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SANTA BARBARA • SANTA CRUZ

Pamela M. Ling, Professor
Director, Center for Tobacco Control Research and Education
Department of Medicine
530 Parnassus Avenue, Ste. 366
San Francisco, CA 94143-1390
Pamela.ling@ucsf.edu

Phone: 415-514-8627
Fax: 415-514-9345

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Francisco Armada
Advisor Tobacco Control
Noncommunicable Diseases and Mental Health
Pan American Health Organization

Dear Dr. Armada,

In October 2020 the Pan American Health Organization (PAHO) made a request to the Center for Tobacco Control and Education (CTCRE) of the University of California San Francisco (UCSF) to conduct a study to answer questions from Brazil's Agencia Nacional de Vigilancia Sanitaria (Anvisa) on potential for harm reduction of Electronic Nicotine Delivery Systems (ENDS). As a WHO Collaborating Center, CTCRE engaged in further discussions and, within the time frame provided, agreed that an original study or a systematic review was not feasible. However, we agreed to provide answers to the questions based on the research we have conducted, and other available evidence. We understand that a more comprehensive study might be desired, and we will continue to discuss with you and with WHO on how to proceed.

CTCRE serves as a focal point for a broad range of research, education, and public service activities for over 70 faculty in all four schools (Medicine, Nursing, Pharmacy and Dentistry) at UCSF.[i] CTCRE is a part of UCSF's Cardiovascular Research Institute and the UCSF Helen Diller Family Comprehensive Cancer Center's Cancer Control Program. Additionally, CTCRE administers one of nine Tobacco Centers for Regulatory Science (TCORS) grants in the United States, which is funded by the U.S. Food and Drug Administration (FDA) and the National Institutes of Health.

In its first five years (2013 – 2018), the TCORS grants were extremely productive in understanding data needed to inform regulation,[ii] published 135 peer-reviewed papers,[iii] and submitted 81 public comments to the FDA and other agencies on tobacco regulation.[iv]

[i] https://tobacco.ucsf.edu/about
[ii] https://tobacco.ucsf.edu/sites/g/files/tkssra4661/f/wysiwyg/TCORS%201.0%20Accomplishments%202013-2018.pdf
[iii] https://tobacco.ucsf.edu/sites/g/files/tkssra4661/f/wysiwyg/P50%20CA180890%20TCORS%202021-01-19a.pdf
[iv] https://tobacco.ucsf.edu/list-public-comments-fda-and-other-agencies-ucsf-faculty-and-fellows-and-others-links-comments

The work of the current TCORS is ongoing, and has three primary goals:[v]

1) Evaluate the short-term health effects of the new tobacco products and how specific product characteristics influence health effects and behavior
2) Scientifically inform product standards and marketing regulations for the new products
3) Build the tobacco regulatory science research community

It accomplishes these goals through five main projects:

1) The impact of different e-cigarette characteristics (components and e-liquids) on acute lung injury.[vi]
2) The short-term cardiovascular effects of e-cigarettes and how e-cigarettes compare with HTPs.[vii]
3) Cardiovascular health effects of Heated Tobacco Products.[viii]
4) Product characteristics, use behaviors and role in nicotine exposure of smokeless tobacco in rural high schools.[ix]
5) The impact of changing tobacco product use on health care costs among general and vulnerable populations.[x]

In addition to the TCORS grant, faculty at the CTCRE are funded to conduct a range of other tobacco-related research,[xi] including tobacco use cessation. Each of the past[xii] and current[xiii] TCORS have published (and continue to publish) hundreds of research papers addressing ENDS (or DEF in its Portuguese abbreviation[xiv]) in addition to the thousands of papers published in the past decade from scientists worldwide. Below we address each of the four questions submitted by Anvisa via PAHO based on our own research.

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[v] https://tobacco.ucsf.edu/tobacco-center-regulatory-science

[vi] https://tobacco.ucsf.edu/research/impact-different-e-cigarette-characteristics-acute-lung-injury-20

[vii] https://tobacco.ucsf.edu/research/short-term-cardiovascular-effects-e-cigarettes-influence-device-power-and-e-liquid-ph-and-how-e-cigarettes-compare-heat-not-burn-products-20

[viii] https://tobacco.ucsf.edu/research/cardiovascular-health-effects-emerging-heat-not-burn-tobacco-products-20

[ix] https://tobacco.ucsf.edu/research/current-and-emerging-tobacco-products-rural-context-influences-product-characteristics-perceptions-behaviors-and-biologic-exposures-20

[x] https://tobacco.ucsf.edu/research/impact-changing-tobacco-product-use-healthcare-costs-general-and-vulnerable-populations-20

[xi] https://tobacco.ucsf.edu/tobacco-faculty

[xii] https://web.archive.org/web/20180725113926/https:/www.fda.gov/TobaccoProducts/PublicHealthScienceResearch/Research/ucm369005.htm

[xiii] https://www.fda.gov/tobacco-products/research/tobacco-centers-regulatory-science-tcors

[xiv] Note that within the Brazilian legal definition DEFs include all products that have any electronic component, such as electronic cigarettes, electronic waterpipes, heated tobacco products, hybrid electronic cigarettes, among others. These products differ vastly from each other including in their toxicity, safety, health impact, potential for cessation of cigarette smoking. Studies' conclusions and recommendations are limited to the product or products included. There are thousands of DEFs in the United States and other markets.

1.a) What would be the concept of harm reduction?

At CTCRE we do not have a concept of harm reduction that is different than the broadly understood definition of harm reduction as "an effort to implement public health measures to decrease the social or individual impact of various health behaviors that are harmful to society, families, communities and persons."[xv]

Within this public health approach, we considered whether these policies could have unintended consequences that would exacerbate harm or create new harms at the population level.

1.b) How is this concept applicable (or not) to tobacco products, especially DEFs?

The harm reduction concept, as applied to tobacco products, is based on the idea that there is a continuum of risk[1] among tobacco products and in the several forms of nicotine delivery.[xvi] It is often used interchangeably with a nicotine continuum of risk, the latter based on the knowledge of the addictive powers of nicotine. It is also based on an assumption that available, health-authorities approved, tobacco dependence treatments have failed,[xvii] and that there might be a proportion of tobacco users who can't or won't quit. We conducted a systematic review of the published literature on tobacco harm reduction, and found that tobacco, e-cigarette or drug industry funding was significantly associated with support for promotion of tobacco products as harm reduction.[2 and xviii]

The application of this concept to DEF is an assumption that these products are safer that combustible (or conventional) cigarettes and that they would promote cigarette smoking quitting.[3] Whether DEF would be a harm reduction option for users of other types of tobacco products, including but not limited to, smokeless tobacco and waterpipe have not been the focus of as much research. Therefore, the concept of harm reduction when applied to DEFs mostly uses combustible cigarettes as the comparison point.

An important caveat is that there is a huge variance amongst the several DEFs currently in the market in the United States and in different countries.[4] Therefore, it is, to date, impossible to make a clear and precise statement that could be applied to the safety and relative risk of DEFs as a group or groups of

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[xv] Harm reduction: An approach to reducing risky health behaviours in adolescents. Paediatr Child Health. 2008;13(1):53-60. DOI: 10.1093/pch/13.1.53

[xvi] See also https://tobacco.ucsf.edu/fda-should-not-adopt-nicotine-"harm-reduction"-paradigm-because-doing-so-likely-increase-amount-smoking-caused-disease-and-death

[xvii] It is important to note that tobacco dependence treatment, as contemplated by Article 14 of the WHO Framework Convention on Tobacco Control, has yet to be fully implemented as recommended by scientific evidence, in the vast majority of countries (See WHO Global Tobacco Control Report, 2019. Many consider this lack of implementation a missed opportunity given the high proportion of tobacco users that express a wish to quit.

[xviii] Supplemental files available at https://ajph.aphapublications.org/doi/suppl/10.2105/AJPH.2019.305106

products that will provide certainty that these products are safe and effective in promoting smoking cessation.

1.c) Has the tobacco industry used it related to its products? If so, how has the tobacco industry used it?

Yes, the tobacco industry has embraced the concept of harm reduction and has been active in funding science, developing new products, marketing and lobbying to persuade countries to adopt a harm reduction approach, focused on promotion and sales of new electronic and heated tobacco products. This approach often serves as a distraction from, or an alternative to, implementing tobacco control policies against cigarettes.[5, 6] This tobacco industry strategy follows decades of well documented efforts by the tobacco industry to develop a "safer" cigarette, and to maintain nicotine addiction, and ultimately, tobacco use. [2, 6-21]

Within this discussion it is also important to differentiate risk reduction to exposure reduction.[xix] Reducing exposure of consumers to certain substances have not yet been determined to reduce health risks.[18, 22] This is an important distinction, however it is unlikely to be well understood by the public.[8, 9, 11-13, 16, 17, 19, 23, 24]

2.a) Is there evidence that DEF promote harm reduction by replacing conventional cigarettes? If so, what are the pathologies for which damage reduction is observed?

There is no conclusive evidence that at a population level DEF have significantly reduced to incidence, prevalence or mortality from any particular disease. There is growing evidence that several types of DEF may cause harm.[25, 26]

The potential for DEF to serve as a smoking cessation device, on the assumption that switching from cigarettes to DEF would reduce harm, have yet to be confirmed,[27-31] particularly given the differences among different products[3] and the rapid innovations introduced by the manufacturers. A few studies demonstrated that certain types of DEF may help smokers quit when integrated into a smoking cessation service that include behavioral counseling and support.[29] However, these studies also found that use of DEF under real world conditions by consumers outside of smoking cessation clinical trials did not increase successful smoking cessation. Studies indicate that the efficacy of DEF is similar, within smoking cessation settings, to the efficacy of varenicline.[1] The safety of using e-cigarettes for cessation needs further studies.

A very significant point related to the potential for harm reduction is whether DEF are considered a cessation aid or a consumer product. As a cessation aid, these products would need to go through the same steps as other cessation drugs to ensure not just efficacy, but safety for a range of conditions.[29]

[xix] https://tobacco.ucsf.edu/fda-should-not-permit-modified-exposure-claims-iqos-because-they-are-likely-be-misunderstood-modified-risk-claims

As a consumer product, widely available, the harm reduction potential of DEFs are unlikely to be observed.

2.b) Is there a percentage by which damage reduction is expressed?

None that has been scientifically and independently (from tobacco industry) established.

3.a) Would the dual use of conventional cigarettes and DEFs promote harm reduction? If so, what are the pathologies for which damage reduction is observed?

No, on the contrary. Dual use, which is the most common pattern of use of DEF[32, 33] present no health benefit and in fact may increase harm.[34]

3.b) Is there a percentage by which damage reduction is expressed?

No.

4. How does a possible harm reduction behave, in the aspects of individual and collective health?

As previously , at the individual level, and within the context of a smoking cessation clinic, with the supervision of a health professional, there is a possibility that DEF could help an individual person with cessation of cigarette smoking, if complete cessation is achieved (i.e. no dual use).[29] That is not the experience in most countries and by most users. In terms of collective health, no benefits have been documented.

On a follow-up email from PAHO, also in October 2020, additional questions were proposed, for which a more detailed response could be provided at a later date. In summary, the additional three questions: 1) What is the target consumer for the END, ENNDS and HTP?; 2) Are such products only intended for people who wish to quit smoking? 3) Are there ways to ensure that these devices are used only by the target consumers?

These questions address the allegedly intent of the manufacturers of DEF versus the real-world impact. To our knowledge, no manufacturer has applied to market and sell DEF cessation devices. (The one that was approved in the United Kingdom is no longer in production.[xx]-[xxi]) It refers to the question on whether these are consumer products, as currently marketed, or cessation aids. Countries that have allowed these products to be sold as consumer products have experienced an increase in use among youth, even in countries where there are tobacco control measures restricting advertisement. Australia recently changed its policy to ensure that only those seeking cessation would have access to DEF. the success of this policy remains to be seen.

[xx] https://www.reuters.com/article/us-health-ecigarettes-brit-am-tobacco/bats-novel-e-cigarette-rival-wins-uk-medical-approval-idUSKBN0H70F520140912

[xxi] https://www.totallywicked-eliquid.co.uk/vaped/the-only-medically-licensed-e-cig-is-axed/

Our research has demonstrated that adolescents and youth are highly susceptible to DEF marketing, which leads to initiation of use. Our research also shows that marketing of DEF conveys messages of safety that are not supported by available evidence. [10, 13, 14, 16, 17, 23, 35-42]

If there are any questions, please do not hesitate in contacting us. As a WHO Collaborating Center, we remain committed to support PAHO and the Member States to the best of our ability.

Yours Sincerely,

Pamela Ling, Professor of Medicine

CC: Mr. Diogo Alves, PAHO Brazil
Dr. Ranti Fayokun, WHO

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