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White Paper on Electronic Nicotine Delivery Systems by the Indian Council of Medical Research: A Critical Appraisal of the Scientific Evidence

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FOREWORD

The Indian Council of Medical Research (ICMR), New Delhi is India's most authoritative voice on matters related to pursuing highest scientific achievements on the one hand, and finding practical solutions to the health problems of the country on the other hand. The ICMR's core responsibility is to communicate to the public the best available scientific information regarding ways to improve personal and public health.

On 31st May 2019, an ad-hoc Expert Committee of the ICMR published its first report on e-cigarettes, "White Paper on Electronic Nicotine Delivery Systems".[1] Their conclusion recommends a "*…complete prohibition on ENDS or e-cigarettes in India in the greater interest of protecting public health*".

We are concerned that ICMR has issued this radical policy recommendation in light of the broad consensus in the scientific community that e-cigarettes are much less harmful than combustible cigarettes including bidis. Because the White Paper is based on uncritical reporting of the evidence, it fails to report a balanced overview of the risk-benefit ratio of these new technologies, and grossly misrepresents the actual evidence base.[2-4]

To correct these misperceptions, we present a critical rebuttal to the "White Paper on Electronic Nicotine Delivery Systems" that challenges the scientific claims advanced by the ICMR Expert Committee and therefore argues against the Committee's proposal of banning e-cigarettes in India.

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The major arguments in support of the Committee's conclusions are: 1) adverse health effects and unknown health risks, 2) risks from second-hand exposure, 3) risk of dual use and initiation of tobacco addiction among non-smokers and e-cigarette use by youth, and 4) lack of effectiveness for smoking reduction and cessation. In the following sections, we will explore in detail these arguments and provide an insight on the omissions that were noticed in the paper.

HEALTH RISKS AND EFFECTS OF E-CIGARETTES

The evidence that e-cigarettes are by far less harmful than tobacco cigarettes and overall carry a small health risk is clear. Some studies have reported potential adverse effects, yet on balance multiple literature reviews from scientists and health organizations clearly acknowledge the lower harm potential of e-cigarettes.[2-4] When examining the overall safety/risk profile of e-cigarettes (both absolute and relative to smoking), it is vital to review all the available literature rather than selectively choosing a limited number of studies, many of which either misinterpret research findings or have no meaningful clinical significance.

The first review on e-cigarette safety in 2014 reported that "*electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes*".[5] Other review teams have also come to similar conclusions.[6,7] In recent years, several health organizations have acknowledged the harm reduction potential of e-cigarettes in their official reports. In 2014 and 2015, Public Health England (PHE) published a report stating that e-cigarettes are unlikely to have more than 5% of the risk of tobacco cigarettes.[8,9] While there was some criticism of the 2015 PHE for one of the studies in the review report,[10,11] the conclusion was based on an extensive review of the literature citing

multiple studies, and the 5% calculation was based on the much lower toxin emissions and toxicological impact of e-cigarettes compared to tobacco cigarettes.[12] PHE updated their report in 2018, assessing all new evidence since 2015, and reported no change in their original conclusion.[3] The Royal College of Physicians (RCP) repeated the conclusions of PHE that e-cigarettes are 95% less harmful than smoking in their report about tobacco harm reduction and e-cigarettes in 2016.[2] The American Heart Association (AHA) acknowledged the lower harm of e-cigarettes in 2014 by stating that, for those smokers who are unable or unwilling to quit smoking with currently approved methods, an effort to quit smoking with e-cigarettes should be supported.[13] The American Cancer Society in 2018 released a position statement about e-cigarettes mentioning that exclusive use of e-cigarettes is preferable to continuing to smoke combustible products for smokers who are unwilling or unable to quit.[14] Last year, the National Academies of Sciences, Engineering and Medicine (NASEM) published an extensive review of the literature on e-cigarettes, over 750 pages long, in which they acknowledged the lower levels of toxic emissions from e-cigarettes compared to tobacco cigarettes, and the significantly lower toxicological and clinical impact of e-cigarettes compared to smoking.[4] In India, the Heart Care Foundation of India (HCFI) recently released a consensus statement supporting e-cigarette use as a smoking cessation aid for those unable to quit with other means.[15]

In addition to the evidence provided by systematic reviews of the literature, clinical evidence is mounting that switching from smoking to e-cigarette use could improve disease conditions such as asthma and high blood pressure.[16-18] No adverse health effects were reported in a 3-year follow-up of healthy never-smoking e-cigarette users in a small study.[19] Clinical studies measuring biomarkers of exposure have found that e-cigarette users who have quit smoking have levels similar to never smokers and former smokers on nicotine replacement therapies.[20,21] ICMR raised safety concerns based on a recent smoking cessation trial that reported 27 serious adverse events in the e-cigarette arm.[22] However, ICMR failed to consider that the study authors stated that no serious adverse event was related to product use, and a similar number of serious adverse effects were observed in the nicotine replacement therapy arm.

ICMR rightly argues that there are no long-term clinical studies to assess the health impact of e-cigarettes. This is to be expected because e-cigarettes have been widely available in the market for less than 10 years. The lack of availability of long-term studies is a common occurrence with medications – for example, antihypertensive and cholesterol-lowering medications did not conduct clinical trials with decades of use before being marketed despite expecting use by patients for many years. In fact, it would be practically and economically impossible for any product to be marketed only after decades of clinical and epidemiological research. The accepted practice, applied even to pharmaceutical products, is to perform post-marketing surveillance in order to examine the long-term health effects. The same procedures should be applied to e-cigarettes. Based on the available evidence, implementing a ban based on the lack of long-term studies is not justified. At the same time, authorities need to consider the long-term adverse effects of smoking that are well-established and documented. In summary, an extensive review of the literature overwhelmingly supports the lower risk potential of e-cigarettes while no clinical evidence exists for established, long-term adverse health effects in any human body system caused by e-cigarette use. We have no doubt that, from a health perspective, e-cigarettes represent an important tool for smokers to reduce their risk. The position by ICMR is not in line with the recommendations of many health organizations worldwide and fails to consider the substantial body of literature that demonstrates the harm reduction potential of e-cigarettes.

SECOND-HAND EXPOSURE TO E-CIGARETTES

ICMR claims in its report that second-hand exposure to e-cigarettes has adverse health effects. To the best of our knowledge, there is no published scientific evidence of harm to bystanders from exposure to an e-cigarette. The available evidence on e-cigarette aerosol chemistry indicates that any risk of harm, if present, is extremely low, and orders of magnitude lower compared with tobacco smoke.[23] Besides the substantial differences in e-cigarette aerosol compared to smoke chemistry, an important characteristic of e-cigarettes is their lack of side-stream emissions so that any environmental exposure is derived only from the exhaled and diluted aerosol of e-cigarette users. One systematic review has raised concerns about environmental emissions from e-cigarettes, but no actual health risks were identified because the study did not report on the level of exposure of e-cigarette aerosol.[24] Research shows that >99.9% of e-cigarette emissions from exhaled breath of vapers consist of the base ingredients (propylene glycol, vegetable glycerol), water and nicotine[25] and the nicotine levels are approximately 10 times lower than

in tobacco smoke.[26] Nicotine exposure from second-hand tobacco smoke has never been associated with disease or health risks, so it is a reasonable assumption that traces of nicotine detected in the environment are unlikely to result in any health risk. More importantly, no carcinogenic tobacco-specific nitrosamines were measured in the environment after e-cigarette use.[26] Considering the composition of exhaled e-cigarette aerosol, studies on particulate matter levels and size are generally irrelevant to health risks. Unlike tobacco smoke, which increases carbonyl levels in room air, exhaled e-cigarette vapor is unlikely to do so because it contains minimal levels of carbonyls.[27,28] In one study, after e-cigarette use, acetaldehyde levels increased minimally relative to background levels (from 9.0 μg/m^3 to 12.4 μg/m^3), but remained more than one order of magnitude lower than the European Union (EU) Indoor Air Quality guideline for acetaldehyde of 200 μg/m^3.[29] Metal emissions have been found in some samples of e-cigarette aerosol, but at levels well below established safety limits.[30,31] Because environmental exposure to e-cigarettes is derived from exhaled breath and is diluted in the large volume of room air, based on the available data, such emissions are very unlikely to cause any substantial health concern.

The ICMR suggested that passive exposure to vapors during pregnancy could severely affect the health of both the mother and the fetus. We are not aware of any study assessing environmental exposure of pregnant women to e-cigarette aerosol. In fact, the only study on pregnant women, presented recently in a scientific conference, found that the newborns of women who had quit smoking and were using e-cigarettes had the same birth weight as never-smoking women, while the newborns of women who smoked had 316 g lower birth weight.[32]

In conclusion, contrary to the ICMR statement, the research data overall demonstrates that environmental exposure to e-cigarette emissions does not appear to impose any significant health risk.

EFFECTS OF E-CIGARETTES ON SMOKING REDUCTION AND CESSATION

Quitting smoking is the ideal goal, the most valuable (and cost-effective) measure to improve prognosis and reduce disease risk.[33] In just a few years, e-cigarettes have become the most popular smoking cessation aid in several countries. Up to 35% of US smokers have used e-cigarettes in their most recent smoking cessation attempt, and similarly high popularity has been observed elsewhere including UK and France.[34-36]

Several of the earliest studies, including small and randomized controlled trials, have shown a positive association between e-cigarette use and smoking cessation or reduction.[37-41] Results were best for those with long-term and daily e-cigarette use,[42,43] which is to be expected because consistent, regular use of any smoking cessation aid is required for successful substitution. Not all studies have reported positive findings, failing to find a positive association, and in some cases finding a negative association between e-cigarette use and smoking cessation.[44-46] Looking at reviews of multiple studies, Cochrane systematic reviews and meta-analyses have reported that e-cigarettes may help smokers to quit.[47,48] Other meta-analyses of randomized controlled and cohort studies found inconclusive evidence on the association between e-cigarette use and smoking cessation and, in one review, a negative association.[49,50] The difficulty with utilizing these reviews and meta-analyses is that they are based on studies with a high probability of bias from sources such as combining subjects with and without a quit motivation, classifying subjects reporting ever use or occasional use together with regular/daily users, or conducting studies with subjects who had already failed to quit with the use of e-cigarettes.[51,52]

Identifying these biases in earlier studies is important to consider when assessing evidence for e-cigarettes and smoking cessation. More recent studies that have differentiated between occasional or experimental users from regular users, and research designs that have included the assessment of the time of quitting smoking have found a consistent and strong association between e-cigarette use and smoking cessation.[53-55] A randomized controlled trial with a 1-year follow-up found that e-cigarette use had no adverse effects and was almost twice as effective as nicotine replacement therapies in smoking cessation.[22] An analysis of a large US population survey indicated that the substantial increase in e-cigarette use between 2010 and 2015 was significantly associated with an increase in smoking cessation,[56] the first significant increase in the smoking cessation rate in the past 25 years. Population data from the UK tracked the increase in e-cigarette use with an increase in smoking cessation rates, while e-cigarette users were 60% more likely to quit smoking compared to nicotine replacement therapy users.[57,58] E-cigarette users, especially frequent users, have been found to have higher rates of smoking cessation attempts and success.[41,59-62] This is linked to quitting smoking being a main reason for e-cigarette use for the majority of current and former smokers.[36,63-66]

Some concerns have been raised by public health scientists about the dual use of e-cigarettes and tobacco cigarettes. Dual use does occur, and it can be a transition phase during an attempt to quit smoking, the same transition period that occurs during quit attempts with pharmaceuticals. It is certainly to be expected that many smokers will fail to completely quit smoking with e-cigarettes and may instead become dual users. This is also the case with most smokers who choose to use smoking cessation medications and eventually fail to quit and relapse to being "single users" of tobacco cigarettes.[67-69] These failed quit attempts do not represent an argument against the use of smoking cessation medications or e-cigarettes. Does dual use increase health risks? One study measuring biomarkers of toxin exposure found that dual users of tobacco and e-cigarettes had similar levels compared to smokers even with the dual users smoking the same number of cigarettes daily as smokers.[21] For the many dual users who have substantially reduced their smoking consumption,[63] exposure to toxins is expected to be reduced compared to smoking at their previous consumption rate. To date one small clinical study has found improvements in the respiratory health of smoking asthmatics who significantly reduced their smoking (by >80%), but did not quit, with e-cigarette use.[17]

ICMR seems to be criticizing the sustained use of e-cigarettes by people who have managed to quit smoking because it may lead to sustained nicotine dependence. That would become an important public health issue, if long-term nicotine use was associated with adverse health effects. Studies evaluating long-term use of pharmaceutical nicotine replacement therapies and of a low-risk smokeless tobacco product, snus, have shown that the risks from nicotine intake are minimal and by far outweigh the benefits of smoking cessation.[70-75] For this reason, health organizations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) recommend the long-term use of nicotine in the form of nicotine replacement therapies if this is needed to maintain smoking cessation, to prevent relapse or even to reduce smoking.[76,77] Therefore, smoking cessation through long-term use of nicotine in a less harmful product such as e-cigarettes is by far preferable to continuous smoking.

Our conclusion based on the evidence from the newer, better-designed studies support that e-cigarettes have a strong potential as a smoking cessation aid, particularly for those smokers who fail at cessation or are unwilling to attempt to quit with currently approved medications.

E-CIGARETTE USE BY YOUTH AND GATEWAY TO SMOKING AND ADDICTION EFFECTS

Public health is rightly concerned with any potential increase in nicotine use by youth, and the 2016 US Surgeon General Report reports a large increase in e-cigarette use among youth.[78] The bias in these reports is that it confounds ever-use (even once) and experimental use (any past month) with regular use, even as infrequently as use once or twice a month. One-time or experimental use of an e-cigarette is extremely unlikely to increase any risk for developing any disease, particularly given the very low risk profile of e-cigarettes. Moreover, there is evidence that most youth are not using nicotine-containing e-cigarettes.[79] For public health surveillance, it is critical to survey the prevalence of regular (weekly and daily) e-cigarettes use, e-cigarette use by youth who smoke, and e-cigarette use by never-smoking youth. Another important indicator is changes in smoking prevalence since the introduction of e-cigarettes. The two large youth population surveys in the US, Monitoring the Future and National Youth Tobacco Survey, have shown that frequent (i.e., daily or almost daily) e-cigarette use is confined almost completely to smoking youth, and the rates of use among never smokers is low.[80-82] The surveys also reported that adolescents who smoked daily or almost daily during the past month were more likely to have used e-cigarettes as well as other tobacco products. Therefore, the issue of addiction to nicotine from e-cigarettes is irrelevant since many may already have been addicted to nicotine from tobacco cigarettes.

The White Paper argues that e-cigarettes are a "gateway" to tobacco cigarette use. Certainly, several youth studies have shown that e-cigarette use at baseline predicts use of tobacco cigarettes at follow-up.[83-87] A meta-analysis synthesized the findings of individual studies and interpreted the results as demonstrating a gateway to smoking effect.[88] However, the data also shows a bi-directional association, with tobacco cigarette use at baseline predicting e-cigarette use at follow-up.[83,89] Thus, no strict cause-and-effect association between e-cigarette use and tobacco cigarette use has been proven. A number of researchers have proposed a common liability model as a better fit for the data than the gateway hypothesis.[90,91] Another possibility is that youth who use e-cigarettes may eschew tobacco cigarettes or may substitute e-cigarette use for tobacco use as a social display. The strongest argument for youth using e-cigarette substitution is the marked and rapid decline (by more than 50%) in smoking prevalence among US youth observed since 2011,[92] the period when

e-cigarettes became popular. Where substitution is not readily available (due to strict regulation), US state-based data suggest that there are increased smoking rates among adolescents in states with stricter regulation compared to those with fewer regulations.[93,94]

There is no debate about the absolute need for monitoring e-cigarette use by youth. Appropriate regulatory actions should be undertaken in every case, including the regulation of advertising and promotion, and age requirements for purchase. The current evidence shows that frequent e-cigarette use by youth is largely confined to those who smoke. The good news is that youth smoking rates are continuously declining at a rapid pace even with the increase in e-cigarette experimentation. For public health surveillance, we must keep the relative harm of e-cigarettes in context because risks related to e-cigarette use are vastly lower than the risks from smoking. While any use of e-cigarettes by youth is not desirable, the health risks for non-smoking youth adopting e-cigarette use are projected to be substantially lower compared to initiating smoking.

MONITORING AND REGULATION: THE INDIAN PERSPECTIVE

For e-cigarettes to be an effective harm reduction and tobacco cessation public health strategy, a robust and proportionate regulatory framework is a requirement. The best example of a comprehensive and fully implemented regulatory framework on e-cigarettes exists in the EU: the Tobacco Products Directive (TPD), promulgated in 2014, and adopted into national legislation of all member states in 2016.[95] The TPD integrates e-cigarettes into the regulation for tobacco products, but under a separate section for e-cigarettes that does not classify them as tobacco products. This is appropriate because e-cigarettes do not contain any tobacco. While nicotine in e-cigarettes is derived from the tobacco plant, as is nicotine in pharmaceutical nicotine replacement therapies, this cannot scientifically justify the classification as a tobacco product in the same way that biodiesel cannot be considered a vegetable product because it is derived from plants.[96] For specific cases, the TPD allows the regulation of e-cigarettes as medicinal products, but almost in all cases they are marketed as consumer products with many of the same regulations as tobacco products. We note that the ICMR white paper incorrectly states that UK regulates e-cigarettes as medicines. The TPD regulation of e-cigarettes includes quality standards, nicotine concentration and volume limits in e-cigarette liquids and prefilled cartridges, marketing restrictions and a defined registration process for all products. Product sales are monitored and reported to an adverse effects registry. To minimize the uptake of e-cigarette use by youth, the regulation includes a ban on the sales to minors below the age of 18. The TPD is being continuously assessed with the goal of revising it every few years based on the monitoring process. In the TPD, e-cigarettes are treated differently from tobacco products and are excluded from many of the restrictions on combustible tobacco products, including the prohibition of flavors and the placement of health warning messages and pictorials on the packaging. The TPD, although not perfect, is realistic and largely applicable to any other country, including India.

Another model for regulation comes from Canada. In less than 4 years, Canadian authorities went from a ban on nicotine products to a legal framework for them. Canada legalized nicotine products in 2018 with the *Vaping and Tobacco Products Act* with the goal of "providing a balance between protecting youth from nicotine addiction and tobacco use, and allowing adults to legally access vaping products as a less harmful alternative to cigarettes".[97] Like the TPD, products without health claims are regulated as consumer products, and products making health claims are to be regulated as medicines, although no products have yet been marketed as medicines. The *Act* prohibits some flavors and additives, restricts advertising, and requires purchasers to be at least 19 years old. *The Consumer Chemicals and Containers Regulations*[98] specifies the labeling and composition of vapor products, with nicotine concentrations higher than permitted in the TPD (66 mg/mL compared to 20). The Canadian legislation has some differences compared to the TPD, but it offers another regulatory structure that is comprehensive and reasonably proportionate to the risks and benefits offered by vapor products.

Despite some recent improvements in tobacco control in India, demonstrated by the reduction in tobacco use from the Global Adult Tobacco Survey (GATS) 1 to GATS 2, India is still facing a huge challenge with tobacco use both for public health and economic consideration. The National Tobacco Control Program supports one tobacco cessation center per district and one center in each dental college[99] that is clearly inadequate to provide the essential assistance to the millions of India's tobacco users. The financial resources needed to provide smoking cessation services in a country of the size of India would be substantial. With the toll of the smoking epidemic and the heavy financial cost of

smoking treatment, endorsing tobacco harm reduction as a supplement to all other tobacco control measures could represent a historical opportunity for India to accelerate the decline in smoking rates without any cost to the taxpayers and the government.

E-cigarettes are mostly unregulated in India. In light of the current evidence, health authorities have the responsibility to respond to the innovative and disruptive challenges introduced by e-cigarettes. Such regulatory adjustments could be enacted as they have in countries such as Canada, New Zealand, Switzerland and in the EU. In the UK, the National Institute for Health and Care Excellence (NICE) actively recommends that health care workers advice smokers about the potential value of e-cigarettes as smoking cessation modalities,[100] while the UK Parliament Science and Technology Committee recommended an even more liberal regulatory framework for e-cigarettes in order to further strengthen their effect as a smoking cessation measure.[101] All these indicate the acceptability of evidence on the safety and efficacy of these products, and the valuable prospects of strengthening the tobacco control measures through a harm reduction strategy with e-cigarettes. With an effective regulatory framework that maximizes potential benefits and minimizes unintended consequences, tobacco harm reduction could bring about a revolution in India.

By excluding tobacco harm reduction from a comprehensive tobacco control strategy by prohibiting the most popular harm reduction product, e-cigarettes, India would miss the opportunity to promote public health to its large population of smokers and tobacco users. There is little logic in allowing the sale of lethal combustible tobacco cigarettes while banning the sale of e-cigarettes, a substantially less harmful product and alternative to smoking. Additionally, banning e-cigarettes will effectively push these products in the underground grey market and will make it more likely that consumers seeking these products may be exposed to harmful or even banned substances. An underground market will be largely uncontrollable, both in terms of quality and marketing and promotion, while demand is likely to exist considering the growing evidence from other countries about the prospects of e-cigarettes for smokers unable to quit with other means. India has endorsed some forms of harm reduction such as needle exchange programs and opioid substitution therapy.[102] While positive outcomes have been recorded from such actions,[103-106] there is criticism that an anachronistic approach is being followed, based on prejudice rather than evidence, and is thus missing an opportunity to fully explore the potential of harm reduction for people who inject drugs.[107] With the current environment on tobacco harm reduction and e-cigarettes, India may miss an important opportunity to tackle the long, pressing problem of tobacco use in the country. This can be avoided by following the approach of other regions where e-cigarettes have been available, regulated and their use monitored for years. Regulatory frameworks that have already been implemented successfully elsewhere (such as in the EU and in Canada) could offer a valuable starting point for India to create its own a regulation scheme incorporating tobacco harm reduction. Scientific authorities throughout India should be encouraged to review the available evidence with rigor, impartiality and an open mind, assessing both the potential benefits and risks of a new policy implementation and its potential impact on a population level.

CONCLUSIONS

Public health is a public good, and the best of scientific knowledge must be brought into a bright spotlight in the public domain. Access to information, and with it, health literacy, is a right enshrined in all constitutions and it is the solemn duty of States to ensure that information, especially one that affects life and living, reaches people without delay.

Biomedical research is critical to understanding the health impact of e-cigarettes, but this understanding has to be encouraged and strengthened, with health authorities accurately weighting the science and documenting the well-known damaging effects of smoking against the risks and harm reduction potential of e-cigarettes. Several extensive literature reviews have concretely established the lower risk potential of e-cigarettes. We have no doubt that e-cigarettes represent an important tool for smokers to reduce their risk of smoking-related illness, and e-cigarettes can be a tool for public health to promote tobacco harm reduction.

We believe the time has come to do something more for smokers who want to quit, and India and its agencies could be a world leader in crafting a new path of e-cigarettes and harm reduction and cessation. This opportunity to improve public health will be lost if India bans e-cigarettes, and with no new strategies the tobacco epidemic will continue. India is the world's largest democracy and now its fifth largest economy. The Indian leadership in public health is a natural corollary of its growing international presence. We look forward to a constructive exchange. We urge ICMR to

reconsider its recommendation on a ban, and we hope that this discussion will enable them to understand the science and evidence on e-cigarettes and tobacco control.

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