

References related to the abstract (Attachment to the submission)

- 1) A growing body of international, independent scientific evidence indicates that exclusive e-cigarette use reduces users' exposure to toxicants and that an effective component of tobacco harm reduction is helping smokers to quit. See below scientific literature:**

Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. *Electronic cigarettes for smoking cessation*. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4.

- 2) LN13-14 “the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong” is inconsistent with available evidence. A significant amount of scientific literature on the cardiovascular effects of e-cigarettes was omitted. This statement should be reconsidered to reflect the current scientific evidence as referenced below:**

George, J., Hussain, M., Vadiveloo, T., *et al.* (2019). Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. *The Health Impact of Electronic Nicotine Delivery Systems: A Systematic Review. J Am Coll Cardiol* 74: 3112-3120, D'Ruiz, C.D., O'Connell, G., Graff, D.W., *et al.* (2017). Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Regulatory Toxicology and Pharmacology* 87: 36-53; Farsalinos, K., Cibella, F., Caponnetto, P., *et al.* (2016). Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Internal and emergency medicine* 11: 85-94; Polosa, R., Morjaria, J.B., Caponnetto, P., *et al.* (2016). Blood pressure control in smokers with arterial hypertension who switched to electronic cigarettes. *International journal of environmental research and public health* 13; Kuntic, M., Oelze, M., Steven, S., *et al.* (2020). Short-term e-cigarette vapour exposure causes vascular oxidative stress and dysfunction: Evidence for a close connection to brain damage and a key role of the phagocytic NADPH oxidase (NOX-2). *European Heart Journal* 41, 2472–2483; Farsalinos, K.E. (2020). Acute vs. Chronic effects of e-cigarettes on vascular function. *European Heart Journal* 41, 1525; Benowitz, N., Fraiman, J. Cardiovascular effects of electronic cigarettes. *Nat Rev Cardiol* 14, 447–456 (2017); Price LR, Martinez J. Cardiovascular, carcinogenic and reproductive effects of nicotine exposure: A narrative review of the scientific literature. *F1000Res.* 2019;8:1586. Published 2019 Sep 4. doi:10.12688/f1000research.20062.2; 33. Benowitz, N.L *et al.*: “Cardiovascular toxicity of nicotine: Implications for electronic cigarette use”, *Trends in Cardiovascular Medicine*, 2016). Hajat, C., Stein, E., Shantikumar, S., Niaura, R., *et al.* (2020) The health impact of electronic nicotine delivery systems: A systematic review. *medRxiv* 2020.10.07.20208355; doi.

- 3) LN42-44 “there is strong evidence that electronic cigarettes are a gateway to smoking for young people” is inconsistent with evidence presented in available studies. This statement should be reconsidered to reflect a more comprehensive review of the literature, based on the references outlined below:**

Etter, J.F. (2018). Gateway effects and electronic cigarettes. *Addiction* 113: 1776-1783 ; Stanton, C.A., Bansal-Travers, M., Johnson, A.L., *et al.* (2019). Longitudinal e-cigarette and cigarette use among us youth in the path study (2013–2015). *JNCI: Journal of the National Cancer Institute* 111: 1088-1096; Lee PN and Fry JS. Investigating gateway effects using the PATH study. *F1000Research* 2019, 8:264; Mendelsohn, C.P., and Hall, W. (2020). Does the gateway theory justify a ban on nicotine vaping in Australia? *International Journal of Drug Policy* 78: 102712; Collins, L.K., Villanti, A.C., Pearson, J.L., *et al.* (2017). Frequency of youth e-cigarette, tobacco, and poly-use in the united states, 2015: Update to Villanti *et al.*, "frequency of youth e-cigarette and tobacco use patterns in the united states: Measurement precision is critical to inform public health". *Nicotine Tob Res* 19: 1253-1254; Cole, A.G., Aleyan, S., Battista, K., and Leatherdale, S.T. (2020). Trends in youth e-cigarette and cigarette use between 2013 and 2019: insights from repeat cross-sectional data from the COMPASS study. *Can J*

Public Health; Hammond, D., Rynard, V.L., and Reid, J.L. (2020). Changes in Prevalence of Vaping Among Youths in the United States, Canada, and England from 2017 to 2019. *JAMA Pediatric* 174(8):797-800; Chan, G.C.K., Stjepanovic, D., Lim, C., *et al.* (2020). Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. *Addiction*; Chyderiotis, S., Benmarhnia, T., Beck, F., Spilka, S., and Legleye, S. (2020). Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France? *Drug Alcohol Depend* 208: 107853; McNeill., *et al.* (2018). Evidence review of e-cigarettes and heated tobacco products. A report commissioned by Public Health England. London: Public Health England. Royal College of Physicians. Nicotine without smoke: Tobacco harm reduction. London: RCP, 2016; O’Leary R., *et al.* (2017) Clearing the Air: A systematic review on the harms and benefits of e-cigarettes and vapour devices Victoria, BC: Centre for Addictions Research of BC; Action on Smoking and Health (ASH). Fact Sheet: Use of e-cigarettes (vapes) among adults in Great Britain. October 2020; Shahab L, Beard E, Brown J (2020) Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents: a cross-sectional, matched control study *Tobacco control*; Glasser AM, Johnson AL, Niaura RS, Abrams DB, Pearson JL (2020) Youth Vaping and Tobacco Use in Context in the United States: Results from the 2018 National Youth Tobacco Survey *Nicotine & Tobacco Research* doi:10.1093/ntr/ntaa010); Glasser AM, Johnson AL, Niaura RS, Abrams DB, Pearson JL (2020) Youth Vaping and Tobacco Use in Context in the United States: Results from the 2018 National Youth Tobacco Survey *Nicotine & Tobacco Research* doi:10.1093/ntr/ntaa010; Bauld, L., *et al.*, Young People's Use of E-Cigarettes across the United Kingdom: Findings from Five Surveys 2015-2017. *Int J Environ Res Public Health*, 2017. 14(9).

4) LN50-52 “there is weak evidence for the support of electronic cigarettes’ effectiveness in helping smokers to quit” is inconsistent with scientific evidence. Based on the scientific literature below, this statement should be reconsidered, and evidence should not be ‘weak’:

Glasser, A., Vojjala, M., Cantrell, J., *et al.* (2020). Patterns of e-cigarette use and subsequent cigarette smoking cessation over two years (2013/2014 to 2015/2016) in the Population Assessment of Tobacco and Health (PATH) study. *Nicotine Tob Res* ntaa182; Grabovac, I., Oberndorfer, M., Fischer, J., *et al.* (2020). Effectiveness of electronic cigarettes in smoking cessation: A systematic review and meta-analysis. *Nicotine Tob Res*; Kalkhoran, S., Chang, Y., and Rigotti, N.A. (2020). Electronic cigarette use and cigarette abstinence over 2 years among US smokers in the Population Assessment of Tobacco and Health study. *Nicotine Tob Res* 22: 728-733; Glasser, A.M., Collins, L., Pearson, J.L., *et al.* (2017). Overview of electronic nicotine delivery systems: A systematic review. *American journal of preventive medicine* 52: e33-e66; Villanti, A.C., Feirman, S.P., Niaura, R.S., *et al.* (2018). How do we determine the impact of e-cigarettes on cigarette smoking cessation or reduction? Review and recommendations for answering the research question with scientific rigor. *Addiction* 113: 391-404; Zhu, S.H., Zhuang, Y.L., Wong, S., *et al.* (2017). E-cigarette use and associated changes in population smoking cessation: Evidence from us current population surveys. *BMJ* 358: j3262; Johnson, L., Ma, Y., Fisher, S.L., *et al.* (2019). E-cigarette usage is associated with increased past-12-month quit attempts and successful smoking cessation in two us population-based surveys. *Nicotine Tob Res* 21: 1331-1338; Beard E., *et al.* (2016) Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *British Medical J*; 354 :i4645; Caraballo RS *et al.* (2017) Quit Methods Used by US Adult Cigarette Smokers, 2014–2016. *Prev Chronic Dis* 14:160600; Adriaens K., *et al.* (2014) Effectiveness of the electronic cigarette: an eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. *Int. J. Environ. Res. Public Health* 11:11220–48; Bullen C., *et al.* (2013) Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 382:1629–37; Caponnetto P., *et al.* (2013) Efficiency and Safety of an eElectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized

control design study. PLOS ONE 8:e66317; Farsalinos KE., et al. (2016) Electronic cigarette use in the European Union: analysis of a representative sample of 27,460 Europeans from 28 countries. *Addiction* 111(11):2032–40; Giovenco DP and Delnevo CD. (2018) Prevalence of smoking cessation by electronic cigarette use status in a national sample of recent smokers. *Addict Behav* 76:129–34 ; Levy DT., et al (2017) The relationship of e-cigarette use to cigarette quit attempts and cessation: insights from a large, nationally representative U.S. survey. *Nicotine Tob. Res*; McRobbie H., et al (2014) Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4. E-cigarettes versus NRT for smoking reduction or cessation in people with mental illness: secondary analysis of data from the ASCEND trial. *Tob. Induc. Dis.* 13:5; Parks SH., et al. (2017) Characteristics of adults who switched from cigarette smoking to e-cigarettes. *Am. J. Prev. Med.* 53(5):652–60; Tseng TY., et al. (2016) A randomized trial comparing the effect of nicotine versus placebo electronic cigarettes on smoking reduction among young adult smokers. *Nicotine Tob. Res.* 18:1937–43; *Tob. Use Depend. Guidel. Panel.* 2008. *Treating Tobacco Use and Dependence: 2008 Update.* Rockville, MD: US Dep. Health Hum. Serv; Hajek P., et al. (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy *N Engl J Med* 2019; 380:629-637; Cox S., et al. (2019) Effects of e-cigarettes versus nicotine replacement therapy on short-term smoking abstinence when delivered at a community pharmacy *Addictive Behaviors Reports* 10: 100202; Farsalinos KE, Barbouni A (2020). Association between electronic cigarette use and smoking cessation in the European Union in 2017: analysis of a representative sample of 13 057 Europeans from 28 countries *Tobacco Control*; Public health consequences of e-cigarettes, US National Academy of Science, Engineering and Medicine, January 2018; Royal College of Physicians. *Nicotine without smoke: Tobacco harm reduction.* London: RCP, 2016; McNeill., et al. (2018). Evidence review of e-cigarettes and heated tobacco products. A report commissioned by Public Health England. London: Public Health England. Special Eurobarometer 458 “Attitudes of Europeans towards tobacco and electronic cigarettes”. Tackett, A. P., W. V. Lechner, E. Meier, D. M. Grant, L. M. Driskill, N. N. Tahirkheli and T. L. Wagener (2015). "Biochemically verified smoking cessation and vaping beliefs among vape store customers." *Addiction* 110(5): 868-874); Brown, J et al: “Real-world effectiveness of e-cigarettes when used to aid smoking cessation”, *Addiction*, 2014; Hajek, Peter, Anna Phillips-Waller, Dunja Przulj, Francesca Pesola, Katie Myers Smith, Natalie Bisal, Jinshuo Li, Steve Parrott, Peter Sasieni, Lynne Dawkins, Louise Ross, Maciej Goniewicz, Qi Wu, and Hayden J. McRobbie. "A Randomized Trial of E-Cigarettes Versus Nicotine-Replacement Therapy." *New England Journal of Medicine* (2019); Filippidis, F. T., A. A. Lavery, U. Mons, C. Jimenez-Ruiz and C. I. Vardavas (2018). "Changes in smoking cessation assistance in the European Union between 2012 and 2017: pharmacotherapy versus counselling versus e-cigarettes." *Tobacco Control*; Jackson S, Kotz D, West R, Brown J (2019) Moderators of real-world effectiveness of smoking cessation aids: a population study *Addiction* (Abingdon, England) 0 doi:10.1111/add.14656; Beard E, West R, Michie S, Brown J (2019) Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time series analysis between 2006 and 2017 *Addiction* (Abingdon, England) 0 doi:10.1111/add.14851); Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. *The Lancet Respiratory Medicine* 2020; 8(1): 54-64).