Critical evaluation of the review article: "*Respiratory impact of electronic cigarettes and 'low risk' tobacco*", by Thirion-Romero I., Pérez Padilla R., Zabert G. and Barrientos-Gutiérrez I., Revista de Investigación Clínica. 2019:71"17-27. DOI 10.24875/RIC.18002616

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Abstract. *Thirion-Romero et al present a review of the evidence on various topics related to the usage and health impact of electronic cigarettes (EC). Unfortunately, this is not an objective nor balanced review. It follows the line of argumentation espoused by similar reviews by other neumologists and positioning papers of respiratory societies, all of which selectively search and cite uncritically studies that report a litany of adverse effects, often exaggerated or taken out of context by these studies, while ignoring sources reporting more nuanced or beneficial outcomes. Thirion-Romero et al (following similar reviews and positioning statements of respiratory societies) invoke an extreme interpretation of a Precautionary Principle in which EC usage can only be endorsed to smokers after extensive research has shown that they are completely safe in the long term (something that could take decades to achieve). Thirion-Romero et al summarily dismiss on the basis of weak and frivolous arguments the estimation by Public Health England of a 95% harm reduction respect to smoking for smokers switching to EC usage, an estimation that has been endorsed by more recent PHE reports, the Royal College of Physicians and health authorities in the United Kingdom. While the authors grudgingly recognize that EC aerosols are less toxic than tobacco smoke, they fail to evaluate (or at least consider) the potential health benefits that this fact may afford for smokers who might continue nicotine consumption through a delivery method that, without being innocuous, represents for them a viable health gain at least in the short to medium term. If translated into official health policy, the refusal to even consider the potential benefits of this harm reduction approach necessarily limits the available options for millions of smokers for whom abstinence is a difficult task. As an unintended consequence many of these smokers will continue smoking.*

SUMMARY OF THE REVIEW AND GUIDE TO OUR RESPONSE

The present review by Thirion-Romero et al is very similar to reviews published by the European [1] and Spanish [2] (see our reply [3]) respiratory societies and by various groups of neumologists [4,5]. They begin with a brief description of the devices and the properties of the aerosols they release, continuing with a summary of physiological effects (mostly cardiovascular and respiratory) that emerge from in vitro studies, animal models, clinical studies, looking also at their utility for smoking cessation and their usage by adolescents. While the authors admit that "*the aerosols contain fewer toxins than tobacco smoke*", they do not regard this fact as sufficiently significant and convincing to recommend EC usage as part of a viable harm reduction strategy aimed at smokers. In what follows we provide a critical appraisal on how Thirion-Romero et al address various issues following the order listed below:

I. Negative evaluation of the 95% reduced risk estimation by Public Health England
II. Invoking utopian "clean air" perfection to dismiss EC Harm reduction
III. Lack of evidence on long term effects
IV. Pathway to nicotine addiction
V. Uptake and transition to smoking by adolescents
VI. Lack of evidence of utility in smoking cessation
VII. Toxicity of EC aerosols
VIII. Emerging evidence of mechanisms of damage and harmful systemic effects.
IX. Conclusions
X. Epilogue: the EVALI outbreak.

I. NEGATIVE EVALUATION OF THE 95% REDUCED RISK ESTIMATION BY PUBLIC HEALTH ENGLAND

In their section "The health risk dilemma of e-cigarettes" Thirion-Romero et al hint (without providing any proof) that the claim of a reduced risk profile of EC is a marketing strategy of the tobacco industry, a novel step in the sequence of previous deceptive efforts by this industry to market less harmful products like "low tar" and filtered cigarettes. In the authors' own words the "*EC is now reloading the dilemma of low risk nicotine consumption through the respiratory system*", a statement which serves them as a prelude to extend this innuendo in their critique to the main scientific sources that sustain such low risk nicotine consumption: the reports by British institutions, specially Public Health England (PHE) [6,7,8] and the Royal College of Physicians (RCP) [9], which provide the scientific basis of tobacco control policy of the UK that officially supports the recreational EC usage in substitution of conventional cigarettes [10].

The extensive report "*E-cigarettes: an evidence update*" published in 2015 by PHE (PHE-2015) [6] estimated that EC's in total replacement of conventional cigarettes offers smokers a 95% reduction of harms with respecto to smoking. The evaluation undertaken by Thirion-Romero et al of this relative harm estimation consists only of their critique of a single article (*Estimating the harms of nicotine-containing products using the MCDA approach,* by Nutt et al [11]*),* which in their opinion suffers from a deficient methodology (and conflicts of interest). Thirion-Romero et al further declare that:

> *This paper was the pillar for the Public Health England e-cigarette report, translated into two questionable statements: "e-cigs are 95% safer than smoking" and "tobacco health burden can be reduced by 95% if all smokers move to e-cigarettes" .*

Evidently, the PHE-2015 report is not free from criticism, but it is a gross disservice to the truth to describe it as based on a single paper (by Nutt et al cited above). Thirion-Romero et al also misquote the PHE-2015 report: nowhere in the report it is stated that *"tobacco health burden can be reduced by 95% if all smokers move to e-cigarettes".* The PHE-2015 report cites the above mentioned Nutt et al paper and acknowledges agreement with its evaluation, but other evaluations available at the time were considered and examined as well. In fact, irrespective of the merits or defects of the Nutt et al paper, the report cites other 184 references and offers a broad and deep discussion of many relevant topics.

A thorough critique of the PHE-2015 report would be very valuable, as it would contribute to a better knowledge of EC's and to a better evaluation of the merits or defects of the harm reduction arguments. Unfortunately, Thirion-Romero et al are not attempting such a critique, they are simply dismissing the PHE-2015 report by means of superficial and quasi libelous arguments (the ad hominem innuendo about "conflicts of interests" which as been categorically rejected by PHE). Moreover, Thirion-Romero et al are not alone in misrepresenting the PHE-2015 report, they are merely voicing the same flawed uncritical dismissal espoused by an editorial of The Lancet [12] published soon after the publication of the PHE-2015 report, a dismissal that has been further repeated by other authors [13,14,15] without any one of these critics ever attempting a well argued alternative risk estimation.

The response to the editorial of The Lancet by the authors of the Nutt et al paper and the PHE-2015 report was published in the correspondence section in the same volume [16,17,18,19] (see a more recent response and swift rejection of the innuendo of "conflicts of interest" in [20]). Moreover, the risk estimation of the PHE-2015 report has been upgraded, reaffirmed and endorsed by subsequent PHE reports [7,8] and by the Royal College of Physicians (RCP) [9], which stated (page 87) it in more nuanced and precise terms that acknowledges uncertainty:

> *Although it is not possible to precisely quantify the long-term health risks associated with EC's, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products, and may well be substantially lower than this figure*

This risk estimate is currently endorsed by all major health institutions in the UK and by the Committee of Science and Technology of the House of Commons [21]. As a consequence, the recreational usage of EC's is currently an integral part of the official tobacco control policy of the UK [10].

Could it be possible that all major British health institutions and the UK government were so utterly incompetent to let themselves be deceived by Nutt et al in such a preposterous way? If we take Thirion-Romero et al at face value, we must conclude that the core of the fundamental evidence based tenets of the tobacco control policy of the UK would rest on very feeble grounds (a single defective paper marred by conflicts of interest). Consequently, thousands of health professionals and activists over the world promoting a Tobacco Harm Reduction approach, broadly agreeing with the official policy of the UK, would be either dishonest or grossly misled incompetents. This disastrous deception would also include (at least partially) the report on EC's of the National Academies of Sciences Engineering and Medicine of the USA [22] and many other institutions and extensive reviews outside the UK [23,24,25,26], which without providing a numerical risk estimate and sustaining disagreements with the British sources on other issues, broadly endorse the significant reduction of risk afforded to smokers by switching to EC.

Evidently, to claim that the core harm reduction arguments on EC's that guides British health institutions can be readily dismissed in such a demolishing way is an extraordinary claim, and thus requires extraordinary evidence. Are Thirion-Romero et al and other critics of PHE providing such evidence? Certainly not. While it is true that the estimate 95% risk reduction by British institutions is an inferred qualitative estimate not obtained quantitatively by a proper risk analysis based on specific toxicological data, the critique by Thirion-Romero et al (and critics arguing along their lines of argumentation) fails to provide an alternative toxicological risk estimate. Some critics have even proposed that EC's can be as risky as 50% relative to smoking [14,15], but have never provided any valid supporting arguments for this figure. Other critics [27] have suggested that the PHE-2015 report omitted dealing with long term cancer risks related to tobacco specific nitrosamines TSNA detected in cell studies, when epidemiology of smoke free nicotine (either NRT's [28] or snus users in Sweden [29,30,31]) reveals no association of smoke free nicotine consumption with any cancer.

Moreover, there are studies (which Thirion-Romero et al do not cite) that do offer a very basic (even rudimentary) toxicological analysis of EC's. A study by Burstyn [32] that analyzed available experimental data before 2014 showed that user exposure to toxic and carcinogenic compounds (aldehydes, tobacco specific nitrosamines and metals) in the aerosol emissions are well below the occupational Limit Threshold Values (TLV) of the National Institute of Occupational Safety and Health (NIOSH) of the USA. This result holds even if the exposure doses are multiplied by a factor of 10, hence it would still be valid for more recent high powered devices. Two other studies [33,34] showed that the doses of aldehydes (formaldehyde and acetaldehyde) and "particulate matter" (droplets) account for about 1% of cancer potential of smoking. While the literature contains studies (some cited by Thirion-Romero et al) that claim to have found aldehyde concentrations that would surpass toxicological TLV's [35,36], these studies can be readily refuted from their methodological flaws [37,38]: examination of the devices under abnormal usage conditions (see extensive discussion in [39]). Likewise, studies claiming high concentrations of metals [40,41] where refuted [42,43]. As we argue further ahead, numerous studies based on *in vitro* and animal models that bear no relevance for human exposure.

In summary, the 95% risk reduction estimate by PHE and other British institutions is not cast in stone, it can (and should) be challenged or improved. Unfortunately, the critique by Thirion-Romero et al is very weak and superficial (the same remark applies to critiques by other authors [14,15,27]). As Professor Britton (who directed the team of experts behind the RCP report) stated [19], the exact number accounting for the risk relative to smoking might be very difficult to obtain, but its exact value is irrelevant, the relevant scientific result that matters is that EC's completely replacing conventional cigarettes do afford smokers a significant harm reduction.

II. INVOKING UTOPIAN "CLEAN AIR" PERFECTION TO DISMISS EC HARM REDUCTION.

Towards the end of the article Thirion-Romero et al grudgingly admit that EC aerosols "*contain less toxins than tobacco smoke*". Notwithstanding that the real qualitative statement must be "*contain **far less** toxins than tobacco smoke*", they dismiss this fact on the grounds that on evaluating respiratory effects "breathing clean air" must be the only "safety comparator".

By placing as the only acceptable benchmark the perfect safety of "clean air" Thirion-Romero et al are invoking the utopia of absolute perfection in order to dismiss the pragmatic effort by smokers to achieve a modest, but realistic (and achievable), harm reduction benchmark in reference to the toxic cigarette smoke they inhale when smoking. Nobody living in an urban environment really breathes "clean air", though smokers inhale toxic smoke besides breathing atmospheric pollution. It is evident that smokers will greatly benefit if they quit smoking and thus avoid this extra pollutant, but Thirion-Romero et al display an extreme lack of empathy to smokers by dismissing the health benefit that represents for them the option of replacing this smoke by a much more benign aerosol whose long term inhalation surely represents health risks, but risks that are extremely unlikely to be comparable in the long term to those of continuing smoking.

III. LACK OF EVIDENCE ON LONG TERM EFFECTS.

Thirion-Romero et al, following the stance of respiratory societies, espouse an extreme precautionary approach that recommends deterring EC's usage until their safety profile has been fully and accurately quantified, even if this requires decades of dedicated observation and medical tests. No product (or medication) is judged under such a strict standard. The following quote from Dr K Farsalinos [44] illustrates this point:

> *I challenge anyone to show me a product that was marketed only after collecting 20 or 30 years of* ***clinical epidemiological evidence****. This is simply* ***impossible to happen****.* [original emphasis] *I wonder, was it a 40 years experiment for the population when ACE-inhibitors, one of the commonest antihypertensive medications, were recently found to increase the risk for lung cancer by 20-30% when used for more than 5 years? ACE-inhibitors were first marketed in 1980 (captopril). These very common antihypertensive medications are expected to be used for years, even decades, by some patients (for example, my father takes an ACE-inhibitor daily for the past 20 years). The recent study* [45] *that found a higher risk for lung cancer was published in October 2018. Of course, before marketing ACE-inhibitors, there was no study examining the effects of intake for 10, 20 or 30 years, despite knowing that these medications will be used for such long periods by millions of patients. In an accompanying editorial* [46] *to the recent study, the author correctly and appropriately mentioned that: "Nonetheless, in an individual patient, concerns about the long term risk of lung cancer should be balanced against gains in life expectancy associated with use of ACEIs." This is a reasonable and appropriate statement, and common practice for all medications (since all medications and medical procedures have side effects and complications). But we apply double standards for e-cigarettes.*

Besides the demand of full long term risk quantification, Thirion-Romero et al further disapprove of the devices by emphasizing, as if these were accomplished facts, the societal harms of EC usage: it maintains a nicotine addiction seen as a negative behavioral feature irrespective of the actual harms it may cause, it promotes the uptake by never smoking youth and adults, who (in their opinion) will eventually transition to smoking, and its efficiency in smoking cessation is in doubt.

Given this approach, Thirion-Romero et al propose a regulation of the devices to be, at least, as strict as that of tobacco products. Meanwhile, the only alternatives they leave to current smokers is to rely on traditional "approved" quit smoking methods (Nicotine Replacement Therapies or medication) until they only breath "clean air" by total nicotine abstinence (likely they also discourage recreational oral consumption), or else to become ill or die prematurely from smoking.

This uncompromising and rigid stance is ethically indefensible. Some smokers might quit unaided, some might use traditional "approved" quit smoking methods, but It is not outlandish to assume (as shown by demographic data [47,48] see also British sources [7,9]) that millions would prefer to try and use EC's or other non-combustible devices instead of pharmaceutic products. How many millions of smokers must become ill or die prematurely by being prevented, or actively discouraged, from migrating to less harmful products of their choice until Thirion-Romero et al and authors with a similar stance are fully satisfied that they are as safe as "clean air" and do not contribute to any societal harm?

IV. PATHWAY TO NICOTINE ADDICTION

In their section "Smoking cessation with EC's" Thirion-Romero et al claim that EC usage is a pathway to nicotine addiction, supporting this claim by stating that "*EC's saturate the nicotinic receptors in the brain as as much as conventional cigarettes do*". Although the authors might see this feature as a negative effect because of the allegedly addictive nature of nicotine, it is a actually one of the positive features that explain the success and popularity of EC's: they can deliver nicotine as efficiently as tobacco cigarettes [49,50] at a reduced fraction of the health risks. Given the epidemiological evidence that nicotine consumption without smoke is not a cause of concern for healthy adults [28,29,30,31], and since this consumption through EC does not involve toxic cigarette smoke, then seeing this "addiction" negatively can only be supported on the basis of moral, not medical, grounds. Moreover, the concept of "addiction" is still loosely defined [51] (see a critique of the excessive medicalization of this concept in [52]). It is often confused with dependence, which can be quantified empirically. The interaction between nicotine and brain receptors has only been studied when nicotine is delivered through cigarettes and is potentiated by various compounds in tobacco smoke besides nicotine [53]. Observations reveal a continuum of nicotine dependence [54,55] varying among different delivery paths: it is very intense when delivered through cigarette smoking, but much less intense through dermal delivery in pharmaceutical patches, oral pathways and EC's (there are several observational studies showing that EC users experience less intense nicotine dependence than cigarette smokers [57,58,59]). Observations also reveal that nicotine dependence through smoking has important psychological components that cannot be reduced to pharmacological effects [56]. Considering the definition of the American Psychiatric Society [60] in which dependence is a necessary but not sufficient condition for considering the consumption of a substances as "addictive" (i.e. a syndrome), then the risk reduction with respect to cigarette smoking and the mild dependence observed among EC users would suggest that nicotine delivered by EC usage is not addictive.

V. UPTAKE AND TRANSITION TO SMOKING BY ADOLESCENTS

Thirion-Romero et al correctly identify EC experimentation and usage by children and adolescents as a major health concern. However, they take as an accomplished indisputable fact that this constitutes a pathway to initiation and progress to smoking conventional cigarettes and nicotine addiction. Their analysis of under age experimentation and usage is extremely selective and biassed, omitting references that dispute their claims. At the very least, Thirion-Romero et al should cite these sources and mention that the effects of under age experimentation and usage remains a controversial issue.

In their section Epidemiology Thirion-Romero et al mention that EC usage and experimentation "*may lead or progress to conventional smoking of cigarettes*", citing two studies: by Thrasher et al [61] and Lozano et al [62] (their references 22 and 23) undertaken on a sample of junior high school students in Mexican public schools (in Mexico City, Guadalajara and Monterrey). However, these studies do not provide a robust proof of this progress to conventional smoking: Thrasher et al is cross sectional and the longitudinal one by Lozano et al found an association between EC trial and past 30 days smoking that is weak and lacks statistical significance (adjusted relative risk 1.43 with 95% CI [0.94,2.36]). Thirion-Romero et al mention in the same paragraph that:

> *A 2016 survey among teenagers 11 and 16 years old in Mexico City, Monterrey and Guadalajara revealed a prevalence of having ever experienced e-cig of 35% and 31%, and regular use, 14% and 13%, respectively; of them, 5-7% declared having initiated tobacco smoking after experiencing with e-cigarettes*

A 5-7% of tobacco initiation due to EC usage is certainly a worrying figure, however their cited references (27 and 28) that sustains this figure comes from an unpublished survey that is not publicly available (it was impossible to find it in a google search). Therefore, this survey cannot support the authors' claim because it is impossible for external reviewers to verify its methodology and scope.

In the same section Thirion-Romero et al explain the cause of under age EC usage as a deliberate marketing

effort by advertisement and social media (presumably sponsored and promoted by vendors or manufacturers). However, they offer no proof of such a deliberate effort. EC publicity directed to young adults (18 to 24 years old) does attract teenagers simply because they tend to imitate adults who are close to their age. Teenagers are also prone to challenge adult disapproval and they are constantly exposed to the stimulation by publicity on all other adult usage legal products (alcohol beverages or energetic drinks or caffeine). While it is a popular tobacco control narrative in the USA, there is no proof of an existing conspiracy by EC manufacturers or vendors to deliberately market under age costumers. The references cited by Thirion-Romero et al [63,64] (their references 79 and 80) do not prove this deliberate marketing effort, in fact [63] is based on the National Youth Tobacco Survey (NYTS) in which about 19% of they surveyed students are adults (over 18 years old).

Thirion-Romero et al claim as an accomplished fact the role of EC experimentation in a transition to conventional cigarette smoking by adolescents. To sustain this claim they cite studies in the USA [65,66] (their references 81 and 82) and Great Britain [67] (their reference 29). However, [67] merely found associations in both directions of product initiation (EC to cigarettes and vice versa), which points out as a plausible hypothesis that common propensity to nicotine consumption is a shared cause of both products initiation rather than EC initiation causing smoking initiation. Thirion-Romero et al did not bother to (at least) recognize the existence of British studies that do not support the claim that EC experimentation propitiates smoking initiation of never smoking adolescents [68] (see also [7,8]).

The USA references cited by Thirion-Romero et al (specially Soneji et al [66], their reference 82) have been criticized for claiming that EC initiation is a gateway to smoking, while disregarding the more plausible common propensity hypothesis and not dealing properly with residual confounding [69] and for not considering the fact that smoking prevalence among adolescents in the USA has decayed much faster as EC experimentation and usage increased since 2011 [70,71,72]. The claim that availability of a wide selection of EC flavors increases the probability of smoking initiation [73,74] (their references 83, 84) suffers from the same methodological problems. Yes, flavors attract adolescents as they attract adults, but it takes a big leap of imagination (and disregard for proper handling of confounders and alternative hypothesis) to assume that this translates into propitiating smoking initiation among never smoking adolescents.

VI. LACK OF EVIDENCE OF UTILITY IN SMOKING CESSATION.

Since their paper was published in 2018, Thirion-Romero et al can be dispensed for not being aware of a recently published high quality Randomized Controlled Trial (RCT) by Hajek et al [75], which showed EC's being nearly twice as effective as combined Nicotine Replacement Therapies in achieving 12 months smoking abstinence (18% vs 9.9%). Still, the revision of smoking cessation by Thirion-Romero et al is very sketchy, outdated and negatively selective even considering only available evidence before this RCT. They cite the Cochrane reviews of 2014 [76] and 2016 [77] (their references 71 and 75), quoting from the 2016 review low quality evidence based on a small number of studies. The Cochrane review of 2016 reported several RCT's [78,79,80] (references 72, 73, 74 of Thirion-Romero et al) dated between 2011 and 2014, emphasizing in particular reference [80] (Bullen et al), an RCT in which the effectiveness of EC and nicotine patches was comparable. However, the EC models used by Bullen et al did not deliver nicotine effectively and are now obsolete and thus their relevance of this result is today questionable. Besides mentioning these RCT's, Thirion-Romero et al conclude that "*so far there is insufficient evidence of whether e-cigarettes increase the likelihood of smoking cessation*", citing (or rather misquoting) the observational study by Biener and Hargrave [81] (their reference 19) whose results do not support this negative assessment:

"*Logistic regression controlling for demographics and tobacco dependence indicated that intensive users of e-cigarettes were 6 times more likely than non-users/triers to report that they quit smoking (OR: 6.07, 95% CI = 1.11, 33.2). No such relationship was seen for intermittent users. There was a negative association between intermittent e-cigarette use and 1 of 2 indicators of motivation to quit at follow-up*."

Thirion-Romero et al failed to cite several other observational studies (cross sectional and longitudinal) reporting the effectiveness of CE in smoking cessation [82,83,84,85]. They also failed to cite an extensive methodological review of 91 studies published up to 2017 on smoking cessation by Villanti et al [86], whose

conclusion was that the the best quality studies (observational and RCT's) objectively support the utility of EC's in smoking cessation.

VII. TOXICITY OF EC AEROSOL

Thirion-Romero et al deal with the compounds of EC aerosols (gas and particulate phases) in their introductory section. They provide a list of detected gas phase compounds besides the vapors of the liquid carriers propylene glycol and glycerol and nicotine: formaldehyde, acetaldehyde, acrolein, acetone, benzaldehyde, siloxanes, reactive oxygen species, volatile organic compounds (VOC's), polycyclic aromatic hydrocarbons (PAH's), and tobacco-specific nitrosamines (TSNAs), including N-nitrosonornicotine (NNN), plus metals. Most of these compounds formed by thermal decomposition (low temperature pyrolysis) of the carriers and flavorings are toxic, but under normal operation conditions formaldehyde, acetaldehyde and acrolein appear in minute concentrations well below those of tobacco smoke, while the other compounds are found at truly negligible levels just above detection thresholds [39,87,88,89]. However, the most useful result on the chemistry of EC aerosol is furnished by Burstyn [32], who computed actual exposures to these compounds (including metals, see further ahead) and found that they are well below the TLV's of the NIOSH even if multiplied by a factor of 10 (and thus his toxicological evaluation remains valid for recent high powered devices and low power pods used under normal operational conditions).

It is true that concentrations or exposures can vary for several orders of magnitude (specially in recent high powered devices [89]), but under normal conditions of operation that avoid overheating they do remain below concern [39]. Thirion-Romero et al mention the presence of nano-particles made of nickel-chromium, chromium-aluminum-iron, copper, silver, zinc, tin, or manganese. In particular, they emphasize that "*nickel contained in the e-cig aerosol was 2-100 times higher than in tobacco smoke*". It is not strange to find higher metal concentrations in EC aerosols than in tobacco smoke because (unlike cigarettes) the devices are made of metals, but exposure to these metals is well below toxicological thresholds. Thirion-Romero et al cite a 2014 study of metals in EC aerosol by Williams et al [40] (their reference 8) that examined emissions from cartridge based devices that are now obsolete. Moreover, the exposures found in this study were all below toxicological thresholds [42] and the 2-100 times higher than in tobacco smoke nickel concentration is misleading because the latter concentration in tobacco smoke is negligible (100 times a negligible quantity is still negligible).

It is also true that emissions depend on the power/temperature of operation of the devices, and sufficiently high power/temperature release worrying levels of toxins, but emissions are not worrying when the devices are evaluated in the power/temperature ranges in which they are normally used [39] (most cars can run at 200 km/hr but evaluating their safety at such top speeds is unrealistic).

Regarding environmental emissions, Thirion-Romero et al mention that "*in chamber studies and model café environments, a low level of most of the vapor components can be found in the air*", citing Czogala et al [90] (their reference 9) whose conclusion is that save for the presence of nicotine bystanders are exposed to toxic compounds in concentrations barely distinguishable from background levels. Thirion-Romero et al further argue that exposure to nicotine in these EC emissions is comparable to exposure from environmental tobacco smoke "*using machine-smoked e-cigarettes and cigarettes*" [91] (their reference 10). This is a highly misleading and unrealistic result, since machine generated emissions are a poor proxy for environmental emissions generated by actual vapers or smokers. In fact, chamber experiments reveal that nicotine exposure from environmental EC aerosol emissions is 20 to 50 times less than in environmental tobacco smoke [92], something that is easy to understand since about 75% of the nicotine in the latter originates from sidestream smoke emissions that are absent in EC's [93].

Thirion-Romero et al mention exposure to fine particles in concentrations similar to those of tobacco smoke, stating further that particle lung deposition is also similar to that of tobacco smoke. However, they omit to mention what really matters in evaluating toxicity: the fact that the chemical composition of the particles is radically different. EC aerosols are produced by the condensation of liquid droplets from the vaporized e-liquid solution at 180-220 degrees C, thus it follows from any text book on physics and chemistry of aerosols that its particulate phase consists of liquid droplets made almost exclusively of the liquid propellent and carrier (propylene glycol and glycerol) [94,95]. These droplets evaporate in minutes

[96,97], and since propylene glycol and glycerol are not reactive at room temperatures they must impact and dissolve in the lungs linings and be rapidly absorbed without systemic harm. As a contract, tobacco smoke is a chemically complex aerosol produced by combustion, thus its particles can be solid or liquid droplets of chemically complex composition and high toxicity (the TAR, tobacco aerosol residue obtained by filtering water and nicotine). It is well known that the pulmonary absorption of this type particulate matter is slow and problematic and that it cause significant systemic harm [98].

VIII. MECHANISMS OF DAMAGE AND HARMFUL SYSTEMIC EFFECTS.

Perhaps the argument that Thirion-Romero et al regard as most relevant to justify their negative evaluation of EC's is their appreciation that a growing evidence already exists of "*toxic products in vaporizing liquids that result in chemical, morphologic and functional deleterious effects in in vitro and in vivo models*". This appreciation follows from a very selective examination of the literature: they cite and comment uncritically only articles and reviews that highlight adverse effects, with bare or no mention of the limitations of these sources and omitting articles and reviews that highlight different outcomes or interpretations. Thirion-Romero et al can be dispensed for not having cited a recently published comprehensive review on the effects of EC emissions on respiratory health [99] which covers these topics, discussing many of the references they have presented.

Mechanisms of damage of EC's.

Thirion-Romero et al begin this section by stating that significantly lower concentrations of "ingredients" than in tobacco smoke does not mean that EC aerosols are "harmless vapor". This is a "straw man" argument, as no serious harm reduction source has ever claimed that EC aerosols are 100% harmless.

A brief summary is presented of potential harms from submicron particles and toxic compounds of EC aerosols. However, as discussed previously, these "particles" are droplets made almost exclusively by propylene glycol and glycerol that have nothing to do with the particulate phase of tobacco smoke or suspended particles of air pollution, all of which originate from combustion processes. Thirion-Romero et al mention sources [35,36] (their reference 6 and 42) that have found concentrations of toxic aldehydes and metals above toxicological thresholds, but omit mentioning that aldehyde concentrations in [35] found only at overheating conditions [37,38], while the metals study in [41] was refuted by [43]: it had a fatal methodological flaw (computed doses from continuous exposures when users are only exposed to the aerosols while they use the devices). Thirion-Romero et al mention the presence of flavorings, such as diacetyl and acetyl propionyl, allegedly related to the obstructive lung disease bronchiolitis obliterans ("popcorn lung"). However, they fail to mention that not a single case of this disease has been reported in years of usage by millions of vapers. In fact, these compounds are found in much smaller concentrations than in tobacco smoke and the connection between this disease and smoking remains unclear.

Thirion-Romero et al claim that nicotine levels reported in the labels are often inaccurate, a valid concern. However this is not a generic feature of EC's, it depends on the quality control and on the regulatory processes. A "back of the envelope" calculation reveals that approximately 15 EC puffs deliver the same 2 mg dose of a cigarette and then mention that the letal dose is 60 mg (citing the review by Chun et al [4]). This value of a letal nicotine dose is often stated but it is false: it comes from unreliable XIX century observations. The right letal dose is far higher, of the order of magnitude of gm, which is orders of magnitude higher that any reasonable delivery by cigarettes or EC's (see [100]).

To describe further damage mechanisms Thirion-Romero et al provide a quick summary of the review by Reidel et al [101] (their reference 12). Citing this review they mention that

> *"… exposure to aldehydes (formaldehyde and acrolein) "has been associated with altered epithelial response, mucus hypersecretion, activation and degranulation of neutrophils and induction of neutrophil apoptosis",*

also from the same source

> *"E-cigarette users show increased proteins secretion in sputum related to the innate defense functions of leukocytes, bronchial inflammation and structural damage. These include neutrophil elastase, proteinase 3, azurocidin 1 and myeoloperoxidase as well as other secondary neutrophil granule proteins."*

What Thirion-Romero et al fail to mention is that Reidel et al [101] (which was cited and commented by Polosa et al in [99]) is a study of cross sectional design, and thus it does not allow to establish causation of these effects by EC's. Also, Reidel et al did not give proper consideration to the fact that the vapers from whom sputum samples were collected were all smokers or ex-smokers, a significant confounder that renders any possible causality highly unlikely.

In vitro damage by EC's and evidence in animal models.

Thirion-Romero et al discuss other pathways of potential systemic lung damage (for example, oxidative stress and macrophage mediated inflammation, increase of bacterial loads) that emerge from in vitro or animal model studies, all of which merely reveal a potential biological plausibility of harm in idealized experiments that needs to be corroborated by clinical or epidemiological studies. The mechanisms of systemic damage they have presented (see Table 1) are potential and speculative. However, as discussed extensively in Polosa et al [99], most pre-clinical (in vitro and animal model) studies on EC's suffer from several methodological flaws: lack of a an appropriate dosimetric protocol to relate aerosol exposures to realistic human exposures and lack of a comparative standard with tobacco smoke. Pre-clinical studies that are free from these flaws reveal negligible harms from EC aerosol exposure in comparison with exposure to tobacco smoke [102,103,104] (including lack of mutagenesis from the Ames test [105]). None of these studies were cited by Thirion-Romero et al.

Systemic impact of EC's in humans

Effects of nicotine. Thirion-Romero et al begin this section by enlisting known acute effects of nicotine (increase in blood pressure, myocardial oxygen consumption, vasoconstriction) that cannot be considered harmful in healthy subjects [106,107].

Cardiovascular disease. Thirion-Romero et al mention recent evidence of population impact on cardiovascular health, citing two studies [108,109] (Moheimani et al and Qasim et al, their references 56 and 57) published in the Journal of the American Heart Association. These two studies have cross sectional design and thus merely show associations that provide no evidence of causation (it is not evident if the heart infarction or another coronary problem happened before or after EC usage). Thirion-Romero et al did not cite studies reporting CV benefits of EC usage [107,110], which also emerge in studies published in 2019 [111,112,113] (in particular [113] is a longitudinal study showing CV improvement after just 1 month of EC usage even in dual users).

Cancer. Thirion-Romero et al do recognize lack of association between EC usage and cancer, mentioning the existence of a large time gap between biological plausibility revealed by pre-clinical studies and actual clinical or epidemiological outcomes. However, they omit to mention the existence of toxicological modeling studies of Excess Lifetime Cancer Risks (ELCR), which do provide at least a preliminary answer to cancer risks of EC usage compared to smoking [33,34]. The ELCR that emerges from these studies is at most 1% relative to smoking, a result that is consistent with the fact that EC's users are exposed to a small fraction of the dose of carcinogenic compounds present in tobacco smoke.

Evidence of pulmonary damage associated with exposure in humans.

Thirion-Romero et al recognize that practically all studies of alteration of lung structure and function and respiratory symptoms have examined EC users who are either smokers or ex-smokers. They fail to cite a 3.5 years duration longitudinal study [114] involving young EC users who never smoked (a population sample that is hard to find), which revealed complete lack of adverse respiratory symptoms pulmonary damage. The study has evident limitations, specially a small sample of 9 users and lack of a smokers control group.

Thirion-Romero et al also recognize that short term deleterious respiratory symptoms in EC users are marginal compared with those of smokers. Yet, citing Chun et al [4] (their reference 2) they mention that

> "*exposure to EC aerosol has been associated with respiratory symptoms in healthy individuals, changes in respiratory physiology and host defense, and with increased symptoms in asthma, cystic fibrosis (CF) and COPD"*.

However, Chun et al is an extremely biassed review. As mentioned in the following extract taken from a letter to the editor criticizing this review [115], which (just as Thirion-Romero et al) failed to cite four studies that contradict its negative evaluation:

> "*The review examined studies reporting adverse effects but failed to include a range of clinical studies with smokers who switched to ECs* [116,117,118,119]. *These studies have consistently shown that ECs are unlikely to raise significant health concerns for the human respiratory tract under normal condition of use and showed improvement in many cases. A more comprehensive study selection would have provided a more accurate reflection of the available research*."

Thirion-Romero et al then proceed to describe a litany of studies revealing adverse outcomes in adolescents from EC usage but taking them as face vale without considering their limitations and shortcomings:

- "*There is growing evidence that adolescents who were exposed to EC's more often have cough and phlegm*" (cited studies: McConnel et al [120] and Cho et al [121], references 62 and 63 of Thirion-Romero et al)

- "*Adolescents using EC's more frequently report not only respiratory symptoms but also school absenteeism*" (cited study: Clapp et al [122], reference 64 of Thirion-Romero et al)

- "*Airway exposure to nicotine containing EC vapor inhibits bronchial and nasal mucociliary clearance, with the production of a cough and rhino-nasal symptoms compared to unexposed individuals*" (cited study: Kumral et al [123], reference 65 of Thirion-Romero et al)

All these studies cited by by Thirion-Romero et al were reviewed by Polosa et al [99], who point in the following extract out various of their limitations omitted by Thirion-Romero et al:

> "*Four studies examined respiratory symptoms in adolescents using or who have used EC (their references* [120,121,122,123]*) and all show an association between respiratory symptoms and EC use. All these surveys are cross-sectional, relying on inaccurate self-reporting of respiratory symptoms and respiratory illnesses, and failing to take into account relevant key confounders. These studies should be expanded in more appropriate longitudinal cohorts. In particular, the analysis conducted by McConnell et al* [120]*. fails to confirm the association between asthma symptoms and EC use when controlling for tobacco smoking and second-hand smoke exposure*."

Thirion-Romero et al proceed listing studies showing that EC usage produces changes in the increase of airway resistance, fractional exhale of nitric oxide FENO, etc as if they were evidences of actual damage of pulmonary function, when these are just acute reversible effects. They terminate this section by reporting lung damage in the form of lipoid pneumonia (citing Shields et al [124], reference 58 of Thirion-Romero et al), an impossible outcome since EC liquids and aerosol do not contain lipids.

EC's and more common lung diseases.

Thirion-Romero et al provide an extremely selective review of the relation between EC usage and pre-existent respiratory disease, including asthma and COPD. They mention higher EC usage among adults with one or more comorbidities (citing Kruse et al [125], reference 68 of Thirion-Romero et al), as well as studies showing higher odds of asthma and respiratory symptoms and exacerbations. All these are associations in

cross sectional studies that fail to reveal any causal relation (besides the deficient handling of previous smoking history of EC users, an important confounder). They also cite a cross sectional study (Bowler et al [126], reference 70 of Thirion-Romero et al) on COPD patients in which EC users showed higher rates of cough, phlegm and exacerbations. Bowler et al claim to have adjusted tobacco usage and age, but (as mentioned by Polosa et al [99]) they did not measure frequency of EC usage and incurred in a selection bias: the vapers were selected patients with much higher smoking levels and dependence, who are more likely to be associated with poorer COPD outcomes from the outset (hence it is a poor indication of EC usage in generic COPD patients).

In their poor and biassed selection of the literature Thirion-Romero et al omitted mentioning various relevant studies reporting beneficial effects of EC usage on patients with pre-existing respiratory disease. This omission can be appreciated from the following extracts from Polosa et al [99] on asthma and COPD (reference numbers are ours):

Asthma

> *The asthmatic smoker is a distinct disease phenotype with increased susceptibility to exacerbations and poor asthma-specific health status* [127] *(this was a landmark review on smoking and asthma. An important reference for those interested in the impact of smoking and smoking cessation in asthma). Quitting smoking can reverse the negative impact of tobacco smoke on asthma symptoms and lung function* [128]*, and switching to EC use may produce significant respiratory benefits as well. A retrospective cohort study of regular EC users with mild to moderate asthma did not show any deterioration in respiratory physiology and subjective asthma outcomes* [129,130]*. On the contrary, smokers with asthma who quit or substantially decreased tobacco consumption by switching to EC's showed progressive significant improvement in the Juniper's Asthma Control Questionnaire (ACQ), FEV_1, FVC, and forced expired flow between 25% and 75% of the FVC (FEF25-75), as well as airway hyper-responsiveness (AHR) to inhaled methacholine* [129]*. A 2-year follow-up study confirmed that EC use ameliorated objective and subjective asthma outcomes and suggests that these beneficial effects may persist in the long term* [130]*. Remarkably, similar findings were found in the dual users of EC's and cigarettes. EC use was well tolerated, and exposure to e-liquid aerosol in this vulnerable population did not trigger any asthma attacks*.

COPD

> *Another disease associated with tobacco smoking is COPD, a progressive disease characterized by a persistent inflammatory and remodeling response of the airways* [131,132]*. Smoking cessation is the only evidence-based strategy known to favorably modify the course of COPD and reduce mortality* [133,134]*. Reducing cigarette consumption by switching to EC use may yield considerable respiratory benefits in COPD. A retrospective-prospective study of patients with COPD found no deterioration in respiratory physiology (post-bronchodilator FEV_1, FVC, and %FEV1/FVC) in COPD patients who quit or substantially reduced their tobacco consumption by switching to EC use* [135] *(First study to provide evidence that switching to e-cigarette use may reverse some of the harm resulting from cigarette smoking in COPD patients). In smokers with COPD and irreversible airway obstruction, the lack of significant improvements in spirometric indices after smoking cessation is not unusual* [136,137]*. Nonetheless, participants in a three-year study experienced significant declines in yearly respiratory exacerbations, much improved overall health status (measured by the COPD Assessment Test [CAT]), and boosted physical activity (measured by the Six-Minute Walk Test)* [135]*.*

IX. CONCLUSIONS

We have provided a comprehensive critique of the review of electronic cigarettes (EC) by Thirion-Romero et al. We have shown how this review (like similar reviews by respiratory societies [1,2] and other neumologists [4,5]) is extremely slanted and selective, citing and commenting literature that is exclusively focused on identifying and highlighting risks and shortcomings of the devices, ignoring and/or dismissing independent articles, reports and reviews by health professionals and prestigious institutions that reveal their potential for public health improvement. In particular, it is regrettable that Thirion-Romero et al resort to weak arguments to dismiss a large body of literature supporting the estimation of a 95% of risk reduction of EC's respect to smoking by Public Health England [6,7,8], the Royal College of Physicians [9] and the health authorities of the United Kingdom [10].

While Thirion-Romero et al grudgingly recognize that EC usage is less toxic than smoking, they dismiss the benefit of a harm reduction approach based on substitution of cigarettes by EC's because the latter do not achieve the state of absolute perfection defined by "*breathing only clean air*". From their negative evaluation Thirion-Romero et al recommend that EC's must be regulated exactly as tobacco cigarettes and its usage must not be recommended to smokers unable or unwilling to quit smoking, even if traditional "approved" methods have not worked for them. Thirion-Romero et al follow the stance of the European and Spanish respiratory societies in their that EC usage can only be endorsed to smokers until (and if) all doubts on their safety have been fully resolved decades in the future, a stance they claim to follow strictly from the "Precautionary Principle", which states that a given policy must be opposed as long as there is a lack of a complete knowledge of the involved risks. However, this principle also requires to consider if this harsh opposition compensates potentially negative (undesired) consequences of not supporting the policy, at least cautiously. Since the stance of Thirion-Romero et al (and the respiratory societies) on EC's is based on a deficient and selective evaluation of the available evidence that yields a disproportionate appreciation of risks, this strict and uncompromising opposition to EC is a flawed interpretation of the Precautionary Principle that will necessarily give rise to an undesired harmful consequence: millions of smokers continuing smoking.

X. EPILOGUE: THE EVALI OUTBREAK

Thirion-Romero et al published their review in 2018, well before the outbreak of acute pulmonary intoxications in the USA (known as EVALI: e-cigarette, or vaping-associated lung illness), allegedly associated with "vaping" (EC usage), which have resulted in over 2400 cases and 54 deaths from June 2019 up to this day. In their latest public communication (dated 20 December 2019) [138,139] the Centers of Disease Control and Prevention (CDC) of the USA have recognized that the main preponderant cause of EVALI is not "vaping" generically, but vaping of closed pre-filled cartridges ("carts") containing the main psychoactive cannabis compound Tetrahydrocannabinol (THC) that were acquired from black market (or informal) sources and vaped in "vape pens" (which are different from the devices used to vape nicotine e-liquids). This connection with illegal THC was pointed out as early as August by the Food and Drugs Administration (FDA) [140]. After an initial period of uncertainty, the CDC also recognized this type of vaping as the most plausible cause of EVALi in its public communication of 27 September [141].

The CDC has also reported a strong connection between EVALI and usage of vitamin E acetate (an additive oil) to thicken the THC based solution for its vaporization [138,139]. Representative samples of vaped consumables reveal this compound (none reveal the compounds used in nicotine based vaping) [142]. Yet, the CDC still mention that other substances and chemical paths are under investigation and points out that a connection with nicotine should still be investigated because 13% of those affected reported having vaped only nicotine based e-liquids (though recognizing that these are self-reported testimonies that are impossible to verify in most cases). Notwithstanding this comment, it is evident that the CDC are now placing a very strong emphasis on explaining EVALI by THC vaping with consumables from informal sources, with nicotine based vaping with e-liquids acquired in legal retail shops playing (at most) a merely token role, in fact, their recommendation to discontinue all e-cigarette usage (including nicotine based usage) must be understood just as the need to include the most extreme (but unrealistic) warning level of precaution to be 100% completely safe. Moreover, the CDC is sufficiently pragmatic to recognize that it is not realistic to expect 10-14 million vapers in the USA to follow this extreme level of precaution and simply stop using the

devices, thus they recommend users to vape only with consumables (cannabis or nicotine based) acquired in legal retail stores and to use the devices along the ways and substances they have been design to operate. Specifically, the CDC recommends the millions of nicotine vapers who have used EC's to quit smoking not to return to smoking cigarettes.

In spite of the fact that the CDC have placed such a strong emphasis in identifying EVALI with a specific type of vaping (with informally acquired THC cartridges), two of the authors of Thirion-Romero et al (Pérez Padilla and Barrientos Gutiérrez) and other health professionals in Mexico have stated in public forums [143,144,145] by November and early December that the EVALI outbreak provides the first evidence that "vaping" (in general) produces serious acute pulmonary injury (on top of possible long term chronic effects). In these statements Pérez Padilla and Barrientos Gutiérrez refer generically to "vaping", thus conflating THC and nicotine based vaping as the cause of EVALI. While this argumentation (as for example in the CDC communications of early September) was somehow justified then it was factually mistaken by November when there was indisputable evidence of the connection with illegal THC vaping. As we argue further ahead, the type of vaping based on nicotine e-liquids acquired in legal retail stores can be definitely ruled out as a cause (even as a contributing cause) of the EVALI outbreak.

While there is still ongoing research on the details and the CDC have not officially ruled out "other substances", the overall medical diagnosis identifies various types of pneumonia (lipoid pneumonia, chemical pneumonitis, crypotogenic organizing pneumonia, acute eosinophilic pneumonia) associated with various pulmonary responses (and in various stages) to oils and lipids whose etiology is consistent with damage from inhalation of vitamin E acetate [146]. However, the examination of biopsias from 17 patients by a team of Mayo Clinic pathologists [147] did not find traces of lipids, identifying instead as causing agent the inhalation of toxic vapors associated with exogenous combustion (dark colored particles normally seen in smokers were found in macrophages even in subjects who did not smoke).

Pérez Padilla and Barrientos Gutiérrez (and other health professionals in Mexico) have argued in public forums [143,144,145] that nicotine based vaping cannot be ruled out as a cause of EVALI because 16% of those affected reported having vaped only traditional e-liquids with nicotine and not cartridges containing THC (the percentage dropped to 13% in December). However, this claim by Pérez Padilla and Barrientos Gutiérrez is based on very weak arguments, these are self-reported testimonies whose veracity is highly suspect: whenever urine tests have been performed the markers of THC usage readily appear. Most EVALI affected subjects come from states of the USA where recreational THC is still illegal, hence recognizing its consumption carries for them legal sanctions and stigma [148]. In fact, the CDC have been criticized for delaying excessively the recognition of the preponderant role of vitamin E acetate in order to artificially keep the opportunity to target nicotine vaping [149].

The lack of incriminating samples of nicotine based e-liquids in EVALI cases is not surprising: these e-liquids do not involve lipids, only water soluble compounds (alcohol carriers: propylene glycol and glycerol, plus nicotine and flavorings), whereas THC vaping in carts and vape pens involves liposoluble compounds. Hence, THC based vaping provides a consistent chemical path to the detected type of pneumonia characterized by lipid remnants. This chemical pathway does not exist for nicotine based vaping (there is also no possible association with toxic vapors in the Mayo Clinic biopsias because EC aerosols do not produce this type of dark colored particles).

Besides these arguments, it is possible to definitely rule out nicotine based vaping as a cause of EVALI because traditional e-liquids with nicotine:

- have been used for over 12 years (since 2008) by more than 40 millions EC users worldwide. The same type of e-liquids and devices have been extensively used much before the fist EVALI case emerged. If these e-liquids would cause acute pulmonary intoxications (such as those of EVALI) thousands of cases (not one or two or a few isolated cases) would have appeared years ago everywhere.

- were used in other countries (Europe, Canada, Australia, Asia, Russia, Latin America, Africa) in the same period when EVALI cases appeared in the USA since June 2019 [149]. If nicotine based e-liquids would be a cause of EVALI many cases (not one or two) would have appeared outside the USA since the e-liquids and the devices used in the USA are on average the same as outside the USA.

While a few cases before 2019 (or outside the USA) could have been mistaken with other diseases or some affected by pulmonary disease could have failed to report previous vaping (a plausible but unlikely scenario in poor countries where EC's are illegal), it is practically impossible that such misplacements or errors could have occurred in large numbers of cases in developed countries where nicotine based vaping is popular. Evidently, the EVALI outbreak affecting 2500 out of over 40 million users of EC's is a clear case of contamination by black market sources, it is factually mistaken and highly irresponsible to blame the EVALI outbreak on "vaping" in general.

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