than was measured bythe ISO method. For nicotine and carbon monoxide, the levels are respectively 2 to 17 and 2 to 20 times higher with the CI (Canadian Intense) method. It is striking that the largest differences between the two measurement methods are reported for cigarettes with relatively low TNCO (Tar, nicotine and carbon monoxide) levels measured using the ISO (International Organization for Standardization) method. These low TNCO

(Tar, nicotine and carbon monoxide) levels from the ISO (International Organization for Standardization) method are mainly caused by a high degree of filter ventilation. Because the filter holes are blocked in the CI (Canadian Intense) method, the degree of filter ventilation does not affect the measurement results. As a result, the differences in TNCO levels between cigarette brands are smaller with this method.

During the measurement with the CI (Canadian Intense) method, no cigarette contained less tar, nicotine or carbon monoxide than was measured using the ISO (International Organization for Standardization) method. With the exception of one cigarette, all measured TNCO (Tar, nicotine and carbon monoxide) levels exceed the legal limits.

The results of this research support the conclusion that the prescribed ISO (International Organization for Standardization) method underestimates the amounts of TNCO (Tar, nicotine and carbon monoxide) that a smoker ingests. The committee that drew up this method is largely influenced by the tobacco industry. RIVM (Dutch National Institute for Public Health and the Environment) therefore recommends that an independent measurement method, such as that of WHO (World Health Organization) TobLabNet, be included in the law, instead of the ISO (International Organization for Standardization) method.

Tar and Nicotine Report

govtlab.gov.hk/english/pub_tnrpt.htm

Jump to the beginning of content

Government Laboratory

As determined by the Government Chemist from samples obtained during the period of January - December 2017

BRAND	TAR YIELD (mg/cig)	NICOTINE YIELD (mg/cig)
MEVIUS BLIZZARD MINT LSS FTKS SIDE SLIDE 20S BOX (<=90MM)	1	0.1
MEVIUS ONE 1 FTKS ROUND 20S BOX (<=90MM)	1	0.1
MEVIUS PREMIUM MENTHOL OPTION YELLOW 1MG 100S ROUND FT 20S BOX (<=90MM)	1	0.1
MEVIUS LSS PIANISSIMO ONE FT 20S BOX (<=90MM)	1	0.1
KENT CORE 1 FTKS (NAKED-WRAP) 20S BOX (<=90MM)	1	0.1
KENT (MINTEK) 1MG FTKS (NAKED-WRAP) 20S BOX (<=90MM)	1	0.2
MEVIUS WIND BLUE 4 FTKS ROUND 20S BOX (<=90MM)	4	0.4
KENT CORE 4 FTKS (NAKED-WRAP) 20S BOX (<=90MM)	4	0.4
KENT NANOTEK 4 FTKS (NAKED-WRAP) 20S BOX (<=90MM)	4	0.4
DUNHILL GOLD FTK (NAKED-WRAP) 20S BOX (<=90MM)	4	0.5
BOHEM CIGAR MOJITO DOUBLE FT 20S BOX (<=90MM)	4	0.5
ZHONG NAN HAI FIVE 5MG CHARCOAL FTKS 20S BOX (<=90MM)	5	0.4
PALL MALL CHILLED FTKS (NAKED-WRAP) 20S BOX (<=90MM)	5	0.4
ESSE BLUE SUPER SLIM FT 20S BOX (<= 90MM)	5	0.5
ESSE MENTHOL SUPER SLIM FT 20S BOX (<= 90MM)	5	0.5
MEVIUS PREMIUM MENTHOL OPTION YELLOW 5MG ROUND FT 20S BOX (<=90MM)	5	0.5
MEVIUS SILVER MENTHOL FTKS ROUND 20S BOX (<=90MM)	5	0.5
MARLBORO REFINED MENTHOL FTKS 20S BOX (<=90MM)	6	0.5
MARLBORO ADVANCE SILVER 6MG FTKS 20S BOX (<=90MM)	6	0.5
MARLBORO DOUBLE BURST FTKS 20S BOX (<=90MM)	6	0.5

WINNER SUPER COOL FTKS 20S BOX (<= 90MM)	6	0.6
CAPRI SLIMS FT 20S BOX (<=90MM) (NAKED-WRAP)	6	0.6
DUNHILL BLUE FTK (NAKED-WRAP) 20S BOX (<=90MM)	6	0.7
LUCKY STRIKE CHOICE DOUBLE CLICK (PURPLE GREEN) FTKS (NAKED-WRAP) 20S BOX (<=90MM)	7	0.6
LUCKY STRIKE CHOICE DOUBLE CLICK (YELLOW GREEN) FTKS (NAKED-WRAP) 20S BOX (<=90MM)	7	0.6
CHESTERFIELD MINT BURST FTKS 20S BOX (<=90MM)	7	0.6
MARLBORO DOUBLE BLACK FTKS 20S BOX (<=90MM)	7	0.6
DAVIDOFF GOLD FT 20S BOX (<=90MM)	7	0.6
WINSTON BLUE FTKS 20S ROUND CORNER BOX (<=90 MM)	7	0.6
LUCKY STRIKE CLICK BOOST (GREEN) (NAKED-WRAP) FTKS 20S BOX (<=90MM)	7	0.6
CAMEL BLUE FTKS 20S BOX (<=90 MM)	7	0.6
MEVIUS GREEN MENTHOL FTKS ROUND 20S BOX (<=90MM)	7	0.6
MEVIUS PREMIUM MENTHOL OPTION YELLOW 8MG ROUND FT 20S BOX (<=90MM)	7	0.7
MEVIUS SKY BLUE 7 FTKS ROUND 20S BOX (<=90MM)	7	0.7
MARLBORO MINT STORM FTKS 20S BOX (<=90MM)	7	0.7
PALL MALL CLICK ON (GREEN) FTKS (NAKED-WRAP) 20S BOX (<=90MM)	7	0.7
MARLBORO GOLD FTKS 20S BOX (<=90MM)	8	0.6
LUCKY STRIKE FRESH FTKS (NAKED-WRAP) 20S BOX (<=90MM)	8	0.6
MARLBORO BLACK MENTHOL FTKS 20S BOX (<=90MM)	8	0.6
MARLBORO WHITE MENTHOL FTKS 20S BOX (<=90MM)	8	0.6
KENT CORE 8 FTKS (NAKED-WRAP) 20S BOX (<=90MM)	8	0.7
CHESTERFIELD MENTHOL FTKS 20S BOX (<=90MM)	8	0.7
PALL MALL COOL FTKS (NAKED-WRAP) 20S BOX (<=90MM)	8	0.7
PALL MALL BLUE FTKS (NAKED-WRAP) 20S BOX (<=90MM)	8	0.7
PALL MALL KRYSTAL STORM FTKS (NAKED-WRAP) 20S BOX (<=90MM)	8	0.7
CAPRI SUPERSLIMS FT (NAKED-WRAP) 20S BOX (<=90MM)	8	0.7
PALL MALL (BLUE) CLICK ON FTKS (NAKED-WRAP) 20S BOX (<=90MM)	8	0.7
LUCKY STRIKE BLUE FTK (NAKED-WRAP) 20S BOX (<=90MM)	8	0.7
MEVIUS SKY BLUE LSS FTKS SIDE SLIDE 20S BOX (<=90MM)	8	0.8
DAVIDOFF CLASSIC FTKS 20S BOX (<=90MM)	9	0.7
MEVIUS ORIGINAL BLUE 9 FTKS ROUND 20S BOX (<=90MM)	9	0.7

FURONGWANG (BLUE BOX) FT 20S BOX (<= 90MM)	9	0.8
WINSTON MORE BLUE FTKS ROUND CORNER 20S BOX (<=90MM)	9	0.8
DOUBLE HAPPINESS (9 MG) FTKS 20S BOX (<= 90MM)	9	0.9
WINSTON CLASSIC FTKS 20S SOFT PACK (<=90 MM)	10	0.8
MARLBORO FLAVOR MIX FTKS 20S BOX (<=90MM)	10	0.8
WINSTON CLASSIC FTKS 20S ROUND CORNER BOX (<=90 MM)	10	0.8
CAMEL FTKS 20S BOX (<= 90 MM)	10	0.9
DUNHILL RED FTK (NAKED-WRAP) 20S BOX (<=90MM)	10	0.9
LESSER PANDA FT 20S BOX (<= 90MM)	10	0.9
DOUBLE HAPPINESS FTKS 20S BOX (<=90MM)	11	0.9
YUXI FT 20S BOX (<=90MM)	11	1.0
MARLBORO MENTHOL FTKS 20S BOX (<=90MM)	12	0.9
FURONGWANG 20S BOX (<=90MM)	12	1.0
LIQUN FTKS 20S BOX (<=90MM)	12	1.0
PALL MALL (RED) CLICK ON FTKS (NAKED-WRAP) 20S BOX (<=90MM)	12	1.0
PALL MALL RED FTKS (NAKED-WRAP) 20S BOX (<=90MM)	12	1.0
WUYESHEN FT 20S RED BOX (<=90MM)	12	1.0
CHUNGHWA FTKS 20S SOFT PACK (<=90MM)	12	1.1
DOUBLE HAPPINESS FTKS CLASSIC DELUXE 20S BOX (<= 90MM)	12	1.3
WEALTH FTKS 20S SOFT PACK (<=90 MM)	13	1.0
MARLBORO RED FTKS 20S BOX (<=90MM)	13	1.0
GENTORI FILTER KING SIZE 20S PACK (<=90MM)	13	1.0
CHUNGHWA (RED) FTKS 20S BOX (<=90MM)	13	1.0
WINSTON MORE RED FTKS ROUND CORNER 20S BOX (<=90MM)	13	1.0
MARLBORO RED 20S SOFT PACK (<=90MM)	13	1.0
LUCKY STRIKE ORIGINAL RED FTK (NAKED-WRAP) 20S BOX (<=90MM)	13	1.0
WUYESHEN FT 20S GOLD BOX (<=90MM)	13	1.1
VICEROY RED FTKS 20S BOX (<= 90MM) (NAKED-WRAP)	14	1.0
DOUBLE HAPPINESS FTKS 20S SOFT PACK (<=90MM)	14	1.1

Remarks:

1. The published figures represent mean values of determinations undertaken over the whole sampling period.
2. Brands with the same figure for tar and nicotine yields are listed in alphabetical order.
3. International Standards methods employed for the determination are ISO 3308:2012,

ISO 4387:2000, ISO10362-1:1999, ISO 8243:2013, and ISO 10315:2013.

4. The estimates of uncertainty for the methods summarized below are based on data published by the International Organization for Standardization and results reported by recent Asia Collaborative Study.

Mean tar yield, mg	**Uncertainty, mg**
1 to 4	± 1.0
5 to 9	± 1.5
10 to 14	± 2.2
15 to 17	± 2.6

Mean nicotine yield, mg	Uncertainty, mg
0.1 to 0.4	± 0.10
0.5 to 1.0	± 0.18
1.1 to 1.5	± 0.25

- Top -

Money a better motivator to stop smoking than free e-cigs or quit aids

(Reuters Health) - Providing free electronic cigarettes or other stop-smoking products to employees to get them to give up real cigarettes is less effective than the threat of taking away a cash reward for quitting, according to a new study that weighs the effectiveness of a variety of workplace incentive programs.

The findings, published in The New England Journal of Medicine, call into question the claims by e-cigarette enthusiasts that the devices may be better than traditional quit aids at helping smokers to stop.

“Do they help people stop smoking? The answer to that is clearly no,” lead author Dr. Scott Halpern, of the University of Pennsylvania Perelman School of Medicine in Philadelphia, said in a telephone interview. “We cannot detect any evidence that they are better than offering free conventional smoking cessation aids or just providing information.”

The study is also significant because it may be the first to look at programs to get all smoking employees to quit, whether or not they’ve decided they want to do so.

The results show that if the motivation isn’t there, neither are the positive results.

Among 6,006 employees at 54 U.S.-based companies, the six-month smoking abstinence rates for all the strategies were less than 3 percent.

“It’s a pragmatic study, and most studies start with people who want to quit,” said Norman H. Edelman, senior science adviser for the American Lung Association, who was not involved in the research. Because this study included all smokers in a company, “that’s why the numbers are so low. If you separate out people who want to quit, you get rates in the teens.”

In this case, employees who logged on to the study’s website just once - and only 1,191 did - were classified as being willing to quit.

Some of these “engaged” participants were assigned to a group that only received information regarding the benefits of quitting and got access to a service that offered text messages designed to encourage them; in this group, less than 1 percent stayed off cigarettes for six months.

The “engaged” workers who also received free smoking cessation aids such as nicotine patches, lozenges and gum, or one of the two FDA-approved stop-smoking drugs, had a quit rate of only 2.9 percent.

Free e-cigarettes, where the participant could pick their flavors, brought the rate up to 4.8 percent, but the difference compared to free patches and the like was not statistically meaningful.

In the fourth group, whose participants got the free smoking cessation products plus a cash reward for staying away from tobacco - $100 for the first month, an additional $200 at the three-month mark and $300 if they stayed smoke-free for six months - 9.5 percent quit.

That was significantly better performance than workers getting the free cessation aids alone but not a statistically meaningful difference from the e-cigarette group.

The employees who did the best got whatever cessation products they wanted plus $600 in an account with the threat that they would lose the money if they didn't stay smoke-free for six months.

Their success rate was 12.7 percent, which was clearly better than those who got e-cigarettes or free cessation aids alone.

It reflects an odd psychological quirk about human behavior: "People are much more motivated to avoid losing $100 than they are to gain $100, even though, economically, they are flip sides of the same coin," Halpern noted.

Most large companies offer the promise of healthcare premium reductions for smokers who quit. "The problem with that approach is that the money you effectively save is not very tangible," he said. "It's not actively handing out money," so such programs don't work well.

The study team estimates that the average cost for each person who succeeded in quitting for six months was $3,461. It was $3,623 when cash was paid out every few months, $5,416 for providing free e-cigarettes and $7,798 for providing free cessation aids.

"The best estimates are, it costs $3,000 to $6,000 more per year to employ a smoker rather than a non-smoker. So even if these programs cost $800 to $1000, they would be highly cost-saving from the standpoint of the employer and the insurer," Halpern said.

About half the smoking workers who were tobacco-free at the six-month mark were still not smoking after one year.

SOURCE: bit.ly/2GM2xra The New England Journal of Medicine, online May 23, 2018.

The online version of the story has been refiled to fix typo in paragraph one

Our Standards:The Thomson Reuters Trust Principles.

Scottish smokers offered £160 incentive to quit

scotsman.com/news/scottish-smokers-offered-160-incentive-to-quit-1-4755709

Claire McKim

Published: 23:06 Saturday 16 June 2018 Updated: 08:11 Sunday 17 June 2018

Smokers across Scotland are being handed shopping vouchers in a publicly funded attempt to help them ditch the habit.

In Lanarkshire, about half of smokers living in the poorest parts of the area ditched cigarettes after being offered a financial incentive.

Pregnant women have been targeted in one voucher scheme. Photograph: Getty

From next month, a new initiative in Greater Glasgow and Clyde will see pregnant smokers paid up to £160 to ditch cigarettes, after a successful pilot scheme.

A similar project in Tayside will see smokers rewarded for quitting.

Medical experts have welcomed the schemes as a “cost effective” way to improve the health of patients. But opposition politicians warn many taxpayers will be “sceptical” about this approach, despite the early results being positive.

In NHS Lanarkshire, employees at a number of public and private sector organisations have been offered up to £20 in shopping vouchers if they can prove they are cigarette free for 12 weeks.

The scheme, which has been running since August last year, has shown early promise, with 71 per cent of participants saying the vouchers were an incentive to stop smoking. For patients in the most deprived areas, there was a quit rate after 12 weeks of 50 per cent.

From next month, health bosses at NHS Greater Glasgow and Clyde will hand pregnant women up to £160 in vouchers in instalments for every week the mothers-to-be go smoke free.

Sheila Duffy, chief executive of health charity ASH Scotland, said incentive schemes have a proven worth. She added: “It’s an innovative approach and seems to be bringing positive results. Voucher schemes are cost-effective when you consider the significant financial implications of tobacco use for the NHS and wider society.”

In Scottish prisons, inmates are also rewarded for quitting smoking.

A spokesman from NHS Lanarkshire said incentive schemes offered a “wide range of benefits” for patients.

He said: “The risks of smoking during pregnancy are serious, from premature delivery to increased risk of miscarriage, stillbirth or sudden infant death.”

Scottish Conservative shadow health secretary Miles Briggs said: “There is evidence to suggest this tactic can be effective... but we can’t get away from the fact a vast number of people will be sceptical.”

A spokeswoman for NHS Greater Glasgow and Clyde said: “Research carried out in Greater Glasgow and Clyde showed that pregnant women are more likely to use stop smoking services and successfully give up when incentives like shopping vouchers are offered, in conjunction with stop smoking support.”

The Tobacco industry's latest scam: How Big Tobacco is still facilitating tobacco smuggling, while also attempting to control a global system designed to prevent it.

BMJ blogs.bmj.com/tc/2018/06/19/the-tobacco-industrys-latest-scam-how-big-tobacco-is-still-facilitating-tobacco-smuggling-while-also-attempting-to-control-a-global-system-designed-to-prevent-it

Becky Freeman, Web Editor June 19, 2018

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by **AB Gilmore, A Rowell, University of Bath**

The major tobacco companies are acting as corporate chameleons, spending millions on make-overs, trying to convince the world they have changed. But shattering this expensive illusion is the latest evidence (published this week in Tobacco Control) uncovering one of their greatest scams: not only are tobacco companies still involved in tobacco smuggling, but they are positioning themselves to control the very system governments around the world have designed to stop them from doing so. Their elaborate and underhand effort, implemented over years, involves front groups, third parties, fake news and payments to the international regulatory authorities meant to hold them to account.

Understanding the **background** to this latest industry scam is essential. First, **tobacco smuggling benefits the tobacco companies**. They make their profit when they sell to the distributor and so their profit per pack is the same whether their cigarettes then end up in the smuggled market or not. But, because smuggled tobacco is largely untaxed, it is way cheaper to buy than legal tobacco. The cheaper it is, the more they sell and the more profit they make. Cheap smuggled tobacco is also particularly attractive to those short of cash – children and the least well off – key tobacco industry targets.

Second, and in line with the above, in the late 1990s **the major tobacco companies were caught orchestrating the smuggling of their cigarettes in vast quantities**. A third of global cigarette exports were going missing and the industry's own documents showed that smuggling was a core part of their business strategy – they were supplying some markets almost entirely with smuggled cigarettes. From 1998 to 2008, the industry faced an embarrassing series of inquiries, court cases, fines and legal agreements, all intended to stop this illegal behaviour. By 2012, governments around the world had adopted the Illicit Trade Protocol which requires, among other things, the implementation of a global 'Track and Trace' system. Packs of cigarettes and rolling tobacco are to be marked with a unique ID so they can be tracked from manufacture to point of sale and, if they end up on the illicit market, traced back to see where things went awry. This system is designed to stop the tobacco companies from smuggling and the Protocol specifically says that responsibility for it cannot be delegated to the tobacco industry.

Fearful of these developments, the tobacco companies claimed they had changed – no longer were they the perpetrators of tobacco smuggling, but they were now the victims of an apparently vast increase in counterfeited tobacco. No longer did governments need to

hold them to account for smuggling, but should instead work in partnership with them to counter the real perpetrators.

But using publicly available data on smuggling, leaked industry documents, trademark and patent filings, we have identified a major tobacco industry conspiracy.

Our latest evidence indicates **the tobacco companies are still involved in tobacco smuggling**. Despite their claims that *"illicit trade is a growing threat to legitimate business. The threat comes from different sources, the most important of which are counterfeit",* various data (including the industry's own) show that the majority of smuggled cigarettes – approximately 60 to 70% – are the tobacco company's own products. By contrast counterfeited cigarettes make up a small fraction (approximately 5-8%) of the illegal cigarette market. At very best this indicates a wholescale failure by Big Tobacco to secure its supply chain. Yet evidence from government investigations, whistleblowers and leaked tobacco industry documents all points the same direction – suggesting tobacco companies are still involved and, in BAT's case, still using distributors known to have previously been involved in smuggling; the latter in direct contravention of a legal agreement reached with the European Union.

Simultaneously they developed their own track and trace system, Codentify, and are **trying to hoodwink governments** around the world to implement it as the global track and trace system of choice under the Illicit Trade Protocol. This could of course leave them able to continue smuggling with impunity. Aware of their own lack of credibility, leaked documents show that the four major transnational tobacco companies hatched a joint plan to use front groups and third parties to promote Codentify to governments and convince them it would be run independently of industry and under full government control. These documents specifically identify one "credible third party technology company" as FractureCode. Later leaked documents show how these plans were operationalised. For example, the documents suggest that FractureCode operated as a "front" for BAT in the tender for a track and trace system in Kenya, with BAT appearing to direct FractureCode's conduct, organising consultants and drafting letters on its behalf. BAT whistleblower Paul Hopkins' alleged in his Employment Tribunal that FractureCode was "in the pay" of BAT.

To help them get away with this monumental scam the tobacco companies engaged in a whole gamut of activities to **confuse and cajole the very organisations that should have been holding them to account,** as well as the press. They funded large numbers of 'surveys' and reports exaggerating the scale of the counterfeiting problem in particular. They used these to secure extensive and misleading press coverage promoting the message that the tobacco companies were now the victim of tobacco smuggling. They funded ex-policemen and front groups to be their "credible voice". They poured money into INTERPOL and the International Anti-Corruption Academy. Through their discredited third party, the Digital Coding and Tracking Association, they funded the World Customs Organization conference on illicit and paid KPMG and GS1 to produce a report promoting Codentify. They spied on the Illicit Trade Protocol negotiations, getting hold of the text, despite being excluded from negotiations. They engaged in corporate espionage – BAT paid staff in small competitor companies to provide data suggesting that its competitor was smuggling. BAT would then share that data with tax authority staff to put them off the scent. Most recently Philip Morris International set up, with great fanfare, a $100M initiative to

support research on illicit – PMI Impact. This has simply allowed it to continue funding the organisations producing its misleading and widely criticised data, while creating further confusion and influence, not least because it has managed to convince high level ex-UN staff to join PMI Impact's Expert Council.

The scale of the effort and funding poured into this conspiracy are unparalleled. So too is the extent of regulatory capture. Many intergovernmental organisations and national tax and customs authorities around the world appear to have swallowed, without question, the tobacco industry's misleading version of events.

It is vital that they wake up and realise what is at stake: if the tobacco industry's tricks work, they will be left in charge of the very system meant to keep them in check, the system meant to stop them from smuggling their own products, the system meant to safeguard government revenues. Yet identifying which are the industry's latest front groups, spokespeople, linked companies or coalitions is increasingly difficult given the lengths industry will go in order to disguise these interests. If there is a simple message it is this: no government should implement a track and trace system linked in any shape or form to the tobacco manufacturers. In short, no-one can trust the tobacco industry chameleons.

OPEN ACCESS

Tobacco industry's elaborate attempts to control a global track and trace system and fundamentally undermine the Illicit Trade Protocol

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ABSTRACT

Background The Illicit Trade Protocol (ITP) requires a global track and trace (T&T) system to reduce tobacco smuggling. Given the tobacco industry's (TI) historical involvement in tobacco smuggling, it stipulates that T&T 'shall not be performed by or delegated to the tobacco industry'. This paper explores the rationale for & nature of the TI's effors to influence the ITP & its T&T system.

Methods Analysis of leaked TI documents and publicly available data; ,investigation of front groups, trademark and patent ownership.

Findings Growing & diverse sources of evidence indicate that the TI remains involved in tobacco smuggling and that TI cigarettes account for around two-thirds of the illicit cigarette market. The TI therefore has a vested interest in controlling the global T&T system aimed to curtail this behaviour. To this end, Philip Morris International (PMI) adapted its pack marker system, Codentify, to meet T&T requirements, licensed it for free to its three major competitors who then collectively promoted it to governments using front groups and third parties including companies claiming to be independent despite clear TI links. PMI also sought to suggest Codentify was independent by selling some parts of its intellectual property on Codentify while retaining others, leaving a complex web of shared interests. In Africa, British American Tobacco used payments to obtain data suggesting its smaller competitor companies were evading taxes and secure influence with tax authorities. Regulatory capture has been enhanced by a public relations effort involving TI funding for conferences, training, research, and international police and anti-corruption organisations. Collectively this has created public messaging and a powerful network of organisations supportive of the TI's misleading postion on illicit.

Conclusions Governments should assume the TI seeks to control T&T systems in order to avoid scrutiny and minimise excise tax payments and that any T&T system based on Codentify, on intellectual property currently or previously owned by the TI, or being promoted or implemented by companies with TI links, is incompatible with the ITP and would not serve to reduce illicit trade.

Linked

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INTRODUCTION

The Framework Convention on Tobacco Control's (FCTC) Illicit Trade Protocol (ITP), adopted in November 2012 following 4 years of negotiation[1] (see Timeline in table 1), aims to eliminate all forms of illicit tobacco, but focuses particularly on securing the supply chain of legally manufactured tobacco products. A global track and trace (T&T) system which can track a tobacco product through its distribution chain and, should it enter the illicit market, 'trace' it back to determine at what point it entered the illicit channel is therefore central.[1] This will be achieved by each party to the protocol requiring that every pack manufactured in or imported to their territory has a unique, secure marking providing information on manufacture, shipping and distribution. This focus and the stipulation that obligations for T&T systems 'shall not be performed by or delegated to the tobacco industry' were driven by overwhelming evidence of the transnational tobacco companies' (TTCs) historical involvement in cigarette smuggling.[1–10]

This paper aims to examine the nature and purpose of TTC efforts to undermine the ITP and the implications for global tobacco control. Through analysing data on the structure of the illicit tobacco market, leaked industry documents, patent and trademark filings and investigating front groups, it shows that TTCs are engaged in an elaborate campaign to control the global T&T system the ITP envisages by promoting its own pack marker system, Codentify (box 1), as the T&T system of choice.

EVIDENCE OF HISTORICAL AND ONGOING TOBACCO INDUSTRY INVOLVEMENT IN TOBACCO SMUGGLING

Pre-1990

TTCs have a long history of complicity in tobacco smuggling.[2 4–10] They profit when they sell to the distributor regardless of whether their product then enters the illegal market.[4] Tobacco smuggling can benefit them in numerous ways (box 2).

Through the 1990s, overwhelming evidence from TTC documents detailed their involvement in global cigarette smuggling.[2–10] The scale was unprecedented—a third of global cigarette exports were estimated to end up on the illicit market[4] with TTCs supplying some markets almost entirely via illicit channels.[9 10]By the late 1990s, investigations and lawsuits (table 1)[11–14] had led to guilty verdicts[14 15] and legal agreements including between the European Union (EU) and all four TTCs—Philip Morris International (PMI), British American Tobacco (BAT), Japan Tobacco International (JTI) and Imperial Tobacco.[16]

Post-1990: a change in the competitive landscape for illicit tobacco products

With their activities exposed, TTCs changed their export practices.[17] Total illicit cigarette volumes declined,[17] but new types of illicit products began

Table 1 Timeline of events, 1998 to 2017

Timeline			
Date	**Framework Convention on Tobacco Control (FCTC) and Illicit Trade Protocol (ITP)**	**European Union (EU)**	**Tobacco industry (TI)**
1998		EU investigation of transnational tobacco company (TTC) cigarette smuggling starts[16]	
December 1998			An affiliate of RJ Reynolds pleads guilty in US tobacco smuggling lawsuit and is fined $15 million[170]
June 1999			RJR MacDonald's parent company under investigation by the Royal Canadian Mounted Police (RCMP) for complicity in tobacco smuggling between 1989 and 1994[171]
December 1999			Through US Courts, the Canadian government sues RJ Reynolds and affiliates in alleging they were part of a conspiracy to smuggle cigarettes into Canada[12]
June 2000			Canada's lawsuit rejected on the grounds that US courts cannot be used to collect the taxes of another country[172]
November 2000		EU files Racketeer Infuenced & Corrupt Organizations Act (RICO) case in New York Court against TTCs accusing the companies of 'an ongoing global scheme to smuggle cigarettes'[16 173 174]	
August 2001		10 EU member states join the lawsuit[174]	
January 2002		Additional charges filed against Japan Tobacco International (JTI) and its affiliates[175]	
October 2002		Additional allegations filed against RJR MacDonald [16]	
February 2003			The RCMP file criminal charges against RJ Reynolds and affiliates over cigarette smuggling in the 1990s[14]
May 2003	The FCTC is adopted by the World Health Assembly[176]		
July 2004		EU and member states drop case against Phillip Morris International (PMI) in return for enforceable and legally binding agreement. PMI pays the EC $1250 million over 12 years.[16] Through this and subsequent agreements with the other TTCs, they collectively had to make payments of US$1.9 billion to the EU and its member states, additional payments if their tobacco products were, through seizures, found on the illicit market (although only in large numbers)[16] and to mark their products with trackable codes[177–180]	
October 2004			PMI files priority international patent for 'methods and systems for marking, tracking and authentication of products' (Codentify)[77]
February 2005	The FCTC enters into force[181]		
September 2005			International Codentify patent filed[77]
February 2006	Conference of the Parties (COP) 1—officers elected and main committees established[182]		
September 2006			Codentify patent enters the European regional phase[183]
June 2007	COP 2—decision to establish an intergovernmental negotiating body (INB) on the ITP[182]		
December 2007		EU reaches agreement on illicit trade with JTI. JTI agrees to pay the EC $400 million over 15 years[179]	
February 2008	INB—first meeting (negotiations for ITP begin)[182]		During 2008–September 2010, the four major tobacco companies in Canada plead guilty to tobacco smuggling and were collectively fined $C1.7 billion[14]
October 2008	INB, second meeting[182]		
November 2008	COP 3[182]		
February 2009			Codentify patent is granted by Eurasian Patent Organization[184]
April 2009			Codentify patent is granted in Europe[185]
June 2009	INB, third meeting[182]		
March 2010	INB, fourth meeting[182]		
July 2010		EU reaches agreement on illicit trade with British American Tobacco (BAT). BAT agrees to pay the EC $200 million over 20 years[177]	
September 2010		EU reaches agreement on illicit trade with Imperial Tobacco Limited. Imperial agrees to pay the EC $300 over 20 years[178]	

Continued

Table 1 Continued

Timeline			
Date	**Framework Convention on Tobacco Control (FCTC) and Illicit Trade Protocol (ITP)**	**European Union (EU)**	**Tobacco industry (TI)**
November 2010	COP 4—decision to establish informal working group on the ITP[182]		PMI licences Codentify for free to its main competitors.[65] Tobacco Industry Working Group on Digital Tax Verification formed[67]
May 2011			The first Project Star report published on illicit tobacco in the EU, commissioned by PMI from KPMG[25]
July 2011	ITP working group holds its first meeting[186]		
October 2011			Digital Coding and Tracking Association (DCTA) registered in Zurich[187]
March 2012	INB, fifth meeting[182]		
June 2012			PMI makes €15 million donation to Interpol to work with DCTA[132]
November 2012	COP 5—ITP adopted and Interpol (in receipt of pounds from PMI) applies for observer status[182 188]		
December 2012			SICPA awarded Kenyan Revenue Authority tender, despite lobbying efforts for Codentify by BAT and FractureCode[189]
January 2013	ITP opened for signature[190]		
April 2013			European Codentify patent is updated to change the applicant from PMI to the DCTA[191]
September 2013			PMI donates €55 000 to International Anti-Corruption Academy (initiated by European Antifraud Office and UN Office on Drugs and Crime)[131]
December 2013	EU signs ITP[192]		US Codentify patent is filed[193]
April 2014		The Revised Tobacco Products Directive (TPD) agreed. Articles 15 and16 relate to T&T and operationalise the ITP in the EU[194]	DCTA is the major sponsor of World Customs Organization conference on illicit tobacco[6]
May 2014			KPMG & GS1 UK release a DCTA-funded report promoting Codentify[138]
June 2014			First Project SUN report is published—a continuation of Project Star but now commissioned by all TTCs[195]
October 2014	COP 6—Report on the status of the ITP. Request for establishment of ITP expert panel[182]		
November 2014			BAT is fined £650 000 (later reduced to £10 000)[35] for oversupplying products to Belgium[34]
March 2015		Feasibility assessment on EU T&T system published[117]	
June 2015			Coalition Against Illicit Trade is formed[118]
April 2016			Inexto established[101]
May 2016	Coordinating meeting of the ITP expert panel[196]		PMI launches PMI IMPACT[197]
June 2016	EU ratifies ITP[198]	Inception impact assessment for delegated acts under Articles 15 and 16 of TPD published[200]	DCTA announces that it has sold Codentify to Inexto, and PMI claims it now complies with the TPD[199] PMI IMPACT announces first call for proposals to fund[160]
July 2016		EU agreement on illicit trade with PMI expires[201] EU public consultation on EU system of T&T in line with Articles 15 and 16 of the TPD (ends in November 2016)[202]	
September 2016			DCTA transfers ownership of Codentify's European patent to Inexto[203]
November 2016	COP 7—Parties urged not to consider tobacco industry proposals or assistance on T&T. Requests ITP expert panel to report at next COP[182]		Two trademarks for Codentify, covering Switzerland and the EU member states, are transferred to Inexto[112–114];
June 2017	First meeting of ITP expert panel[196]		
September 2017		Consultation on draft implementing regulation on technical standards for T&T system[168]	PMI IMPACT funds 32 projects and many led by organisations with previous TI links[159]

Box 1 Codentify versus enhanced tax stamp systems

Codentify: A code-generating system developed and promoted by the transnational tobacco companies (TTCs). Initially developed as a non-secure authentication system (to determine if a product is authentic or counterfeit), it was subsequently adapted for use as a digital tax verification system.[65 204] Installed at the production line, the system prints two unique codes on each tobacco/cigarette packet—a production information code detailing, inter alia, line and time of production, and a 12-character alphanumeric code generated through an encrypted digital signature to the production information code.[66 193] There is no linked security feature. Tobacco industry insiders, academics and the Framework Convention on Tobacco Control's Secretariat have criticised Codentify as an inefficient[205] and ineffective track and trace (T&T) mechanism.[79 206]

Enhanced stamp systems: Developed initially to focus on individual packs (not cartons, master cases or pallets) intended for the domestic market and to enable volume reporting and revenue collection, tax stamps have now been advanced through the addition of enhanced security features and database linkage to allow T&T and authentication of genuine versus counterfeit products. The key feature is the combination of digital (the unique identification code on a pack) and physical security elements (these may be overt, eg, holograms; covert, eg, fluorescent fibres; or forensic) which make new tax stamps difficult to counterfeit.[167]

Codentify-based system has close links to the tobacco industry, while tax stamp systems were developed independently. Tax stamp producers, also in the business of printing secure documents for government (passports, ID documents, currency), are subject to international standards that control their production and distribution processes.

to appear alongside tobacco industry illicit—counterfeits and cheap whites (box 3).[17 18] Simultaneously, TTCs sought to shift the issue from a public relations (PR) disaster where they were the pariah supplier of illicit product[8] to a PR success story identifying them as both the victim of and solution to tobacco smuggling.[6] They did so by using their resource advantage to purchase data, access and influence,[6] exaggerate the threat of illicit tobacco (particularly counterfeit and cheap whites) and present them as a consequence of tobacco control policies.[19–22]

Ongoing industry involvement: emerging evidence and data

Recent data consistently show that at global, European and national level, the majority of the illicit cigarette market still comprises tobacco industry product (table 2). Latest estimates suggest that approximately 60%–70% of the illicit market is tobacco industry product with specific figures varying from 58% (2016, EU level, industry funded data) to 69%–73% (seizure data for 2011 and 2012 at global level and 2014 and 2016 at UK level). This has occurred despite the use of Codentify in, according to industry claims, over 100 countries worldwide (online supplementary appendix 1).[23]

By comparison, the problem of counterfeit, which the industry continuously emphasises,[6 19 20 24 25] comprises only 5%–8% of the illicit market (other than in the 2016 *Operation Henry* data which are problematic—see footnote to Table 2). The contribution of cheap whites represents, in most of these data, around a fifth to a third of the illicit market. There has, however, been some confusion in defining and measuring cheap whites. For example, industry-commissioned *Project Star* report, undertaken by KPMG, incorrectly classified the Imperial Tobacco brand, Classic, as a cheap white during a period (2006–2012) when it

Box 2 The ways in which tobacco smuggling can benefit transnational tobacco companies (TTCs)

- Smuggled tobacco has either no excise duties or duties from a lower tax jurisdiction applied. Consequently, it is sold for less than it should be. The cheaper a product, the more it sells, especially to the most price-sensitive smokers—the young and the least well off.[6]
- Smuggling undermines tobacco control measures making them less effective in reducing smoking. An obvious example is tobacco taxes, but because illicit product is not usually sold through standard outlets, it also undermines age of sale controls and licensing.[6 17 207]
- Smuggling is a key market entry technique that the TTCs have used extensively[208] to bypass tariff and non-tariff barriers to trade and move tobacco into closed or protected markets. Simultaneously, TTCs argue that the presence of illicit products signals a need for them to invest in that market (rather than resulting from their involvement in the illegal trade).[9 208]
- TTCs use tobacco smuggling to oppose tobacco control policies, arguing that demand for the illicit product, rather than its supply, drives the problem and the tobacco control policy in question will only make this worse. Historically TTCs mainly applied this argument to tobacco taxes,[24] often causing countries to reduce their tobacco excise rates.[4 207] The problem of tobacco smuggling is now used to oppose almost every tobacco control policy.[19 24 209]

Source: Adapted from Gilmore et al.[6]

Box 3 Types of illicit tobacco products now being seen

Counterfeits

- Products bearing a trademark of a cigarette manufacturer that are manufactured by a third party without consent from that cigarette manufacturer.

Cheap whites (also known as illicit whites)

- Non-transnational tobacco company (TTC)-branded cigarettes that are legally produced but have no legitimate market. This confusing term initially used by TTCs is defined by the European Commission as: 'brands manufactured legitimately in one market, either taxed for local consumption or untaxed for export, and sold knowingly to traders who transport them to another country where the products are sold illegally without domestic duty paid.'[210]

Tobacco industry illicit (tobacco industry product present in the illicit market)

- Product of one of the cigarette manufacturers that was en route to, imported into, distributed in or sold in a jurisdiction in violation of that jurisdiction's fiscal laws. That this product was manufactured by a tobacco company does not imply the company is always responsible when that product ends up on the illicit market.

Source: Adapted from Gilmore et al.[25]

Table 2 The make-up of illicit cigarette market by type (tobacco industry illicit, cheap whites and counterfeit): recently available data at global, European and UK levels

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016*
Global (WCO data)										
Illicit white					20%	25%	NA	NA	NA	
Counterfeit					7%	7%	4%	2%	2%	
TI illicit					73%	69%	NA	NA	NA	
EU (Project Star and Project Sun)										
Illicit white	4%	8%	13%	15%	23%	26%	33%	37%	35%	34%
Counterfeit†	6%	6%	5%	5%	4%	0%	6%	7%	9%	8%
TI illicit	89%	86%	82%	80%	74%	74%	61%	56%	56%	58%
UK (Operation Henry 1&2)										
Illicit whites								24%		14%
Counterfeit								5%		18%
TI illicit‡								72%		69%

Blank cells are where no reports were published. NA indicates where a report was published but a specific data item was not available.
WCO data taken from the WCO Illicit Trade Reports: 2014 and 2015 data from 2015 report[211]; 2013 data from 2014 report[212]; 2012 and 2011 data from 2012 report (the first such report)[213] (please note figures differ very slightly between reports) (based on seizure data).
EU data taken from the Project Sun and Project Star reports published by KPMG and funded by the tobacco industry and the Royal United Services Institute[214–220] (based on industry data and modelling by KPMG).
UK data taken from the Operation Henry reports published by the Chartered Trading Standards Institute and commissioned by the Department of Health Tobacco Policy Team[27 221] (based on systematically collected seizure data).
*2016 Operation Henry data were collected from December 2015 to April 2016 inclusive.
†The Counterfeit data in the Project Sun/Star reports comprise just counterfeit PMI brands from 2007 to 2011 and counterfeited brands for all four TTCs from 2013 onward.
‡The 2016 Operation Henry report listed the two most seized products, West and Winston which are tobacco industry brands (sold in the UK by Imperial Tobacco and Japan Tobacco International, respectively), as cheap white products. In our analysis, these have instead been included as TI illicits. This is more likely to give an accurate picture because, although it is unclear if a determination was made as to whether these products were genuine or counterfeit, as they are not widely sold in the UK it is thought unlikely that counterfeiters would target them at the UK market.
EU, European Union; PMI, Philip Morris International; TI, tobacco industry; TTCs, transnational tobacco companies; WCO, World Customs Organization.

was one of the most seized brands in Europe.[26] Similarly, in the latest *Operation Henry* report, the two most seized brands, West and Winston, were coded as cheap whites yet are TTC brands.[27] Consequently, data may underestimate tobacco industry illicit.

While the smuggling of some tobacco industry cigarettes may be outside their control, the sheer volume suggests some involvement. Whistleblowers,[28] researchers,[16] investigative journalists,[29 30] alongside government reports,[31 32] investigations,[33] accusations[33] and fines[34 35] suggest that industry involvement has continued since the 1990s. At best, evidence indicates that tobacco companies are failing to control their supply chain, overproducing in some markets (eg, Ukraine[29]) and oversupplying to others (eg, Belgium) in the knowledge their products will end up on the illicit market. At worst, ex-employees insist JTI remained actively involved, describing 'rampant smuggling' throughout the Middle East, Russia, Moldova and the Balkans.[28] Leaked documents suggest that BAT staff suspected JTI was facilitating smuggling into the Democratic Republic of Congo (DRC)[36 37] but that BAT also clandestinely moved millions of dollars in cash from Uganda to the DRC to buy tobacco leaf which was presumably then illegally exported.[38 39] In 2011–2012, BAT cigarettes being distributed by a company previously implicated in tobacco smuggling were ending up in the illicit market across Africa, the Middle East and Europe with BAT staff agreeing not to discuss the problem by email.[40–42]

Evidence suggests that smaller tobacco companies in Africa are also involved in smuggling and that, despite evidence of its own involvement,[33 39–42] BAT sought to prove these companies were evading tax payments, using this knowledge to undermine them and gain influence with tax authorities.[30 33 43–57] In South Africa, critics claim BAT engaged in money laundering to fund a large spy network and used its funding and the data obtained to secure a seat on the multiagency Illicit-Tobacco Task Team where it could then drive the law enforcement agenda.[33 43 44 48 57] While such detailed evidence is limited to South Africa, BAT documents indicate the company was also paying informants to obtain competitor data elsewhere in Africa and using these data, alongside payments to staff,[58 59] to ingratiate itself with tax authorities.[60–64] Collectively this evidence suggests a very real danger of regulatory capture.

Implications for T&T

It is unsurprising that tobacco industry illicit has not fallen further given that the incentives (box 2) have hardly changed and, where evaluated, fines are too small to offer sufficient deterrent to ongoing involvement.[16 25] At EU level, for example, seizure payments paid by the TTCs from 2006 to 2012 cover only 0.08% of estimated government excise losses despite TTC product representing at least 74% of illicit tobacco over that period (table 2).[16 25]

Effective and well-implemented T&T systems run independently of the tobacco industry would make ongoing TTC involvement in illicit almost impossible. And, as they can only be applied to legally manufactured product, would disadvantage TTCs compared with operators selling counterfeit and cheap whites, providing an incentive for TTCs to control them.

TOBACCO INDUSTRY INTERESTS IN AND INFLUENCE ON T&T SYSTEMS: EVIDENCE FROM LEAKED INDUSTRY DOCUMENTS AND LINKED INVESTIGATIONS

Tobacco industry's fears and aims

Leaked industry documents highlight TTCs' fears and aims around illicit, tax stamps, T&T systems and the ITP.[65–69] In 2003, BAT outlined how the industry was perceived as 'part of the problem' in illicit yet needed 'to be part of solution to

combat threat to our business'.[68] It was identified as 'VITAL for Big Tobacco to be involved in shaping final regulation' in this area.[68] To this end 'cooperation with Governments and Customs authorities worldwide' was key.[68] A later BAT document outlining the 'building blocks' of an Anti-Illicit Trade Advocacy strategy stressed the need 'To reinforce British American Tobacco as being part of solution, not part of the problem'.[70]

Documents suggest TTCs feared the implementation of enhanced tax stamp systems such as those of a leading company in the field, SICPA,[65 66] most notably the cost and lack of TTC control.[65 66] The TTCs' strategy appeared to involve three key elements: to collectively develop their own alternative, Codentify (box 1), and promote it to governments as a digital tax verification (DTV) and T&T system[65 66 71]; to actively oppose tax stamp systems and convince governments they were inferior to Codentify[65 66 71]; and to 'proactively shape T&T regulation'[66] to enable the above.[66] BAT Whistleblower Paul Hopkins' Employment Tribunal documents allege that he was tasked by the company's lead for Anti-Illicit Trade 'to disrupt and if possible stop other service providers of DTV and T&T products from winning tenders …[because]…. BAT had developed its own preferred system in conjunction with Philip Morris International called Codentify and wanted this system to be adopted by as many countries as possible'.[72]

Engaging governments and tax authorities in order to promote common standards on T&T that would help secure the implementation of Codentify over tax stamps appear to have been key.[65 71] Documents note, for example, that: 'Manufacturers should be involved in providing advice and assistance on best practice solutions to governments intending to institute new systems and, where appropriate, should participate in the drafting process, for example in relation to any proposed Framework Convention on Tobacco Control (FCTC) Illicit Trade Protocol'.[69]

The TTCs closely monitored ITP negotiations[73] and, despite being formally excluded, BAT was, at different stages, able to obtain confidential information[74 75] apparently including the text of the protocol.[76] A 45-page document setting out BAT's campaign plan for the fifth Conference of the Parties in November 2012, where the ITP was adopted, noted BAT's preferred outcome on T&T as 'Stamping and coding should be digital (Codentify).'[71]

Developing Codentify as a pan-industry product

Codentify was originally patented by PMI in the mid-2000s following its legal agreement with the EU[77] (see Timeline in table 1). In late 2010, 2 years after ITP negotiations had begun, PMI licensed Codentify for free to the other TTCs who collectively established a Working Group to collaborate on 'DTV',[65 67] promoting Codentify to governments as an alternative to tax stamps.[67]

Promoting Codentify via an increasingly elaborate set of front groups

In line with the ITP specification that T&T systems cannot be 'delegated to the tobacco industry',[78] the pan-industry agreement and linked documentation stipulated the importance of making Codentify appear independent.[65 67] This need was later underscored when BAT noted that the South African Department of Health 'voiced its concern and will not support an "Industry" solution.'[66] The TTCs therefore began giving the impression of independence via a complex system of front groups and third parties.

Digital Coding and Tracking Association

The first of these front groups, the Digital Coding and Tracking Association (DCTA), was created by the TTCs in 2011 to promote Codentify to governments,[67 79] a role it continues to perform.[80 81] DCTA's glossy brochure claimed Codentify could 'meet the expected licensing provisions of [ITP] Article 5' and deliver 'Full Government control' but failed to acknowledge it was developed and patented by the tobacco industry.[82] It has promoted Codentify in a recent consultation, again failing to acknowledge industry links.[83]

FractureCode and ATOS

The pan-industry agreement also outlined the role for 'an independent reputable organisation' to promote Codentify:

> When discussing DTV with authorities, it is important to stress that while the solution is developed and supported by the major industry players, the operation and control of the system will be handled by an independent reputable organization assigned by the respective government.[65 67]

Documentation outlines that this was necessary because governments 'need to be convinced for themselves that this [Codentify] is a high quality solution, which works totally under their control and supervision, and which is supplied to them by a credible third party technology company.'[65]

Yet simultaneously it suggests that TTCs (rather than governments) would select these 'independent' organisations and had already pre-selected two—FractureCode and Siemens.[65] Their role was to: 'guarantee to governments that the "Codentify" system works'; 'promote and sell the system to governments'; and 'after winning a government tender… install the system'.[65]A later (2012) BAT email indicates that it was working 'globally with two approved suppliers to represent Codentify,' this time naming FractureCode and ATOS,[84] both of which subsequently appear to have been involved in tendering for T&T systems on the TTCs' behalf (see below). We identified no further evidence of Siemens fulfilling this role. However, Siemens is a long-standing supplier of tobacco manufacturing machinery, produces its own code reading systems[85] and was reported to be involved in operationalising a T&T system for BAT in Poland, providing both hardware (a code reading system) and software.[86] Moreover, ATOS was involved in developing Codentify[87 88] and in December 2010 acquired Siemens' IT services division for €850 million.[89]

FractureCode, a Danish company established in 2002, offers T&T, digital authentication and volume verification solutions including Codentify.[90] Its web page claimed that Codentify is 'Aligned with expected requirements of WHO FCTC Protocol on Illicit Trade in Tobacco Products'.[91] Although the industry's exact relationship with FractureCode was unclear even to BAT staff,[84 92] interactions during a tender process in Kenya suggest a close relationship with and degree of control by BAT (box 4). BAT Whistleblower Paul Hopkins' Employment Tribunal documents state that by 2011 FractureCode was 'in the pay' of BAT.[72] As the first T&T system to be implemented in Africa post-ITP, Kenya's tender outcome would have significant ramifications, making BAT fearful that SICPA's product would be approved.[93] Documents suggest that FractureCode was also representing Codentify in Mauritius, Uganda and possibly Germany.[84 92]

French company, ATOS, originally involved in Codentify's development[87 88] and named in leaked BAT documents[84] may have played a similar role to FractureCode. It has promoted Codentify in Asia[94] and been involved in the implementation of Codentify in Lithuania alongisde DCTA.[95–98]

In 2012, Kenya held a tender for tobacco revenue stamps with T&T and integrated product accounting systems. BAT did not tender for the service directly but instead used FractureCode to promote Codentify. As Eric Jones, BAT's International Solutions Engagement Manager for Global Supply Chain Tracking and Verification, noted: "following the launch by the KRA [Kenyan Revenue Authority] of the tender that clearly favoured SICPA, we agreed the use of FractureCode (FCC) to support you [BAT Kenya] in fighting/amending/cancelling this tender." He added: "It is worth noting that not using a third party such as FCC to respond to the tender is likely to severely reduce our ability to shape events and prevent SICPA from winning".[93]

Other emails note that BAT had 'purchased' the tender on FractureCode's behalf,[92] 'organised a consultant to represent them [FractureCode]' at a KRA question and answer session and drafted a letter on FractureCode's behalf.[92] It appears this letter was to be sent by FractureCode to the Commissioner General of the KRA, saying: "We, FractureCode Corporation/Codentify, a well established Security Company in Denmark, promoting and selling Digital Tax Verification for Tobacco and Alcohol Products, would like to formally protest about the conduct of the recent KRA tender carried out by your authority." [222] Other documents suggest BAT wrote the original draft.[223]

BAT also required FractureCode to 'Work with the Danish Embassy/Foreign Affairs to get tender cancelled. (This borne by FCC).'[84] Documents indicate that the Danish Embassy wrote a letter on FractureCode's behalf and met with the KRA to help get the tender extended.[224] On 4 May 2012, a Danish Embassy staff member in Nairobi emailed the minutes of their meeting with the KRA to FractureCode stating: "We believe the result of this meeting leaves room for your company to submit your bid and have a direct dialogue with the KRA throughout the process. The Embassy would be happy to assist you in facilitating the contract."[225] The Embassy sent FractureCode an invoice for 9 hours work at Kr915 (Danish Kroner) an hour.[225] It is not known whether the KRA and Embassy understood the BAT link.

Despite these efforts, at the end of 2012, KRA awarded the tender to SICPA.[189] The subsequent implementation of the T&T system was completed by March 2014 and government figures indicate a 49% increase in legal cigarette and cigar sales and a 20% increase in tobacco tax revenue from 2013 to 2015.[167]

Inexto

The outing of DCTA as a tobacco industry front group in 2012[17] limited the TTCs' ability to argue that Codentify was independent. With efforts to operationalise the ITP accelerating, this was becoming increasingly important.[17]

On 24 June 2016, the EU became the 19th party to ratify the ITP.[99] Three weeks before, DCTA announced it had sold Codentify to a company called Inexto, an affiliate of the French Group Impala,[100 101] reportedly for only 1 Swiss Frank.[102–104] Inexto had been established just a few weeks previously[101] and when the handover was reported in the press, a PMI spokesperson claimed Codentify "now complies with … the WHO's Framework Convention on Tobacco Control."[105]

Yet Inexto's links to PMI are clear. Its managing director is Philippe Chatelain, previously PMI's Director of Product Tracking Intelligence & Security for 14 years.[105 106] Other top officials are Erwan Fradet, PMI's Product Manager for Codentify for 5½ years,[107] and Patrick Chanez, who worked for PMI for over 10 years developing anti-illicit trade technology.[108] All three are coinventors of Codentify and still (as of November 2017) hold numerous patents with various PMI companies although now also hold some with Inexto and one with DCTA (Espacenet search 13 November 2017). Four months after the June 2016 announcement, Philip Morris Products SA still owned the global trademark rights to Codentify (online supplementary appendix 2, figure 1a) and Chatelain still held signing authority for that company (this ended 3 November 2016).[109]

Following public criticism of the close link between PMI and Inexto,[105 110 111] two of the trademarks for Codentify, covering Switzerland and the EU member states (online supplementary appendix 2, figure 1b), were transferred to Inexto in late November 2016.[112–114] Chatelain has since suggested that the Codentify system has been redeveloped from scratch, again publicly implying it would be compliant with the ITP.[81] Yet, an additional 20 Codentify trademarks in the WIPO database are still listed as being held by PMI companies covering, for example, Chile, USA, Indonesia, Israel, Mexico, Malaysia, Jordan and UAE, some with application dates as recent as March 2017.[115]Nevertheless, in June 2018 PMI stated to the Guardian newspaper: "We confirm that the worldwide assignment of all Codentify trademarks, previously owned by Philip Morris Products SA, to Inexto SA (part of Impala Security Solutions B.V.) was completed. It is up to Inexto SA to take steps to record the change of ownership at all relevant trademark registries, including WIPO."

The Coalition Against Illicit Trade (CAIT)

The latest group promoting 'an industry operated solution'[116] is the CAIT (figure 1), formed in June 2015 (3 months after the EU T&T feasibility assessment was published)[117] and described as 'a new worldwide coalition of businesses and organisations dedicated to fighting the trade of counterfeited and contraband goods'.[118] As of November 2017, six of the seven members (an eighth, Aegate, has gone into administration[119]) can be linked to the tobacco industry. Yet its submissions to the EU T&T consultation[116] and EU transparency register[120] fail to mention tobacco industry links.

ATOS and FractureCode (see previous section) are members[121] as is Inexto's sister company within the Impala Group, Arjo Solutions.[121 122] Of the other three, FATA Logistics was associated with the development and promotion of Codentify.[123] Domino, a printing and technology company,[124] claims to have worked closely with the Codentify development team and the tobacco industry for over a decade.[125] Describing itself as a global provider of Codentify[126] and the 'tobacco industry's coding technology supplier of choice'[127] it is involved in a project to adapt Codentify to pharmaceuticals.[128] Essentra, which produces cigarette filters and packaging (including security solutions such as holographic products and specialist inks), has been working with the tobacco industry for 65 years.[129 130]

Engaging regulatory agencies and enhancing public relations efforts

A 2012 BAT presentation identified 'key influencer stakeholder groups' as central to 'proactively shap[ing]Track and Trace regulation'. Listed stakeholders included the World Customs Organization (WCO), International Monetary Fund, Interpol and Organisation for Economic Cooperation and Development (OECD) alongside 'Key influencer' governments.[66] Evidence suggests such efforts have been extensively operationalised creating a powerful network that promotes the TTCs' position on illicit.

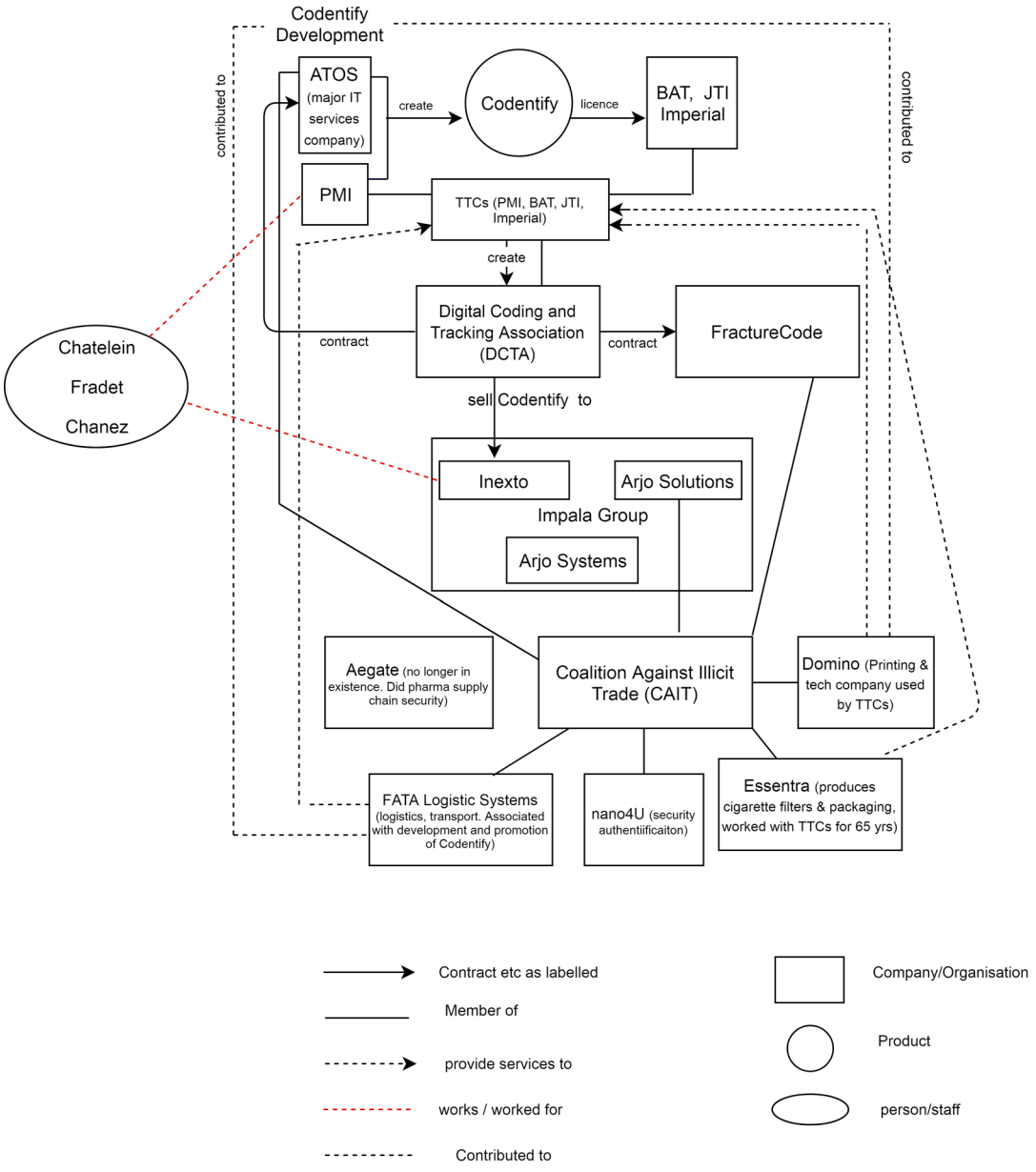

Figure 1 Diagram showing relationships between the creators and promoter of Codentify and the TTCs. BAT, British American Tobacco; JTI, Japan Tobacco International; PMI, Philip Morris International; TTCs, transnational tobacco companies.

In 2011, PMI donated €55 000 to the *International Anti-Corruption Academy*, an organisation initiated by the European Antifraud Office (OLAF) and *UN Office on Drugs and Crime (UNODC)* to provide anti-corruption education and research.[131]

In 2012, PMI donated €15 million to *Interpol*, the world's largest police organisation, to work with DCTA to promote Codentify.[79] It made Codentify accessible to law enforcement agencies via Interpol's Global Register[79 132 133] and Interpol's then Secretary General publicly promoted it.[134] BAT's Eric Jones outlined the importance of Interpol's involvement stating it "will reinforce the credibility of the DCTA (and BAT) when talking to Governments as a credible provider of technology on DTV and T&T."[135]

BAT flagged cooperation with WCO as important because of the 'need for cross border/regional solutions shaped by WCO not WHO.'[68] In 2014, the industry's DCTA was a major sponsor of the WCO conference on illicit tobacco in Brisbane, Australia. KPMG's Robin Cartwright presented in DCTA's time slot and, despite then taking £10 million a year from PMI,[6 136] failed to acknowledge this in his slides.[137] Simultaneously, KPMG and GS1 UK launched a new report promoting Codentify[138] which mentioned DCTA funding but not DCTA's tobacco industry status.[6] WCO also works closely with Interpol[139] and other tobacco industry-linked groups, including the International Tax and Investment Centre,[140 141] with whom WCO has cohosted conferences and training on tobacco smuggling.[142–144]

The *International Chamber of Commerce* has close links to and has repeatedly supported the tobacco industry.[140] All four TTCs are members of its *Business Action to Stop Counterfeiting and Piracy* (BASCAP) initiative which purports to 'combat product counterfeiting'.[140 145] Through events which BASCAP organises or participates in, including an August 2016 UN Counter-Terrorism Centre meeting, TTCs are given a platform to present their position on illicit trade, counterfeiting and crime.[140 146–149]

In addition to these international efforts, TTCs have been working with national Governments[3] and via ex-policemen and front groups established by or representing policemen[150–155]; BAT describing them as 'the credible voice for contraband tobacco'.[156]

In 2016, PMI launched *PMI Impact* with $100 million to fund projects addressing illicit trade, corruption, organised crime and money laundering.[157] With applications judged by an Expert Council of individuals closely linked to multiple UN agencies[158] and Interpol,[159] and PMI Impact's September 2017 event featuring presentations from (and enabling PMI executives to link with), among others, WCO, OECD, Europol and numerous UN agencies including the UNODC (see second paragraph in this section), it would appear the initiative's purpose is to further cement PMI's access to authorities and undermine the WHO and the FCTC Secretariat among UN agencies. The first 32 recipients of funding (totalling approximately US$28 million) announced in September 2017[160] include KPMG, Oxford Economics, Transcrime and others previously commissioned by PMI to produce widely criticised reports[20 25 161 162] on illicit favourable to the TTCs.[159 161 162]

DISCUSSION

This evidence outlined in this paper indicates that the tobacco industry has created a T&T system it can control and, through an elaborate campaign involving front groups, third parties and increasingly complex relationships with other companies, all underpinned by a massive public relations effort, is aiming to have this system implemented as the global T&T system of choice under the ITP. Simultaneous evidence suggests it remains involved in tobacco smuggling. This combination of events would fundamentally undermine the ITP by enabling tobacco companies, with a vested interest in minimising their tax payments, to control the very system aimed to maximise those payments and reduce tobacco smuggling.

Three key findings underpin this conclusion. First, diverse and growing evidence shows that tobacco industry illicit outstrips the problems of cheap whites and counterfeits and remains the single largest problem in illicit tobacco; that incentives for industry involvement have barely changed since their well-documented involvement in the 1990s; that tobacco companies likely continue to be involved in and benefit from tobacco smuggling; and that this problem has persisted since the widespread introduction of Codentify. Possible interpretations are that Codentify is technically unfit for purpose or that TTC control renders Codentify useless.

Second, TTCs have a vested interest in controlling a T&T system intended to address tobacco industry illicit and fear T&T systems outside their control. This drove them to work collaboratively to oppose competitor systems, promote their own digital system, Codentify, and influence regulation on T&T to favour it. This collaborative campaign involved extensive subterfuge including the creation of front groups like DCTA to promote Codentify and channel funding to others who further promoted Codentify (eg, KPMG and WCO), and use of companies like FractureCode. Later elements of their intellectual property on Codentify were sold to other companies with Codentify now being promoted by companies and coalitions purporting to be independent yet having clear TTC links, including co-ownership of intellectual property rights to Codentify by former PM staff now at Inexto.

Third, underpinning all the above, was an extensive and well-funded stakeholder management and public relations effort involving funding for conferences, training, research, ex-policemen to act as spokespeople, and major organisations in the field including intergovernmental organisations. Such efforts are often operationalised via third parties (eg, DCTA, BASCAP) or specific initiatives (eg, PMI Impact). They serve to: cement the TTCs' previously observed control over data and research on tobacco smuggling[6]; create and disseminate discourses favourable to industry; and build a network of influential organisations and individuals that support, promote and enhance the credibility of these misleading industry discourses. These efforts should be seen as part of a broader strategy to rehabilitate the TTCs' image,[163–165] reintegrate TTCs into policy-making circles from which they have been excluded, and undermine WHO and the Convention Secretariat among UN agencies. The concern that such efforts lead to regulatory capture is enhanced by findings from Africa that BAT has been paying to obtain data suggesting its competitors were smuggling and to gain influence with tax authorities.

Limitations

Like any illegal activity, tobacco smuggling is complex, hidden and hard to investigate. We are limited to data that are publicly available and documents provided to us and cannot, therefore,

What this paper adds

What is already known on this subject

- The Framework Convention on Tobacco Control's Illicit Trade Protocol (ITP) aims, inter alia, to secure the supply chain of legally manufactured tobacco products through a global track and trace (T&T) system. Given evidence of the tobacco industry's (TI) historical involvement in cigarette smuggling, the protocol stipulates that such systems 'shall not be performed by or delegated to the tobacco industry'. Philip Morris International developed a code-generating system, Codentify, and licensed it for free to its competitors in a deal which saw the four transnational tobacco companies agree to promote Codentify to governments as a T&T system.

What this paper adds

- Growing evidence indicates the TI remains involved in tobacco smuggling and therefore has a vested interest in controlling any T&T system aimed to control its supply in order to avoid scrutiny and minimise its excise payments.
- The TI's attempts to have its Codentify-based system implemented as a T&T system have become increasingly underhand. They include claiming Codentify is independent of the TI by using front groups and front companies to promote it; selling some parts of its intellectual property on Codentify while retaining others, leaving a complex web of shared interests; paying networks of spies to obtain data showing its competitors are smuggling; and providing significant funding (administered directly and via third parties) for conferences, training, research and international police and anti-corruption organisations which serves to foment confusion over tobacco smuggling and create a powerful network supportive of the TI's position.
- Governments should assume that any system based on Codentify, on intellectual property currently or previously owned by the TI, or being promoted by companies with TI links, is incompatible with the ITP and would not serve to reduce illicit trade within the legal supply chain.

access legal agreements between TTCs, DCTA and the various companies now promoting Codentify.

Policy implications

The findings signal a very real danger of regulatory capture of the governmental and intergovernmental institutions responsible for addressing tax evasion and TTCs coming to control a global T&T system thereby fundamentally undermining it. Recent press reports from Argentina suggest these dangers may already be being realised with legal charges against PMI alleging its use of Codentify to hide levels of cigarette production in order to avoid paying taxes.[166] By contrast we note the increase in legal tobacco sales and tobacco tax revenue in Kenya postimplementation of an independent T&T system (box 4).[167]

The findings indicate that determining independence from industry when operationalising the ITP is increasingly difficult. Experience in the EU[168] suggests that definitions which require countries, possibly repeatedly, to search patent and trademark registers, investigate industry links and company sources of income, and so on, are best avoided.

We therefore suggest, broadly in line with Convention Secretariat recommendations,[169] that governments should be alert to the likelihood that TTCs will continue to disguise their links to Codentify and that Codentify will be promoted under different names and by different companies. The safest response is for governments to assume that (1) the TTCs remain involved in any T&T system based on Codentify or on intellectual property currently or previously owned by a TTC and (2) such a system would be incompatible with the ITP and ineffective in reducing illicit trade within the legal supply chain. The industry's own use of Codentify to help address counterfeiting should be seen as entirely separate. To help address potential regulatory capture, decisions on T&T should be cross-governmental and it is vital that health ministries are involved.

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Contributors ABG conceived the idea for the study, undertook the data analysis and drafted the first version. ABG and AR investigated trademark ownership and ABG and AWAG produced timeline. ABG, AR, AWAG all contributed to document analysis, investigation of third parties and patent ownership, and editing of paper.

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E-cigarettes are a gateway to real cigarettes for Britain's young

theconversation.com/e-cigarettes-are-a-gateway-to-real-cigarettes-for-britains-young-82466

Mark Conner

Young people in Britain who use e-cigarettes (vape) are nearly four times more likely to start smoking cigarettes than their non-vaping peers, our latest study has found.

When e-cigarettes first entered the market a decade ago, they were considered to be as dangerous as cigarettes. But views have changed since then, and e-cigarettes are now widely believed to be a far safer option than smoking.

In 2015, Public Health England published a detailed review of the evidence around the safety of e-cigarettes and said, at best guess, they were 95% less toxic than conventional cigarettes.

But concerns remain because e-cigarettes usually contain the addictive ingredient of cigarettes: nicotine. While recognising the harm reduction impact of e-cigarettes, it is important to ask what role, if any, e-cigarettes play in encouraging non-smoking adolescents to try their first cigarette.

For a number of years, my colleagues and I have been tracking data from several thousand schoolchildren in England to assess the impact of various anti-smoking interventions. We set about trying to identify any associations between e-cigarette use and starting to smoke within a year.

We started by looking at those children, aged 14 and 15, who had not smoked. We asked them to fill out a questionnaire at the start of the survey, and then a year later. Of those who had tried an e-cigarette, just under 34% reported having a cigarette within a year compared with just under 9% who had not. In other words, there was an almost fourfold increased chance of starting to smoke among those young people who had used an e-cigarette. This is worrying because it is known that once someone starts to smoke, the chances that they will continue to smoke are high.

Would they have started smoking anyway?

Last year, researchers in the US published their findings on smoking among a group of teenagers (average age 17) in southern California. As with our study in England, they were surveyed at the start of the study and again 16 months later. The US researchers found that e-cigarette users had six times risk of starting to smoke compared with their peers, who had not used an e-cigarette.

Perhaps these young people were going to smoke anyway, whether e-cigarettes existed or not? It is a question that gets to the heart of the risks that might be associated with e-cigarette use among the young.

We looked at those adolescents whose friends did or did not smoke, because having friends who smoke is a known risk factor for starting smoking. The data – which surprised us – suggested that e-cigarette use was a greater risk factor in starting to smoke in those *without* friends who smoked, compared with those*with* friends who smoked.

Using e-cigarettes meant they were five-and-a-half times more likely to start smoking in the group with no friends who smoked but only one-and-a-half times more likely to start smoking in the group with most or all friends who smoked.

Again, the picture in the US seems very similar to what we found in the UK. Researchers there found associations between e-cigarette use and starting to smoke among those young people who during the initial survey stated they had no intention of starting to smoke.

Once people take up smoking, they tend not to stop.Sasa Prudkov/Shutterstock

So what do the associations suggest is going on? The unanswered question is whether the young people who go on to smoke are simply experimenting or whether they are becoming regular smokers.

The long-term trend in the UK is for e-cigarette use to go up while smoking declines. Future research is now needed to disentangle these apparently contrary findings, and whether there is any link between the intensity of e-cigarette use among adolescents and cigarette use.

Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study

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ABSTRACT

Background In cross-sectional surveys, increasing numbers of adolescents report using both electronic cigarettes (e-cigarettes) and cigarettes. This study assessed whether adolescent e-cigarette use was associated prospectively with initiation or escalation of cigarette use.

Methods Data were from 2836 adolescents (aged 13–14 years at baseline) in 20 schools in England. At baseline, breath carbon monoxide levels, self-reported e-cigarette and cigarette use, sex, age, friends and family smoking, beliefs about cigarette use and percentage receiving free school meals (measure of socioeconomic status) were assessed. At 12-month follow-up, self-reported cigarette use was assessed and validated by breath carbon monoxide levels.

Results At baseline, 34.2% of adolescents reported ever using e-cigarettes (16.0% used only e-cigarettes). Baseline ever use of e-cigarettes was strongly associated with subsequent initiation (n=1726; OR 5.38, 95% CI 4.02 to 7.22; controlling for covariates, OR 4.06, 95% CI 2.94 to 5.60) and escalation (n=318; OR 1.91, 95% CI 1.14 to 3.21; controlling for covariates, this effect became non-significant, OR 1.39, 95% CI 0.97 to 1.82) of cigarette use.

Conclusions This is the first study to report prospective relationships between ever use of e-cigarettes and initiation and escalation of cigarette use among UK adolescents. Ever use of e-cigarettes was robustly associated with initiation but more modestly related to escalation of cigarette use. Further research with longer follow-up in a broader age range of adolescents is required.

INTRODUCTION

Electronic cigarettes (e-cigarettes) deliver inhaled aerosol usually containing nicotine. E-cigarettes are thought to have minimal impact on morbidity and mortality[1 2] and are recognised as harm reducing for adult smokers.[2–4] Although rates of adolescent regular use of e-cigarettes are low, rates of ever use are substantial (13%–22%) and have increased over recent years, whereas rates of cigarette use have decreased over the same period both in the USA[5–7] and UK.[8–15] Nevertheless, the possible relationship between adolescent e-cigarette use and the initiation and escalation of cigarette use remains under-researched.

Longitudinal data on e-cigarette use and subsequent cigarette use are currently limited to US samples based on unverified self-reported measures.[16–19] For example, two US studies reported baseline e-cigarette use to be positively associated with the initiation of cigarette use 12 months later in 14-year olds controlling for various predictors of smoking (OR 1.75, 95% CI 1.10 to 2.77; OR 2.87, 95% CI 2.03 to 4.05).[17 18] Barrington-Trimis *et al*[16] reported similar findings over 16 months in 17-year-olds (OR 6.17, 95% CI 3.30 to 11.6), whereas Wills *et al*[19] reported that e-cigarette use was linked to initiation (OR 2.87, 95% CI 2.03 to 4.05) but not to escalation of smoking over 12 months in a sample of adolescents aged 14–15 years.

This study is novel in assessing these relationships between e-cigarette use and subsequent cigarette use in a sample of UK adolescents and in exploring a number of previously unexamined smoking risk factors as covariates and moderators. In particular, we investigated the extent to which baseline ever use of e-cigarettes was associated with the initiation or escalation of cigarette use (objectively validated) 12 months later in a sample of UK adolescents aged 13–14 years. The impact of controlling for various smoking risk factors such as friends and family smoking and their moderating effects was also explored.

METHODS

Participants and procedures

Data were collected as part of a 4-year cluster randomised controlled trial of a school-based smoking initiation intervention[20 21] based on implementation intentions.[22] Data from 2836 adolescents (13–14 years at baseline) in the 20 control schools are reported here. Head teachers consented to school participation with parents given the option to withdraw children from the study. Adolescents consented by completing questionnaires matched across time points using a personally generated code. The data reported here are from waves 3 (September–December 2014; referred to as *baseline*) and 4 (September–December 2015; referred to as *follow-up*) of the trial when e-cigarette use measures were added to the data collection.

The Faculty of Medicine, University of Leeds, UK, ethical review committee approved the study (reference 12–0155).

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Table 1 Descriptive data for the full sample and subsamples

		Cross-sectional sample (total N=2836)		Longitudinal sample of baseline never used cigarettes (total n=1726)		Longitudinal sample of baseline once/ used to use cigarettes (total n=318)	
		N/M	(%/SD)	N/M	(%/SD)	N/M	(%/SD)
Age		13.18	(0.39)	13.18	(0.39)	13.17	(0.39)
Sex	Boy	1411	(49.8%)	898	(48.0%)	164	(51.6%)
	Girl	1425	(50.2%)	898	(52.0%)	154	(48.4%)
Heard of e-cigarettes (baseline)	No	346	(12.2%)	227	(13.2%)	24	(7.5%)
	Yes	2383	(84.2%)	1381	(80.0%)	286	(90.0%)
	Don't know	103	(3.2%)	118	(6.8%)	8	(2.5%)
Ever used e-cigarettes (baseline)	No	1867	(65.8%)	1383	(80.1%)	70	(22.0%)
	Yes	969	(34.2%)	343	(19.9%)	248	(78.0%)
Ever used cigarettes (baseline)	No	2196	(77.4%)	1726)	(100.0%	0	(0.0%)
	Yes	640	(22.6%)	0	(0.0%)	318	(100.0%)
Family smokers = none		898	(31.7%)	666	(38.6%)	42	(13.2%)
Family smokers = one		852	(30.0%)	534	(30.9%)	88	(27.7%)
Family smokers = two		517	(19.2%)	298	(17.3%)	74	(23.2%)
Family smokers = three or more		569	(20.1%)	228	(13.2%)	114	(35.8%)
Friend smokers = none		1384	(48.8%)	1050	(60.8%)	67	(21.1%)
Friend smokers = a few		1135	(40.0%)	613	(35.5%)	189	(59.4%)
Friend smokers = most		317	(11.2%)	63	(3.7%)	62	(19.5%)
Intentions		4.69	(0.77)	4.87	(0.50)	4.48	(0.76)
Attitude		4.73	(0.57)	4.88	(0.32)	4.51	(0.65)
Perceived norms		4.81	(0.57)	4.91	(0.30)	4.66	(0.50)
Perceived behavioural control		4.61	(0.72)	4.78	(0.49)	4.43	(0.71)
Self-efficacy		4.64	(0.77)	4.83	(0.47)	4.41	(0.82)
Free school meals*		14.24	(6.63)	13.82	(6.55)	15.57	(6.35)

*Mean and SD for this variable based on school-level data.

Measures

Cigarette use was assessed using a standardised measure[23] at both time points; adolescents ticked one of the following: 'I have never smoked; I have only tried smoking once; I used to smoke sometimes, but I never smoke cigarettes now; I sometimes smoke cigarettes now, but I don't smoke as many as one a week; I usually smoke between one and six cigarettes a week; and I usually smoke more than six cigarettes a week'. Self-reported smoking was validated against a measure of breath carbon monoxide (CO) levels (using Micro+ Smokerlyzer CO Monitor; Bedfont Scientific Limited, Kent, England, UK). Such measures are reliable and valid ways of assessing regular cigarette smoking[24 25] but not occasional smoking due to the short half-life (4–6 hours) of breath CO.

E-cigarettes/vapourisers were described as 'a tube that sometimes looks like a normal cigarette and has a glowing tip. They all puff a vapour that looks like smoke but unlike normal cigarettes, they don't burn tobacco'. Awareness ('Have you ever heard of e-cigarettes or vapourisers?' yes I have; no I haven't; I don't know) and use ('Which ONE of the following is closest to describing your experience of e-cigarettes or vapourisers?' I have never used them; I have tried them once or twice; I use them sometimes (more than once a month but less than once a week); I use them often (more than once a week)) of e-cigarettes were tapped by single items.

Other measures were assessed as covariates/moderators. Percentage of children at a school eligible for free school meals was used as an indicator of socioeconomic status.[26] Sex and age were measured (age not used in analyses as adolescents from one school year). Family smoking was assessed using the question, 'Who smokes in your family now? Tick all the people who smoke at the moment', followed by a list of family members (zero to nine family members marked; scored as 0, 1, 2 or 3 or more). Friends' smoking was assessed using the question, 'How many of your friends smoke?' none of them; only a few; half and half; most but not all; all of them (scored as none of them, a few or most (last three categories)).

Baseline health cognitions about smoking[21] were assessed as mean of multiple items on five-point scales (high scores indicated negative views of smoking): intention was tapped by three statements ('I plan not to smoke', 'I don't want to smoke' and 'I will try not to smoke'; strongly disagree to strongly agree; Cronbach's alpha 0.90), attitude by seven statements ('For me, smoking would be… good–bad; beneficial–harmful; pleasant–unpleasant; enjoyable–unenjoyable; wise–foolish; fun–not fun; healthy–unhealthy'; Cronbach's alpha 0.87), norms by five statements ('Most of my friends think…'; 'My best male friend thinks…'; 'My best female friend thinks…'; 'My family think…'; 'People who are important to me think…'; I should smoke–I should not smoke; Cronbach's alpha 0.79), perceived behavioural control by three statements ('I am confident I could resist smoking', strongly disagree to strongly agree; 'For me to not smoke would be…', difficult–easy; 'How much control do you feel you have over not smoking?' no control–complete control; Cronbach's alpha 0.69) and self-efficacy by six statements ('I can say no to smoking, even at school'; 'I can say no to smoking even when I am offered a cigarette'; 'I can say no to smoking, even if my friends want me to smoke'; 'I can say no to smoking, even if I was the only one in the group not smoking'; 'I can say no to smoking, even if I feel a bit left out of the group'; 'I can say no to smoking, even if I feel like smoking'; strongly disagree-strongly agree; Cronbach's alpha 0.91).

Table 2 Relationships between cigarette and e-cigarette use: (A) cross-sectional relationships between baseline cigarette and e-cigarette use; (B) prospective relationships between cigarette use at 1-year follow-up and e-cigarette use at baseline among baseline never used cigarettes; (C) prospective relationships between cigarette use at 1-year follow-up and e-cigarette use at baseline among baseline used once or used to use cigarettes

	Baseline e-cigarette use			
	Never	Tried	Infrequent	Frequent
		(1–2 times)	(1/month–1/week)	(>1/week)
Cigarette Use	n (%)	n (%)	n (%)	n (%)
A. Cross-sectional relationships at baseline (n=2836)				
Never	1743 (61.5)	407 (14.4)	40 (1.4)	6 (0.2)
Once	90 (3.2)	201 (7.1)	57 (2.0)	10 (0.4)
Used to	20 (0.7)	59 (2.1)	38 (1.3)	22 (0.8)
Rarely (<1/week)	8 (0.3)	15 (0.5)	31 (1.1)	19 (0.7)
Occasional (1–6/week)	1 (0.0)	6 (0.2)	20 (0.7)	10 (0.4)
Frequent (>6/week)	5 (0.2)	7 (0.2)	6 (0.2)	15 (0.5)
B. Longitudinal relationships for baseline never users of cigarettes (n=1726)				
Never	1259 (72.9)	211 (12.2)	13 (0.8)	1 (0.1)
Once	86 (5.0)	65 (3.8)	8 (0.5)	0 (0.0)
Used to smoke	19 (1.1)	19 (1.1)	1 (0.1)	1 (0.1)
Rarely (<1/week)	11 (0.6)	12 (0.7)	1 (0.1)	0 (0.0)
Occasional (1–6/week)	5 (0.3)	3 (0.2)	2 (0.1)	0 (0.0)
Frequent (>6/week)	3 (0.2)	1 (0.1)	3 (0.2)	2 (0.1)
C. Longitudinal relationships for baseline triers of cigarettes (n=318)				
No change	61 (19.2)	131 (41.2)	43 (13.5)	14 (4.4)
Escalation	9 (2.8)	38 (11.9)	17 (5.3)	5 (1.6)

Data analysis

We tested for differences on each baseline measure between adolescents who had complete versus missing values on one or more measures using χ^2 tests and t-tests. Among respondents completing all measures, we report descriptives on baseline measures for three subsamples: full cross-sectional sample, longitudinal subsample of baseline never users of cigarettes and longitudinal subsample of baseline occasional users of cigarettes. The relationship between e-cigarette and cigarette use was examined next in the same three subsamples. Self-rated smoking was validated against breath CO levels at baseline and follow-up using Games–Howell post hoc tests based on 1000 bootstrapped resamples because the data were skewed and had unequal variances.

Given the problems with imputing values for outcome variables,[27] attrition analyses were used to assess biases in all baseline measures in those with and without matched follow-up data (at follow-up 1=data missing; 0=data available) in the two longitudinal subsamples using multilevel logistic regressions (in R) to assess model fit (Akaike Information Criterion) and, for each predictor, the odds ratios (OR), 95% CIs and p value. The main analyses used the same analysis to predict follow-up initiation (1=smoked; 0=never smoked) or escalation (0=never, once or used to smoke cigarettes; 1=rarely, occasional or frequent cigarette smoking) of smoking based on ever use of e-cigarettes and covariates. E-cigarette use was dichotomised into never versus ever use due to few regular users. Model 1 controlled for the clustering of adolescents within schools, and baseline e-cigarette ever use was a predictor; model 2 added baseline covariates; and model 3 tested interactions between each covariate and e-cigarettes ever use. To assess the impact of baseline missing values, we repeated the regressions with imputation.[28]

RESULTS

Sample description

At baseline, full data were available on 2836 adolescents, who did not differ (p>0.05) from those with missing data (N=58–92) on all measures except sex (p=0.001; boys less likely to have complete data) and norms (p=0.02; those with lower norms to not smoke less likely to have complete data).

Table 1 provides descriptive data on baseline measures for respondents who completed all measures. The cross-sectional sample (table 1) was mostly aged 13 years, approximately half boys, and a majority not having ever used e-cigarettes or cigarettes. Levels of e-cigarette awareness and use were lower in the never smoking subsample (table 1: 80.0% heard of, 19.9% used e-cigarettes) compared with the subsample reporting occasional smoking (table 1: 90.0% heard of, 78.0% used e-cigarettes).

At baseline and follow-up, CO levels were low and not significantly different between those reporting they never smoked, had only tried smoking once, used to smoke sometimes or smoked sometimes but not as many as one per week; CO levels were significantly higher (p<0.05) among those reporting they smoked 1–6 or >6 cigarettes per week but not significantly different across these latter two categories.

Simple relationships between use of e-cigarettes and cigarettes

Table 2 reports the relationship between e-cigarette and cigarette use in the three subsamples. Table 2A shows the cross-sectional relationship: 61.5% of the sample had tried neither e-cigarettes nor cigarettes, 16.0% had tried e-cigarettes but not cigarettes, 4.4% had tried cigarettes but not e-cigarettes and 18.2% had used both.

Table 2B shows the longitudinal relationship between baseline e-cigarette use and follow-up cigarette use in the baseline

Table 3 Association of baseline measures with missingness (1=absent) at follow-up for baseline never used cigarettes (n=2196; left-hand column) and baseline once or used to use cigarettes (n=497; right-hand column)

	Baseline never used cigarettes		Baseline once or used to use cigarettes	
Predictors	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Never used e-cigarettes	1.00		1.00	
Ever used e-cigarettes	1.11 (0.85 to 1.46)	0.43	0.83 (0.51 to 1.35)	0.44
Friend smokers= none	1.00		1.00	
Friend smokers=a few	1.18 (0.93 to 1.49)	0.18	2.08 (1.12 to 3.82)	0.019
Friend smokers= most	1.36 (0.78 to 2.39)	0.28	4.33 (2.10 to 8.95)	<0.001
Male	1.00		1.00	
Female	0.70 (0.56 to 0.86)	<0.001	0.84 (0.6 to 1.26)	0.40
Family smokers = none	1.00		1.00	
Family smokers = one	1.29 (0.99 to 1.67)	0.057	0.90 (0.47 to 1.71)	0.74
Family smokers = two	1.10 (0.79 to 1.51)	0.58	0.97 (0.50 to 1.89)	0.93
Family smokers = three or more	1.53 (1.10 to 2.12)	0.01	0.81 (0.43 to 1.53)	0.51
Intentions	0.77 (0.62 to 0.96)	0.02	0.99 (0.71 to 1.38)	0.95
Attitudes	0.93 (0.65 to 1.31)	0.66	1.29 (0.86 to 1.93)	0.22
Norms	0.95 (0.66 to 1.37)	0.78	0.99 (0.65 to 1.52)	0.97
Perceived behavioural control	0.91 (0.73 to 1.14)	0.42	0.64 (0.46 to 0.88)	0.006
Self-efficacy	1.25 (0.95 to 1.64)	0.11	1.15 (0.79 to 1.67)	0.46
Free school meals	1.03 (0.97 to 1.08)	0.34	1.01 (0.97 to 1.06)	0.49

Baseline never used cigarettes, AIC=2222.6; baseline once or used to use cigarettes, AIC=658.7.

never smokers; initiation of cigarette use in the next 12 months rose from 9.0% to 34.4%, respectively, in baseline never versus ever used e-cigarettes. Baseline CO levels were low among the self-reported never smokers, and exclusion of adolescents with higher baseline CO levels (>2 ppm) did not substantively change the regression findings. CO levels at follow-up were significantly higher among those classified as initiating compared with not initiating cigarette use ($p<0.05$).

Table 2C shows the longitudinal relationship between e-cigarette use at baseline and escalation of cigarette use at follow-up among baseline occasional smokers; escalation in the next 12 months rose from 12.9% to 24.2%, respectively, in those never versus ever having used e-cigarettes at baseline. Baseline CO levels were low among those self-reporting that they had only once used or former smokers and exclusion of adolescents with higher baseline CO levels (>2 ppm) did not substantively change the regression findings. CO levels at follow-up were significantly higher among those classified as escalating versus not escalating smoking ($p<0.001$).

Attrition analyses

At baseline, 2196 adolescents (77.4%) reported never having smoked but only 1726 adolescents (78.6%) could be matched across time points. The similar number of adolescents completing questions at each time point (total N=2928 and 2747 at baseline and follow-up, respectively) suggests that attrition was principally due to a failure to match personally generated codes.

Analyses (table 3) indicated no significant effects for baseline ever used e-cigarettes, friends' smoking, attitude, norms, perceived behavioural control, self-efficacy or free school meals on missingness; however, there were significant effects for sex (OR 0.70, 95% CI 0.56 to 0.86; girls less likely to be missing), family smoking (OR 1.53, 95% CI 1.10 to 2.12; with three or more family members who smoked more likely to be missing) and intention (OR 0.77, 95% CI 0.62 to 0.96; with weaker intentions not to smoke more likely to be missing).

At baseline, 497 adolescents reported trying or past use of cigarettes. We matched 318 adolescents (64.0%) across time points. Analyses indicated no significant effects for baseline ever used e-cigarettes, sex, family smoking, intention, attitude, perceived behavioural control, self-efficacy and free school meals on missingness (table 3); however, there were significant effects for friends' smoking (OR 2.08, 95% CI 1.12 to 3.82 for few friends smoking; OR 4.33, 95% CI 2.10 to 8.95 for most friends smoking; with a few or most friends who smoked more likely to be missing) and perceived behavioural control (OR 0.64, 95% CI 0.46 to 0.88; with weaker perceived behavioural control over not smoking more likely to be missing).

Prospective analyses

Initiation of cigarette use at follow-up was predicted by having ever used e-cigarettes at baseline (table 4, model 1; OR 5.38, 95% CI 4.02 to 7.22) and remained so when controlling for covariates (table 4, model 2; OR 4.06, 95% CI 2.94 to 5.60). Initiation of cigarette use was significantly higher in adolescents who at baseline were ever users of e-cigarettes, had either a few or most friends who smoked and had one, two or three or more family members who smoked, but was significantly lower in adolescents with stronger intentions (not to smoke). Exploratory analyses revealed that baseline friends' smoking was a statistically significant moderator ($p<0.001$; all other moderators $p>0.43$). Decomposition of the moderation effect (table 4, model 3) indicated that the the impact of ever used e-cigarettes on likelihood of initiating cigarette use was attenuated among those with a few or most friends who smoked at baseline. Multiple imputation resulted in an additional 28 cases in this analysis. The estimated model coefficients showed very little change (mostly <1%), and there was no change in the interpretation.

Table 4 also reports the results of the regressions to predict escalation of cigarette use at follow-up. In model 1, ever use of e-cigarettes at baseline was a significant predictor of escalation of cigarette use (OR 2.16, 95% CI 1.01 to 4.62). In model 2, ever use of e-cigarettes at baseline became a non-significant predictor of escalation when controlling for covariates (OR 1.89, 95% CI 0.82 to 4.33). Escalation of cigarette use was significantly higher in adolescents who had most friends who

Table 4 Association of baseline ever used e-cigarettes with ever used cigarettes at follow-up (among never users of cigarettes at baseline; n=1726; left-hand column) or increased use of cigarettes at follow-up (among baseline once or used to use cigarettes; n=318; right-hand column) controlling for clustering by school

	Baseline never used cigarettes		Baseline once or used to use cigarettes	
Predictors	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Model one without covariates				
Never used e-cigarettes	1.00		1.00	
Ever used e-cigarettes	5.38 (4.02 to 7.22)	<0.001	2.16 (1.01 to 4.62)	0.046
Model two with covariates				
Never used e-cigarettes	1.00		1.00	
Ever used e-cigarettes	4.06 (2.94 to 5.60)	<0.001	1.89 (0.82 to 4.33)	0.13
Friend smokers = none	1.00		1.00	
Friend smokers = a few	1.87 (1.35 to 2.58)	<0.001	1.15 (0.50 to 2.66)	0.75
Friend smokers = most	2.99 (1.52 to 5.87)	0.001	3.23 (1.19 to 8.77)	0.022
Male	1.00		1.00	
Female	1.32 (0.97 to 1.79)	0.08	0.83 (0.45 to 1.52)	0.55
Family smokers = none	1.00		1.00	
Family smokers = one	0.76 (0.51 to 1.13)	0.18	1.69 (0.61 to 4.68)	0.31
Family smokers = two	2.05 (1.37 to 3.06)	<0.001	1.41 (0.48 to 4.12)	0.53
Family smokers = three or more	1.90 (1.23 to 2.94)	0.004	1.23 (0.45 to 3.41)	0.69
Intentions	0.70 (0.52 to 0.96)	0.03	1.50 (0.87 to 2.57)	0.14
Attitudes	0.68 (0.44 to 1.04)	0.08	0.51 (0.28 to 0.90)	0.020
Norms	0.89 (0.57 to 1.39)	0.61	1.12 (0.56 to 2.23)	0.75
Perceived behavioural control	1.00 (0.73 to 1.37)	0.99	0.99 (0.58 to 1.69)	0.96
Self-efficacy	1.09 (0.75 to 1.57)	0.66	0.57 (0.35 to 0.94)	0.027
Free school meals	0.99 (0.97 to 1.02)	0.60	1.01 (0.96 to 1.07)	0.62
Model three with covariates and interactions				
Never used e-cigarettes and Friend smokers = none	1.00			
Ever used e-cigarettes and friend smokers = none	7.74 (4.68—12.79)	<0.001		
Never used e-cigarettes and Friend smokers = a few	2.57 (1.72 to 3.84)	<0.001		
Ever used e-cigarettes and friend smokers = a few	7.84 (5.08–12.09)	<0.001		
Never used e-cigarettes and friend smokers = most	6.32 (2.68 to 14.91)	<0.001		
Ever used e-cigarettes and friend smokers = most	8.75 (3.68–20.83)	<0.001		
Male	1.00			
Female	1.37 (1.01 to 1.86)	0.04		
Family smokers = none	1.00			
Family smokers = one	0.76 (0.51 to 1.14)	0.19		
Family smokers = two	2.02 (1.35 to 3.03)	<0.001		
Family smokers = three or more	1.87 (1.21 to 2.90)	0.005		
Intentions	0.70 (0.52 to 0.96)	0.03		
Attitudes	0.67 (0.44 to 1.01)	0.06		
Norms	0.91 (0.59 to 1.41)	0.69		
Perceived behavioural control	1.00 (0.73 to 1.37)	0.99		
Self-efficacy	1.09 (0.75 to 1.59)	0.65		
Free school meals	0.99 (0.96 to 1.02)	0.47		

Follow-up ever used cigarettes: model without covariates, AIC=1281.3; model with covariates, AIC=1226.5; model with covariates and interactions, AIC=1218.7; follow-up escalation of cigarette use: model without covariates, AIC=334.1; model with covariates, AIC=327.5.

smoked, but was significantly lower in those adolescents with stronger attitudes (not to smoke) and intentions (not to smoke). Exploration of moderation effects revealed that two interactions were statistically significant (attitudes, p=0.01; intentions, p=0.02), although decomposition of these effects did not reveal significant effects of e-cigarette use on escalation of cigarette use at different levels of either moderator (p>0.20). None of the other moderators approached statistical significance (p>0.16). Multiple imputation did not change any values or the analyses.

The ORs based on logistic regression analyses reported in table 4 may overestimate the degree of association between e-cigarette use and subsequent smoking because the prevalence of the outcome exceeds the usual 15% cut-off. To assess the degree of overestimation, we ran the initial models (model 1 in table 4) using a log binomial model. For the analyses of never smokers, the degree of association was reduced but remained statistically significant: incidence relative risk (IRR) was 3.85 (95% CI 3.07 to 4.82), p<0.001. For the analyses of smoking escalation, the degree of association was also reduced and no longer statistically significant: IRR=1.81 (95% CI 095 to 3.44), p=0.071.

DISCUSSION

We showed that ever use of e-cigarettes is associated with initiation of cigarette use; an effect that remains when controlling for various predictors of smoking. Our study in UK adolescents (13–14 years old) found patterns similar to those reported in longitudinal studies among adolescents aged 13–14 years and older[16–19] in the USA with comparable sized ORs (the IRR was also of a comparable magnitude). Together, these studies suggest that it is unlikely that the high rates of dual use of e-cigarette and cigarette use observed in the USA[5–7] and UK[8–15] in cross-sectional surveys of adolescents are entirely attributable to cigarette users subsequently taking up e-cigarettes. A significant minority of adolescents try e-cigarettes first (19.9% here) and later initiate cigarette use. Our findings also indicated that the association between ever use of e-cigarettes and initiation of cigarette use was particularly strong among adolescents with no friends who smoked, a group usually considered to be less susceptible to smoking initiation (see the study by Barrington-Trimis *et al*[16] for similar moderation effect among those with low intentions to smoke). In relation to escalation of cigarette use, the OR showed that ever use of e-cigarettes is associated with subsequent escalation, although this effect was attenuated when using the IRR or when controlling for covariates. However, given the limited numbers escalating their cigarette use in this study and lack of support in other studies, these findings should be treated cautiously (eg, other studies either did not find e-cigarette use to be related to change in frequency of smoking among baseline ever-smokers,[19] or found that baseline frequency of use of e-cigarettes was only associated with follow-up smoking frequency among baseline non-smokers and not among baseline infrequent or frequent smokers[29]).

Our research provides limited insights into the mechanism relating ever use of e-cigarettes to subsequent initiation and escalation of cigarette use. In principle, it is possible that e-cigarette use in adolescents is a marker for those who would have initiated or escalated cigarette use even if e-cigarettes had not been available. Among such adolescents, the availability of e-cigarettes may have simply delayed initiation or escalation. However, at least in relation to initiation, the fact that e-cigarette use was a bigger risk factor in groups considered least at risk (ie, no friends who smoke at baseline) argues against this (see the study by Barrington-Trimis *et al*[19] for a similar moderator effect also difficult to reconcile with this explanation). It is also plausible that the use of e-cigarettes might lead to initiation and escalation in cigarette use by normalising any kind of nicotine use, by developing nicotine addiction (if the e-cigarettes contain nicotine) or by developing friendship networks with smokers and decreasing the perceived risks of smoking.[30–32] However, there is no direct evidence yet to suggest that ever use of e-cigarettes normalises cigarette use.

Given the lack of clarity regarding the mechanism linking e-cigarette and cigarette use, we need to be cautious in making policy recommendations based on our findings. We acknowledge that since our survey, UK legislation has been put in place, including bans on marketing and selling e-cigarettes to minors. UK agencies are required to enforce age of sale, child and tamper proof packaging and display age of sale signage and health warnings on e-cigarette packaging. Nevertheless, our findings emphasise the value of regulating the marketing and sale of e-cigarettes to minors in countries without such measures, particularly given that e-cigarette advertising has been shown to reduce perceived harm of occasional smoking.[33]

Our study's strengths include a large demographically diverse sample, measurement of e-cigarette and cigarette use over 12 months, exploration of initiation and escalation of cigarette use, validation of smoking measures and exploration of covariates and moderators not previously examined. There are also weaknesses. First, our study had a relatively high attrition. This was principally attributable to problems in matching participants' personally generated anonymous codes, although attrition analyses indicated relatively modest biases in the final compared with initial sample. Second, like other similar studies, we focused on self-reported e-cigarette and cigarette use. Although we validated the self-reported smoking against an objective measure of CO, we did not have a way of validating e-cigarette use. Third, we failed to distinguish types of e-cigarette use (e-cigarettes vary in a number of ways, including the delivery method and whether they contain nicotine). Furthermore, our description of e-cigarettes and the timing of our survey might have restricted our study to first-generation devices, in which their nicotine delivery profile mimic less closely to cigarettes than do more recent generations.[34] Exploring relationships between use of new generations of e-cigarettes both containing nicotine or not and subsequent cigarette use is an important issue for further research. The current research focused on cigarette use, although other studies have reported similar effects with various tobacco products.[18]

A fourth limitation concerns our main analyses (table 4), which were restricted to ever use of e-cigarettes, and we were unable to test whether more regular use of e-cigarettes was more strongly associated with initiating or escalating cigarette use (see table 2; see the study by Warner[6] for cross-sectional data). Relatedly, our analyses of impacts on escalation should be treated cautiously given the limited numbers escalating cigarette use during the period studied and the fact that our findings conflict with published work.[19] Fifth, our research was restricted to a limited geographical area (two English counties), although it did extend findings from several US states. Sixth, our research focused on a limited age range (baseline: 13–14 years; most published studies[17–19] are with this age group). Future studies should explore effects in different aged adolescents and over varying time periods. Finally, our research could only consider a finite number of covariates and moderators, and it is plausible that important factors were omitted. Previous related studies[16–19] have examined various other factors (eg, sensation seeking, impulsivity, other substance use, delinquent behaviour, academic performance and race/ethnicity). It would be valuable to test these additional covariates and moderating variables in future work.

In summary, this is the first study to report longitudinal relationships between ever use of e-cigarettes and initiation or escalation of cigarette use among UK adolescents. Despite measuring and accounting for the influence of a broad range of variables in this and other studies,[16–19] it is possible that any third variables could have been responsible for the observed relationships. Therefore, while acknowledging that a causal relationship may be plausible, we cannot confirm this based on our findings and the trends observed over the same time period in the UK; rates of e-cigarette use have increased, but the rates of cigarette use have continued to decline. Future research could seek to disentangle these apparently contrary findings and assess dose–response relationships between e-cigarette and cigarette use over longer-time periods in a broader age range of adolescents while controlling for a range of covariates and assessing the impact of antismoking interventions.

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What this paper adds

Previous research: In cross-sectional surveys of UK adolescents, electronic cigarette (e-cigarette) use is increasing, cigarette use is decreasing and increasing numbers of adolescents report using both e-cigarettes and cigarettes. Several studies among US adolescents suggest that self-reported e-cigarette use is associated with subsequent initiation of cigarette use, whereas one study in US adolescents found no association between e-cigarette use and escalation of cigarette use. However, these studies were all conducted in the USA, did not validate their self-reported smoking measures against objective measures and assessed only a limited range of risk factors for smoking as covariates and moderators of these relationships.
Interpretation: Associations similar to those found in the previous studies are reported in a sample of UK adolescents and are validated against breath CO measures. Data collected over a 12-month period confirmed a sizeable relationship between ever use of e-cigarettes and subsequent initiation of cigarette use and showed that e-cigarette use is modestly associated with subsequent escalation of cigarette use. The former but not the latter relationship remained after controlling for various other risk factors for smoking (eg, intentions to smoke), only some of which had been assessed in previous studies. These findings support the robustness of the relationship between ever use of e-cigarettes and initiation of cigarette use but suggest the relationship between ever use of e-cigarettes and escalation of cigarette use may be explainable by other factors. Ever use of e-cigarettes was a stronger predictor of initiation of cigarette use in those with no friends who smoked at baseline compared with those with a few or most friends who smoked at baseline. The latter finding would not appear to be consistent with the suggestion that e-cigarette use may simply be a marker for those who would go on to smoke cigarettes even without having tried e-cigarettes.

review or approval of the manuscript; and the decision to submit the manuscript for publication. The authors thank the trial steering committee (Professor Amanda Amos, Dr Ian Cameron, Dr Christopher Gidlow and Dr Thomas Webb) for advice on measuring e-cigarette use. All available data can be obtained by contacting the corresponding author; the study team will retain exclusive use until the publication of major outputs. The authors of this article affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Contributors MC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: MC, SG, RL, CJA, CT, RW and KS . Acquisition, analysis or interpretation of data: MC, SG, RSE, KF, BSM, LC, RL, CJA, DM, CT, RW and KS . Drafting of the manuscript: MC and SG. Critical revision of the manuscript for important intellectual content: MC, SG, RL, CJA, DM, CT, RW and KS. Statistical analysis: RW and MC. Obtained funding: MC, SG, CJA, CT, RW and KS. Administrative, technical or material support: RS-E, KF, BSM and LC. Study supervision: MC, SG, RL and DM.

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A Federal Court has ordered Altria, R.J. Reynolds Tobacco, Lorillard, and Philip Morris USA to make these statements:

- Health effects of smoking
- Addictiveness of smoking and nicotine
- Low tar and light cigarettes being as harmful as regular cigarettes
- Designing cigarettes to enhance the delivery of nicotine
- Health effects of secondhand smoke
- *Para información en español, clic aquí*

Adverse Health Effects of Smoking

A Federal Court has ordered Altria, R.J. Reynolds Tobacco, Lorillard, and Philip Morris USA to make this statement about the health effects of smoking:

- Smoking kills, on average, 1,200 Americans. Every day.
- More people die every year from smoking than from murder, AIDS, suicide, drugs, car crashes, and alcohol, **combined**.
- Smoking causes heart disease, emphysema, acute myeloid leukemia, and cancer of the mouth, esophagus, larynx, lung, stomach, kidney, bladder, and pancreas.
- Smoking also causes reduced fertility, low birth weight in newborns, and cancer of the cervix.

Addictiveness of Smoking and Nicotine

A Federal Court has ordered Altria, R.J. Reynolds Tobacco, Lorillard, and Philip Morris USA to make this statement about the addictiveness of smoking and nicotine:

- Smoking is highly addictive. Nicotine is the addictive drug in tobacco.
- Cigarette companies intentionally designed cigarettes with enough nicotine to create and sustain addiction.
- It’s not easy to quit.
- When you smoke, the nicotine actually changes the brain – that’s why quitting is so hard.

Lack of Significant Health Benefit from Smoking "Low Tar," "Light," "Ultra Light," "Mild," and "Natural" Cigarettes

A Federal Court has ordered Altria, R.J. Reynolds Tobacco, Lorillard, and Philip Morris USA to make this statement about low tar and light cigarettes being as harmful as regular cigarettes:

- Many smokers switch to low tar and light cigarettes rather than quitting because they think low tar and light cigarettes are less harmful. They are **not**.
- "Low tar" and "light" cigarette smokers inhale essentially the same amount of tar and nicotine as they would from regular cigarettes.
- **All** cigarettes cause cancer, lung disease, heart attacks, and premature death – lights, low tar, ultra lights, and naturals. There is no safe cigarette.

Manipulation of Cigarette Design and Composition to Ensure Optimum Nicotine Delivery

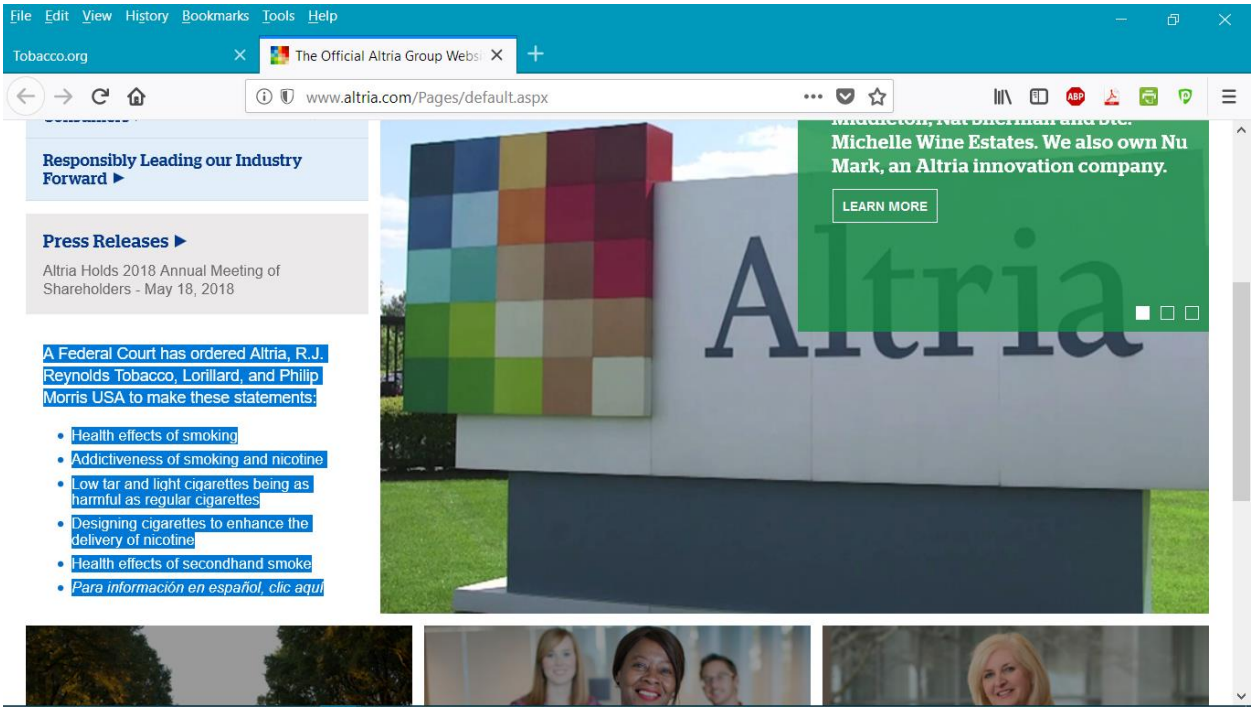
A Federal Court has ordered Altria, R.J. Reynolds Tobacco, Lorillard, and Philip Morris USA to make this statement about designing cigarettes to enhance the delivery of nicotine:

- Altria, R.J. Reynolds Tobacco, Lorillard, and Philip Morris USA intentionally designed cigarettes to make them more addictive.
- Cigarette companies control the impact and delivery of nicotine in many ways, including designing filters and selecting cigarette paper to maximize the ingestion of nicotine, adding ammonia to make the cigarette taste less harsh, and controlling the physical and chemical make-up of the tobacco blend.
- When you smoke, the nicotine actually changes the brain – that's why quitting is so hard.

Adverse Health Effects of Exposure to Second Hand Smoke

A Federal Court has ordered Altria, R.J. Reynolds Tobacco, Lorillard, and Philip Morris USA to make this statement about the health effects of secondhand smoke:

- Secondhand smoke kills over 38,000 Americans each year.
- Secondhand smoke causes lung cancer and coronary heart disease in adults who do **not** smoke.
- Children exposed to secondhand smoke are at an increased risk for sudden infant death syndrome (SIDS), acute respiratory infections, ear problems, severe asthma, and reduced lung function.
- There is no safe level of exposure to secondhand smoke.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