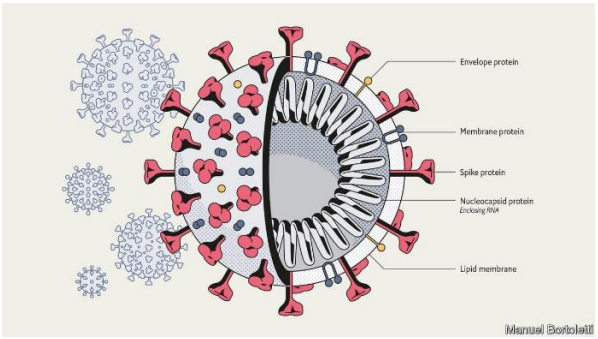
STOP the virus spread – BAN VAPING – BAN ENDs

Vapers intake then expel large volumes of PG/VG and harmful chemicals into their lungs and respiratory systems.
The expelled respiratory suspended particulate sidestream aerosols will include SARS-CoV-19 virus from infected people – many of whom are asymptomatic but highly infectious.
Vaping chemicals contain harmful ingredients which mutate when heated and cause lung, respiratory tract, bladder and immune system damage. Ban Vaping and ENDs.



SARS-CoV-2 is spread by infected droplets and from infected fomite surfaces reaching faces via hand contact. ENDs' users and smokers can touch handrails, chairs, door handles, taxi seats, desks etc on which infected droplets have landed. They then bring the electronic or combustible nicotine delivery systems to their mouths and transfer the virus into their bodies.

Transfer complete!

Group Urges Statewide Vaping Ban Amid Pandemic

spectrumlocalnews.com/nys/central-ny/ny-state-of-politics/2020/03/23/group-urges-statewide-vaping-ban-amid-pandemic

STATE OF POLITICS

By Nick Reisman New York State
PUBLISHED 7:05 AM ET Mar. 23, 2020

A statewide medical group on Sunday called for a complete ban on the sale of vaping products, arguing the use of e-cigarettes and similar devices will help spread coronavirus in New York.

The group, the New York State Academy of Family Physicians, urged Governor Andrew Cuomo to issue an executive order banning the sale of vaping products in New York during the crisis.

"As our state and country struggle to respond to the rapidly evolving and escalating COVID-19 pandemic affecting our residents and straining our healthcare system, mounting evidence demonstrates the link between tobacco use and increased risk for progressive COVID-19," said Dr. Barbara Keber, the group's president.

New York had already moved toward a ban on flavored vaping products amid health concerns that arose last year. State lawmakers were expected to take further action in the budget, which is due to be approved next week.

The group pointed to studies that found linkages between e-cigarette usage or smoking and the elevated risk of contracting the virus.

"People with decreased lung function caused by smoking or vaping are more likely to

develop serious complications caused by infections," Keber said.

"Now more than ever, it is critical for the State and medical community to take actions to prevent our youth from ever using these highly addictive deadly products and to help our patients to reduce their risks through FDA-approved cessation and telehealth during this pandemic."

Experts: Vaping Could Make Coronavirus Infection More Severe

futurism.com/neoscope/experts-vaping-could-make-coronavirus-infection-more-severe

Scientists say it's reasonable to assume that smoking or vaping could make COVID-19 symptoms more severe once infected, according to *Scientific American*.

To be clear, a direct link has yet to be investigated by researchers — but there's plenty of evidence that smoking or vaping suppress immune function in the lungs and trigger inflammation.

Scientists have also found that more severe COVID-19 cases were associated with chronic lung conditions — which in turn is linked to smokers and vapers as well. Some preliminary studies in China have found links between more severe COVID-19 cases and a history of smoking, but it's too early to draw conclusions as many of them still await peer review.

"All these things make me believe that we are going to have more severe cases—especially [in] people who are [long-term] smokers or vapers," said Melodi Pirzada, chief of pediatric pulmonology at NYU Winthrop Hospital on Long Island, to *Scientific American*.

"There's a very coordinated series of events that take place when you do become infected with a virus," associate professor of microbiology and immunology at the University of North Carolina Ray Pickles told *Scientific American*. "I think once you start perturbing this sequence of events in any which way or direction, that's when things can go awry."

Scientists have found plenty of evidence for smoking being a risk factor for influenza. The link to vaping, however, is definitely less clear on the matter. Mice studies have found a link between e-cigarette aerosol lowering the chances of surviving influenza A, a common influenza virus.

Health experts warn smoking, vaping could affect impact of coronavirus

wsbtv.com/news/georgia/health-experts-warn-smoking-vaping-could-affect-impact-coronavirus/NGBEPRROYNFFNESJAFCPKI6OUM

By: Samantha Manning Updated: March 24, 2020 - 8:09 PM

WASHINGTON — Health experts are warning that people who vape or smoke could face a greater threat than nonsmokers from the coronavirus.

“Because it attacks the lungs, the coronavirus that causes COVID-19 could be an especially serious threat to those who smoke tobacco or marijuana or who vape,” wrote Dr. Nora Volkow, with The National Institute on Drug Abuse.

“Thus far, deaths and serious illness from COVID-19 seem concentrated among those who are older and who have underlying health issues, such as diabetes, cancer, and respiratory conditions. It is therefore reasonable to be concerned that compromised lung function or lung disease related to smoking history, such as chronic obstructive pulmonary disease (COPD), could put people at risk for serious complications of COVID-19,” she wrote.

Anti-tobacco advocates are urging people to quit in the wake of the pandemic.

"The coronavirus is in fact a lung disease,” said Matthew Myers, president of the Campaign for Tobacco Free Kids. “Anything that weakens your lungs or immune system puts you at greater risk. If you get it, it makes it more likely you will get it more severely and have a harder time getting through it. If you're a smoker or a vaper, this is the time to quit."

The Centers for Disease Control and Prevention has not specifically placed smokers or vapers in the high-risk category for being seriously impacted by the coronavirus.

So far, it lists the elderly and people with underlying health conditions, which does include chronic lung disease.

Experts said there isn’t enough research or evidence right now to show whether there is a direct link between people who vape and people who get the coronavirus.

Research on the effects of smoking and vaping and the coronavirus is ongoing.

Vaping advocates blasted the suggestion that there might be a connection between vaping and the impact of the coronavirus.

“Even during a pandemic, activists and government bureaucrats are willing to risk their credibility by trying to tie nicotine vaping products to COVID-19,” said Gregory Conley, president of the American Vaping Association. “Lung injuries and deaths that occurred

last year were caused by illicit, contaminated THC products, not nicotine vaping products, so during this pandemic, it is important that cannabis consumers stay away from street-bought vape pens. However, adult smokers should not be scared away from using these smoke-free products by misplaced fears being pushed by those with no care or regard for adults desperately seeking to quit smoking."

Smokers At Higher Risk Of Severe COVID-19 During Coronavirus Outbreak

forbes.com/sites/victoriaforster/2020/03/23/smokers-at-higher-risk-of-severe--covid-19-during-coronavirus-outbreak

March 23, 2020

A leading expert has warned that smokers are likely at increased risk of more severe COVID-19, compared to non-smokers, suggesting that now would be a particularly good time to try and quit or cut down.

"There's not very much data at this point on COVID-19 in smokers, but we do know from reports from China, smokers seem to be over-represented in groups of people who have severe or critical COVID-19," said J. Taylor Hays, M.D. Director of the Nicotine Dependence center at Mayo Clinic in Rochester, Minnesota and Professor of Medicine, Mayo Clinic College of Medicine.

Increasing evidence is suggesting that smokers are at higher risk of severe COVID-19 than those who don't smoke. One study published in the *New England Journal of Medicine* in February looked at 1,099 patients in China with COVID-19, showing that of 173 patients who had severe symptoms, 16.9% of them were current smokers and 5.2% had previously smoked. Among the patients with less-severe symptoms, 11.8% were current smokers and 1.3% former smokers.

Today In: Healthcare

More worryingly, the study showed that in a group of patients that either needed mechanical ventilation, admission to an intensive care unit, or ultimately died, 25.5% were current smokers, which was more than twice the rate of current smokers in a group of patients that did not have these severe adverse outcomes.

"These observations about more severe illness in smokers vs people who have never smoked seems to parallel what is seen in respiratory viruses such as respiratory syncytial virus and seasonal influenza, where smokers tend to do worse than non-smokers," said Hays, also mentioning that no data is currently available on people who vape or use e-cigarettes. "We know that inhalation of combustible tobacco of any sort seems to be associated with more severe disease from respiratory viruses," he added.

Studying other coronavirus outbreaks provides further suggestions that smokers may fare worse with these types of viral infections than non-smokers. In a study of a small number of patients with Middle-East Respiratory Syndrome (MERS) in South Korea, patients who smoked were less likely to survive than those who did not. There was also some evidence that smokers had higher levels of a protein called DPP4, a receptor which allows the MERS coronavirus to enter cells in the lung, which could make their lung cells

more susceptible to attack from the virus. SARS-CoV2, the coronavirus responsible for the current outbreak, uses a different receptor to gain access to lung cells called ACE2. However, the news here isn't any better for smokers either.

"The ACE2 receptor is up-regulated in the respiratory cells of smokers. This might be a mechanism by which it is more likely to cause severe illness," said Hays.

There are also other, well-proven reasons for smokers to be concerned about their risk of severe or fatal COVID-19.

"There is a long history of smokers having more severe respiratory illness in general and this is for a few well-established reasons. They clear mucus less efficiently, the cilia which get infectious particles and secretions out of the lungs, work less efficiently. Smoking also causes inflammation in the airways, which is made worse with respiratory illnesses," said Hays.

So if you are reading this and you smoke or know someone who does, is it too late now to stop or cut down?

"People who quit for even a short time see an improvement in lung health quite quickly. For most smokers who don't already have serious lung injury, they will see immediate improvements in their health, and less opportunity for severe diseases including COVID-19," said Hays.

In 2015, the CDC reported that almost 7 out of 10 adult smokers wanted to try and quit, with over half of all of them trying to quit at least once in that year, but the large majority not succeeding. Is it likely that people will try to quit, and succeed, especially at such a stressful time for many?

"I understand people turn to things because it's a coping mechanism, especially at stressful times. I would say to them - try and flex other coping muscles, there is a real opportunity to break routines – even a short period of abstinence from smoking improves lung function," said Hays.

"People could look at this as an opportunity – a time of crisis is a time of opportunity. If you've been looking for an opportunity to quit, this is it," he added.

Victoria Forster
I am a postdoctoral research scientist focusing on childhood cancers and new, targeted cancer therapies. As a survivor of childhood leukemia myself, I am a determined

...

Coronavirus concerns: Smoking and vaping risk

turnto10.com/features/health-landing-page/coronavirus-concerns-smoking-and-vaping

People who smoke or vape are considered at high risk for complications of COVID-19, according to the Rhode Island Department of Health.

Dr. Doug Martin, who is a pulmonologist at Lifespan, said while it's no secret that there are health ramifications from smoking and vaping, including the potential to damage our lungs, that risk has increased amid the coronavirus pandemic.

"What I tell my patients about smoking is, unfortunately, when you smoke and you breathe this stuff into your nose and out into your lungs, you're delivering it throughout your body and in the blood stream, and so that's why we get all these different cancers and then the injury to the lung," Martin said.

In addition to the health department, Martin said there's evidence from China that it can worsen the illness.

"They took 78 patients that had it and they looked at people that got sicker versus people that didn't, and with the people that got sick, 27 percent of them had a history of smoking," Martin said.

Smoking and vaping, he said, impacts the integrity and immune function in the lungs.

He said everyone, including young adults, need to pay attention.

"There's an emerging concern that we've seen in the U.S., where there does look to be some younger people that are getting sicker with this coronavirus than you would expect," Martin said. "There are now a large number of anecdotal reports that at least a good number of these do have a vaping or smoking history."

Martin and other health officials continue to say that hand-washing and physical distancing are two easy ways to prevent the spread.

But he said we need our lungs to be healthy to help fight this respiratory illness.

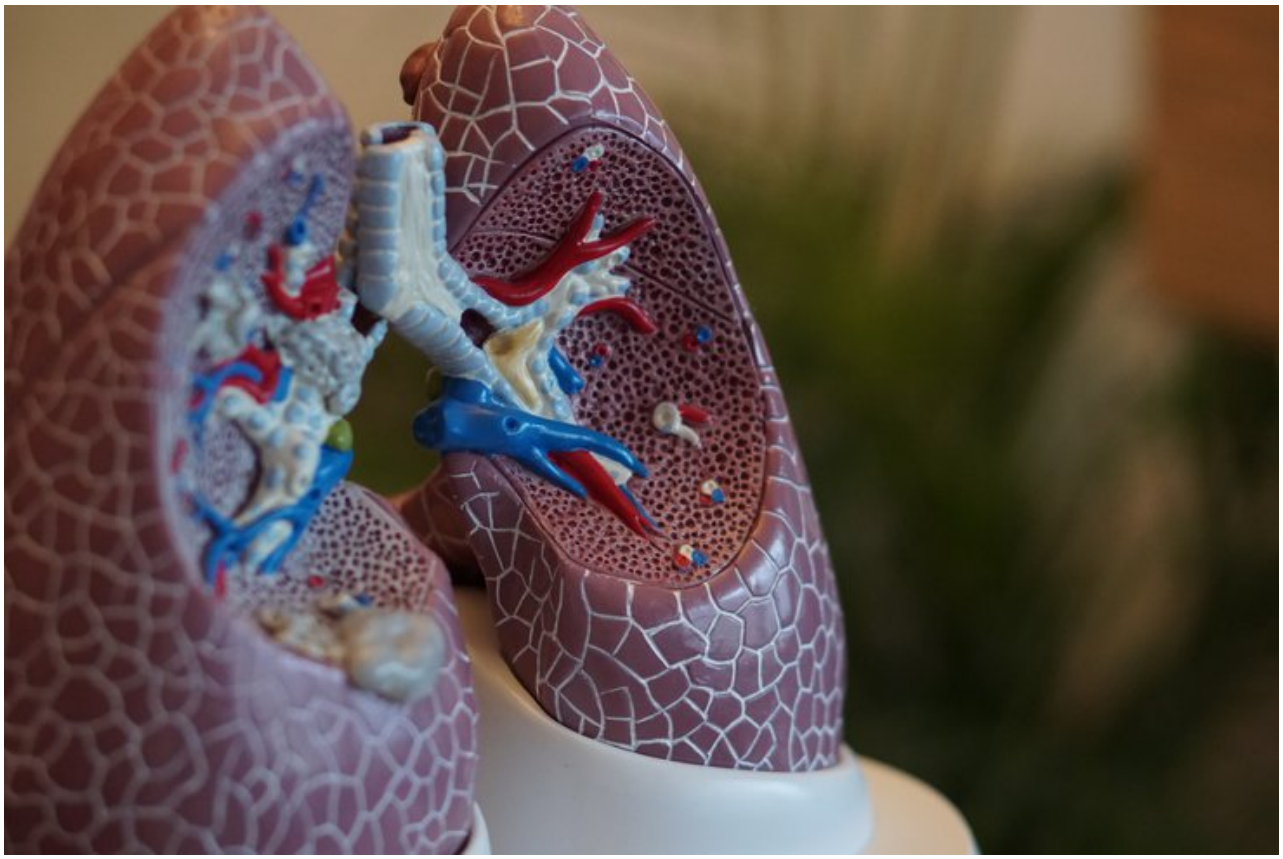
If you're looking to quit smoking or vaping, the American Heart Association has a list of resources.

Smokers are at greater risk of severe illness caused by COVID-19, researchers find

phillyvoice.com/coronavirus-smoking-risk-severe-complications-copd-covid-19

March 23, 2020

Illness Coronavirus



Smokers and people with lung diseases have a greater risk of developing severe coronavirus cases, according to research from China, where the COVID-19 pandemic originated. The virus attacks the lungs, making it particularly dangerous for people who smoke tobacco or marijuana, according to the National Institute on Drug Abuse.

As scientists compile more data on the ways COVID-19 affects the body, one thing has become clear: smokers and people living lung disease have a greater risk of developing severe illness.

Early studies out of China, where the coronavirus pandemic originated, show a higher fatality rate among people with respiratory disease. One study conducted by the Chinese Center for Disease Control found a 6.3% fatality rate among people with chronic respiratory disease compared to a 2.3% fatality rate among all patients infected with the virus.

- Digestive symptoms, diarrhea could be signs of coronavirus, Chinese study finds

Another study published in the Chinese Medical Journal found that smokers were 14 times more likely to have serious complications than nonsmokers.

Because the coronavirus attacks the lungs, it can be particularly dangerous for people who smoke tobacco or marijuana, or those who vape, according to the National Institute on Drug Abuse.

Smokers are already at greater risk for pneumonia – a complication related to COVID-19 – than the general population because the habit weakens the lung's ability to fight off infection. They are also more likely to develop chronic obstructive pulmonary disease, an umbrella term for various progressive lung diseases, including emphysema and chronic bronchitis.

A study published on the MedRxiv scientific study site helps connect the dots between smoking, COPD and COVID-19 complications.

Shortness of breath, a common characteristic of COPD and a coronavirus symptom, has been continuously linked to more severe coronavirus cases. While patients with shortness of breath were 3.7 times more likely to have severe COVID-19 than those without it, patients with COPD were 6.4 times more likely.

Vageesh Jain of University College London's Institute for Global Health, pooled data from seven smaller studies from China, analyzing data on more than 1,813 patients hospitalized with COVID-19. Those who suffered from shortness of breath, formally known as dyspnoea, tended to have more severe cases.

"Whilst dyspnoea was not a particularly common symptom in COVID-19 patients, its significant association with both severe disease and ICU admission may help clinicians discriminate between severe and non-severe COVID-19 cases," Jain said in a statement.

So what is the takeaway from all this data? Health experts are encouraging smokers to make quitting a priority. And they are urging people with lung disease to carefully monitor any changes to their health.

"It is vital to heed public health warnings on social distancing and avoiding public places when possible," The American Lung Association advises. "If you are at-risk, be attentive to any possible symptoms – fever, increased cough or shortness of breath from your baseline and be more communicative with your caregivers. Stay on your medication as directed and be careful to make sure you don't run out."

Locally, Trinity Health is instituting new measures to help smokers.

"Trinity Health has prioritized reducing tobacco use across our 22-state health system through a commitment to tobacco screening and referral connecting patients to cessation resources, and advocacy for anti-tobacco policies at the federal, state and local levels," Dr. Daniel Roth, chief clinical officer and Dr. Mouhanad Hammami, senior vice president of community health and well being, said in a statement.

The Philadelphia Department of Public Health also has resources at SmokeFreePhilly.

DPP4, the Middle East Respiratory Syndrome Coronavirus Receptor, is Upregulated in Lungs of Smokers and Chronic Obstructive Pulmonary Disease Patients

academic.oup.com/cid/article/66/1/45/4083573

Abstract

Background

Middle East respiratory syndrome coronavirus (MERS-CoV) causes pneumonia with a relatively high case fatality rate in humans. Smokers and chronic obstructive pulmonary disease (COPD) patients have been reported to be more susceptible to MERS-CoV infection. Here, we determined the expression of MERS-CoV receptor, dipeptidyl peptidase IV (DPP4), in lung tissues of smokers without airflow limitation and COPD patients in comparison to nonsmoking individuals (never-smokers).

Methods

DPP4 expression was measured in lung tissue of lung resection specimens of never-smokers, smokers without airflow limitation, COPD GOLD stage II patients and in lung explants of end-stage COPD patients. Both control subjects and COPD patients were well phenotyped and age-matched. The mRNA expression was determined using qRT-PCR and protein expression was quantified using immunohistochemistry.

Results

In smokers and subjects with COPD, both DPP4 mRNA and protein expression were significantly higher compared to never-smokers. Additionally, we found that both DPP4 mRNA and protein expression were inversely correlated with lung function and diffusing capacity parameters.

Conclusions

We provide evidence that DPP4 is upregulated in the lungs of smokers and COPD patients, which could partially explain why these individuals are more susceptible to MERS-CoV infection. These data also highlight a possible role of DPP4 in COPD pathogenesis.

Middle East Respiratory Syndrome coronavirus (MERS-CoV) is a newly emerging pathogen that mainly causes pneumonia with a relatively high case-fatality rate [1, 2]. Since 2012, ~1900 laboratory-confirmed cases have been reported to the World Health Organization (WHO) [2]. The majority of cases occurred in familial or hospital-related clusters through human-to-human transmission [3–5]. The clinical course of MERS-CoV

infection ranges from asymptomatic to acute respiratory distress syndrome with need for ventilatory support [3, 5–7]. To infect its host, MERS-CoV attaches to its receptor, an exopeptidase called dipeptidyl peptidase 4 (DPP4), also known as CD26 [8].

DPP4 is a type II transmembrane glycoprotein that is expressed in many cell types and organs in the body. It serves multiple functions among which post-translational cleavage of hormones and chemokines, T-cell activation, cell adhesion, and apoptosis [9–11]. In lungs, however, DPP4 is expressed at a minimum level [12], mainly in alveolar epithelial cells and endothelial cells, and to a lesser extent in bronchiolar epithelial cells, airway submucosal glands, alveolar macrophages, lymphocytes, and plasmacytoid dendritic cells [13–16]. Importantly, the alveolar epithelial cells are the main target for MERS-CoV [13, 17].

Several underlying comorbidities, including chronic lung diseases, have been reported to increase the risk of acquiring MERS-CoV infection [18]. Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic lung disease in older subjects and is currently the leading cause of death worldwide [19, 20]. The most common cause of COPD is chronic cigarette smoking. The inflammatory response to cigarette smoke results in an excessive release of chemokines and cytokines with a subsequent high influx of immune cells [20]. Because smoking has also been reported to increase susceptibility to MERS-CoV infection [18], we aimed to investigate the expression of the MERS-CoV receptor, DPP4, in a large well-phenotyped cohort of smokers, with and without airflow limitation, in comparison to age-matched individuals that never smoked (never-smokers).

METHODS

Human Lung Tissue Samples

Lung resection specimens were obtained from patients diagnosed with solitary pulmonary tumors at Ghent University Hospital (Ghent, Belgium) or from explant lungs from end-stage COPD patients (UZ Gasthuisberg, Leuven, Belgium). Based on preoperative spirometry, diffusion capacity tests and questionnaires, patients were categorized as never-smokers with normal lung function, smokers without airflow limitation or patients with COPD. COPD severity was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [19]. None of the patients were treated with neo-adjuvants chemotherapy. Lung tissue of patients diagnosed with solitary pulmonary tumor was obtained at a maximum distance from the pulmonary lesions and without signs of retro-obstructive pneumonia or tumor invasion and collected by a pathologist. Lung tissue of patients with COPD GOLD III-IV was obtained from lung explants of end-stage COPD patients undergoing lung transplantation. Written informed consent was obtained from all subjects. This study was approved by the medical ethical committees of the Ghent University Hospital (2011/114) and the University Hospital Gasthuisberg Leuven (S51577). Patient characteristics are listed in Table 1. Detailed patient characteristics per read-out are provided in

supplementary Tables S1 and S2.

Table 1.

Characteristics of study population (n = 117)

	Never-smokers	Smokers[a]	COPD II[b]	COPD III–-IV[c]
Number	21	32	37	27
Sex (M/F)	6/15[d]	23/9[d]	34/3[d]	12/14[d]
Age (years)	65 (58–71)	64.5 (55–71)	65 (58–69)	56.5 (54–60)[e,f,g]
Current- / ex-smoker	-	19/13[d]	24/13[d]	0/27[d]
Smoking history (PY)	0 (0–0)	33 (14–51)[e]	45 (40–60)[e,f]	30 (25–36)[e,g]
FEV_1 post (L)	2,4 (2,1–3)	2,7 (2,3–3,3)	2,1 (1,8–2,4)[e,f]	0,7 (0,5–1)[e,f,g]
FEV_1 post (% predicted)	103 (92–117)	95 (92–112)	69 (61–75)[e,f]	27 (21–33)[e,f,g]
FEV_1 / FVC post (%)	78 (74–83)	76 (72–79)	56 (51–61)[e,f]	30 (27–35)[e,f,g]
DLCO (% predicted)	88 (81–103)	83 (65–104)	67 (51–86)[e,f]	34 (32–37)[e,f,g]
KCO (% predicted)	95 (86–121)	93 (78–106)	85 (65–107)[e]	52 (46–59)[e,f,g]
ICS (yes/no)	1/19[d]	2/30[d]	16/21[d]	25/1[d]

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Human Proximal Bronchi Samples

Biopsy samples of proximal bronchi were obtained from 21 patients (17 male and 4 female) with moderate-to-severe COPD previously recruited for a separate study [21]. Inclusion criteria were the following: chronic productive cough, age between 40 and 70 years, current smokers, negative skin tests for inhalation allergens, FEV_1 < 70% of

predicted normal value or $FEV_1/VC < 0.70$, reversibility of $FEV_1 < 10\%$ pred after 750 μg terbutaline inhalation, and suffering from moderate-to-severe bronchial hyper-responsiveness, as determined by PC_{20} value upon challenge with histamine and methacholine. Exclusion criteria were a history of asthma, complaints of wheezing, recent respiratory tract infection, and recent or concurrent usage of anti-inflammatory drugs. Oral anti-inflammatory medication was discontinued for at least 3 months and inhaled glucocorticoids at least 6 weeks before the start of the study. Bronchoscopy was performed with an Olympus BF 1T10. At least 6 biopsies were taken from the bronchi of the right and the left upper and lower lobes using a fenestrated forceps (FB-18C or FB-20C). All was according to published guidelines [22]. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center Rotterdam, and written informed consent was obtained from all participants. Patient characteristics are listed in Table 2. Proximal bronchi biopsy samples of 16 healthy individuals (8 male and 8 female), previously described in the earlier study [23], were used as negative control.

Table 2.

Characteristics of the Patients in Which Proximal Bronchi Biopsy Samples Were Obtained

	Mean ± SD	Median	Range
Age, years	56.3 ± 8.9	60	42–46
Actual smoking, cigarettes/day	15.4 ± 7.4	13	6–30
Pack-years	25.3 ± 11.2	21	5–50
FEV_1, % predicted	62.5 ± 12.9	65	34–93
Reversibility, % predicted	5.3 ± 3.1	5	0–9.0
PC_{20}, mg/ml			
For histamine	1.7 ± 2.1	0.87	0.11–8
For methacholine	4.6 ± 5.5	1.72	0.6–17.4

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Table 3 provides an overview of the different cohorts and samples used in this study.

Table 3.

Overview of the Cohorts and Samples Used in This Study

Overview of cohorts and samples used

90 patients (21 never-smokers, 32 smokers without airflow limitation and 37 patients with COPD GOLD stage II) who underwent lobectomia or pneumectomia due to lung cancer.
•73/90 patients: samples for both qRT-PCR and IHC analyses. •5/90 patients: samples only for qRT-PCR analysis. •12/90 patients: samples only for IHC analysis.
27 patients with COPD GOLD stage III–IV who underwent lung transplantation due to end-stage COPD.
•14/27 patients: samples for qRT-PCR analysis. •13/27 patients: samples for IHC analysis.
37 patients who underwent bronchial biopsies.
•21/37 patients with moderate-to-severe COPD (ref): samples used for IHC staining. •16/37 control patients with airflow limitation (ref): samples used for IHC staining.

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Purification of Human Lung Dendritic Cell-subsets

Lung dendritic cells (DC) were isolated from single cell suspensions of lung tissue of 3 patients, as described previously [24]. Lung tissues were rinsed, cut into small fragments, and incubated in digestion medium. Next, the samples were resuspended in Ca2+ and Mg2+–free PBS containing 10 mM EDTA and passed through a 40 μm filter. Subsequently, pulmonary mononuclear cells were separated on a Ficoll density gradient. The cells were labeled with anti-CD3-FITC, anti-CD19-FITC, anti-CD207-PE, anti-CD209-PerCp-Cy5 and anti-BDCA2-APC and sorted on a FACSAria (BD Biosciences).

RNA Extraction and Real-Time Polymerase Chain Reaction Analysis

RNA extraction and polymerase chain reaction (PCR) analysis of lung tissue were performed as described previously [25]. RNA extraction from lung tissue blocks of 92 subjects (18 never-smokers, 26 smokers without airflow limitation, 34 patients with COPD GOLD II, 14 patients with COPD GOLD IV) was performed with the miRNeasy Mini kit (Qiagen, Hilden, Germany), following manufacturer's instructions. Next, complementary DNA (cDNA) was prepared with the iScript™ Advanced cDNA Synthesis Kit for RT-qPCR (Bio-Rad, Hercules, California). Taqman Gene Expression Assays (Applied Biosystems, Forster City, California) were used to measure the expression of DPP4 and the reference genes Glyceraldehyde-3-phosphate dehydrogenase (GAPDH), Hypoxanthine phosphoribosyltransferase-1 (HPRT-1) and Succinate Dehydrogenase

complex flavoprotein subunit A (SDHA). Data were analyzed using the standard curve method, and expression of DPP4 was calculated relative to the expression of the 3 reference genes, using the geNorm applet according to the guidelines and theoretical framework previously described [25, 26].

For human lung DC subsets, RNA extraction was performed with miRNeasy Mini kit (Qiagen, Hilden, Germany), whereas RNA amplification was with the Qiagen QuantiTect Whole Transcriptome kit, both following manufacturer's instructions. DPP4 expression in the DC subsets was calculated relative to the expression of GAPDH, HPRT1 and peptidylprolyl isomerase A (PPIA) as described previously [25].

DPP4 Immunohistochemistry and Analyses

Sections obtained from formalin-fixed paraffin-embedded lung tissue blocks of 98 subjects (19 never-smokers, 30 smokers without COPD, 36 subjects with COPD GOLD II, and 13 subjects with COPD GOLD III-IV) were incubated with anti-DPP4 antibody (polyclonal goat-anti-human, R&D Systems, AF1180) [15] after antigen retrieval with citrate buffer (Klinipath, Olen, Belgium). Next, slides were colored with diaminobenzidine (Dako, Carpinteria, California) and counterstained with Mayer's hematoxylin (Sigma-Aldrich, St-Louis, Missouri). The isotype control was goat immunoglobulin G (IgG) from R&D Systems (Abingdon, UK) (AB-108-C). To co-stain DPP4 with alveolar epithelial cells, anti-aquaporin 5 (Abcam, Cambridge, UK) (ab92320) and pro-surfactant C (Abcam) (ab90716) were used to detect, respectively, type I and type II alveolar cells and subsequently colored with Vector Blue (Vector, Peterborough, UK).

Quantitative scoring of the amount of DPP4-positive scoring in alveolar tissue and airway epithelium was performed using the Axiovision software (Zeiss, Oberkochen, Germany). In order to measure the area of DPP4-positive signal in alveolar tissue, 15 images of alveolar tissue were recorded from an average of 3 tissue blocks per patient. The intensity of brown staining we wished to score was selected by means of selecting specific hue, lightness, and saturation values. The hue, saturation, and lightness values were identical for all images, therefore restricting our scoring to a specific signal. In every image the alveolar tissue was selected and the DPP4-positive signal was calculated only within the alveolar tissue and normalized to the area of alveolar tissue present in each image. The final score of each patient was the average ratio of DPP4-positive signal of the 15 images. In the airway epithelium, the amount of DPP4 signal was normalized to the length of the basement membrane (Pbm). The final score of each patient was the average DPP4 staining in all airways present in all tissue blocks available of that patient. The number of airways per patient was between 3 and 20.

DPP4 detection in the frozen samples of proximal bronchi was performed with 1 μg/mL mouse anti-DPP4 monoclonal antibody (Santa Cruz Biotechnology, Dallas, Texas) [15], after previously fixed with acetone and incubated with 10% normal goat serum (Dako, Glostrup, Denmark) for 1 hour at room temperature. These slides were subsequently stained with biotinylated goat antimouse Ig serum (1:50 in PBS/BSA plus 10% human

serum) and with streptavidin alkaline phosphatase (1:50 in PBS/BSA plus 10% human serum; Biogenex, Klinipath, Duiven, The Netherlands) for 30 minutes each. A positive signal was revealed with New Fuchsin substrate (Chroma, Kongen, Germany). Counterstaining was performed with Gill's hematoxylin. Negative control staining was performed by the substitution of the primary monoclonal antibody with an isotype antibody.

Statistical Analysis

Statistical analysis was performed with Sigma Stat software (SPSS 23.0, Chicago, Illinois), using Kruskal-Wallis, Mann-Whitney *U*, Fisher exact test, and Spearman correlation analysis. In addition, one-way analysis of variance (ANOVA) and *T*-tests were used for statistical analyses of the DC subsets. Characteristics of the study population are presented as a median and interquartile range. Differences at *P*-values < .05 were considered to be significant (**P* < .05, ***P* < .01, and *** *P* < .001).

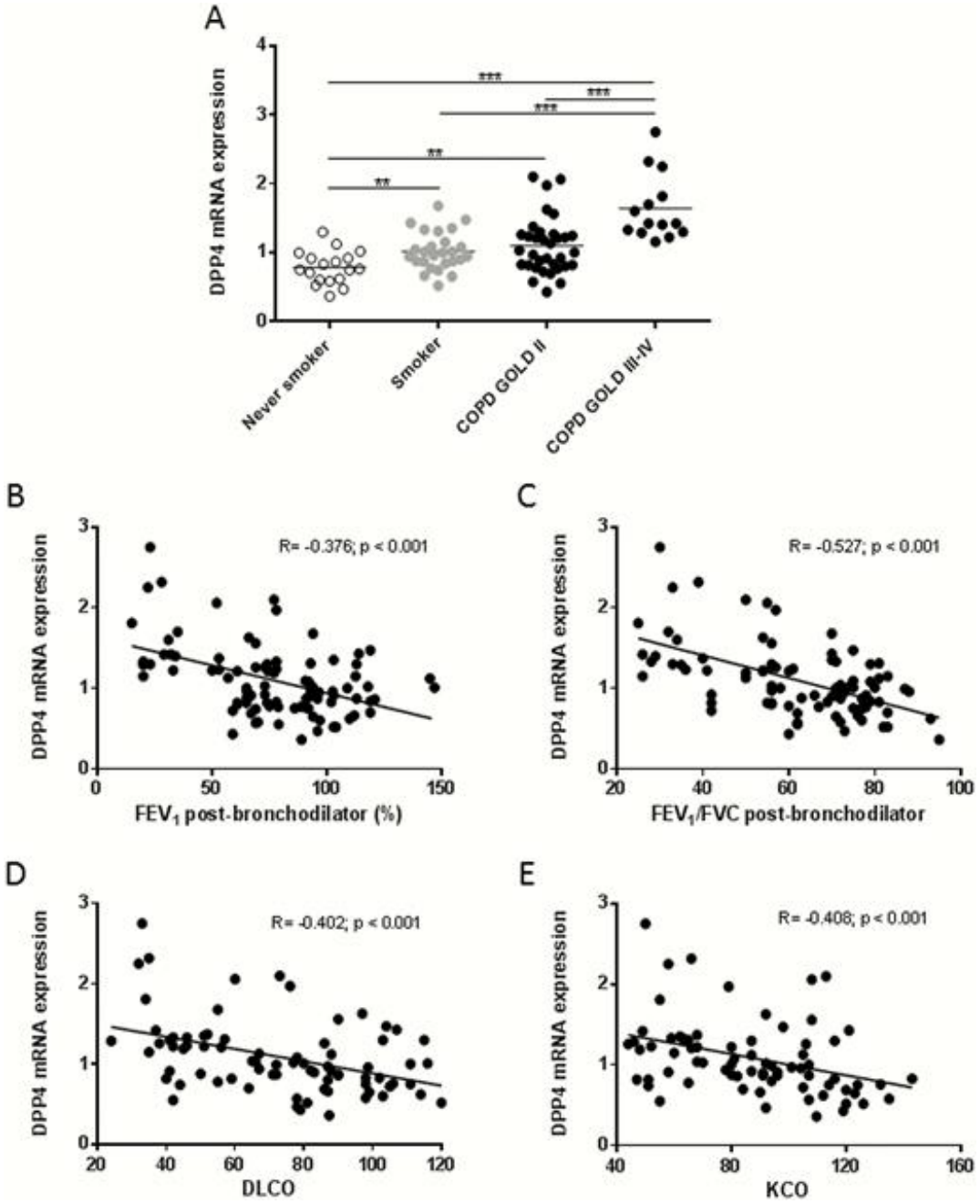
RESULTS

DPP4 mRNA Expression is Upregulated in Lungs of Smokers and COPD Patients

Messenger RNA (mRNA) expression of DPP4 was analyzed in lung tissue of 92 subjects. Lung tissue was derived from either resection tissue of lobectomy (never smokers, smokers without airflow limitation and patients with COPD GOLD stage II) or explant lungs of lung transplantation (patients with COPD GOLD stage III–IV). Patient characteristics are described in supplementary Table 1.

Compared to never-smokers, mRNA expression of DPP4 in lung tissue of smokers without airflow limitation and patients with COPD was significantly increased (Figure 1A). Moreover, DPP4 mRNA expression in lung tissue of patients with COPD GOLD stage III–IV was significantly higher than in lung tissue of smokers without airflow limitation and patients with COPD GOLD stage II (Figure 1A). Quantification according to smoking status (ex- vs. current smokers) is shown in Supplementary Figure S1. Furthermore, DPP4 mRNA expression was inversely correlated with the severity of airflow limitation: FEV_1 (R = −0.376, *P* < .001) and FEV_1/FVC ratio (R = −0.527, *P* < .001) (Figure 1B–C). In addition, the mRNA expression of DPP4 was also correlated inversely with the diffusing capacity of the lung, DLCO (R = −0.402, *P* < .001) and KCO (R = −0.408, *P* < .001) (Figure 1D–E). Linear regression analysis revealed that the association of DPP4 mRNA expression with the presence of COPD was significant even when corrected for age, sex, pack-years, and use of inhaled corticosteroids (Supplementary Table S3).

Figure 1.



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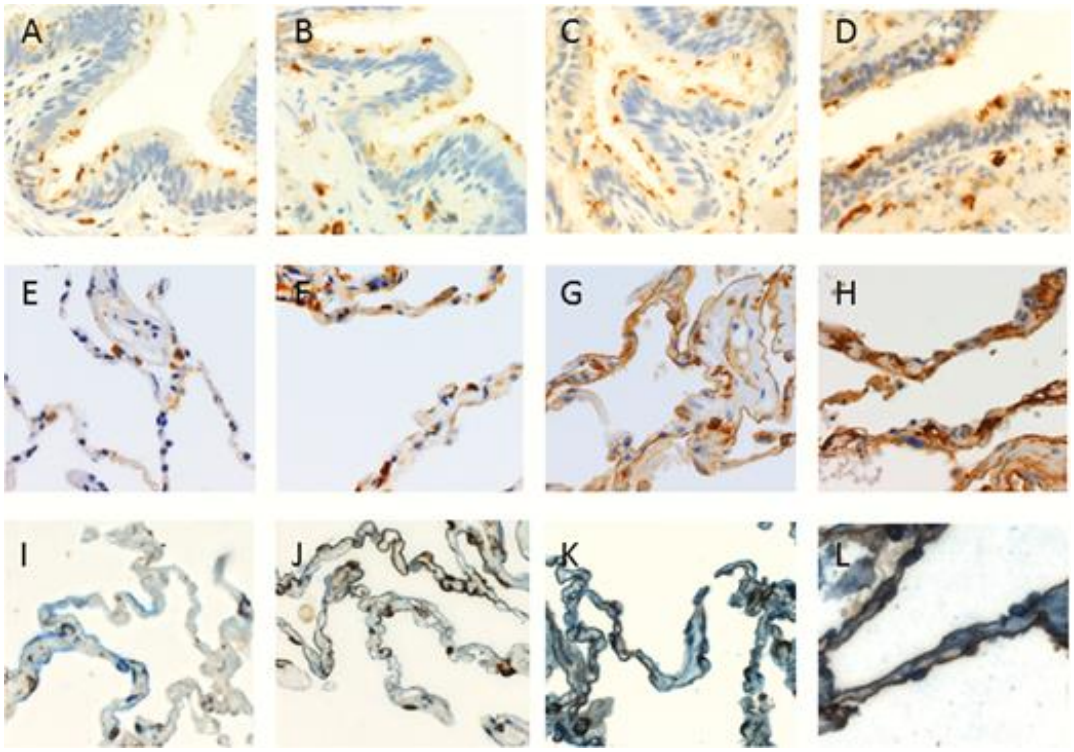
DPP4 mRNA expression in the lung tissues of smokers and COPD patients. *A*, DPP4 mRNA expression was measured by qRT-PCR and normalized to three reference genes (GAPDH, HPRT-1, SDHA). DPP4 mRNA expression in the lungs of smokers and COPD patients is significantly higher in comparison to that of never smokers. *B*, Correlation of DPP4 mRNA expression with post-bronchodilator FEV_1 values. *C*, Correlation of DPP4 mRNA expression with post-bronchodilator Tiffeneau index (FEV_1/FVC). *D*, Correlation of DPP4 mRNA expression with DLCO (diffusing capacity or transfer factor of the lung for carbon monoxide). *E*, Correlation of DPP4 mRNA expression with KCO (carbon monoxide transfer coefficient). $^{**}P < .01$, $^{***}P < .001$. Abbreviations: COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; FEV/FVC, forced expiratory volume in 1 second/forced vital capacity; GOLD, global initiative for obstructive lung disease; KCO, transfer of carbon monoxide coefficient; mRNA, messenger RNA; qRT-PCR, quantitative reverse-transcription polymerase chain reaction.

Additionally, because dendritic cells (DCs) play a crucial role in antiviral immunity, we investigated whether DPP4 mRNA expression differs between DC subsets. Three DC subsets were sorted: langerin-positive DCs, DC-SIGN-positive DCs, and plasmacytoid DCs (pDCs). DPP4 mRNA was merely detected in pDCs (Supplementary Figure S2).

DPP4 Protein Expression is Upregulated in Lungs of Smokers and COPD Patients

DPP4 protein expression was studied in lung tissue of never-smokers, smokers without airflow limitation, and COPD patients by using immunohistochemistry (IHC) staining. DPP4 was detected on the apical surface of bronchiolar epithelium and in the alveolar epithelial cells. In the alveoli, we observed that DPP4 protein was gradually increased from never-smokers to COPD GOLD stage III–IV (Figure 2). Additionally, we performed immunohistochemical staining of DPP4 with both aquaporin 5 (marker of type I alveolar epithelial cells) and pro-surfactant C (marker of type II alveolar epithelial cells), confirming that the upregulation of DPP4 protein can mainly be contributed to the alveolar epithelial cells (Figure 2I–L). In contrast, this increment was not observed in the bronchiolar epithelium (Figure 2A), as well as in the proximal bronchial epithelium (Figure 3). Furthermore, DPP4 was also detected in the endothelial cells, alveolar macrophages, immune cells in the submucosal region of airway epithelium, and lymphoid aggregates (Supplementary Figure S3). We further quantified DPP4 signals in the lung tissues of 98 subjects using the Axiovision software (Zeiss). Characteristics of these patients are presented in supplementary Table 2.

Figure 2.



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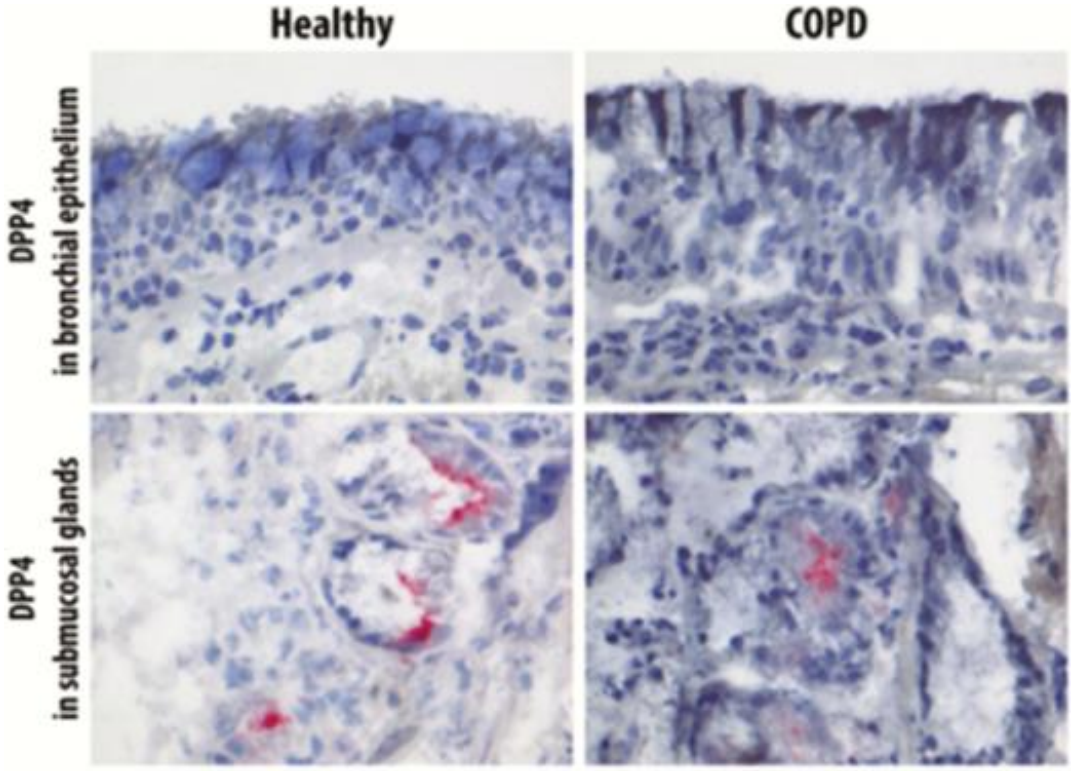
DPP4 protein expression in the bronchiolar epithelium and the alveolar tissues of never smoker, smoker, and COPD patients. Representative images of DPP4 staining in the bronchiolar epithelium (top row) and alveoli (middle and bottom row) of *A,E,I,* never-smoker, *B,F,J*, smoker without airflow limitation, *C,G,K*, subject with COPD GOLD stage II and *D,H,L*, subject with COPD GOLD stage III–IV. *I–-L*, are immunohistochemical stainings of DPP4 (brown) and aquaporin 5 (marker of type I alveolar epithelial cells) and pro-surfactant C (marker of type II alveolar epithelial cells) (both in blue). Co-staining of DPP4 with either one of the alveolar epithelial cell types results in a dark brown stain. DPP4 was mainly expressed in the alveolar epithelial cells and expressed the most intense in the COPD GOLD stage III–IV group. A 400× magnification was used for all photomicrographs in this figure. Abbreviation: COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease.

Figure 3.



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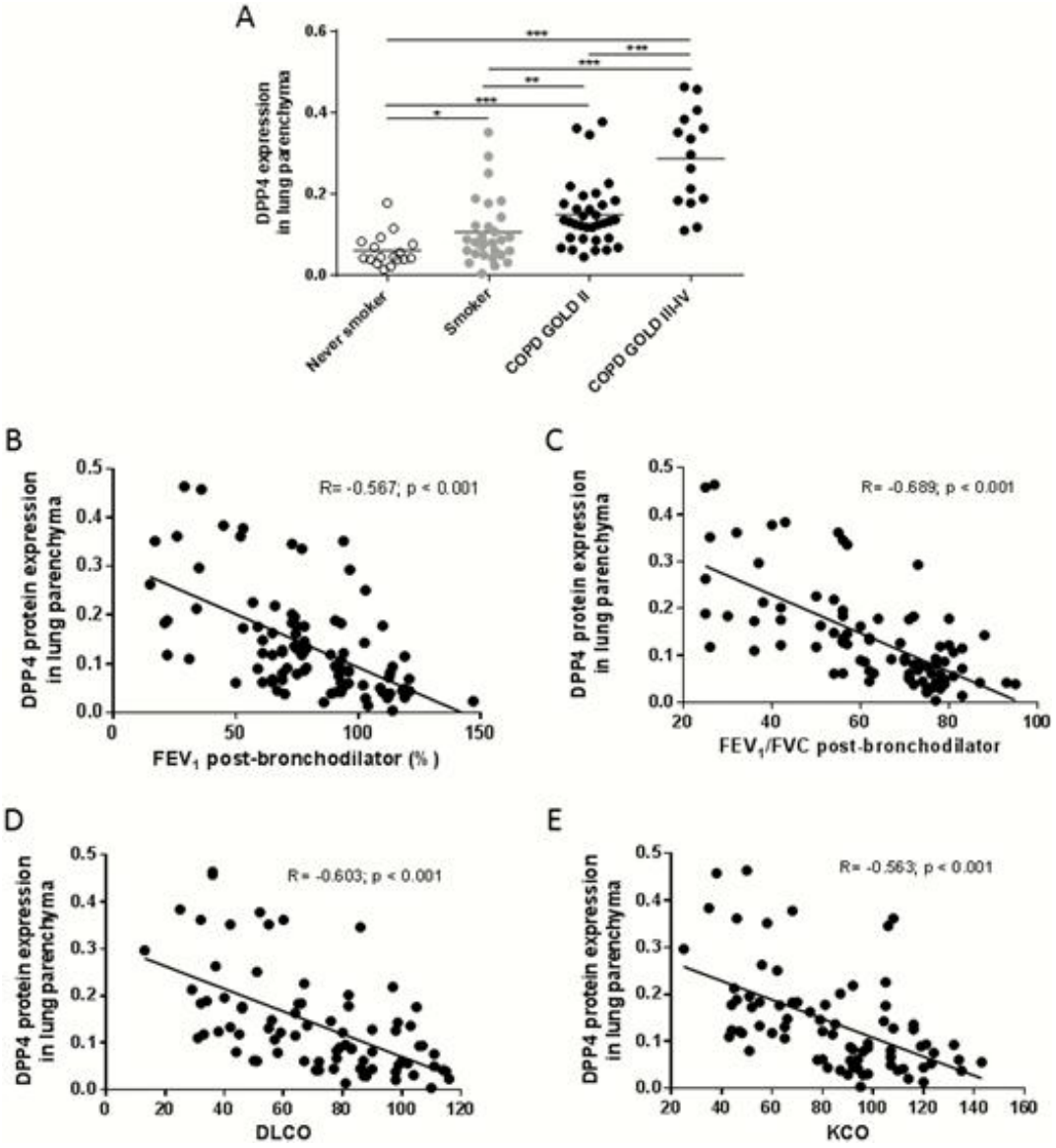
DPP4 staining in the proximal bronchi epithelium. Representative images of DPP4 staining in proximal bronchial epithelium and submucosal glands of the healthy control subject with COPD GOLD stage II. DPP4 was hardly detected in the apical surface of the proximal bronchi epithelium of both healthy control and COPD patients. Submucosal glands here served as positive control for DPP4 staining. Abbreviation: COPD, chronic obstructive pulmonary disease.

Compared to never-smokers, DPP4 protein expression was significantly increased in the alveolar epithelial cells of smokers and patients with COPD. DPP4 protein expression was the highest in patients with COPD GOLD stage III–IV (Figure 4A). Quantification of DPP4 protein expression according to smoking status (ex- vs. current smoking) is shown in

Supplementary Figure S4. Similar to DPP4 mRNA expression, DPP4 protein was also inversely correlated with lung function parameters FEV_1 (R = −0.567, $P < .001$) and FEV_1/FVC ratio (R = −0.689, $P < .001$); as well as diffusing capacity parameters DLCO (R = −0.603, $P < .001$) and KCO (R = −0.563, $P < .001$). Linear regression analysis revealed that the association of alveolar DPP4 expression with the presence of COPD was significant even when corrected for age, gender, pack-years, and use of inhaled corticosteroids (Supplementary Table S4).

Figure 4.



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DPP4 protein expression in the lung tissues of smokers and COPD patients. , DPP4 protein expression was analyzed by using Axiovision software (Zeiss). The area of DPP4 positive signal was normalized to the total area of cells present in each analyzed image. DPP4 protein expression in the lungs of smokers and COPD patients is significantly higher in comparison to that of never smokers. *B*, Correlation of alveolar DPP4 protein expression with post-bronchodilator FEV_1 values. *C*, Correlation of alveolar DPP4 protein expression with post-bronchodilator Tiffeneau index (FEV_1/FVC). *D*, Correlation of alveolar DPP4 protein expression with DLCO (diffusing capacity or transfer factor of the lung for carbon monoxide). *E*, Correlation of alveolar DPP4 protein expression with KCO (carbon monoxide transfer coefficient). $^{**}P < .01$, $^{***}P < .001$. Abbreviation: COPD, chronic obstructive pulmonary disease.

DISCUSSION

Our study investigated the expression of the MERS-CoV receptor, DPP4, in lung tissues of smokers without airflow limitation and COPD patients in comparison to never-smokers. As previously reported, DPP4 is mainly detected in the alveolar epithelial cells of the lungs, the main target of MERS-CoV infection [13, 15]. Among the dendritic cells, we found that DPP4 mRNA is mainly expressed in pDCs; confirming in vitro data showing that among the antigen presenting cells, pDCs produce large amounts of type I and III interferon upon contact with MERS-CoV [14]. Most importantly, we provide evidence that DPP4 is upregulated in the lungs, both at mRNA and protein level, not only in COPD patients but also in that of smokers. This indicates that these individuals may be more susceptible to MERS-CoV, supporting both smoking and COPD as risk factors for MERS-CoV infection [18]. These results are in line with a recent study describing a higher DPP4 expression in lungs of 4 COPD patients compared to 16 control subjects of different ages [13].

In this study, we did not find any evidence of DPP4 upregulation in the bronchial and bronchiolar epithelium in the lungs of smokers and COPD patients, suggesting that DPP4 upregulation in pulmonary epithelia is restricted to the alveolar epithelial cells. Previous studies have shown that DPP4 is limitedly expressed in the bronchial and bronchiolar epithelium, and even absent at the apical surface of the nasal respiratory and olfactory epithelium of humans [13, 15]. Future studies are needed to assess whether DPP4 upregulation is specific for the alveolar epithelial cells or also occurs in the upper respiratory tract epithelium. Additionally, the importance of alveolar macrophages in the pathogenesis of MERS-CoV needs further research as these cells also express DPP4 and patrol the alveoli while being in close contact with the alveolar epithelial cells.

It is currently unclear how DPP4 is upregulated in the lungs of smokers and COPD patients. Several cytokines have been reported to upregulate DPP4 in vitro. TGF-β2, for instance, could upregulate DPP4 protein expression and enzymatic activity in primary human endothelial cells [27], whereas interleukin (IL) 13 has been reported to increase DPP4 mRNA expression in human primary bronchial epithelial cells [28]. On the other hand, in COPD pathogenesis, several cytokines—such as IL-6, IL-8, and the TGF-β

superfamily—have been described to play important roles [29, 30]. Further studies are needed to identify cytokines that could both upregulate DPP4 in the lung and influence COPD pathogenesis.

We also showed that DPP4 mRNA and protein expression were inversely correlated with lung function and diffusing capacity parameters. These data suggest a possible role of DPP4 in COPD pathogenesis. DPP4 is an exopeptidase responsible for cleaving chemokines and this alters the biological function. Moreover, DPP4 is able to activate T cells and induce production of pro-inflammatory cytokines, which later could affect the development of COPD [20, 31–33]. Furthermore, DPP4 is also capable of influencing migration of immune cells by activating or deactivating chemokines in an inflammatory or tumor environment [10, 11]. Interestingly, soluble DPP4 in the serum of COPD patients has been reported to be significantly lower compared to that of non-COPD controls [34, 35]. It remains possible that in COPD patients, DPP4 concentration is low in the serum and high in the lungs to facilitate migration of certain immune cells into or out of the lungs.

Our study has several strengths; first, we included a large number of patients which have been thoroughly characterized. Second, to eliminate the possible interference of the presence of malignancy in our patients, we also included lung tissue derived from explant lungs of end-stage COPD patients, devoid of malignancy. A possible limitation of our study might be the sex imbalance in the groups with, respectively, a male predominance in the COPD groups and a female predominance in the never-smokers. However, it should be noted that linear regression analyses indicated that sex does not significantly contribute to the differences in expression of membrane-bound DPP4. Our data are in line with recent analyses of soluble DPP4 in serum in patients with COPD versus non-COPD controls indicating that there is no relationship between sex and DPP4 levels [35]. It is also important to acknowledge that there are other factors related to COPD that could contribute to the increased MERS-CoV susceptibility independent of DPP4. For instance, COPD patients are mostly in advanced age and more prone to many other pulmonary infections during hospitalization [36]. Besides that, COPD is associated with systemic inflammation, which might also cause insufficient host immune response against pathogens [20, 37].

In conclusion, because smoking is the most common etiology of COPD [19], our data highlight the association between chronic exposure to cigarette smoking and DPP4 upregulation in the lungs, as well as partially explain the increased susceptibility of smokers and COPD patients to MERS-CoV infection [18]. It is imperative to try replicating this observation in an animal model in order to further dissect the molecular pathway of DPP4 upregulation in the lungs.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgements. The authors thank Greet Barbier, Indra De Borle, Katleen De Saedeleer, Anouck Goethals, Marie-Rose Mouton, and Ann Neesen, from the laboratory for Translational Research in Obstructive Pulmonary Diseases, Department of Respiratory Medicine (Ghent University Hospital, Ghent, Belgium) for their excellent technical assistance. Furthermore, we thank Dr. Geert Van Pottelberge (Maatschap Longartsen Zeeuws-Vlaanderen / Dept. of Respiratory Medicine, ZorgSaam Ziekenhuis Zeeuws-Vlaanderen, Terneuzen, The Netherlands) for his contribution to the sorting of human DC and Prof. Bart Vanaudenaerde and Dr. Stijn Verleden (Department of Pneumology, Leuven) for providing us with the explant lungs of patients with severe chronic obstructive pulmonary disease.

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Potential conflicts of interest. W. J. reports grants from Boehringer Ingelheim, Astra Zeneca, Novartis, Chiesi, GSK, outside the submitted work; G. F. J. reports grants from AstraZeneca, grants from Boehringer Ingelheim, grants from Chiesi, grants from GlaxoSmithKline, grants and personal fees from Novartis, personal fees from Teva, outside the submitted work. All other authors have no reported disclosures. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Sci Rep

It is also important to safeguard your mental health, especially during times of physical distancing

Older people, and people with pre-existing conditions (such as heart diseases, diabetes, respiratory conditions) appear to be more susceptible to becoming severely ill with the virus.

Information note

COVID-19 and NCDs

World Health Organization

COVID-19

https://www.who.int/emergencies/diseases/novel-coronavirus-2019

NCDs and mental health

www.who.int/ncds
www.who.int/mental_health

COVID-19 and NCDs

For people living with or affected by non-communicable diseases:

- People of all ages can be infected by the new coronavirus (COVID-19).
- The risk of becoming severely ill with the virus appears to increase if you are 60+.
- People with pre-existing non-communicable diseases (NCDs) also appear to be more vulnerable to becoming severely ill with the virus. These NCDs include:
  - Cardiovascular disease (e.g. hypertension, persons who have had, or are at risk for, a heart attack or stroke)
  - Chronic respiratory disease (e.g. COPD)
  - Diabetes
  - Cancer.

Risk factors and conditions that make people more vulnerable to becoming severely ill with COVID-19:

- Smokers are likely to be more vulnerable to COVID-19 as the act of smoking means that fingers (and possibly contaminated cigarettes) are in contact with lips which increases the possibility of transmission of virus from hand to mouth. Smokers may also already have lung disease or reduced lung capacity which would greatly increase risk of serious illness.
- Smoking products such as water pipes often involve the sharing of mouth pieces and hoses, which could facilitate the transmission of COVID-19 in communal and social settings.
- Conditions that increases oxygen needs or reduces the ability of the body to use it properly will put patients at higher risk of the consequences of bilateral viral pneumonia.

Coronavirus disease (COVID-19) technical guidance: Patient management*

- **Understand the patient's co-morbid condition(s) to tailor the management of critical illness and appreciate the prognosis**
- **Communicate early with patient and family**

During intensive care management of COVID-19, determine which medications should be continued and which should be stopped temporarily. Communicate proactively with patients and families and provide support and prognostic information. Understand the patient's values and preferences regarding life-sustaining interventions.

A **healthy lifestyle** will make all bodily functions work better, including immunity. Eating healthy diets, with plenty of fruit and vegetables, keeping physically active, quitting smoking, limiting or avoiding alcohol intake, and getting enough sleep are key components of a healthy lifestyle.

Tips for people living with or affected by NCDs:

1. Continue to take your medication and follow medical advice
2. Secure a one month supply of your medication or longer if possible
3. Keep a distance of at least one metre from people with a cough, cold or flu
4. Wash your hands often with soap and water
5. Quit smoking and avoid using coping strategies involving alcohol or drugs
6. Safeguard your mental health

* See https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

World Health Organization

From: <fca_all@lists.fctc.org> on behalf of Bungon Ritthiphakdee via fca_all list <fca_all@lists.fctc.org>
Reply to: Rahipakdee Bungon <**bungon@seatca.org**>
Date: Wednesday, 25 March 2020 at 11:03 AM
To: "fca_all@lists.fctc.org" <fca_all@lists.fctc.org>
Subject: [fca_all] Alert Covid 19 and tobacco industry interference

Dear Colleagues:

Smokers infected with COVID-19 run the risk of developing severe disease, and are more likely to be admitted to an intensive care unit (ICU), need mechanical ventilation, or die. As the world stops for those of us who are anxious about smokers, it is business as usual for the tobacco industry.

The circumstances of the global health crisis provide a remarkable opportunity to urge smokers to quit outright, including quitting cold turkey. But the tobacco industry is downplaying the link between smoking and COVID-19 while promoting vaping or heated tobacco products, even when there is no evidence that these products are safe in the context of transmitting or acquiring COVID-19.

In various places, the tobacco industry is lobbying governments to ensure continuous delivery of its products during the lockdown; while in developing nations, it is offering donations to health ministries. The tobacco industry tactics during this time of COVID-19 are documented in a brief produced by the Global Center for Good Governance in Tobacco Control (GGTC), a partner of Stopping Tobacco Organizations and Products (STOP).

Please share this brief and urge your health ministry to seize this opportunity to save lives by **asking smokers to quit outright and finding ways to make the tobacco industry accountable for the harm caused by its products, including smoking-aggravated harms of COVID-19**. We need to remind governments that any partnership with the tobacco industry would undermine their capacity and credibility to protect their citizens and the planet from a scourge that kills 8M people a year (roughly 22,000 persons a day).

The tobacco industry must be held accountable for the harm caused by its products.

If you see incidents of the tobacco industry undermining quit smoking messages, promoting its products, or using CSR related to COVID-19 in your country, send us a tip here.

Thank you

Bungon

Ms Bungon Ritthiphakdee
Executive Director
Global Center for Good Governance in Tobacco Control
WHO FCTC Secretariat's Knowledge Hub on Article 5.3
School of Global Studies, Thammasat University, Thailand
Advisor and Founder | SEATCA

Global Center for Good Governance in Tobacco Control

COVID-19 AND TOBACCO INDUSTRY INTERFERENCE

GGTC BRIEF 2020 S1

I. Background

On February 14, 2020, the head of the WHO Health Emergencies Programme posited that smoking is a risk factor for the severity of any lower respiratory tract infection, and that the same would be expected in COVID-19, a respiratory disease.[1] To identify smokers as a potential vulnerable group for COVID-19, health experts have subsequently called for outright quitting of smoking in Indonesia (WHO),[2 3] Israel (Israeli Medical Association for Smoking Cessation and Prevention),[4] Japan (Tokyo Medical Association),[5] Ireland (Health Service Executive),[6] and South Africa (National Council Against Smoking [NCAS]).[7] To avoid COVID-19 transmission, some countries in the Eastern Mediterranean Region have banned the use of shisha in public places.[8]

On March 2, 2020, when the New York City mayor announced that smoking or vaping makes people "more vulnerable to suffer" with COVID-19 and encouraged individuals to quit;[9 10] authors/ publishers with links to Philip Morris International (PMI) or the PMI-funded Foundation for a Smoke-Free World (FSFW) actively challenged the same. They also reacted negatively[11 12] to an expert who warned against the dangers of vaping during the coronavirus outbreak by asserting that those inhaling the fumes produced by the cigarette substitute is equivalent to "someone spitting in your face."[13] On March 16, 2020, an article published by Reason, an organization with known links to PMI,[14 15] stated that the US Center for Disease Control and Prevention's (CDC) "scaremongering about e-cigarettes undermined its credibility on the eve of a true public health crisis (referring to COVID-19)."[16]

Scientists have opined that the "COVID-19 epidemic provides a 'teachable moment' in which smokers may be uniquely receptive to stop smoking advice" and that "it is plausible that a spike in quit rates could help reduce community transmission of SARS-CoV-2."[17] However, an analysis of the tobacco industry's public relations and social media responses reveals that it is utilizing the global COVID-19 crisis to promote "switching" (to heated tobacco)[18] or vaping;[19] and condemning those who call for outright quitting (see Annex 1).[20 21] To this end, it has even propagated the speculation that the "antiviral" and "antibacterial" properties of a vape ingredient could be beneficial to curb COVID-19 transmission.[22] It has also taken the opportunity to market its stocks,[23 24 25 26] ensure continuous availability of its products despite the lockdowns,[27 28] encourage stocking-up on vaping supplies/ novel tobacco products,[29 30] and even provide discounts for the same.[31] The

tobacco industry has also reportedly approached policymakers in low- and middle-income countries to offer so-called "donations", while at the same time, seeking favors to ensure continuous delivery of its products during the lockdown.[32]

II. Issue

The tobacco epidemic kills 8 million people annually.[33] Because of the tobacco industry's role in the epidemic, it is subject of a global treaty, the WHO Framework Convention on Tobacco Control (WHO FCTC),[34] with over 180 Parties. To date, it is the only industry that a treaty law requires to be strictly monitored.[35] Because of tobacco's adverse impacts on health, environment, and economy, the WHO FCTC is now embedded in the United Nations Sustainable Development Goals (UN SDGs), enshrining the tenet that good governance in public health involves treating tobacco companies differently from the rest of industry.[36]

While the COVID-19 crisis presents an opportunity to encourage the world's smokers to quit smoking outright, including quitting cold turkey, the tobacco industry is taking the opportunity to counter this by camouflaging the links between tobacco and COVID-19; and promoting vaping products or heated tobacco, even when there is no evidence that these products are safe in the context of transmitting or acquiring COVID-19.

While governments can seize the opportunity to save more lives than COVID-19 can take, the tobacco industry is poised to undermine governments' credibility and ability to do so by "partnering with" or "donating to" them in the guise of so-called "corporate social responsibility," and shifting public attention towards the use of vaping products and heated tobacco.

III. Recommendations

1. Use the COVID-19 crisis to urge smokers to quit outright

Smokers are more vulnerable to influenza as well as the corona virus that causes the Middle East Respiratory Syndrome (MERS). [37] [38] Once infected with COVID-19, smokers are likely to suffer more serious conditions [39] that could lead to premature deaths.

The disease progression of smokers with COVID-19 demonstrates what the adverse effects of smoking look like when there is no latency period. This makes the harms of smoking more real, and makes the urgency to quit more imminent. Quarantine and lockdown regulations instill an environment that fosters health and safety, leaving less room for harmful practices such as smoking. There is widespread concern over the under-capacity of healthcare systems and personnel to address COVID-19; and this provides further motivation to maintain healthy practices, especially to those who are concerned that treatment of smoking-related or smoking-aggravated diseases puts undue strains on healthcare systems.

Hence, a growing number of governments and health experts see the COVID-19 crisis as an opportunity to encourage over 1 billion smokers[40] in the world to quit smoking outright, in order to reduce the 8 million deaths annually.

COVID-19 and SMOKING

Smoking can increase your risk of developing severe disease
if you become infected with COVID-19.
--WHO Director General, March 20, 2020

A systematic review of evidence shows that based on limited data "smoking is most likely associated with the negative progression and adverse outcomes of COVID-19;" and based on the largest study, the authors calculated that "smokers were 1.4 times more likely ..to have severe symptoms of COVID-19 and approximately 2.4 times more likely to be admitted to an intensive care unit (ICU), need mechanical ventilation or die compared to non-smokers. [41] The paper also cited previous studies[42] [43] showing "that smokers are twice more likely than non-smokers to contract influenza and have more severe symptoms, while smokers were also noted to have higher mortality in the previous MERS-CoV outbreak."[44]

As to vaping and use of heated tobacco products (HTPs), while no evidence exists to directly link COVID-19 risks, there are also no studies that show the safety of vaping or use of HTPs in the context of COVID-19. Nevertheless, there is a study showing vaping-related damage to parts of the respiratory system (in terms of immune suppression and inflammatory response in nasal cells).[45]

2. Raise awareness about the tobacco industry and its tactics and reject its approaches

As part of treaty obligations, WHO FCTC Parties are required to encourage quitting and to protect their respective tobacco control measures from the commercial and vested interests of the tobacco industry (Article 5.3); and the Guidelines for the Implementation of Article 5.3 recommend that Parties raise awareness about tobacco industry tactics. Tobacco companies must be monitored and their tactics exposed in accordance with treaty guidelines[46] because their corporate behavior resulted in the tobacco epidemic that kills 8 million people annually,[47] Hence, partnerships with the tobacco industry could erode governments' credibility in upholding public health and in delivering anti-smoking messages in the time of COVID-19.

COVID-19 also highlights the affliction caused by tobacco products to society, and provides a sharp contrast to tobacco companies' claims of being "partners in development." Yet, the tobacco industry, despite its claims of having "transformed and committed to make smokers quit," downplays the role of smoking in COVID-19, questions those calling for outright quitting of smoking, and paves the way to promote the use of novel tobacco and nicotine products (i.e., vaping devices and heated tobacco products).[48] Further, tobacco companies' messages to investors reveal the industry strategy to further grow alternative addictive products in order to offset investment declines.[49] [50] Finally, the tobacco industry uses "public relations" activities such as "partnerships" and "donations" to enhance its corporate image to enable itself to better market its addictive products including in a manner that attracts children.[51]

3. *Hold the tobacco industry accountable for harms and deaths suffered by smokers including those suffering from COVID-19*

The COVID-19 pandemic magnifies the liability of the tobacco industry in inducing smokers to use its addictive products. The science linking the health harms, including respiratory damage, to tobacco products is robust;[52] but the tobacco industry has yet to be made accountable for the global scourge.

Tobacco manufacturers can be made accountable for harms suffered and deaths caused by its products and/or its behavior; based on either consumer / product liability laws, or equity and justice provisions in laws that exist in many countries. WHO FCTC Article 19 encourages Parties to strengthen legal and court procedures to facilitate lawsuits against the tobacco industry, while establishing mechanisms for international cooperation. Governments must take the opportunity to exhaust means to recover healthcare costs of tobacco-related harms from large tobacco manufacturers[53] (e.g., cases filed in Canada,[54] Nigeria,[55] South Korea,[56] and United States[57]); and explore other means to make them accountable, including by imposing taxes and surcharges to compensate victims and governments for the massive harms caused.

ANNEX 1: TOBACCO INDUSTRY-BACKED ARTICLES IN RELATION TO COVID-19

Publisher/ Date	Author/ Title	Tobacco Links	Messages relating to COVID-19
Filter Magazine March 17, 2020	Helen Redmond A Scientist Persuaded Italy to Exempt Vape Shops from COVID-19 Lockdown[58]	Filter magazine received funds from FSFW.[59] Dr. Riccardo Polosa who was interviewed for the article, is founder of the Center of Excellence for the Acceleration of Harm Reduction in Catania, Italy, which is funded by FSFW.	Convinced the Ministry of Health and the prime minister of Italy to open vape shops after Dr. Polosa said that a number of vapers would return back to smoking after switching to vape, if vape shops are closed. Furthermore, Dr. Polosa justified that due to stress caused by COVID-19, people will smoke at their homes, and if there are no available vape shops open, children will be at risk when exposed to cigarette smoke. Explained how the vaping industry was mobilized to lobby the prime minister of Italy to keep vape shops open amid a lockdown due to COVID-19.
Filter Magazine, March 10, 2020	McGrady, M. COVID-19 and Tobacco Harm Reduction: What's the Relationship?[60]	Authors declared receiving grants from FSFW. Spokesperson Marewa Glover's links to FSFW was also disclosed.[61] Filter magazine received funds from FSFW.[62]	Concedes the fact that the "general rate of infection from respiratory viruses is higher among smokers" but questioned authorities' statements[63] urging the public to stop smoking and vaping. Highlighted the speculation that large-scale switching (to vaping) would significantly mitigate against future respiratory viruses, utilizing a fallacious argument anchored on tobacco control researchers' theoretical example.[64] Posited that smokers' susceptibility to COVID-19 is an opportunity to encourage switching to "vape" (instead of just quitting smoking).[65]
E-cigarette Research Blog March 9, 2020	Farsalinos, K. Smoking, vaping and the coronavirus (COVID-19) epidemic: Rumors vs. evidence[66]	E-cigarette Research website is linked to Konstantino Farsalinos who is a cardiologist and researcher at the Onassis Cardiac Surgery Center, University of Patras, which is a grantee of FSFW.[67] [68]	Pointed to the evidence linking smoking and COVID-19 disease progression as being "weak and inconclusive," while the vaping link to COVID-19 as being non-existent; highlighted the possibility that e-cigarette liquid's main ingredient (propylene glycol) might have some beneficial "anti-bacterial" effects. Failed to mention evidence on potential harms of inhaled propylene glycol,[69] and encouraged

Publisher/ Date	Author/ Title	Tobacco Links	Messages relating to COVID-19
			inclusion of propylene glycol nebulizing as part of clinical trials.[70]
Vice Media March 5, 2020	Hicks, J. Coronavirus Attacks the Lungs. Here's What That Means for Smokers and Vapers[71]	Vice Media received funds from PMI to create content in 2016.[72] [73] [74] Ties between author and tobacco industry were not found.	Provided facts on the link between smoking and vaping but downplayed the risk factors (of smoking/ vaping) that contribute to respiratory vulnerability by suggesting that smokers and vapers just do what others do—wash hands and cough into elbows—without mentioning the importance of quitting smoking.
Metronome March 2, 2020	Scientific research - Coronavirus mostly affects non-smokers [75]	Metronome is a digital media outlet in Georgia. No further information on tobacco industry link was found. Author not named.	Claimed that the virus is affecting mostly non-smokers and promoted the "benefits" of smoking[76] by utilizing a February 17, 2020 study of 140 Wuhan COVID-19 patients in one hospital, where only 2 were smokers.[77]
Politico February 15, 2020	Owermohle, S. Could tobacco cure coronavirus? Don't laugh.[78] [79]	Politico previously received funds from PMI for advertisements.[80] [81] Ties between author and tobacco industry were not found.	Reported on Reynolds American's ongoing research about a potential cure for COVID-19 by genetically manipulating tobacco plants.[82] [83] (Notably, this news was reported in other media outlets, likely a "press release" from the company.)
American Council on Science and Health (ACSH) January 24, 2020	Alex Berezow WHO Damages Its Reputation On Vaping, Coronavirus	ACSH received funds from BAT, PMI, and Reynolds[84]	Used UK's critique of WHO's "anti-vaping" position as basis to question WHO's credibility as an institution in light of its restraint from calling the then "novel coronavirus" a public health emergency.

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[5] Sakuta M (15 March 2020). "[fca_all] Document Industry Manipulation by COVID19." Email message to fca_all@lists.fctc.org.

[6] Health Service Executive (15 March 2020). At-risk groups and coronavirus. Retrieved from https://www2.hse.ie/conditions/coronavirus/at-risk-groups.html (accessed on 20 March 2020). – "*Announced 4 countermeasures to prevent the spread of COVID-19: (1) If you feel ill, rest at home and do not overexert yourself. (2) If you are worried about infection, consult your doctor by telephone. (3) Smokers should quit smoking. (4) Consider the secondary harm for elderly people in nursing care…Health Service Executive in Ireland emphasized that smoking increases the risk of getting acute respiratory infection; greater risk of infection lasting longer; and, greater risk of infection being more serious than non-smokers. Smoking affects the immune system and lung tissue which leads to serious infection particularly when a smoker acquires COVID-19.*"

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[11] *See*, e.g., tweet of BAT Belgium (@BE_BAT_official) on 17 March 2020.

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[50] Supra note 26. – *While BAT takes pride in stating that the "business is resilient and supported by a geographically diversified supply chain from both a manufacturing and distribution standpoint," and that it has seen "no material impact" on its products, even during the COVID-19 situation.*
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[61] Ibid. – *"The author is a recipient of Tobacco Harm Reduction Scholarship from Knowledge-Action-Change (KAC), independently administered by KAC and supported by a grant from the Foundation for a Smoke-Free World (FSFW). Dr. Marewa Glover's Centre of Research Excellence: Indigenous Sovereignty & Smoking, has also received grants from FSFW. The Influence Foundation which operates Filter, has received restricted and unrestricted grants, respectively, from KAC and FSFW."*
[62] Supra note 59. – *"Now, the Foundation is similarly funding media outlets, with $190,000 allocated to Filter Magazine for 'feature-length pieces, short pieces and original videos.'"*
[63] Supra note 20. – *"Current use of e-cigarettes appears to be an independent risk factor for respiratory disease in addition to all combustible tobacco smoking… high prevalence of dual use, which is associated with increased risk beyond combustible tobacco use. – Bhatta, D. and Glantz, S."…"Dr. Alex Wodak, an addiction medicine physician, prominent drug policy reform advocate and board member of the Australian Tobacco Harm Reduction Association, raised this question in a February 27 email to colleagues…we are in 'uncharted territory' when it comes to determining any efficacy of tobacco harm reduction in curtailing COVID-19. He pointed out that public health authorities in a number of countries are recommending that people refrain from smoking to reduce their risks of infection, 'Although of course that's not proven yet.'"*
[64] Bhatta D & Glantz S (2019). Association of E-Cigarette Use with Respiratory Disease among Adults: A Longitudinal Analysis. American Journal of Preventive Medicine. Vol. 58, Issue 2, pp. 182-190. Retrieved from https://www.ajpmonline.org/article/S0749-3797(19)30391-5/fulltext (accessed on 20 March 2020). – *The author based its argument on Bhatta & Glantz's article that mentions a theoretical reduced risk of respiratory infections for vapers vis-a-vis smokers, when this was mentioned in the context of challenging the value of the alleged theoretical risk reduction due to dual use (use of both vaping devices and cigarettes)—not to prove the matter. "Conclusions: Use of e-cigarettes is an independent risk factor for respiratory disease in addition to combustible tobacco smoking. Dual use, the most common use pattern, is riskier than using either product alone."*
[65] Supra note 20. – *"The fast-developing situation with COVID-19 requires public health authorities to make decisions without the benefit of substantial evidence, but balanced communications are essential. The far more predictable health harms of smoking continue to contrast with the substantial relative benefits of switching to risk-reduced nicotine products (of which some, such as oral snus, have no known respiratory impact). If that key message—already denied by the WHO and many others—were to be further obscured by stop-vaping calls amid the COVID-19 crisis, there's every likelihood that it will further exacerbate the harms of this outbreak."*
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[70] Supra note 22.
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[81] Supra note 59. – "*The tobacco industry has a history of co-opting media outlets in order to disseminate industry-favourable messages. In 2018 and 2019, PMI funded Filter Magazine, Politico and Vice Media.*"
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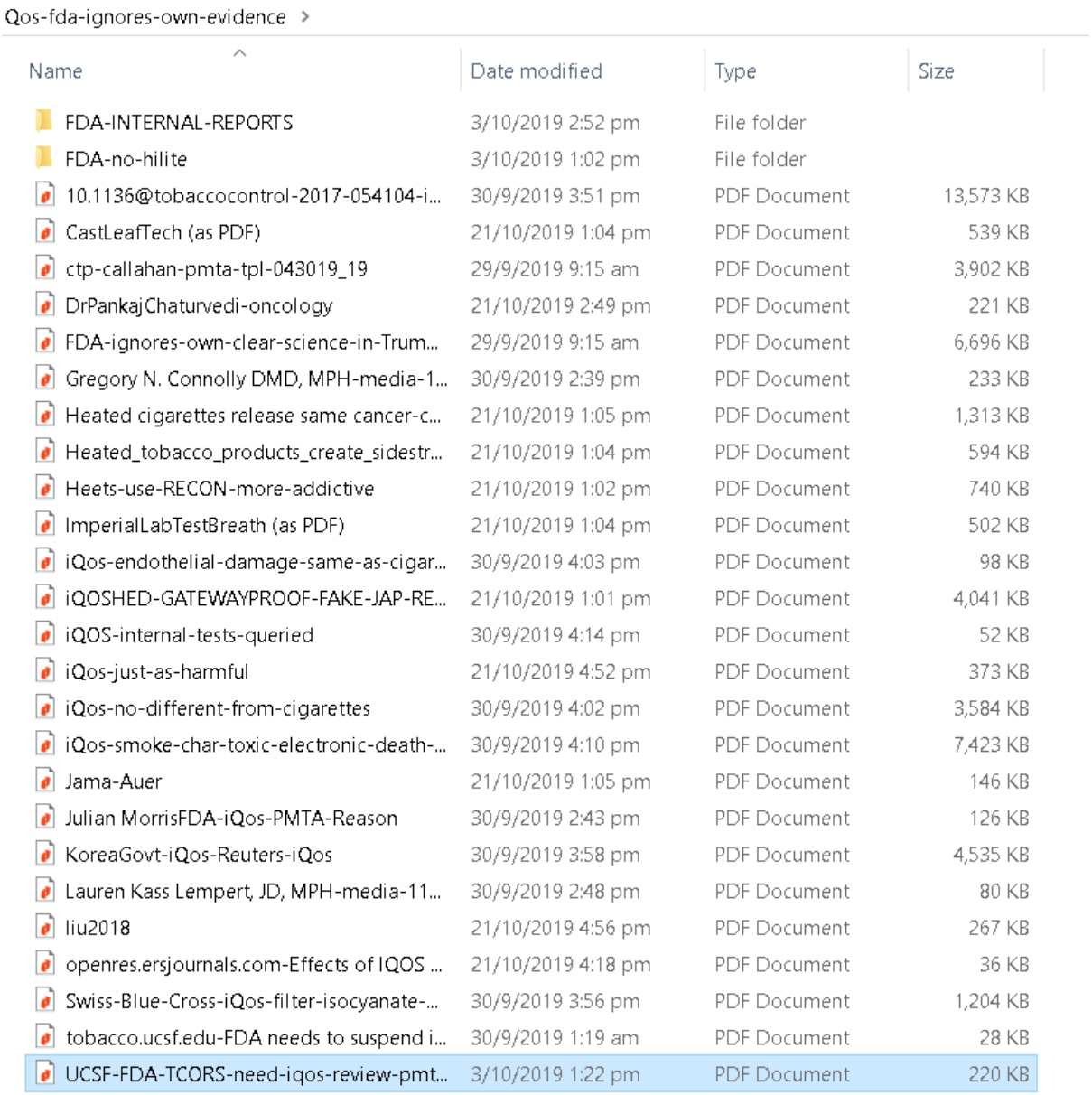
Read the FDA's Internal Test Reports which clearly show the dangers of HNB

https://www.dropbox.com/sh/5v2am1bknyd1tl4/AADBX4TKU3ykBDqEH5vlqtvfa?dl=0

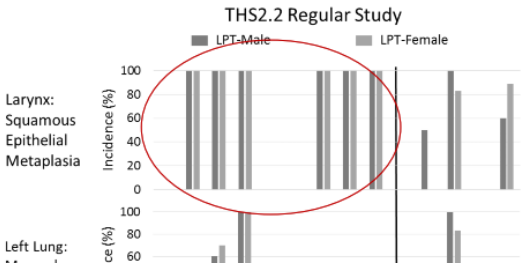


Snapshot of data shown in FDA's own in house testing of iQos

The MLA study reports did ***not*** contain information about clastogenicity, or the capacity to cause damage to chromosomes.

Also, while the MLA study, which is an in vitro test, indicates that *HeatStick* aerosols ***are*** mutagenic, there was no in vivo mutagenicity information which could have further clarified the mutagenic potential of the products.

For squamous metaplasia, a potentially precancerous lesion, the response produced in the larynx by *HeatStick* aerosols was similar to that of the reference cigarette smoke after the 90-day exposure period.



RODENT CARCINOGENICITY STUDY

FDA

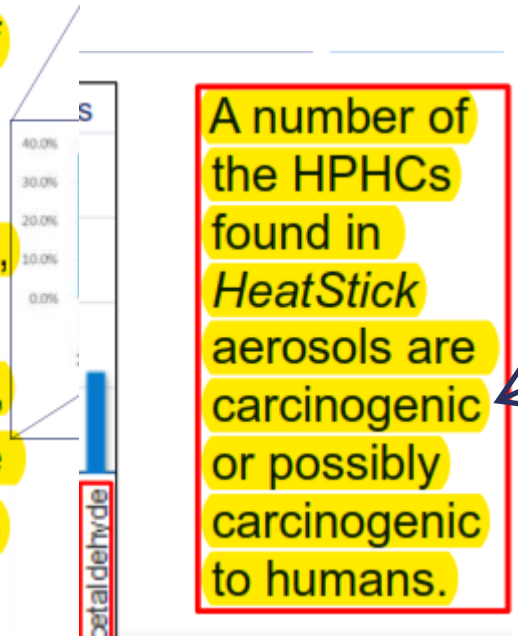
Preliminary data indicate that after 10 months of exposure, neoplastic lesions (e.g., bronchioloalveolar adenoma) were found in the lungs of female mice exposed to reference cigarette smoke and *HeatStick* aerosols.

- The study with male mice was terminated at 15 months due to a high number of deaths

Sham 3R4F THS2.2 Low THS2.2 Med THS2.2 High

- *HeatStick* aerosols demonstrated potential toxicity under the conditions tested by the applicant, but the adverse effects were generally fewer and less severe than what was observed with reference cigarette smoke.
- When *HeatStick* aerosols induced toxicity in the in vitro and in vivo studies, toxicity occurred at higher concentrations compared to reference cigarette smoke.
- *HeatStick* aerosols did not produce any additional adverse effects beyond those observed in test groups exposed to reference cigarette smoke.
- Based on the studies submitted, however, it is unclear if the effects observed in treatment groups exposed to *HeatStick* aerosols translate to a potential risk reduction for noncancer-related effects when chronically used by humans.

smoke. However, consuming 10 *HeatSticks* exposes users to levels of mercury, ammonia, acrylamide, butyraldehyde, acetamide, pyridine, formaldehyde, catechol, propylene oxide, and acetaldehyde that are comparable to smoking 1-3 reference cigarettes.



A number of the HPHCs found in *HeatStick* aerosols are carcinogenic or possibly carcinogenic to humans.

The applicant has recently submitted data identifying at least 12 possibly carcinogenic or genotoxic chemicals that are found at higher levels in *HeatStick* aerosols than in reference cigarette smoke.

- For carcinogens that are mutagenic, cancer potency is assessed using a linear extrapolation from the low-dose region of the dose-response curve. Using this model, any increased exposure increases cancer risk.

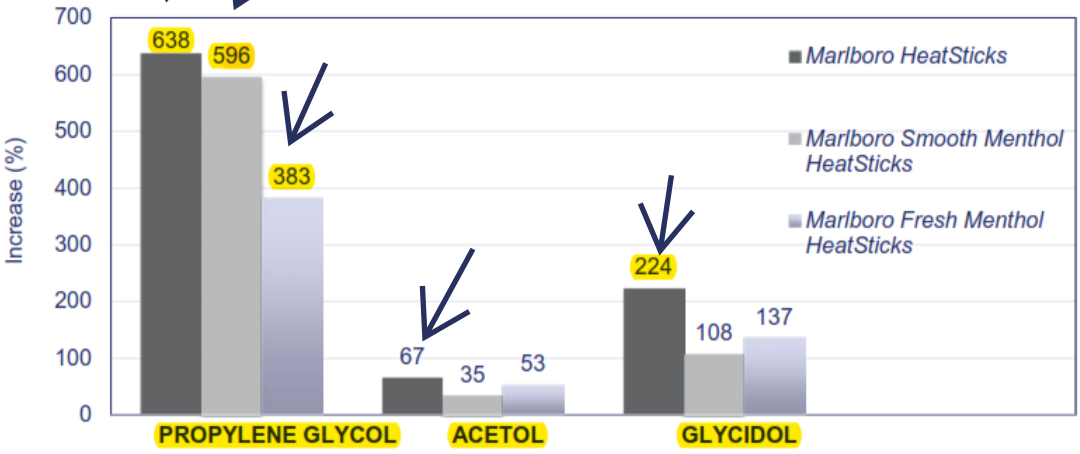
CAS#	Chemical	Fold Increase over 3R4F Cigarette	Designation
98-00-0	2-Furanmethanol	6.8	Possibly Carcinogenic
96-24-2	3-chloro-1,2-Dihydroxyropane	5.7	Possibly Carcinogenic
556-52-5	Glycidol	3.2	Probably Carcinogenic
98-01-1	Furfural	1.6	Possibly Carcinogenic
128-37-0	Butylated hydroxytoluene	23.4	Possibly Genotoxic
25395-31-7	Diacetin	5.9	Possibly Genotoxic
930-60-9	2-Cyclopentene-1,4-dione	5.0	Possibly Genotoxic
106-61-6	Glyceryl 1-acetate	4.0	Possibly Genotoxic
102-62-5	1,2-Diacylclycerol	2.4	Possibly Genotoxic
765-87-7	1,2-Cyclohexanedione	1.8	Possibly Genotoxic
28564-83-2	2,3-Dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one	1.6	Possibly Genotoxic
487-06-9	5,7-Dimethoxycoumarin	1.1	Possibly Genotoxic

Source: MR0000097, *"Tox-Ass-Report-NTDS-2017-fdafixed.pdf"*

- While both reference cigarette smoke and *HeatStick* aerosols contains chemicals that are carcinogenic or possibly carcinogenic to humans (e.g., acetaldehyde, formaldehyde, benzene), *HeatStick* aerosols did not produce a positive response under conditions of the Ames test conducted by the applicant.
- The study reports did not contain information from an Ames test with the gas vapor phase (GVP) of the *HeatStick* aerosol. An Ames test with GVP would provide additional information about the mutagenic potential of *HeatStick* aerosol.

The applicant lists 53 compounds in the *Marlboro HeatSticks*, 58 compounds in the *Marlboro Smooth Menthol HeatSticks*, and 61 compounds in the *Marlboro Fresh Menthol HeatSticks* with higher quantities in the aerosol of the *Heatsticks* compared to mainstream smoke of Kentucky reference cigarette 3R4F

SELECT COMPOUNDS INCREASED IN *IQOS* AEROSOL COMPARED TO KENTUCKY REFERENCE CIGARETTE 3R4F



MRTPA	Analytes	Matrix/ Smoking regimen	PMP SA data			STL# results	Difference between PMP and STL data (%)
			FDA 18 + 6	PMI-58	3R4F		
Marlboro HeatSticks	Tar (mg/stick)	Aerosol/ HCI	21.9 – 23.7	19.4	25.0	15.1	↓28
	Nicotine (mg/stick)		1.15 – 1.19	1.29	1.74	1.25	0
	Acrolein (µg/stick)		8.9 – 11.5	8.3	158	12.25	↑24
	Formaldehyde (µg/stick)		13 – 14	14.1	85.2	19.6	↑45
	NNN (ng/stick)	Tobacco filler	88.4-104	-		86.3	↓10
	NNK (ng/stick)		44.9-47.7	-		38.6	↓15
	Ammonia (µg/stick)		105-111	-		130.1	↑20
Smooth Menthol HeatSticks	Acrolein (µg/stick)	Aerosol/ HCI	8.4-10.3	9.8	157	10.1	0
	Formaldehyde (µg/stick)		13.8-14.1	15.2	79.4	18.7	↑29
	Ammonia (µg/stick)	Tobacco filler	105-113	-		123.3	↑13
Fresh Menthol HeatSticks	Benzo[a]pyrene (ng/stick)	Aerosol/ HCI	0.51-0.55	0.45	14.4	0.99	↑98
	NNN (ng/stick)	Tobacco filler	65-68	-		81.4	↑22
	NNK (ng/stick)		51-54	-		40.0	↓24

*#STL: Southeast Tobacco Laboratory

- Auer *et al*. (2017): reported lower reduction of acrolein (18%) and formaldehyde (26%) in the aerosol of the *HeatSticks* than the reduction reported by the applicant. In addition, reported high quantity of acenaphthene (295%).
- Bekki et al. (2017): found carbon monoxide (99%), NNN (90-94%), and NNK (87-95%) lower in the aerosol of *HeatSticks* compared to the reference cigarettes 3R4F and 1R5F
- Savareear *et al*. (2017), British American Tobacco: reported 205 compounds in the aerosol of *HeatSticks*, including flavor and fragrance agents, humectants, natural substances, and a plasticizer. The paper lists 82 compounds that were not previously reported in cigarette smoke. From those 82 compounds, 43 compounds were previously reported in tobacco filler but not in cigarette smoke.

The applicant reported 53 compounds in the *Marlboro HeatSticks*, 58 compounds in the *Marlboro Smooth Menthol HeatSticks*, and 61 compounds in the *Marlboro Fresh Menthol HeatSticks* with higher quantities in the aerosol of the *HeatSticks*. Compounds other than HPHCs, such as glycidol, acetol, and propylene glycol, are higher in the aerosol of the *HeatSticks* compared to the mainstream cigarette smoke of the Kentucky reference cigarette 3R4F.

Who is iQOS for?

✓ It is for smokers who want to continue using tobacco.

Who is iQOS not for?

x It is not for smokers who want to quit.

x It is not for ex-smokers.

x It is not for non-smokers.

For Claim 1	For Claim 2	For Claim 3
IMPORTANT WARNING: Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. HeatSticks™ contain nicotine, which is addictive. Using the *iQOS* system can harm your health.	IMPORTANT WARNING: • Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • HeatSticks™ contain nicotine, which is addictive.	IMPORTANT WARNING: •It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes. •HeatSticks™ contain nicotine, which is addictive. •Using the *iQOS* system can harm your health.

- From RRC: "Based on the information on the iQOS material, what can be the effect of using iQOS on your health?"

Response Options	% Across LLA Materials
None – it is totally safe	2-3%
It is completely unknown	5-7%
It is more harmful than conventional cigarettes	<1%
It can harm your health	85-86%
Don't know	4-7%

- Among non-smokers, 89-96% responded "It can harm your health."

PRELIMINARY ASSESSMENT

FDA

Overall Preliminary Assessment:

It is not clear whether or how much the chosen biomarkers of exposure and potential harm in these reduced exposure studies are predictive of long-term tobacco-related disease risk.

MARKET STUDY

Tobacco Product Used Concurrently	% of Current "Heat-Not-Burn" Users That Concurrently Use Other Tobacco Products[1] (N=71)
At least one other tobacco product	91.8%
Cigarettes (including roll-your-own)	84.9%
Cigarettes, use daily	79.4%
Cigarettes, use less than daily	5.5%
E-cigarettes	58.9%
"Smokeless tobacco pipe"[2]	38.4%
Chewing tobacco, snus, snuff	30.1%
Cigars/pipes/kiseru	24.7%

- *IQOS* initiation (i.e., using ≥100 *HeatSticks*) varied across countries
  - 33.8% in the US
  - Ranged from 36.1% in Italy to 76.3% in South Korea in the WOT
- Dual use was common across all countries
- Low prevalence of complete switching to *IQOS*
  - In the US, 8% of participants were "exclusive" *IQOS* users in the last week of the study

SUMMARY: LIMITATIONS

- Unknown effect of dual use on reducing health risks and exposure to HPHCs
- Study design may impact behavior relative to true real-world conditions
  - Effect on behavior of receiving *IQOS* free of charge
  - Sustainability of *IQOS* use patterns over time
  - Unclear whether participants noticed or were impacted by reduced risk information on labeling material
- Generalizability of results to US smokers
  - Non-probability sample from marketing research databases
  - Prevalence of switching varied across countries, with highest prevalence in Asia
  - Differences in the availability of products across countries