Hon Aaron Stonehouse MLC
Chair Select Committee Personal Choice and Community Safety
Legislative Council
Parliament of Western Australia

Dear Select Committee

Set out below are answers to the questions raised by Dr Steve Thomas MLC and Dr Sally Talbot MLC during the testimony provided by the Australian Council on Smoking and Health (ACOSH) to the Select Committee on 27 March 2019.

It is important to note that the evidence on the harms caused by e-cigarettes is not confined to a single published scientific, peer reviewed paper. Rather, the totality of the available evidence needs to be assessed to draw firm conclusions.

1.0 Major reviews of the evidence on e-cigarettes

During the testimony, Dr Steve Thomas MLC asked the following question:

> "… but what I am looking for is the definitive study that says that e-cigarettes are equally harmful as standard cigarettes. Does that study exist?"

As conveyed in our statement to the Select Committee, there have been a number of comprehensive reviews of the published evidence on the health effects of e-cigarettes.

Set out below is the title and reference for each of these reviews and their major conclusions, statements, abstracts or key findings.

National Health and Medical Research Council [NHMRC]. NHMRC CEO Statement: Electronic Cigarettes (e-cigarettes). 2017.

"Conclusions

- E-cigarettes may expose users to fewer toxic chemicals than conventional tobacco cigarettes; however, the extent to which this reduces harm to the user has not been determined.
- E-cigarettes may expose users to chemicals and toxins such as formaldehyde, heavy metals, particulate matter and flavouring chemicals, at levels that have the potential to cause adverse health effects.
- There is currently insufficient evidence to conclude whether e-cigarettes can assist smokers to quit. Smokers wishing to quit should consult the Quitline or their general practitioner.
- There is some evidence from longitudinal studies to suggest that e-cigarette use in non-smokers is associated with future uptake of tobacco cigarette smoking.
- Health authorities and policy-makers should act to minimise harm to users and bystanders, and to protect vulnerable groups such as young people, until evidence of safety, quality and efficacy can be produced.
- NHMRC is currently funding a number of studies into the safety and efficacy of e-cigarettes.
- Consumers should seek further information about e-cigarettes from reliable sources, such as the relevant State or Territory Health Department or quit smoking services."

Department of Health. Therapeutic Goods Administration [TGA]. Electronic cigarettes. 2015.

"Statement

- Products claiming to help people quit smoking are therapeutic goods
- The importation and supply (including sale) of therapeutic goods is illegal in Australia unless authorised by the TGA.
- **Nicotine** is classified by law as a dangerous poison. States and territories have responsibility for regulating dangerous poisons. In all states and territories, the retail sale of nicotine is an offence unless a permit has been issued by the relevant state or territory authority. In some states and territories, obtaining, purchasing, possession and/or using nicotine without a permit is an offence. In most jurisdictions there are similar controls on manufacturing (including mixing), storage, labelling and packaging and other aspects of dangerous poisons. For details, contact the relevant state or territory health agency. These state and territory laws have not been overridden by Commonwealth legislation
- Some states and territories have legislation prohibiting the marketing of products that resemble tobacco products
- Electronic cigarettes have not been evaluated for quality, safety or performance by the TGA."

Byrne S, Brindal E, Williams G, Anastasiou KM, Tonkin A, Battams S, Riley MD. E-cigarettes, smoking and health: A Literature Review Update. CSIRO, Australia. 2018.

"Key findings

Health impact of e-cigarettes and personal vaporisers

- The evidence available suggests that regular use of e-cigarettes is likely to have adverse health consequences.
- There is a lack of clarity about the: magnitude of adverse health effects and quantity of e-cigarette use required to trigger adverse health effects.

Impact on smoking tobacco

- In many countries where appropriate evidence is available, it appears that e-cigarette use occurs with cigarette use.
- However, the evidence is consistent in suggesting that use of e-cigarettes by non-smoking youth predicts future smoking.
- While many smokers and former smokers state a preference for e-cigarettes as a smoking cessation method, the effectiveness of this method compared with other smoking cessation methods is not known.

Impact on health of e-cigarettes and personal vaporisers in countries where they have been allowed

- Based on the current evidence it is not possible to ascertain whether e-cigarettes have a positive or a negative effect on health in countries where they are permitted.

Impact on health of e-cigarettes and personal vaporisers in smokers

- When e-cigarettes are used by smokers instead of conventional cigarettes there is evidence for improvement in individual health, probably mainly due to the reduction in smoking.

- However, use of e-cigarettes may also introduce independent health risks, and 'dual use' (using both e-cigarettes and conventional cigarettes) is popular.

Potential for e-cigarettes and personal vaporisers to reduce rates of smoking in Australia

- It is a critical research question to determine the effectiveness of e-cigarettes compared to other smoking cessation methods among Australian smokers generally, but also amongst groups with a high smoking rate.
- The rate at which young people and adults start smoking as a result of using e-cigarettes should be assessed and monitored to fill a research gap.
- On present evidence, it is not possible to determine whether less restrictive access to e-cigarettes would reduce rates of smoking in Australia.

Smoking rates in countries where e-cigarettes and personal vaporisers are available

- There does not appear to be a consistent pattern of rate of e-cigarette use compared to tobacco smoking across countries.
- While tobacco smoking is a well-established practice that varies widely between countries, e-cigarette use has spread across countries in the recent past with different rate of device availability, marketing, familiarity and regulations.
- It is plausible that a consistent pattern between tobacco smoking and e-cigarette use across countries could develop in the future."

World Health Organization Framework Convention on Tobacco Control. Conference of the Parties to the WHO Framework Convention on Tobacco Control. Electronic Nicotine Delivery System and Electronic Non-Nicotine Delivery Systems. 2016.

"Health risks of exclusive ENDS/ENNDS use

7. The typical use of unadulterated ENDS/ENNDS produces aerosol that ordinarily includes glycols, aldehydes, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbon (PAHs), tobacco-specific nitrosamines (TSNAs), metals, silicate particles and other elements. Dicarbonyls (glyoxal, methylglyoxal, diacethyl) and hydroxycarbonyls (acetol) also are thought to be important compounds in the aerosol. Many of these substances are toxicants that have known health effects resulting in a range of significant pathological changes.

8. The number and level of known toxicants generated by the typical use of unadulterated ENDS/ENNDS is on average lower or much lower than in cigarette smoke, with a few new toxicants specific to ENDS such as glyoxal. However, the levels of toxicants can vary enormously across and within brands and sometimes reach higher levels than in tobacco smoke. This is probably due, among other things, to the increased thermal decomposition of e-liquid ingredients with rising applied temperatures in open system devices. A number of metals - including lead, chromium, and nickel and formaldehyde - have been found in the aerosol of some ENDS/ENNDS at concentrations equal to or greater than traditional cigarettes under normal experimental conditions of use.

9. ENDS aerosol contains nicotine, the addictive component of tobacco products. In addition to dependence, nicotine can have adverse effects on the development of the foetus during pregnancy and may contribute to cardiovascular disease. Although nicotine itself is not a carcinogen, it may function as a "tumour promoter" and seems to be involved in the biology of malignant diseases, as well as of neurodegeneration. Foetal and adolescent nicotine

exposure may have long-term consequences for brain development, potentially leading to learning and anxiety disorders. The evidence is sufficient to warn children and adolescents, pregnant women, and women of reproductive age against ENDS use and nicotine.

10. Close to 8,000 e-liquid unique flavours have been reported. The health effects of heated and inhaled flavourants used in the e-liquids have not been well studied. Heated and inhaled popcorn cinnamon and cherry flavourants are potentially hazardous, with the limited literature on the topic indicating that most flavourants may pose appreciable health risks from long-term use, especially those that are sweet. Many are irritants which may increase airway inflammation; some are more cytotoxic than unflavoured aerosol although less so than tobacco smoke, or increase the susceptibility of airway cells to viral infection after direct contact with e-liquid, although the relevance of direct effects of contact with e-liquid, as opposed to aerosol, is unclear.

11. Based mostly on the levels and number of toxicants produced during the typical use of unadulterated ENDS/ENNDS made with pharmaceutical-grade ingredients, it is very likely that ENDS/ENNDS are less toxic than cigarette smoke. However, ENDS/ENNDS are unlikely to be harmless, and long-term use is expected to increase the risk of chronic obstructive pulmonary disease, lung cancer, and possibly cardiovascular disease as well as some other diseases also associated with smoking. The magnitude of these risks is likely to be smaller than from tobacco smoke although there is not enough research to quantify the relative risk of ENDS/ENNDS over combustible products. Therefore, no specific figure about how much "safer" the use of these products is compared to smoking can be given any scientific credibility at this time. Existing modelling studies indicate, however, that in order for there to be a potential population-wide net health benefit from ENDS/ENNDS at present usage rates, these products would need to be at least three times "safer" than cigarettes.

12. There is an urgent need to elucidate the range of relative risks when using the diverse ENDS/ENNDS devices and e-liquids, and about user behaviour compared to smoking and use of other nicotine products, recognizing that:

a. complex mixtures, such as in ENDS liquids and aerosol, have the potential for toxicological effects even if toxicants are at low or very low concentrations;
b. predicting adverse health effects of these complex mixtures solely on the basis of aerosol composition might prove futile without solid evidence from the coordinated use of chemical, in vitro, clinical and epidemiological methods; and that
c. simple comparisons of toxicant levels in ENDS/ENNDS aerosol to the high levels in tobacco smoke, as advocated by the tobacco industry, may be of little value given the absence of science on safe tolerance limits for smoke constituents or their specific effects on the multiple diseases caused by smoking."

National Academy of Sciences, Engineering and Medicine. Public Health Consequences of E-Cigarettes. 2018.

"Health effects of e-cigarettes

Conclusion 7-1. There is substantial evidence that e-cigarette aerosols can induce acute endothelial cell dysfunction, although the long-term consequences and outcomes on these parameters with long-term exposure to e-cigarette aerosol are uncertain.

Conclusion 7-2. There is substantial evidence that components of e-cigarette aerosols can promote formation of reactive oxygen species/oxidative stress. Although this supports the biological plausibility of tissue injury and disease from longterm exposure to e-cigarette

aerosols, generation of reactive oxygen species and oxidative stress induction is generally lower from e-cigarettes than from combustible tobacco cigarette smoke.

Conclusion 8-1. There is substantial evidence that e-cigarette use results in symptoms of dependence on e-cigarettes.

Conclusion 8-2. There is moderate evidence that risk and severity of dependence are lower for e-cigarettes than combustible tobacco cigarettes.

Conclusion 8-3. There is moderate evidence that variability in e-cigarette product characteristics (nicotine concentration, flavoring, device type, and brand) is an important determinant of risk and severity of e-cigarette dependence.

Conclusion 9-1. There is no available evidence whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima-media thickness and coronary artery calcification).

Conclusion 9-2. There is substantial evidence that heart rate increases shortly after nicotine intake from e-cigarettes.

Conclusion 9-3. There is moderate evidence that diastolic blood pressure increases shortly after nicotine intake from e-cigarettes.

Conclusion 9-4. There is limited evidence that e-cigarette use is associated with a short-term increase in systolic blood pressure, changes in biomarkers of oxidative stress, increased endothelial dysfunction and arterial stiffness, and autonomic control.

Conclusion 9-5. There is insufficient evidence that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function.

Conclusion 10-1. There is no available evidence whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for e-cigarette use compared with use of combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products.

Conclusion 10-2. There is limited evidence from in vivo animal studies using intermediate biomarkers of cancer to support the hypothesis that long-term e-cigarette use could increase the risk of cancer; there is no available evidence from adequate long-term animal bioassays of e-cigarette aerosol exposures to inform cancer risk.

Conclusion 10-3. There is limited evidence that e-cigarette aerosol can be mutagenic or cause DNA damage in humans, animal models, and human cells in culture.

Conclusion 10-4. There is substantial evidence that some chemicals present in e-cigarette aerosols (e.g., formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis. This supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes. Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined.

Conclusion 11-1. There is no available evidence whether or not e-cigarettes cause respiratory diseases in humans.

Conclusion 11-2. There is limited evidence for improvement in lung function and respiratory symptoms among adult smokers with asthma who switch to e-cigarettes completely or in part (dual use).

Conclusion 11-3. There is limited evidence for reduction of chronic obstructive pulmonary disease (COPD) exacerbations among adult smokers with COPD who switch to e-cigarettes completely or in part (dual use).

Conclusion 11-4. There is moderate evidence for increased cough and wheeze in adolescents who use e-cigarettes and an association with e-cigarette use and an increase in asthma exacerbations.

Conclusion 11-5. There is limited evidence of adverse effects of e-cigarette exposure on the respiratory system from animal and in vitro studies.

Conclusion 12-1. There is limited evidence suggesting that switching to e-cigarettes will improve periodontal disease in smokers.

Conclusion 12-2. There is limited evidence suggesting that nicotine- and non-nicotine–containing e-cigarette aerosol can adversely affect cell viability and cause cell damage of oral tissue in non-smokers.

Conclusion 13-1. There is no available evidence whether or not e-cigarettes affect pregnancy outcomes.

Conclusion 13-2. There is insufficient evidence whether or not maternal e-cigarette use affects fetal development.

Conclusion 14-1. There is conclusive evidence that e-cigarette devices can explode and cause burns and projectile injuries. Such risk is significantly increased when batteries are of poor quality, stored improperly, or modified by users.

Conclusion 14-2. There is conclusive evidence that intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects including but not limited to seizures, anoxic brain injury, vomiting, and lactic acidosis.

Conclusion 14-3. There is conclusive evidence that intentionally or unintentionally drinking or injecting e-liquids can be fatal."

Livingston CJ et al (2019) Electronic Nicotine Delivery Systems or E-cigarettes: American College of Preventive Medicine's Practice Statement.

"Results

On an individual level, limited evidence suggests that ENDS may be effective at reducing cigarette use among adult smokers intending to quit. There is insufficient evidence addressing potential long-term harms of ENDS, and limited evidence is available about short-term harms of ENDS and the impact of secondhand exposure. Although ENDS appear safer than combustible cigarettes, they are not without risk. Among youth there is no known

benefit and significant concern for harm. On a population level, there may be significant harms associated with ENDS, particularly among youth nonsmokers. The long-term balance of potential benefits versus harms from the individual and population perspectives are unclear."

Bals, R., Boyd, J., Esposito, S., Foronjy, R., Hiemstra, P., & Jiménez-Ruiz, C. et al. (2019). Electronic cigarettes: a task force report from the European Respiratory Society. European Respiratory Journal, 53(2),

"Abstract

ECIG aerosol contains potentially toxic chemicals. As compared to conventional cigarettes, these are fewer and generally in lower concentrations. Second-hand exposures to ECIG chemicals may represent a potential risk, especially to vulnerable populations. There is not enough scientific evidence to support that ECIGs are an aid to smoking cessation due to a lack of controlled trials, including those that compare ECIGs with licensed stop-smoking treatments. So far, there is conflicting data that use of ECIGs results in a renormalization of smoking behaviour or for the gateway hypothesis. Experiments in cell cultures and animal studies show that ECIGs can have multiple negative effects. The long-term effects of ECIGs use are unknown, and there is therefore no evidence that ECIGs are safer than tobacco in the long term. Negative health effects cannot, based on the current knowledge, be ruled out."

Jenssen, B., & Walley, S. (2019). E-Cigarettes and Similar Devices. Pediatrics, 143(2), e20183652. doi: 10.1542/peds.2018-3652

"Abstract

Electronic cigarettes (e-cigarettes) are the most commonly used tobacco product among youth. The 2016 US Surgeon General's Report on e-cigarette use among youth and young adults concluded that e-cigarettes are unsafe for children and adolescents. Furthermore, strong and consistent evidence finds that children and adolescents who use e-cigarettes are significantly more likely to go on to use traditional cigarettes—a product that kills half its long-term users. E-cigarette manufacturers target children with enticing candy and fruit flavors and use marketing strategies that have been previously successful with traditional cigarettes to attract youth to these products. Numerous toxicants and carcinogens have been found in e-cigarette solutions. Nonusers are involuntarily exposed to the emissions of these devices with secondhand and thirdhand aerosol. To prevent children, adolescents, and young adults from transitioning from e-cigarettes to traditional cigarettes and minimize the potential public health harm from e-cigarette use, there is a critical need for e-cigarette regulation, legislative action, and counterpromotion to protect youth."

2.0 Additional evidence on the health effects of e-cigarettes

In addition to the reviews of evidence referred to in our Statement, there have been further studies published on the health effects of e-cigarettes, outlined below.

Glantz SA, Bareham DW. E-cigarettes: use, effects on smoking, risks, and policy implications. *Annu Rev Public Health*. 2018;39:215-235.

"Abstract

Since e-cigarettes appeared in the mid-2000s, some practitioners, researchers, and policy

makers have embraced them as a safer alternative to conventional cigarettes and an effective way to stop smoking. While e-cigarettes deliver lower levels of carcinogens than do conventional cigarettes, they still expose users to high levels of ultrafine particles and other toxins that may substantially increase cardiovascular and noncancer lung disease risks, which account for more than half of all smoking-caused deaths, at rates similar to conventional cigarettes. Moreover, rather than stimulating smokers to switch from conventional cigarettes to less dangerous e-cigarettes or quitting altogether, e-cigarettes are reducing smoking cessation rates and expanding the nicotine market by attracting youth."

Alzahrani T, Pena I, Temesgen N, Glantz SA. Association between electronic cigarette use and myocardial infarction. *Am J Prev Med*. 2018;55(4):455-461.

"Results

Daily e-cigarette use was independently associated with increased odds of having had a myocardial infarction (OR=1.79, 95% CI=1.20, 2.66, *p*=0.004) as was daily conventional cigarette smoking (OR=2.72, 95% CI=2.29, 3.24, *p*<0.001). Former and some day e-cigarette use were not significantly associated with having had a myocardial infarction (*p*=0.608 and *p*=0.392) whereas former (OR=1.70, *p*<0.001) and some day cigarette smoking (OR=2.36, *p*<0.001) were. Odds of a myocardial infarction were also increased with history of hypertension (OR=2.32, *p*<0.001); high cholesterol (OR=2.36, *p*<0.001); and diabetes (OR=1.77, *p*<0.001); and age (OR=1.65 per 10 years, *p*<0.001). Women (OR=0.47, *p*<0.001) had lower odds of myocardial infarction.

Conclusions

Daily e-cigarette use, adjusted for smoking conventional cigarettes as well as other risk factors, is associated with increased risk of myocardial infarction."

Ndunda PM, Muutu TM. Electronic cigarette use is associated with a higher risk of stroke. International Stroke Conference 2019 Oral Abstracts. *Stroke*. 2019;50(suppl 1):abstract 9.

"Results

Overall 21% of BRFSS respondents reported ever using e-cigarettes, with 48.5% of them being female (P <0.0001). Compared with non-users, e-cigarette users had a lower mean age (44 vs 57 years [P <0.0001]), lower mean BMI (27.7 vs 28.1 [P <0.0001]) and a lower rate of diabetes (9.8% vs 12.1% [P <0.0001]). They however had higher rates of cigarette smoking (78.7% vs 37.4% [P <0.0001]). Compared with non-users, e-cigarette users had higher adjusted odds of stroke (OR 1.71 [1.64 - 1.8]), myocardial infarction (OR 1.59 [1.53 - 1.66]), angina or coronary heart disease (OR 1.4 [1.35 - 1.46]).

Conclusion

E-cigarette use is associated with higher odds of stroke, myocardial infarction and angina/coronary heart disease"

Bhatta D, Glantz SA. Electronic cigarette use and myocardial infarction among adults in the United States Population Assessment of Tobacco and Health. Paper presented at: Society for Research on Nicotine and Tobacco Annual Meeting; February 20-23, 2019; San Francisco, CA. Abstract P0S4-99.

"Abstract

Background: Electronic cigarettes are battery operated nicotine delivery devices, popular for smoking cessation tools and as an alternative product to combustible cigarettes. This study aim is to determine the association between electronic cigarette use and myocardial infarction.

Methods: Adults age 18 and older at Wave 1 (n = 32,320; 2013- 2014) and Wave 2 (n=26,447; 2014-2015) of the Population Assessment of Tobacco and Health (PATH) study in the United States of America were used. Multivariable logistic regression was performed to determine the associations between e-cigarette use and myocardial infarction, adjusting for cigarette smoking, demographic and clinical variables.

Results: Every day (adjusted odds ratio 2.29, 95% CI: 1.25, 4.22) and some day (1.91, 95% CI: 1.08, 3.38) e-cigarette use were independently associated with increased odds of having had a myocardial infarction with a significant dose-response (P < 0.0005), controlling for conventional cigarette smoking and demographic and clinical risk factors in a cross-sectional analysis of Wave 1. Odds of having had a myocardial infarction among current dual user is 6.64 compared with a never smoker who never used e-cigarettes. Having had a myocardial infarction at Wave 1 did not predict e-cigarette use at Wave 2 (p>0.62), suggesting that reverse causality cannot explain the cross-sectional association between e-cigarette use and myocardial infarction observed at Wave 1.

Conclusions: Some day and every day e-cigarette use are associated with increased risk of having had a myocardial infarction, in addition to the effect of any combustible cigarette smoking. Dual use is riskier than using either product alone."

Perez M, Atuegwu N, Mead E, Oncken C, Mortensen E. E-cigarette use is associated with emphysema, chronic bronchitis and COPD (A6245). American Thoracic Society Session D22: Cutting Edge Research in Smoking Cessation and E-cigarettes.

"Abstract

Background: There has been an exponential increase in the use of electronic cigarettes (E-cig) in the United States and this has raised concerns about the effects of these products on lung health. Recent publications have shown an association between E-cig use and asthma in youths. In-vitro and animal studies have shown an inflammatory response to E-cigs similar to conventional cigarettes, which can lead to chronic obstructive pulmonary disease (COPD.) The purpose of this study is to examine the association between E-cig use and COPD in adults.

Methods: Adult 2013-2014 Population Assessment of Tobacco and Health (PATH) Study data was used for the analyses. E-cig use was defined as fairly regular use of E-cigs every day or some days and the prevalence of COPD was defined as having either emphysema, chronic bronchitis or COPD. Propensity score matching was used to balance potential confounders (e.g. use of other tobacco products, second-hand smoke) between the E-cig and non E-cig users. Logistic regression was then used to examine the association between E-cig use and COPD, while also adjusting for potential confounders. We utilized replicate weights and balanced repeated replication methods to account for the PATH Study's complex survey design.

Results: 1,575 out of 32,247 people that participated in the survey met the criteria for E-cig use. The prevalence of COPD among E-cig users was 4.45% (95% confidence interval [CI] 3.70-5.19). The propensity-matched group was composed of 1321 E-cig users and 1321 non E-cig users. E-cig users had increased odds of having COPD odds ratio 1.86 95% confidence interval 1.22-2.83.

Conclusion: We showed that fairly regular use of E-cigs every day or some days is associated with an increased odds of having COPD in a large representative US adult cohort. This association exists even after adjusting for potential confounding factors. Due to the fact that the data is cross-sectional, it is unknown whether E-cigs could contribute to COPD development, or if people who have COPD are more likely to use E-cigs (possibly as a harm reduction method). Prospective data are needed to better determine the nature of this association."

Wills TA, Pagano I, Williams RJ, Tam EK. E-cigarette use and respiratory disorder in an adult sample. *Drug Alcohol Depend*. 2019;194:363-370.

"Highlights

- Few data are available on the association of e-cigarette use with health indices.
- We found e-cigarette use associated with asthma and chronic respiratory disorder.
- Results were independent of cigarette smoking, physical and psychosocial covariates.
- Associations with respiratory disorder were significant primarily among nonsmokers."

Bhatta D, Glantz SA. Electronic cigarette use is associated with respiratory disease among adults in the United States Population Assessment of Tobacco and Health: a longitudinal analysis. Paper presented at: Society for Research on Nicotine and Tobacco Annual Meeting; February 22-23, 2019; San Francisco, CA. Abstract P0S2-146.

"Abstract

Background: Electronic cigarettes are marketed as a less harmful nicotine delivery system and as a new smoking cessation tool. This study aim is to determine the longitudinal associations between electronic cigarette use and respiratory disease.

Methods: Longitudinal analysis of the Population Assessment of Tobacco and Health (PATH) Waves 1, 2 and 3. The Wave 1 dataset includes 32,320 adults, Wave 2 has 28,362 and Wave 3 has 28,148 American adults aged 18 years and above, of whom 23,670 completed all three waves. Wave 1 data were collected from September 2013 to December 2014, Wave 2 from October 2014 to October 2015 and Wave 3 from October 2015 to October 2016. PATH uses a four-stage stratified probability sample technique. Multivariable logistic regression was performed to determine the longitudinal associations between e-cigarette use and respiratory disease, controlling for cigarette smoking, demographic and clinical variables.

Results: Among people who did not report respiratory disease at Wave 1, the longitudinal analysis reveals statistically significant associations between former e-cigarette use (adjusted odds ratio, 1.24, 95% CI: 1.03, 1.51) and current e-cigarette use (1.23, 95% CI: 1.00, 1.52) at Wave 1 and having incident respiratory disease at Waves 2 or 3, controlling for cigarette smoking, demographic, and clinical variables. Current cigarette smoking (2.68, 95% CI: 2.10, 3.42) was also significantly associated with having respiratory disease at Waves 2 or 3. Odds of

developing lung disease for a current dual user is 3.30 compared with a never smoker who never used e-cigarettes.

Conclusions: Current use of e-cigarettes is an independent risk factor for respiratory disease that accrues in addition to the effects of any cigarette smoking. Dual use is riskier than using either product alone."

Tommasi S, Caliri AW, Caceres A, et al. Deregulation of biologically significant genes and associated molecular pathways in the oral epithelium of electronic cigarette users. *Int J Mol Sci*. 2019;20(3):738.

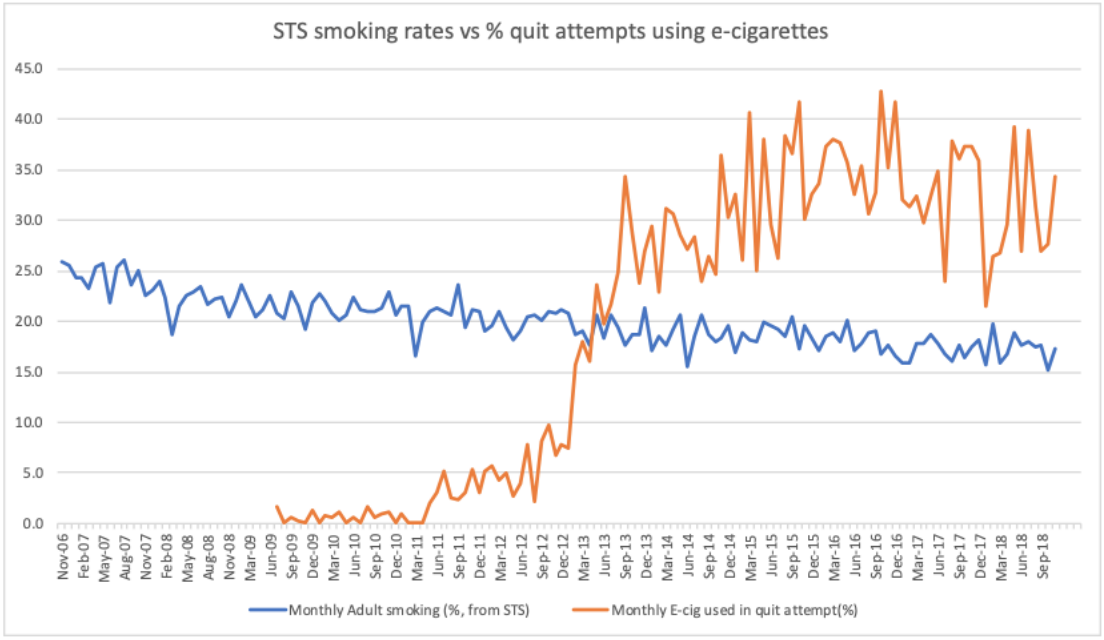
"Abstract

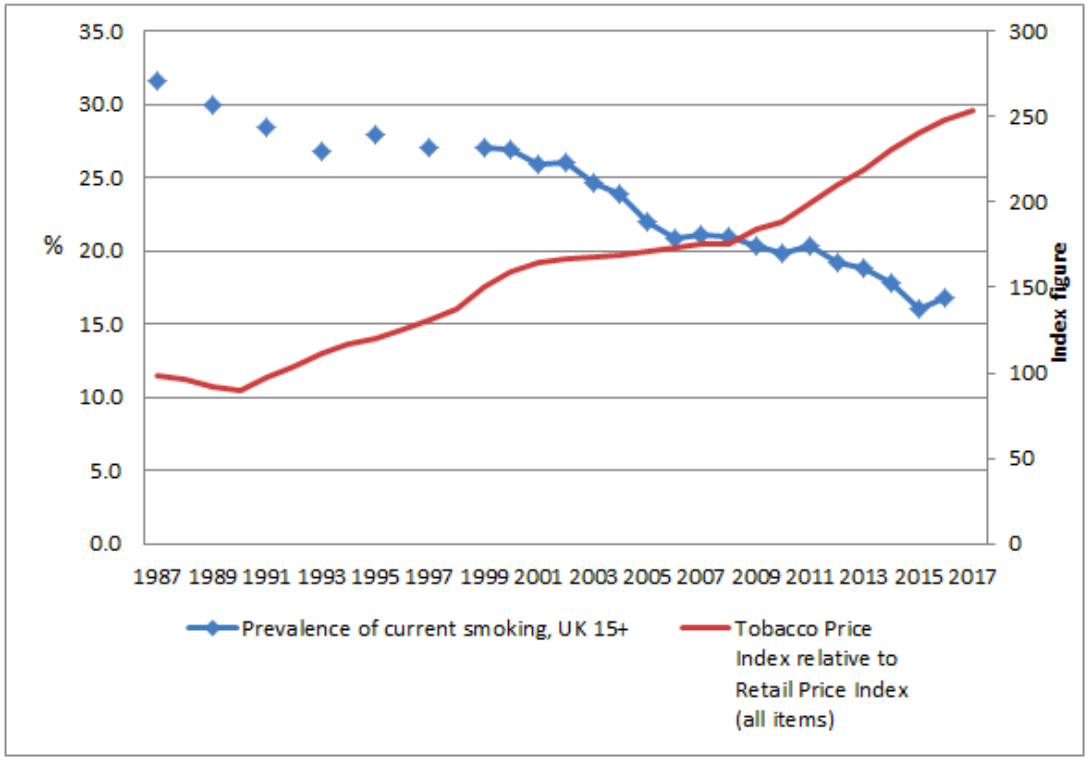
We have investigated the regulation of genes and associated molecular pathways, genome-wide, in oral cells of electronic cigarette (e-cigs) users and cigarette smokers as compared to non-smokers. Interrogation of the oral transcriptome by RNA-sequencing (RNA-seq) analysis showed significant number of aberrantly expressed transcripts in both e-cig users (vapers) and smokers relative to non-smokers; however, smokers had ~50% more differentially expressed transcripts than vapers (1726 versus 1152). Whereas the deregulated transcripts in smokers were predominately from protein-coding genes (79% versus 53% in vapers), nearly 28% of the aberrantly expressed transcripts in vapers (versus 8% in smokers) belonged to regulatory non-coding RNAs, including long intergenic non-coding, antisense, small nucleolar and misc RNA ($P < 0.0001$). Molecular pathway and functional network analyses revealed that "cancer" was the top disease associated with the deregulated genes in both e-cig users and smokers (~62% versus 79%). Examination of the canonical pathways and networks modulated in either e-cig users or smokers identified the "Wnt/Ca^+ pathway" in vapers and the "integrin signaling pathway" in smokers as the most affected pathways. Amongst the overlapping functional pathways impacted in both e-cig users and smokers, the "Rho family GTPases signaling pathway" was the top disrupted pathway, although the number of affected targets was three times higher in smokers than vapers. In conclusion, we observed deregulation of critically important genes and associated molecular pathways in the oral epithelium of vapers that bears both resemblances and differences with that of smokers. Our findings have significant implications for public health and tobacco regulatory science."

3.0 Declines in the prevalence of smoking in the UK

Mr Swanson offered to provide evidence on the decline in prevalence of smoking in the UK, and this decline being more likely related to increases in the price of tobacco rather than use of e-cigarettes in quit attempts.

[Smoking in England]





4.0 Are e-cigarettes 95% safer than traditional cigarettes?

During the ACOSH presentation to the Select Committee, the Hon Sally Talbot MLC referred to the Royal College of Physicians Report, that references the claim e-cigarettes are 95% safer than cigarettes.

British American Tobacco Australia, Philip Morris Limited, Australian Tobacco Harm Reduction Association, Legalise Vaping, and Australian Taxpayers Alliance have all repeated the claim that e-cigarettes 95% safer than traditional cigarettes in their testimony to the Select Committee.

This claim was made originally by Public Health England, followed by the Royal College of Physicians, the Royal Society for Public Health and the National Health Service.

The claim originated from a single consensus meeting of 12 people convened by D.J. Nutt et al. in 2014. They reached this conclusion without citing any specific evidence and included the caveat: "A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria."

This fact has been ignored by many individuals, and organisations, who have subsequently quoted Nutt's Report.

In a further recent review of the health effects of e-cigarettes, Glantz and Bareham (2018) has documented potential conflicts of interest for some of the individuals who generated the guesstimate of 95% less harmful.

> "A 2015 editorial in The Lancet (39) identified financial conflicts of interest associated with Nutt et al. (97), noting that "there was no formal criterion for the recruitment of the experts." The Nutt et al. meeting was funded by EuroSwiss Health and Lega Italiana Anti Fumo (LIAF). EuroSwiss Health is one of several companies registered at the same address in a village outside Geneva with the same chief executive, who was reported to have received funding from British American Tobacco (BAT) for writing a book on nicotine as a means of harm reduction (66) and who also endorsed BAT's public health credentials (127). Another of Nutt's coauthors, Riccardo Polosa, was Chief Scientific Advisor to LIAF, received funding from LIAF, and reported serving as a consultant to Arbi Group Srl, an e-cigarette distributor. He also received funding from Philip Morris International (84, 129). Later in 2015, the BMJpublished an investigative report (51) that raised broader issues surrounding potential conflicts of interest between individuals involved in the Nutt et al. paper. BMJ provided an infographic illuminating undisclosed connections between key people involved in the paper and the tobacco and e-cigarette industries as well as links between the paper and Public Health England via one of the coauthors. Even so, as of June 2017, the "95% safer" figure remains widely quoted, despite the fact that evidence of the dangers of e-cigarette use has rapidly accumulated since 2014. This new evidence indicates that the true risk of e-cigarette use is much higher than the "95% safer" claim would indicate."

5.0 Further information on the harmful health effects of nicotine and the potential role of nicotine in the causation of mental illness

Please see below scientific publications on these topics.

Taylor G, Munafo M. Does smoking cause poor mental health? The Lancet Psychiatry. 2019.

> "Many smokers and health-care providers believe that smoking can reduce stress and other symptoms related to poor mental health. In *The Lancet Psychiatry*, Jentien Vermeulen and colleagues examined the self-medication hypothesis in a prospective cohort study of patients with a non-affective psychosis (n=1094), unaffected siblings (n=1047), and control participants (n=579). The authors measured multi-cross-sectional associations and the associations of smoking status and number of cigarettes smoked per day with positive, negative, and depressive symptoms, and quality of life at baseline and at 3-year and 6-year follow-up. Coefficients derived from multiple linear mixed-effects regression analyses indicated that starting to smoke was associated with an increase in psychotic (positive symptoms: 0·137, SE 0·064, p=0·0330; negative symptoms: 0·170, 0·074, p=0.0214) and depressive symptoms (0·170, 0·076, p=0·0247) in patients compared with those who did not change their smoking status. Patients who quit smoking during the study period did not have any change in their symptoms or quality of life, and siblings who quit smoking had an improvement in quality of life and a larger decrease in negative symptoms compared with those who did not change their smoking status. Similar findings were obtained for the changes in number of cigarettes smoked per day. **These findings add to a growing body of evidence that smoking might be a causal risk factor for a range of psychiatric conditions and that stopping smoking can improve mental health.** Various studies with methods that support strong causal inference in observational data indicate that smoking increases risk of depression and schizophrenia, and that smoking cessation leads to a reduction in prescription of antidepressants and anxiolytics (Taylor and colleagues, unpublished)."

Scott JG, Matuschka L, Niemelä S et al. Evidence of a causal relationship between smoking tobacco and schizophrenia spectrum disorders. Front. Psychiatry, 20 November 2018

> "Abstract: **There has been emerging evidence of an association between tobacco smoking and schizophrenia spectrum disorders (SSD).** Two meta-analyses have reported that people who smoke tobacco have an ~2-fold increased risk of incident schizophrenia or psychosis, even after adjusting for confounding factors. This study aimed to critically appraise the research which has examined the association between tobacco smoking and SSD against the Bradford Hill criteria for causality, to determine the strength of the evidence for a causal relationship. Eight longitudinal studies (seven cohort studies and one case control study) were identified which examined tobacco smoking as an exposure and psychosis as an outcome. All seven cohort studies were assessed as being of high quality using the Newcastle-Ottawa Scale. Six of the eight studies found a statistically significant positive association between tobacco smoking and onset of SSD. These studies reported a consistent association with a moderate to large effect size and a dose response relationship. The studies adjusted for multiple potential confounders including age, sex, socioeconomic status, shared genetic risk, prodromal symptoms, and comorbid cannabis and other substance use. The studies did not adjust for exposure to childhood trauma or prenatal tobacco. There was substantial though inconclusive evidence supporting a causal relationship between tobacco smoking and increased risk of SSD. **If a causal relationship does exist, nicotine is most likely responsible for this association. This raises serious public health concerns about the increasing use of e-cigarettes and other products, particularly by adolescents whose nicotine use may increase their risk of SSD. Research is urgently needed to examine the association between e-cigarette use and incident psychosis, particularly in adolescents and young adults."**

Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. Lancet Psychiatry 2015;2: 718–25.

> "Abstract: Background: Although the association between psychotic illness and cigarette smoking is well known, the reasons are unclear why people with psychosis are more likely to smoke than are the general population. We aimed to test several hypotheses. First, that daily tobacco use is associated with an increased risk of psychotic illness in both case-control and prospective studies. Second, that smoking is associated with an earlier age at onset of psychotic illness. Finally, that an earlier age at initiation of smoking is associated with an increased risk of psychosis. We also aimed to derive an estimate of the prevalence of smoking in patients presenting with their first episode of psychosis.
>
> Methods:We searched Embase, Medline, and PsycINFO and selected observational studies in which rates of smoking were reported in people with psychotic disorders, compared with controls. We calculated the weighted mean difference for age at onset of psychosis and age at initiation of smoking. For categorical outcomes, we calculated odds ratios from cross-sectional studies and risk ratios from prospective studies.
>
> Findings: Of 3717 citations retrieved, 61 studies comprising 72 samples met inclusion criteria. The overall sample included 14 555 tobacco users and 273 162 non-users. The prevalence of smoking in patients presenting with their first episode of psychosis was 0·57 (95% CI 0·52–0·62; p<0·0001). In case-control studies, the overall odds ratio for the first episode of psychosis in smokers versus non-smokers was 3.22 (95% CI 1.63–6.33), with some evidence of publication bias (Egger's test p=0.018, Begg's test p=0.007). **For prospective studies, we calculated an overall relative risk of new psychotic disorders in daily smokers versus non-smokers of 2.18 (95% CI 1.23–3.85). Daily smokers developed psychotic illness at an earlier age than did non-smokers (weighted mean difference –1.04 years, 95% CI –1·82 to –0.26). Those with psychosis started smoking at a non-significantly earlier age than did healthy controls (–0.44 years, 95% CI –1·21 to 0·34).**
>
> Interpretation Daily tobacco use is associated with increased risk of psychosis and an earlier age at onset of psychotic illness. The possibility of a causal link between tobacco use and psychosis merits further examination. [**Note: the discussion section of this paper includes a detailed consideration of the possible role of nicotine in the development of psychosis**]."

Niemelä S, Sourander A, Surcel H-M et al Prenatal nicotine exposure and risk of schizophrenia among offspring in a national birth cohort. Am J Psychiatry. 2016 Aug 1;173(8):799-806.

> "Objective: Cigarette smoking during pregnancy is a major public health problem leading to adverse health outcomes and neurodevelopmental abnormalities among offspring. Its prevalence in the United States and Europe is 12%–25%. This study examined the relationship between prenatal nicotine exposure (cotinine level) in archived maternal sera and schizophrenia in offspring from a national birth cohort.
>
> Method: The authors conducted a population-based nested case-control study of all live births in Finland from 1983 to 1998. Cases of schizophrenia in offspring (N=977) were identified from a national registry and matched 1:1 to controls on date of birth, sex, and residence. Maternal serum cotinine levels were prospectively measured, using quantitative immunoassay, from early- to mid-gestation serum specimens archived in a national biobank.

Results: **A higher maternal cotinine level, measured as a continuous variable, was associated with an increased odds of schizophrenia (odds ratio=3.41, 95% confidence interval, 1.86–6.24). Categorically defined heavy maternal nicotine exposure was related to a 38% increased odds of schizophrenia. These findings were not accounted for by maternal age, maternal or parental psychiatric disorders, socioeconomic status, and other covariates.** There was no clear evidence that weight for gestational age mediated the associations.

Conclusions: To the authors' knowledge, this is the first study of the relationship between a maternal smoking biomarker and schizophrenia. It provides **the most definitive evidence to date that smoking during pregnancy is associated with schizophrenia. If replicated, these findings suggest that preventing smoking during pregnancy may decrease the incidence of schizophrenia."**

Guo, Z-Z1,Cao Q-A, Li Z-Z et al. SP600125 Attenuates Nicotine-Related aortic aneurysm formation by inhibiting matrix metalloproteinase production and CC chemokine-mediated macrophage migration. Mediators of Inflammation 2016 (full text)

"Abstract **Nicotine, a major chemical component of cigarettes, plays a pivotal role in the development of abdominal aortic aneurysm (AAA).** c-Jun N-terminal kinase (JNK) has been demonstrated to participate in elastase-induced AAA. This study aimed to elucidate whether the JNK inhibitor SP600125 can attenuate nicotine plus angiotensin II- (AngII-) induced AAA formation and to assess the underlying molecular mechanisms. SP600125 significantly attenuated nicotine plus AngII-induced AAA formation. The expression of matrix metalloproteinase- (MMP-) 2, MMP-9, monocyte chemoattractant protein- (MCP-) 1, and regulated-onactivation, normal T-cells expressed and secreted (RANTES) was significantly upregulated in aortic aneurysm lesions but inhibited by SP600125. In vitro, nicotine induced the expression of MCP-1 and RANTESin bothRAW264.7 (mouse macrophage) and MOVAS (mouse vascular smooth muscle) cells in a dose-dependent manner; expression was upregulated by 0.5 ng/mL nicotine but strongly downregulated by 500 ng/mL nicotine. SP600125 attenuated the upregulation of MCP-1 and RANTES expression and subsequent macrophage migration. In conclusion, SP600125 attenuates nicotine plus AngII-induced AAA formation likely by inhibiting MMP- 2, MMP-9, MCP-1, and RANTES. **The expression of chemokines in MOVAS cells induced by nicotine has an effect on RAW264.7 migration, which is likely to contribute to the development of nicotine-related AAA."**

Dang N, Meng X, Song H. Nicotinic acetylcholine receptors and cancer (Review). Biomedical Reports 2016;4:515-518 (full text)

"Abstract: **Nicotine, the primary addictive constituent of cigarettes, is believed to contribute to cancer promotion and progression through the activation of nicotinic acetylcholine receptors (nAChRs)**, which are membrane ligand-gated cation channels. nAChRs activation can be triggered by the neurotransmitter Ach, or certain other biological compounds, such as nicotine. In recent years, genome-wide association studies have indicated that allelic variation in the α5-α3-β4 nAChR cluster on chromosome 15q24-15q25.1 is associated with lung cancer risk. The role of nAChRs in other types of cancer has also been reported. **The present review highlights the role of nAChRs in types of human cancer."**

England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the developing human: a neglected element in the electronic cigarette debate American Journal of Preventive Medicine 2015 Aug;49(2):286-93. [full text]

> "Abstract: The elimination of cigarettes and other combusted tobacco products in the U.S. would prevent tens of millions of tobacco-related deaths. It has been suggested that the introduction of less harmful nicotine delivery devices, such as electronic cigarettes or other electronic nicotine delivery systems, will accelerate progress toward ending combustible cigarette use. However, careful consideration of the potential adverse health effects from nicotine itself is often absent from public health debates. **Human and animal data support that nicotine exposure during periods of developmental vulnerability (fetal through adolescent stages) has multiple adverse health consequences, including impaired fetal brain and lung development, and altered development of cerebral cortex and hippocampus in adolescents.** Measures to protect the health of pregnant women and children are needed and could include (1) strong prohibitions on marketing that increase youth uptake; (2) youth access laws similar to those in effect for other tobacco products; (3) appropriate health warnings for vulnerable populations; (4) packaging to prevent accidental poisonings; (5) protection of non-users from exposure to secondhand electronic cigarette aerosol; (6) pricing that helps minimize youth initiation and use; (7) regulations to reduce product addiction potential and appeal for youth; and (8) the age of legal sale."

Mishra M, Chaturvedi P, Datta S et al. Harmful effects of nicotine. Indian J Med Paediatr Oncol. 2015 Jan-Mar;36(1):24-31. (full text)

> "With the advent of nicotine replacement therapy, the consumption of the nicotine is on the rise. Nicotine is considered to be a safer alternative of tobacco. The IARC monograph has not included nicotine as a carcinogen. However there are various studies which show otherwise. We undertook this review to specifically evaluate the effects of nicotine on the various organ systems. A computer aided search of the Medline and PubMed database was done using a combination of the keywords. All the animal and human studies investigating only the role of nicotine were included. Nicotine poses several health hazards. **There is an increased risk of cardiovascular, respiratory, gastrointestinal disorders. There is decreased immune response and it also poses ill impacts on the reproductive health. It affects the cell proliferation, oxidative stress, apoptosis, DNA mutation by various mechanisms which leads to cancer. It also affects the tumor proliferation and metastasis and causes resistance to chemo and radio therapeutic agents. The use of nicotine needs regulation.** The sale of nicotine should be under supervision of trained medical personnel."

Grando SA. Connections of nicotine to cancer. Nature Reviews Cancer (2014) 14:419-429 [Full text]

> "Abstract: This Opinion article **discusses emerging evidence of direct contributions of nicotine to cancer onset and growth. The list of cancers reportedly connected to nicotine is expanding and presently includes small-cell and non-small-cell lung carcinomas, as well as head and neck, gastric, pancreatic, gallbladder, liver, colon, breast, cervical, urinary bladder and kidney cancers. The mutagenic and tumour-promoting activities of nicotine may result from its ability to damage the genome, disrupt cellular metabolic processes, and facilitate growth and spreading of transformed cells. The nicotinic acetylcholine receptors (nAChRs), which are activated by nicotine, can activate several signalling pathways that can have tumorigenic effects, and these receptors might be able to be targeted for cancer therapy or prevention.** There is also growing evidence that the unique

genetic makeup of an individual, such as polymorphisms in genes encoding nAChR subunits, might influence the susceptibility of that individual to the pathobiological effects of nicotine. **The emerging knowledge about the carcinogenic mechanisms of nicotine action should be considered during the evaluation of regulations on nicotine product manufacturing, distribution and marketing."**

Schaal C, Chellappan SP. Nicotine-mediated cell proliferation and tumor progression in smoking-related cancers. Mol Cancer Res. 2014 Jan;12(1):14-23. (full text)

"Abstract: Tobacco smoke contains multiple classes of established carcinogens including benzo(a)pyrenes, polycyclic aromatic hydrocarbons, and tobacco specific nitrosamines. Most of these compounds exert their genotoxic effects by forming DNA adducts and generation of reactive oxygen species, causing mutations in vital genes like K-Ras and p53. In addition, tobacco specific nitrosamines can activate nicotinic acetylcholine receptors (nAChRs) and to a certain extent β-Adrenergic receptors (β-ARs), promoting cell proliferation. Further, **it has been demonstrated that nicotine, the major addictive component of tobacco smoke, can induce cell cycle progression, angiogenesis, and metastasis of lung and pancreatic cancers.** These effects occur mainly through the α7-nAChRs, with possible contribution from the β-ARs and/or epidermal growth factor receptors (EGFRs). This review article will discuss the molecular mechanisms by which nicotine and its oncogenic derivatives such as NNK (4-methylnitrosamino)-1-(3-pyridyl)-1-butanone) and NNN (N-nitrosonornicotine) induce cell cycle progression and promote tumor growth. A variety of signaling cascades are induced by nicotine through nAChRs, including the MAPK/ERK pathway, PI3K/AKT pathway and JAK/STAT signaling. In addition, studies have shown that nAChR activation induces Src kinase in a β-arrestin-1 dependent manner, leading to the inactivation of Rb protein and resulting in the expression of E2F1-regulated proliferative genes. Such nAChR-mediated signaling events enhance the proliferation of cells and render them resistant to apoptosis induced by various agents. These observations highlight the role of nAChRs in promoting the growth and metastasis of tumors and raise the possibility of targeting them for cancer therapy"

Nordenvall C, Nilsson PJ, Ye W, Andersson TM, Nyrén O. Tobacco use and cancer survival: A cohort study of 40,230 Swedish male construction workers with incident cancer. Int J Cancer 2013; 132 (1):155-61. (full text)

"Abstract: On theoretical grounds, **nicotine has been implicated as a modifier of cancer progression.** We investigated possible associations of smoking or use of Scandinavian moist snuff (snus) with survival after cancer among Swedish male construction workers. **Snus use is associated with substantial exposure to nicotine but not to the combustion products in smoke.** Among 336,381 workers with detailed information on tobacco use in 1971–1992, we observed 40,230 incident cancers. Complete follow-up through 2007 was accomplished through linkage to population and health registers. Hazard ratios (HRs) and 95% confidence intervals (CIs) for death from any cause, cancer-specific death and death from other causes were derived from Cox proportional hazards regression models adjusted for age at diagnosis, body mass index at study entry and period of diagnosis. Never users of any tobacco served as reference. **Increased risks of cancer-specific death were observed both among exclusive smokers ($HR_{all\ cancer}$ 1.15, 95% CI: 1.10–1.21) and never-smoking snus users (1.15, 95% CI: 1.05–1.26).** As regards deaths due to other causes, exclusive smokers had higher relative risks than exclusive snus users (p = 0.03). **A history of tobacco use, even exclusive use of the seemingly benign snus, is associated with moderately increased cancer-specific mortality. Although nicotine might play a role, the mechanisms warrant further investigation."**

Bavara JH, Tae H, Settlage RE, Garner HR. Characterizing the Genetic Basis for Nicotine Induced Cancer Development: A Transcriptome Sequencing Study. PLoS One 2013; Jun 18 [Full text]

> "Abstract: **Nicotine is a known risk factor for cancer development and has been shown to alter gene expression in cells and tissue upon exposure.** We used Illumina® Next Generation Sequencing (NGS) technology to gain unbiased biological insight into the transcriptome of normal epithelial cells (MCF-10A) to nicotine exposure. We generated expression data from 54,699 transcripts using triplicates of control and nicotine stressed cells. As a result, we identified 138 differentially expressed transcripts, including 39 uncharacterized genes. Additionally, 173 transcripts that are primarily associated with DNA replication, recombination, and repair showed evidence for alternative splicing. We discovered the greatest nicotine stress response by HPCAL4 (up-regulated by 4.71 fold) and NPAS3 (down-regulated by -2.73 fold); both are genes that have not been previously implicated in nicotine exposure but are linked to cancer. We also discovered significant down-regulation (-2.3 fold) and alternative splicing of NEAT1 (lncRNA) that may have an important, yet undiscovered regulatory role. Gene ontology analysis revealed nicotine exposure influenced genes involved in cellular and metabolic processes. **This study reveals previously unknown consequences of nicotine stress on the transcriptome of normal breast epithelial cells and provides insight into the underlying biological influence of nicotine on normal cells, marking the foundation for future studies."**

Cardinal A, Nastrucci C, Cesario A, Russo P. Nicotine: specific role in angiogenesis, proliferation and apoptosis. Critical Reviews in Toxicology, 2012; 42(1): 68–89

> "Abstract: Nowadays, tobacco smoking is the cause of ~5-6 million deaths per year, counting 31% and 6% of all cancer deaths (affecting 18 different organs) in middle-aged men and women, respectively. Nicotine is the addictive component of tobacco acting on neuronal nicotinic receptors (nAChR). Functional nAChR, are also present on endothelial, haematological and epithelial cells. **Although nicotine itself is regularly not referred to as a carcinogen, there is an ongoing debate whether nicotine functions as a 'tumour promoter'. Nicotine, with its specific binding to nAChR, deregulates essential biological processes like regulation of cell proliferation, apoptosis, migration, invasion, angiogenesis, inflammation and cell-mediated immunity in a wide variety of cells including foetal (regulation of development), embryonic and adult stem cells, adult tissues as well as cancer cells. Nicotine seems involved in fundamental aspects of the biology of malignant diseases, as well as of neurodegeneration.**Investigating the biological effects of nicotine may provide new tools for therapeutic interventions and for the understanding of neurodegenerative diseases and tumour biology."

Momi N, Kaur S, Ponnusamy MP, Kumar S, Wittel UA, Batra SK. Interplay between smoking-induced genotoxicity and altered signaling in pancreatic carcinogenesis. Carcinogenesis. 2012 Sep;33(9):1617-28. [full text]

> "Abstract: Despite continuous research efforts directed at early diagnosis and treatment of pancreatic cancer (PC), the status of patients affected by this deadly malignancy remains dismal. Its notoriety with regard to lack of early diagnosis and resistance to the current chemotherapeutics is due to accumulating signaling abnormalities. Hoarding experimental and epidemiological evidences have established a direct correlation between cigarette smoking and PC risk. **The cancer initiating/promoting nature of cigarette smoke can be attributed to its various constituents including nicotine,** which is the major psychoactive component, and several other toxic constituents, such as nitrosamines, 4-

(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and polycyclic aromatic hydrocarbons. **These predominant smoke-constituents initiate a series of oncogenic events facilitating epigenetic alterations, self-sufficiency in growth signals, evasion of apoptosis, sustained angiogenesis, and metastasis. A better understanding of the molecular mechanisms underpinning these events is crucial for the prevention and therapeutic intervention against PC.** This review presents various interconnected signal transduction cascades, the smoking-mediated genotoxicity, and genetic polymorphisms influencing the susceptibility for smoking-mediated PC development by modulating pivotal biological aspects such as cell defense/tumor suppression, inflammation, DNA repair, as well as tobacco-carcinogen metabolization. Additionally, it provides a large perspective toward tumor biology and the therapeutic approaches against PC by targeting one or several steps of smoking-mediated signaling cascades."

Petros WP, Younis IR, Ford JN, Weed SA. Effects of tobacco smoking and nicotine on cancer treatment. Pharmacotherapy. 2012 Oct;32(10):920-31

"Abstract: A substantial number of the world's population continues to smoke tobacco, even in the setting of a cancer diagnosis. Studies have shown that patients with cancer who have a history of smoking have a worse prognosis than nonsmokers. Modulation of several physiologic processes involved in drug disposition has been associated with long-term exposure to tobacco smoke. The most common of these processes can be categorized into the effects of smoking on cytochrome P450-mediated metabolism, glucuronidation, and protein binding. Perturbation in the pharmacokinetics of anticancer drugs could result in clinically significant consequences, as these drugs are among the most toxic, but potentially beneficial, pharmaceuticals prescribed. Unfortunately, the effect of tobacco smoking on drug disposition has been explored for only a few marketed anticancer drugs; thus, little prescribing information is available to guide clinicians on the vast majority of these agents. **The carcinogenic properties of several compounds found in tobacco smoke have been well studied; however, relatively little attention has been given to the effects of nicotine itself on cancer growth. Data that identify nicotine's effect on cancer cell apoptosis, tumor angiogenesis, invasion, and metastasis are emerging. The implications of these data are still unclear but may lead to important questions regarding approaches to smoking cessation in patients with cancer."**

Catassi A, Servent S, Paleari L, Cesario A, Russo P. Multiple roles of nicotine on cell proliferation and inhibition of apoptosis: implications on lung carcinogenesis. Mutat Res. 2008 Sep-Oct;659(3):221-31.

"Abstract: The genotoxic effects of tobacco carcinogens have long been recognized, the contribution of tobacco components to cancerogenesis by cell surface receptor signaling is relatively unexplored. **Nicotine, the principal tobacco alkaloid, acts through nicotinic acetylcholine receptor (nAChR). nAChR are functionally present on human lung airway epithelial cells, on lung carcinoma [SCLC and NSCLC] and on mesothelioma and build a part of an autocrine-proliferative network that facilitates the growth of neoplastic cells.** Different nAChR subunit gene expression patterns are expressed between NSCLC from smokers and non-smokers. **Although there is no evidence that nicotine itself could induce cancer, different studies established that nicotine promotes in vivo the growth of cancer cells and the proliferation of endothelial cells suggesting that nicotine might contribute to the progression of tumors already initiated. These observations led to the hypothesis that nicotine might be playing a direct role in the promotion and progression of human lung**

cancers. Here, we briefly overview the role and the effects of nicotine on pulmonary cell growth and physiology and its feasible implications in lung carcinogenesis."

Slotkin TA. If nicotine is a developmental neurotoxicant in animal studies, dare we recommend nicotine replacement therapy in pregnant women and adolescents? Neurotoxicol Teratol. 2008 Jan-Feb;30(1):1-19.

"Abstract: Tobacco use in pregnancy is a leading cause of perinatal morbidity and contributes in major ways to attention deficit hyperactivity disorder, conduct disorders and learning disabilities that emerge in childhood and adolescence. **Over the past two decades, animal models of prenatal nicotine exposure have demonstrated that nicotine is a neurobehavioral teratogen that disrupts brain development by preempting the natural, neurotrophic roles of acetylcholine. Through its actions on nicotinic cholinergic receptors, nicotine elicits abnormalities of neural cell proliferation and differentiation, promotes apoptosis and produces deficits in the number of neural cells and in synaptic function. The effects eventually compromise multiple neurotransmitter systems because of the widespread regulatory role of cholinergic neurotransmission**. Importantly, the long-term alterations include effects on reward systems that reinforce the subsequent susceptibility to nicotine addiction in later life. These considerations strongly question the appropriateness of nicotine replacement therapy (NRT) for smoking cessation in pregnant women, especially as the pharmacokinetics of the transdermal patch may actually enhance fetal nicotine exposure. Further, because brain maturation continues into adolescence, the period when smoking typically commences, adolescence is also a vulnerable period in which nicotine can change the trajectory of neurodevelopment. There are also serious questions as to whether NRT is actually effective as an aid to smoking cessation in pregnant women and adolescents. This review considers the ramifications of the basic science findings of nicotine's effects on brain development for NRT in these populations."

Egleton RD, Brown KC, Dasgupta P. Nicotinic acetylcholine receptors in cancer: multiple roles in proliferation and inhibition of apoptosis. Trends Pharmacol Sci.2008 Mar;29(3):151-8.

"Abstract: Nicotinic acetylcholine receptors (nAChRs) constitute a heterogeneous family of ion channels that mediate fast synaptic transmission in neurons. They have also been found on non-neuronal cells such as bronchial epithelium and keratinocytes, underscoring the idea that they have functions well beyond neurotransmission. Components of cigarette smoke, including nicotine and NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone], are agonists of nAChRs. Given the association of tobacco use with several diseases, the non-neuronal nAChR signaling pathway has considerable implications for cancer and cardiovascular disease. Recent studies have shown that alpha7 is the main nAChR subunit that mediates the proliferative effects of nicotine in cancer cells. As a result, alpha7 nAChR might be a valuable molecular target for therapy of cancers such as lung cancer and mesothelioma. Future studies involving the design of nAChR antagonists with improved selectivity might identify novel strategies for the treatment of tobacco-related cancers. **Here we review the cellular roles of non-neuronal nAChRs, including regulation of cell proliferation, angiogenesis, apoptosis, migration, invasion and secretion."**

Zeilder R, Albermann K, Lang S. Nicotine and apoptosis. Apoptosis. 2007 Nov;12(11):1927-43.

"Abstract: Cigarette smoking is associated with a plethora of different diseases. **Nicotine is the addictive component of cigarette but also acts onto cells of the non-neuronal system, including immune effector cells. Although nicotine itself is usually not referred to as a**

carcinogen, there is ongoing debate whether nicotine functions as a 'tumor enhancer.' By binding to nicotinic acetylcholine receptors, nicotine deregulates essential biological processes like angiogenesis, apoptosis, and cell-mediated immunity. Apoptosis plays critical roles in a wide variety of physiologic processes during fetal development and in adult tissue and is also a fundamental aspect of the biology of malignant diseases. This review provides an overlook how nicotine influences apoptotic processes and is thus directly involved in the etiology of pathological conditions like cancer and obstructive diseases."

Wickström R. Effects of nicotine during pregnancy: human and experimental evidence. Curr Neuropharmacol. 2007 Sep;5(3):213-22. [full text]

"Abstract: Prenatal exposure to tobacco smoke is a major risk factor for the newborn, increasing morbidity and even mortality in the neonatal period but also beyond. As nicotine addiction is the factor preventing many women from smoking cessation during pregnancy, nicotine replacement therapy (NRT) has been suggested as a better alternative for the fetus. However, the safety of NRT has not been well documented, and animal studies have in fact pointed to nicotine per se as being responsible for a multitude of these detrimental effects. **Nicotine interacts with endogenous acetylcholine receptors in the brain and lung, and exposure during development interferes with normal neurotransmitter function, thus evoking neurodevelopmental abnormalities by disrupting the timing of neurotrophic actions.** As exposure to pure nicotine is quite uncommon in pregnant women, very little human data exist aside from the vast literature on prenatal exposure to tobacco smoke. The current review discusses recent findings in humans on effects on the newborn of prenatal exposure to pure nicotine and non-smoke tobacco. It also reviews the neuropharmacological properties of nicotine during gestation and findings in animal experiments that offer explanations on a cellular level for the pathogenesis of such prenatal drug exposure. **It is concluded that as findings indicate that functional nAChRs are present very early in neuronal development, and that activation at this stage leads to apoptosis and mitotic abnormalities, a total abstinence from all forms of nicotine should be advised to pregnant women for the entirety of gestation."**

Grozio A, Catassi A, Cavalieri Z et al Nicotine, lung and cancer. Anticancer Agents Med Chem. 2007 Jul;7(4):461-6.

"Abstract: The respiratory epithelium expresses the cholinergic system including nicotinic receptors (nAChRs). It was reported that normal human bronchial epithelial cells (BEC), which are the precursor for squamous cell carcinomas, and small airway epithelial cells (SAEC), which are the precursor for adenocarcinomas, have slightly different repertoires of nAChRs. Studies show that nAChRs expressed on lung carcinoma or mesothelioma form a part of an autocrine-proliferative network facilitating the growth of neoplastic cells; others demonstrated that nicotine can promote the growth of colon, gastric, and lung cancers. **Nicotine and structurally related carcinogens like NNK [4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone] and NNN (N'-nitrosonornicotine) could induce the proliferation of a variety of small cell lung carcinoma cell lines and endothelial cells and nicotine in non-neuronal tissues -including lung- induces the secretion of growth factors (bFGF, TGF-alpha, VEGF and PDGF), up regulation of the calpain family proteins, COX-2 and VEGFR-2, causing the eventual activation of Raf/MAPK kinase/ERK (Raf/MEK/ERK) pathway contributing to the growth and progression of tumors exposed to nicotine through tobacco smoke or cigarette substitutes.** It has been demonstrated that nicotine promotes the growth of solid tumors in vivo, suggesting that might induce the progression of tumors already initiated. **While tobacco carcinogens can initiate and promote tumorigenesis, the exposure**

> **to nicotine could confer a proliferative advantage to early tumors but there is no evidence that nicotine itself provokes cancer.** This is supported by the findings that nicotine can prevent apoptosis induced by various agents – such as chemotherapeutic in NSCLC, conferring a survival advantage as well."

5.0 Further question from the Hon Dr Sally Talbot

In regard to the Royal College of Physicians Report and the claim that e-cigarettes are 95% safer than traditional cigarettes, Mr Swanson replied:

> "But when you look at the long-term health outcomes for those people who continue vaping, they are not discernibly different from those who continued with their smoking, and is it conflicted somewhat by some of them dual-using? That needs to be drilled down. *But we can provide you with those studies. One is by Flacco, an Italian study, and the other is a longer-term follow-up to Hajek's randomised control trial."*

Flacco ME, Ferrante M, Fiore M, et al. Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up. 2019. European Review for Medical and Pharmacological Sciences.

> "RESULTS: Data were available for 228 e-cig users (all ex-smokers), 471 tobacco smokers, 216 dual users. A possibly smoking-related diseases (PSRD; validated through hospital discharge data or visit in 62.6% of the sample) was observed in 73 subjects (8.0%). **No differences emerged across groups in PSRD rates, with negligible variations in self-reported health.** Of e-cig users, 63.6% remained tobacco abstinent; dual users and tobacco smokers showed non-significantly different rates of tobacco (33.8% vs. 26.8%) and all-product (20.2% vs. 19.4%) cessation, and a similar decrease in cigarettes/day. Almost 40% of the sample switched at least once (tobacco smokers: 17.2%; dual users: 81.9%).
>
> CONCLUSIONS: **After four years, a scarce, non-significant harm reduction was observed among e-cig or dual users.** Given the long-lasting health effects of tobacco smoking, the benefits of e-cig use may start being detectable at the next follow-up (six years). The complete switch to e-cig may help tobacco quitters remain abstinent, but e-cig use in addition to tobacco did not increase the likelihood of smoking cessation or reduction."

Supplement to: Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine- replacement therapy. N Engl J Med. 2019. DOI: 10.1056/NEJMoa1808779

In longer term follow-up of this randomised control trial there were numerically more serious adverse events in the e-cigarette arm compared to the NRT arm (27 versus 22), and more tobacco/smoking related serious adverse events in the e-cigarette arm (7 versus 4) including one death in the e-cigarette arm.

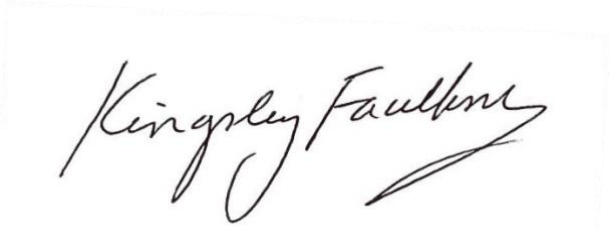
Taken together, these studies do not mean that e-cigarettes alone or in combination with smoking are worse than smoking alone. If the starting position is that a safety benefit is uncertain or small, these studies vindicate that position. If the alternate starting position is a belief that e-cigarettes are 95% safer – these studies cast that into considerable doubt if they do not make it impossible.

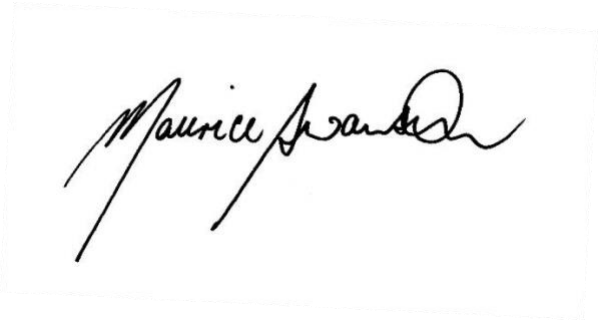
6.0 Conclusion

As stated in our primary submission, e-cigarettes need to be viewed through the prism of previous attempts by the tobacco industry to create so-called harm-reduced products:

> "The history of tobacco control is littered with examples of purported reduced harm products including filters, asbestos filters, reduced carcinogen cigarettes, "low" tar, "lights and milds" and tobacco substitutes.
>
> > "I suspect many people will be surprised to learn that the entire concept of light (or lite) as applied to foods, beer and virtually everything else was a tobacco industry invention, a vehicle to sell cigarettes.[1]"
>
> Many of these products have been promoted by false prophets, commercially driven with little evidence, and none of these have been able to demonstrate reduced harm in those who used them.[2]
>
> In areas where risks and harms for new tobacco products need to be considered as well as potential benefits, adherence to the evidence is critical – evidence that can only be collected, reviewed and reported through a rigorous framework, which considers overall population health."

Yours sincerely





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[1] Proctor NR, Golden Holocaust: Origins of the cigarette catastrophe and the case for abolition. University of California Press. 2011. (p. 406)

[2] Parascandola M. Tobacco Harm Reduction and the Evolution of Nicotine Dependence. American Journal of Public Health. 2011;101(4):632-641. doi:10.2105/AJPH.2009.189274.