



STANTON A. GLANTZ, PhD
Professor of Medicine (Cardiology)
American Legacy Foundation Distinguished Professor of Tobacco Control
Director, Center for Tobacco Control Research and Education

530 Parnassus Suite 366
San Francisco, CA 94143-1390
Phone: (415) 476-3893
Fax: (415) 514-9345
glantz@medicine.ucsf.edu

June 9, 2014

Docket No. FDA-2014-N-0189

Responses to common undocumented assertions about e-cigarettes for harm reduction

The attached letter, "Some Comments on the May 26 letter from public health specialists to WHO Director General Margaret Chan," was written in response to a letter sent to the WHO Director General strenuously advocating for unrestricted access to e-cigarettes. (The letter is available at <http://www.clivebates.com/?p=2185>; all the substantive arguments are quoted verbatim in my comments.

I am submitting this material to the present docket because it is very likely that the same arguments will be submitted to the FDA in the current rulemaking and my comments demonstrate that many of these assertions are incorrect or unsupported by the available data.

Please pay special attention to the discussion on Michael Russell's 1991 paper arguing for nicotine replacement as harm reduction. These arguments are implicit in the "continuum of risk" approach that the FDA is taking and CTP Director Mitch Zeller has often quoted Russell. As discussed in my comment, while Russell's assertions were reasonable 23 years ago when they were made, we have learned a lot about the mechanisms by which smoking and nicotine cause disease that raised questions about his arguments.

Thank you for your consideration.

A handwritten signature in blue ink, appearing to read "Stanton A. Glantz".

Stanton A. Glantz, PhD
Professor and Director

Some Comments on the May 26 letter from public health specialists to WHO Director General Margaret Chan

Stanton A. Glantz, PhD
Professor of Medicine
University of California San Francisco

June 9, 2014

Clive Bates, a private consultant and well-established e-cigarette advocate, has organized a remarkable letter to WHO Director General on 26 May 2014 signed by 53 public health specialists criticising WHO for not enthusiastically embracing e-cigarettes as a harm reduction technique.¹

The most notable thing about the letter, which contains several sweeping scientific statements, is that it does not contain a single reference to the scientific literature, particularly the substantial literature that does not support the political position the letter advocates.

Here are a few broad reactions before getting in to the specifics:

- The letter takes an "ignorance is bliss" position on several important issues, confusing lack of evidence on the long-term adverse effects of e-cigarette use with evidence of no (or minimal) harm from e-cigarette use. It ignores the fact that it will take a long time to determine what the long term effects are because you have to wait for enough time to pass for those effects to occur and be measured (which will be years or decades).
- The letter turns the precautionary principle on its head, by arguing that WHO should embrace e-cigarettes and eschew public health protection through the FCTC despite the fact that we already know that they expose users and bystanders to nicotine and other toxic substances.
- There are several statements (detailed below) that are simply incorrect.
- While several of the signatories were predictable, I was surprised -- even shocked -- to see some of the names on this letter. It will be interesting to see whether they regret putting their names to this letter two years from now.

The entire letter is predicated on the idea that, "We have known for years that people 'smoke for the nicotine, but die from the smoke': the vast majority of the death and disease attributable to tobacco arises from inhalation of tar particles and toxic gases drawn into the lungs."

This view is a restatement of the idea of tobacco harm reduction first proposed by Michael Russell in his 1991 paper "[The future of nicotine replacement](#)."² Here is what Russell actually said:

¹ Clive Bates. [53 public health specialists write to WHO about alternatives to smoking – here's the letter](#).

² Russell M. The future of nicotine replacement. British J Addict 1991;86:653-658.

Since people smoke mainly for nicotine and fail to quit because they are addicted, and since they die mainly from the tar, carbon monoxide and other harmful gases taken in alongside nicotine, and since they chew and snuff tobacco for nicotine but die largely from the nitrosamines and other carcinogens in tobacco, *it seems logical* to offer either a cleaner product or, better still, an acceptable source of purer, less contaminated nicotine. [emphasis added]

Note that Russell presented this idea as a *hypothesis*, not as established fact.

He then summarized the understanding of the biological mechanisms through which smoking causes cancer and heart disease:

Health risks of nicotine

While it is patently obvious that nicotine alone must be less harmful than nicotine plus tar plus noxious gases, decisions about policies for opening the market to cleaner nicotine replacement products and gradually phasing out tobacco will depend crucially on the health risks of nicotine. As mentioned earlier, it is assumed that there is no great objection to drug use and addiction per se. Nicotine addiction is not harmful. Unlike many other addictive drugs, nicotine does not disturb consciousness, impair judgement or social behaviour and, if anything, it enhances rather than impairs cognitive and psychomotor performance and the capacity to work. The key question is the extent to which nicotine or its metabolites contribute to the harmfulness of tobacco.

Nicotine has no role in tobacco-related cancers, which are responsible for 30% of all cancer deaths, neither is it implicated in chronic obstructive lung disease. The possibility of endogenous formation of carcinogenic nitrosamines from nicotine metabolites has been suggested (Hoffmann, 1989). However, it has not been demonstrated and, if it occurs, the amounts would be negligible compared with those present in tobacco and formed when it is burned.

It is likely that nicotine is implicated in the cardiovascular risks of cigarette smoking and that carbon monoxide also plays a part. However, to date no definitive epidemiological studies have identified the cardiovascular risks of individual smoke components. Nicotine activates the sympathetic nervous system and increases circulating levels of adrenaline, noradrenaline and vasopressin. Through these mechanisms it causes peripheral vasoconstriction and may also contribute to atherogenic and thrombogenic processes. It probably increases the adverse consequences of ischaemic heart disease. Propranol largely abolishes the deleterious effects of smoking on mortality following a first heart attack (Jafri et al., 1990) indicating that adrenergic mechanisms are involved. This strongly implicates nicotine which is the only smoke component with effects on adrenergic systems.

In contrast with cigarette smoking, the cardiovascular risks are negligible in primary pipe and cigar smokers who have never smoked cigarettes and who tend not to inhale deeply

(Doll, 1983). It is not clear whether the difference is due to the slower rate of buccal absorption from non-inhaled pipe and cigar smoking, to lower steady-state nicotine levels, or to lower CO levels. Similarly the lack of evidence that use of smokeless tobacco poses a cardiovascular risk is open to various interpretations.

In summary, nicotine has no part in tobacco related cancers and chronic obstructive lung disease, two of the major causes of tobacco-related premature deaths. There is some evidence that it contributes to the overall cardiovascular risks of smoking. These risks appear to be most evident when nicotine is rapidly absorbed through the lungs. However, it must be said that the evidence is discounted by two experts more competent than I am to assess it. They state: "That nicotine has a role in the cause of cardiovascular disease has its adherents, but the evidence is not compelling" (Froggatt & Wald, 1989).

While this was probably a reasonable summary of the evidence in 1991, **23 years ago**, it does not reflect several important things that we now know about the mechanisms by which smoking causes disease and the adverse effects of nicotine:

- There is a highly [nonlinear dose-response for the effects of smoke exposure on cardiovascular disease risk, with large effects at low levels of exposure](#).³
- The [ultrafine particles that cigarettes \(and e-cigarettes\) deliver have substantial adverse effects on the cardiovascular system](#).⁴
- Nicotine may not be a primary carcinogen, [but has carcinogenic effects and likely promotes cancers](#) once established through angiogenic (promoting growth of blood vessels in tumors) effects.⁵
- A dose of nicotine via nasal spray has the same [immediate adverse effect on arterial function](#) as smoking a cigarette.⁶
- [Nicotine is a reproductive toxicant](#).⁷

While we cannot fault Russell for not anticipating these findings, these are well-known effects that the signatories of the Bates letter should have at least acknowledged.

³ Institute of Medicine. *Secondhand Smoke Exposure and Cardiovascular Effects: Making Sense of the Evidence*. 2009. Also see Barnoya J, Glantz S. Cardiovascular effects of secondhand smoke: nearly as large as smoking. [Circulation](#) 2005 May 24;111(20):2684-98.

⁴ Institute of Medicine. *Secondhand Smoke Exposure and Cardiovascular Effects: Making Sense of the Evidence*. 2009. Also see Barnoya J, Glantz S. Cardiovascular effects of secondhand smoke: nearly as large as smoking. [Circulation](#) 2005 May 24;111(20):2684-98 and Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. [Circulation](#) 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

⁵ Grando SA. Connections of nicotine to cancer. *Nature Reviews Cancer* 2014; 14: 419–429. doi:10.1038/nrc3725 Published online 15 May 2014. See also Zhu BQ, Heeschen C, Sievers RE, Karliner JS, Parmley WW, Glantz SA, Cooke JP. Second hand smoke stimulates tumor angiogenesis and growth. [Cancer Cell](#) 2003 Sep;4(3):191-6.

⁶ Neunteufl T, Heher S, Kostner K, Mitulovic G, Lehr S, Khoschorur G, Schmid RW, Maurer G, Stefenelli T. Contribution of Nicotine to Acute Endothelial Dysfunction in Long-Term Smokers. *J Am Coll Cardiol* 2002;39:251–6.

⁷ US Surgeon General. *The Health Consequences of Smoking: 50 Years of Progress*. 2014 Chapter 5: Nicotine.

Here are some comments on the specific assertions in the Bates letter:

1. Tobacco harm reduction is part of the solution, not part of the problem. It could make a significant contribution to reducing the global burden of non-communicable diseases caused by smoking, and do so much faster than conventional strategies. If regulators treat low-risk nicotine products as traditional tobacco products and seek to reduce their use without recognising their potential as low-risk alternatives to smoking, they are improperly defining them as part of the problem.

To date there is no evidence that this "potential" to be part of the solution will be realized, particularly in the face of actual patterns of e-cigarette promotion and use, which show rapid penetration of the youth market, depressed cigarette cessation among all smokers, and high levels of dual use of cigarettes and e-cigarettes among both adults and adolescents.⁸

2. Tobacco harm reduction policies should be evidence-based and proportionate to risk, and give due weight to the significant reductions in risk that are achieved when a smoker switches to a low risk nicotine product. Regulation should be proportionate and balanced to exploit the considerable health opportunities, while managing residual risks. The architecture of the FCTC is not currently well suited to this purpose.

Quite the contrary, the FCTC has created a framework for developing and implementing *evidence-based* policies. If and when there is evidence that the assertions in the letter are correct, the mechanisms established by the FCTC would allow development and implementation of policies that could accommodate use of e-cigarettes in a way that promotes public health. For example, it may be that e-cigarettes used as part of a supervised cessation effort will improve success. If that turns out to be the case it might be good policy for FCTC Parties (and the US FDA) to make e-cigarettes available by prescription just as medicinal nicotine inhalers are now available, which would be consistent with FCTC Article 14.

Of course regulation as a therapeutic product would require the companies, including the tobacco companies who increasingly dominate the e-cigarette business, to submit data to the appropriate authorities demonstrating efficacy and safety, something that no company has yet done anywhere in the world.

Likewise, there are procedures that companies could use to secure approval by competent government authorities for the claims of reduced harm that the letter promotes. To date no company has yet submitted such an application demonstrating actual reduced harm for e-cigarettes as used in the population.

3. On a precautionary basis, regulators should avoid support for measures that could have the perverse effect of prolonging cigarette consumption. Policies that are excessively restrictive or burdensome on lower risk products can have the unintended consequence of protecting cigarettes from competition from less hazardous alternatives, and cause harm as a result.

⁸ Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. [Circulation](#) 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

Every policy related to low risk, non-combustible nicotine products should be assessed for this risk.

This argument turns the precautionary principle on its head. [In particular](#),

The definition of the precautionary principle developed for the Rio Declaration of 1992 is often cited, and the 1998 Wingspread Statement contains similar language: “when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.” The statement also lists 4 central components of the principle: (1) taking preventive action in the face of uncertainty, (2) shifting the burden of proof to the proponents of an activity, (3) exploring a wide range of alternatives to possibly harmful actions, and (4) increasing public participation in decision making.⁹ [references deleted]

Proper application of the precautionary principle requires affirmative evidence of lack of harm (or, at least a clear understanding of the actual level of harm) before a product is approved for general population use. We [already have](#) evidence¹⁰ that e-cigarettes deliver nicotine, ultrafine particles, and a range of carcinogens and other toxins, that among all smokers having tried e-cigarettes is associated with lower likelihood of quitting smoking, that there is aggressive marketing to youth in many countries and that there is rapid penetration into the youth market.

Even if [the one cross-sectional study](#)¹¹ that found that e-cigarettes help motivated smokers who are using them to quit is confirmed, the other problems that have already been identified easily justify proceeding cautiously until we have the evidence needed to make a science-based decision to implement the policies that the Bates letter advocates.

The fact is that [health policy makers in England have thrown the precautionary principle to the wind](#)¹² and are aggressively embracing e-cigarettes, which has turned the whole country into a giant experiment to test whether the e-cigarette optimists' hypotheses are correct. (Fourteen of the 53 signatories of the letter are from England or UK.) Presumably, in a few years there will be actual evidence about the effects of e-cigarette use in England on youth uptake and overall population effects on cessation (as opposed to the effects on the much smaller group of motivated smokers who are using them as cessation aids).

⁹ Kriebel D, Tickner J. Reenergizing Public Health Through Precaution. [Am J Public Health](#) 2001 September; 91(9): 1351–1355. PMC1446776

David Kriebel, ScD and Joel Tickner, ScD

¹⁰ Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation*. 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

¹¹ Brown J1, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction*. 2014 May 20. doi: 10.1111/add.12623. [Epub ahead of print]

¹² National Centre for Smoking Cessation and Training (NCSCT) in partnership with Public Health England. [Electronic Cigarettes](#). 2014. See also ASH UK. [Electronic Cigarettes](#). May 2014.

Once WHO and others have that data, the precautionary principle can be applied properly and, if appropriate, restrictions on e-cigarettes relaxed.

4. Targets and indicators for reduction of tobacco consumption should be aligned with the ultimate goal of reducing disease and premature death, not nicotine use per se, and therefore focus primarily on reducing smoking. In designing targets for the non-communicable disease (NCD) framework or emerging Sustainable Development Goals it would be counterproductive and potentially harmful to include reduction of low-risk nicotine products, such as e-cigarettes, within these targets: instead these products should have an important role in meeting the targets.

As noted above, the letter fails to present any evidence that these assertions are correct. The evidence that has accumulated in the 23 years since Michael Russell first promoted this hypothesis has demonstrated that, at the very least, there are several direct adverse health consequences of nicotine.

5. Tobacco harm reduction is strongly consistent with good public health policy and practice and it would be unethical and harmful to inhibit the option to switch to tobacco harm reduction products. As the WHO's Ottawa Charter states: "Health promotion is the process of enabling people to increase control over, and to improve, their health". Tobacco harm reduction allows people to control the risk associated with taking nicotine and to reduce it down to very low or negligible levels.

When and if the tobacco companies who are profiting from selling e-cigarettes submit evidence that these statements are true to competent authorities they should be permitted to market e-cigarettes for these purposes.

In the meantime England's experience (as well as other countries where there are no meaningful controls on e-cigarette marketing and promotion, including the United States) will provide evidence on the actual effects of e-cigarette use on the population's health.

6. It is counterproductive to ban the advertising of e-cigarettes and other low risk alternatives to smoking. The case for banning tobacco advertising rests on the great harm that smoking causes, but no such argument applies to e-cigarettes, for example, which are far more likely to reduce harm by reducing smoking. Controls on advertising to non-smokers, and particularly to young people are certainly justified, but a total ban would have many negative effects, including protection of the cigarette market and implicit support for tobacco companies. It is possible to target advertising at existing smokers where the benefits are potentially huge and the risks minimal. It is inappropriate to apply Article 13 of the FCTC (Tobacco advertising, promotion and sponsorship) to these products.

It is reassuring that the letter recognizes that e-cigarettes should not be marketed to youth and nonsmokers; unfortunately [e-cigarettes are marketed to youth and nonsmokers](#).¹³ The reality is

¹³ Grana R, Ling P. "Smoking revolution": a content analysis of electronic cigarette retail websites. [Am J Prev Med](#). 2014 Apr;46(4):395-403. doi: 10.1016/j.amepre.2013.12.010. See also de Andrade M, Hastings G, Angus K.

that they are being [heavily marketed on television](#)¹⁴ to these groups, which is being reflected in the rapid increase in youth use in countries where these products are being marketed.

The optimistic view held by many in England (and signatories of the letter) about marketing of e-cigarettes did not anticipate Lorillard Tobacco's June 9, 2014, announcement that it is beginning an advertising campaign for its Blu e-cigarettes in the UK. There will be a national TV commercial to be accompanied by a national tour of music acts. According to an article in the [trade press](#):

Showcasing the *freedom blu e-cigarettes offer to smokers*, the advert is designed to inspire adult smokers to grasp the freedom that's out there waiting for them. Alongside the advertisement, blu eCigs is taking some of the *top electronic music acts* in the UK on a nationwide tour that will call at cities including Edinburgh, Manchester, Brighton, and Bristol. From the end of June, smokers looking to switch to e-cigarettes will find that blu eCigs has taken centre stage in the UK market with availability in Co-op, Asda, WHSmith Travel and other retail outlets across the nation, the company claims.¹⁵ [emphasis added]

At the same time, it is important to recognize that the tobacco companies for decades have claimed that they are not marketing to youth (as e-cigarette companies claim today) despite cigarettes' strong penetration into the youth market. There is no reason to expect that the situation for e-cigarettes would be any different.

Indeed, current e-cigarette advertising tactics, including television commercials featuring celebrities promoting e-cigarettes as a lifestyle product are not consistent with marketing designed to reach established smokers who want to quit using tobacco cigarettes. The strategies are consistent with strategies used for decades to attract youth and young adults to tobacco use.

Application of Article 13 is not only appropriate because of the experience with cigarettes, but also because [youth who experiment with cigarettes are much more likely to have become established cigarette smokers](#) if they use of e-cigarettes than if they do not.¹⁶

7. It is inappropriate to apply legislation designed to protect bystanders or workers from tobacco smoke to vapour products. There is no evidence at present of material risk to health from vapour emitted from e-cigarettes. Decisions on whether it is permitted or banned in a particular space should rest with the owners or operators of public spaces, who can take a wide range of factors into account. Article 8 of the FCTC (Protection from exposure to tobacco smoke) should not be applied to these products at this time.

Promotion of electronic cigarettes: tobacco marketing reinvented? [BMJ](#). 2013 Dec 21;347:f7473. doi: 10.1136/bmj.f7473 and the [Stanford Research into the Impact of Tobacco Advertising collection of e-cigarette ads](#).

¹⁴ Duke JC, Lee YO, Kim AE, Watson KA, Arnold KY, Nonnemaker JM, Porter L. Exposure to Electronic Cigarette Television Advertisements Among Youth and Young Adults. [Pediatrics](#) originally published online June 2, 2014; DOI: 10.1542/peds.2014-0269.

¹⁵ Briggs F. New TV ad from blu eCigs marks the launch of a multi-million pound advertising campaign. [Retail Times](#). 9 June 2014.

¹⁶ Dutra LM, Glantz SA. Electronic Cigarettes and Conventional Cigarette Use Among US Adolescents: A Cross-sectional Study. [JAMA Pediatr](#). 2014 Mar 6. doi: 10.1001/jamapediatrics.2013.5488. [Epub ahead of print]

This statement is incorrect on both counts.

The signatories of the letter seem not to have read Chapter 5 of the 2014 Surgeon Generals' report, which concluded, based on a review of an extensive evidence base, that "[The evidence is sufficient to infer that nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth.](#)"¹⁷

Indeed, all the conclusions of Chapter 5 seem to have been ignored:

1. The evidence is sufficient to infer that at high-enough doses nicotine has acute toxicity.
2. The evidence is sufficient to infer that nicotine activates multiple biological pathways through which smoking increases risk for disease.
3. The evidence is sufficient to infer that nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences for brain development.
4. The evidence is sufficient to infer that nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes such as preterm delivery and stillbirth.
5. The evidence is suggestive that nicotine exposure during adolescence, a critical window for brain development, may have lasting adverse consequences for brain development.
6. The evidence is inadequate to infer the presence or absence of a causal relationship between exposure to nicotine and risk for cancer [but see the comments above about other effects on cancer].

The signatories of the Bates letter might also want to consider the [warning that Altria/Philip Morris/NuMark includes with its MarkTen e-cigarettes](#):¹⁸

WARNING: This product is not a smoking cessation product and has not been tested as such. This product is intended for use by persons of legal age or older, and not by children, women who are pregnant or breast feeding, or persons with or at risk of heart disease, high blood pressure, diabetes, or taking medicine for depression or asthma. Nicotine is addictive and habit forming, and it is very toxic by inhalation, in contact with the skin, or if swallowed. Nicotine can increase your heart rate and blood pressure and cause dizziness, nausea, and stomach pain. Inhalation of this product may aggravate existing respiratory conditions. Ingestion of the non-vaporized concentrated ingredients in the cartridges can be poisonous.

¹⁷ US Surgeon General. *The Health Consequences of Smoking: 50 Years of Progress*. 2014 Chapter 5: Nicotine.

¹⁸ Mark Ten Product and Information Guide. Accessed 8 June 2014. The same information was on the Mark Ten website at <https://www.markten.com/gconnect/inactivity.action> on 8 June 2014.

CA Proposition 65 Warning: This product contains nicotine, a chemical known to the State of California to cause birth defects or other reproductive harm.

(Lest people think that Philip Morris is having an attack of candor, remember that they are still under a court order from Federal Judge Gladys Kessler prohibiting them from lying about the effects of nicotine as a result of her ruling that Philip Morris violated, and is likely to continue violating, the US Racketeer Influenced and Corrupt Organizations Act.) [Mark Ten is also already a brand used for cigarettes in several countries.](#)¹⁹

With regard to exempting e-cigarettes from FCTC Article 8, there is no question that [e-cigarettes pollute the air that bystanders breathe](#)²⁰ and bystanders exposed to secondhand e-cigarette aerosol have detectable levels of cotinine, a metabolite of nicotine, in their body.²¹

While it is too soon to determine precise adverse long-term health effects of this involuntary exposure, there is no health justification for increasing involuntary exposure to ultrafine particles, nicotine, and other toxins. (This is another example of how the Bates letter turns the precautionary principle on its head.)

This is also probably the most radical argument made in the letter, since there is no reason to expect that exempting smokers who use e-cigarettes from clean indoor air laws would help them quit smoking. Indeed, tobacco companies aggressively promote e-cigarettes as a way to deal with smokefree environments. Creating such a bridge with a product designed to imitate smoking behavior will likely undermine the benefits of smokefree environments in terms of promoting and supporting smoking cessation efforts. Nicotine replacement products that do not emit a nicotine-laced aerosol, such as the nicotine patch and lozenge, could continue to be used in indoor environments.

8. The tax regime for nicotine products should reflect risk and be organised to create incentives for users to switch from smoking to low risk harm reduction products. Excessive taxation of low risk products relative to combustible tobacco deters smokers from switching and will cause more smoking and harm than there otherwise would be.

This argument presumes that unrestricted promotion of e-cigarettes as a consumer product will result in net population health benefits, which, as noted above, have not been substantiated.

9. WHO and national governments should take a dispassionate view of scientific arguments, and not accept or promote flawed media or activist misinterpretations of data. For example, much has been made of ‘gateway effects’, in which use of low-risk products would, it is claimed, lead to use of high-risk smoked products. We are unaware of any credible evidence that supports this conjecture. Indeed, similar arguments have been made about

¹⁹ http://www.cigarettespedia.com/index.php/BrandMark_Ten

²⁰ Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. [Circulation](#) 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

²¹ Grana RL, Benowitz N, Glantz SA. E-cigarettes: a scientific review. [Circulation](#) 2014 May 13;129(19):1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667.

the use of smokeless tobacco in Scandinavia but the evidence is now clear that this product has made a significant contribution to reducing both smoking rates and tobacco-related disease, particularly among males.

While there are not yet longitudinal studies of e-cigarette use among youth that will provide a precise answer to what fraction of youth who smoke cigarettes began with e-cigarettes, as noted above we do know that (1) youth use of e-cigarettes is growing rapidly, (2) that there are high levels of dual use of cigarettes and e-cigarettes among youth, (3) that e-cigarette use is associated with progression from experimentation with cigarettes to established smoking, (4) that youth who use e-cigarettes are less likely to have stopped smoking cigarettes, and (5) that some youth who use e-cigarettes report never smoking a cigarettes, mean that some youth are initiating nicotine addiction with e-cigarettes.

The signatories of the letter also ignore longitudinal evidence from the United States that among a cohort of military trainees who experienced a period of forced nicotine abstinence during basic military training "[smokers initiating smokeless tobacco use after basic military training, most demonstrated harm escalation \(87%\), which was 5.4 times more likely to occur than was harm reduction \(e.g., smoking to smokeless tobacco use\).](#)"²²

10. WHO and parties to the FCTC need credible objective scientific and policy assessments with an international perspective. The WHO Study Group on Tobacco Product Regulation (TobReg) produced a series of high quality expert reports between 2005 and 2010. This committee should be constituted with world-class experts and tasked to provide further high-grade independent advice to the WHO and Parties on the issues raised above.

The [TobReg Committee](#) is already considering the issues surrounding e-cigarettes (and has for some time), including by commissioning a [detailed summary of all the available evidence that was presented at its December meeting.](#)²³ TobReg continues to work on this issue and will be issuing a report on e-cigarettes later this year.

Rather than calling for a change to the membership of this committee, the signatories of this letter should allow TobReg to do its work.

A Closing Comment

Unlike the signatories of the Bates letter, Clive Bates is an advocate not a scientist, so his reputation and future prospects depend on his ability to win policies he seeks and stop policies that he opposes.

In contrast, the reputations of the scientists who signed the letter are measured based on a different standard, notably their willingness to assess all the evidence (not just that which

²² Klesges RC, Sherrill-Mittleman D, Ebbert JO, Talcott GW, DeBon M. Tobacco use harm reduction, elimination, and escalation in a large military cohort. *Am J Public Health* 100:2487-92, 2010.

²³ Grana R, Benowitz N, Glantz SA. Background Paper on E-cigarettes (Electronic Nicotine Delivery Systems) Prepared for the WHO Tobacco Free Initiative, December 2013. <http://escholarship.org/uc/item/13p2b72n>.

supports a particular decision or position) and whether the judgments that they make stand the test of time.

It is in that spirit that I urge the signatories of the Bates letter to consider the fact that they have, put their reputations behind everything it says and recommends and carefully review the evidence cited in this comment (as well as the much larger literature cited in the papers and reports cited here) and consider whether they wish to remove their names from Bates' letter.