Complaint under the Code of Conduct of the Committee on Publication Ethics

Letter in the New England Journal of Medicine

Jensen et al (2015) Hidden Formaldehyde in E-cigarette Aerosol

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1 Introduction

This document provides a reasoned case for the editors or editorial board of the New England Journal of Medicine to undertake a review of a research letter published online on 22 January 2015, *Jensen et al, Hidden Formaldehyde in E-cigarette Aerosols*[3] with a view to retracting it. As a member of the Committee on Publication Ethics, the journal has responsibilities under its Code of Conduct[4] and its Retractions Guidelines[5] to uphold the integrity of the academic record and to retract unreliable findings. The relevant sections are as follows:

> ***COPE Code of Conduct for Journal Editors***
> ***12. Ensuring the integrity of the academic record***
> *12.1. Errors, inaccurate or misleading statements must be corrected promptly and with due prominence.*
> *12.2. Editors should follow the COPE guidelines on retractions.*
>
> ***Retractions guidance***
> *Journal editors should consider retracting a publication if:*
> - *they have clear evidence that the findings are unreliable, either as a result of misconduct (e.g. data fabrication) or honest error (e.g. miscalculation or experimental error)*

This document describes the multiple flaws in the research letter. These flaws have created a highly inaccurate and misleading account of the cancer risks associated with e-cigarette use (also known as 'vaping'). This account has gained worldwide media attention (see Appendix 1), promoting false and potentially harmful perceptions of the relative risks of e-cigarette use and of cigarette smoking. The letter continues to be cited in the media and academic discussion.

There are many flaws in the letter that render it highly misleading, but the case for retraction rests on two significant flaws that interact to make the central finding unambiguously unreliable: (1) the operation of the e-cigarette device in conditions that are highly unrealistic for human users, who would find it impossible to inhale the harsh and acrid vapour produced under these conditions; (2) the use of the machine measurements made under these unrealistic conditions to make an estimate of the cancer risk to human users. These failings are discussed in the section 2 below.

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[3] Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols. *N Engl J Med* 2015; **372**: 392–4.

[4] Committee on Publication Ethics, Code of Conduct and Best Practice Guidelines for Journal Editors, 2011

[5] Committee on Publication Ethics, Retraction Guidelines, 2009

We have also noted the publication on 16 April 2015 of correspondence about the research letter and the authors' reply to criticisms made in one of the letters[6]. We do not consider the authors' reply to be a remotely adequate defence of this paper and its conclusions. A detailed examination of this reply is included in section 3 of this complaint.

There are other serious flaws in the letter including: an unwarranted assumption that formaldehyde-related risks can be calculated from measurements of formaldehyde hemiacetals; poor risk communication; ignoring legitimate but reassuring findings; overly simplistic models of cancer risk; and deliberately misleading presentation of error bars. These are discussed in section 4.

The consequences of research that misrepresents smoking or related risks to a wider public can be a cause of actual bodily harm if it deters smokers from switching from smoking or vapers to relapse to smoking. The harmful consequences, and hence the importance of rigorous treatment of studies that purport to describe risks to smokers and vapers, is discussed in sections 5.

The Code of Conduct of the Committee on Publication Ethics requires member journals to have a complaint handling procedure. We would like to request that this complaint is handled under that procedure as implemented at the New England Journal of Medicine, as discussed in section 6.

2 Main arguments for retraction

2.1 Operating e-cigarette equipment in unrealistic artificial conditions

Jensen et al made no attempt to validate that the way they were operating the vaping equipment in their laboratory (i.e. the power output, puff duration, puff frequency) was a realistic representation of the way human subjects use these products. The reporting of the methodology is extremely weak and omits many important experimental details, but crucially there is no account of how *Jensen et al* ensured their test conditions were a realistic representation of human use. It is now clear that this was not done.

The vaping equipment used by *Jensen et al*. was operated at high power. Using a 5.0 volts setting on its battery would give a power output of 12 watts, given the electrical resistance of the atomiser used (power output increases with the square of voltage applied)[7]. This combination of battery and the atomiser chosen is certain to create 'dry puff' conditions in the equipment they were using[8].

This phenomenon is widely discussed on vaping forums and well documented in the peer-reviewed literature. For example, see Farsalinos and colleagues writing in 2013[9].

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[6] Jensen RP, Luo W, Pankow JF, et al. More on Hidden Formaldehyde in E-Cigarette Aerosols – reply by the authors. N Engl J Med 2015;372:1575–7. doi:10.1056/NEJMc1502242

[7] Power output (P) increases with the square of voltage (V) applied (Ohm's law $P=V^2/R$). The atomizer had a resistance (R) of 2.1 Ohms. At 3.3 volts, the power output was about 5.5 watts and at 5 volts it was 12 watts. Note that the information required to make this check was not provided in the research letter.

[8] Farsalinos KE. Verified: formaldehyde levels found in the NEJM study were associated with dry puff conditions. An update. E-cigarette Research, 22 January 2015.

[9] Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. *Int J Environ Res Public Health* 2013; **10**: 2500–14.

> *Vaping topography may have significant implications in production and delivery of potentially harmful substances. The EC evaporation rate and thermal load are directly dependent on the puff duration and interpuff interval. If the device is activated before the temperature is significantly decreased and/or before the wick is sufficiently supplied with liquid, the device will get overheated. This causes a phenomenon called "dry puff". It is an unpleasant, burning taste that forces the user to lower puff duration and increase interpuff interval. […]. The "dry-puff" phenomenon, although easily detected and avoided by the user, cannot be detected in the laboratory setting. Therefore, if this occurs during a laboratory experiment, it will significantly undermine the value of the study results and their applicability to real use. It should be emphasized that each type of atomizer has different cooling and liquid-supply abilities, depending on the design and material used. This should be taken into consideration when preparing laboratory research protocols.*

Jensen et al should have been aware of this phenomenon and taken precautions to avoid it, but it is apparent that they did not. Note that the authors are making affirmative claims about health risks: it is *their responsibility* to show the conditions were realistic, not ours to show that they were not

2.2 Basing cancer risk calculations on measurements made in unrealistic conditions

The human control feedback between harsh flavour and user behaviour means that human users would hardly ever be exposed to the vapour produced under dry puff conditions, and at worst only momentarily before they corrected. However, *Jensen et al* went on to make estimates of the cancer risk to human users that would arise if users had a *lifetime of vaping continuously* under these unrealistic conditions. So, a cancer risk for formaldehyde exposure from e-cigarette use was calculated using estimated exposures that are impossible in human subjects for even very short periods and reported without qualification, and in a comparison with cigarette smoke. These formed the main talking point of the letter, and generated the subsequent worldwide alarmist news coverage.

2.3 Overlooking a crucial human feedback not simulated in laboratory studies

The dry puff condition arises from pyrolysis (thermal degradation) of the main ingredient in e-cigarette vapour, propylene glycol when the coil is running hot – above the normal temperatures for vaping. The thermal breakdown products include carbonyls, such as formaldehyde, which impart a harsh and acrid flavour with a burning sensation to the inhaled vapour that a human user finds painful and intolerable. The human user will respond by stopping, reducing puff frequency, reducing puff duration, adding liquid, improving liquid flow, or resetting the battery to a lower voltage – these responses lower the temperature of the coil to the normal vaping range below the temperatures at which formaldehydes form. This harsh taste experience provides a control feedback to vaping behaviour that ensures the equipment does not operate in 'dry puff conditions: this works for humans, but not the puffing machines used in laboratories. The very presence of measurable formaldehyde-related compounds is a clear sign that the equipment is being used in dry puff conditions. Recent research shows e-cigarettes generate high levels of aldehydes *only* in dry puff conditions[10]. The researchers should have taken the following precautions:

[10] Farsalinos KE., Voudris V., Poulas K. E-cigarettes generate high levels of aldehydes only in "dry puff" conditions. *Addiction*, in press, April 2015.

1. Recognised the widely understood concept of the dry puff phenomenon and designed their experiment to avoid it and to avoid drawing conclusions about human health from measurements undertaken in these conditions. They show no sign of having understood this risk and incorporated into the experimental design.
2. Taken practical steps to avoid operating in dry puff conditions. One obvious way would be to ask one or more human subjects to attempt to use the device under the laboratory conditions tested. *Jensen et al* show no sign of having involved any human subjects or otherwise found a way to verify they were operating in realistic conditions.
3. Used the discussion of the results to reflect at least the highly likely case that the device was operated in unrealistic conditions. Under no circumstances should they have reported a cancer risk without verifying their equipment was operated in a way that human users would use it. Of course, acknowledging that the exposures measured were an unrealistic artefact of equipment configuration and laboratory conditions would have rendered the letter unfit for publication, especially in a medical journal, which is naturally primarily concerned with human health.
4. Reviewed and cited the literature on vaping topography and spoken to users to acquire a better understanding of vapour products and vaping experience.

2.4 Are these measurements still a useful addition to the body of scientific knowledge?

It might be objected that because it is *possible* to operate a vaping device in this way, then it is legitimate to measure it under these conditions. This is not the case. By way of analogy, the procedure followed and calculations made are no more sophisticated, or informative, than toasting bread until it is thoroughly black and charred, measuring toxins on the charred surface and then calculating the cancer risk from consuming a lifelong diet of blackened toast – the *Jensen et al* letter really is as crude as that. Many machines or processes, including toasters and e-cigarettes, can be operated in extreme or unrealistic conditions: but if the purpose is to characterise the risk to humans, they should be operated within the range of conditions in which humans use them.

Even if there were residual curiosity value in measurements made under conditions unrealistic for humans, such findings would need clear caveats about their very limited relevance, and no such caveats were included. However, the fundamental flaw was using these measurements in a calculation of cancer risk: *they could <u>never</u> legitimately be used in a calculation of human exposure and cancer risk*, as they were in the *Jensen et al* letter. Even if measurements outside the range of human experience are an academic curiosity, there is no purpose served in publishing them in a leading *medical* journal.

3 The case for retraction under the COPE Code of Conduct

These errors alone mean that *all the important findings* in the letter are inaccurate, misleading and unreliable in the meanings used in the Code of Conduct of the Committee on Publication Ethics and related Retractions Guidance.

3.1 A correction to the letter would not suffice

The flaw in this letter is fundamental – both miscalculation and experimental design error have led to an erroneous public communication of a cancer risk that does not exist in reality. It would not qualify for a simple correction under the COPE retractions guidance:

"*Journal editors should consider issuing a correction if a small portion of an otherwise reliable publication proves to be misleading (especially because of honest error)".*

3.2 The authors' published response to a critical letter is an inadequate defence

The authors' defence of their work is wholly inadequate. On 16 April 2015, NEJM carried a short letter criticising the study[11] using similar arguments to those laid out in section 2 above, together with a reply from the authors[12]. The reply does not address the failings of this study or justify the flawed conclusions: that the authors should have provided assurance they were operating under realistic conditions for vaping and without that assurance they should not have published an alarmist calculation of cancer risk. The following examines the five main arguments made in the authors' reply:

1. *There is a lack of objective data with which to judge whether these devices are being used as safely as possible*. This does not absolve the authors of the responsibility to ensure their experiment simulates realistic vaping conditions, and so underpins a meaningful risk calculation. The concept of "dry puff" is well understood by vapers and described in the literature – but the authors proceeded as if they were confident that their laboratory settings were realistic. *Jensen et al* are making an affirmative claim about formaldehyde exposure and cancer risk, and they have been challenged to show that their experiment did not rely on conditions that are never found when human subjects, rather than machines, use these products. They have not responded to that challenge at any point, including in the exchange of correspondence with NEJM, and shown their measurements to be realistic, but have instead made a distracting argument about general uncertainty.
2. *It is well known that although inhaling cigar smoke is unpleasant for some, many cigar smokers do inhale*. There is no evidence or experience suggesting that vapers continue vaping through dry puff conditions, which create both a bad taste and a painful burning sensation. The comparison with cigar smoking is misleading and not a reliable basis for claiming that vapers will inhale substantial quantities of formaldehyde or other thermal degradation products. Vapers in fact control their use of the device to avoid this. The more appropriate analogy for the authors' experiment is that of calculating cancer risk from lifetime consumption of toast that has been blackened to a char.
3. *Formation of formaldehyde, formaldehyde hemiacetals, and other possible toxicants will be dictated by a continuum of conditions*. The researchers own experiment only provides two voltage / temperature points – not enough to suggest that the formaldehyde quantities are *ever* above the limits of detection under realistic operating conditions. At the lower voltage no formaldehyde hemiacetals were detected, and it is likely that the 'continuum' is flat and near-zero in the range in which real vapers use these products. Thermal degradation reactions require sufficient energy input to pass a threshold to break otherwise stable chemical bonds, and therefore the formation of these compounds will start to rise only after a certain temperature is exceeded, creating an irregularity in the shape of the continuum – continuously flat and near

[11] Nitzkin JL, Siegel M, Farsalinos KE. More on Hidden Formaldehyde in E-Cigarette Aerosols – letter to the editor. N Engl J Med 2015;372:1575–7. doi:10.1056/NEJMc1502242

[12] Jensen RP, Luo W, Pankow JF, et al. More on Hidden Formaldehyde in E-Cigarette Aerosols – reply by the authors. N Engl J Med 2015;372:1575–7. doi:10.1056/NEJMc1502242

zero and then only rising when a temperature threshold is reached. More recent research[13] confirms this through investigating the relationship between aldehyde emissions and operating power. It shows that aldehyde emissions remain very low at normal operating temperatures and that the onset of dry puff conditions is sudden, showing a rapid spike once these conditions arise. At the point it becomes noticeable (it rarely occurs for most vapers), then human subjects adjust their behaviour and/or the settings to stop the bad taste and burning sensation. There is nothing about this kinked 'continuum' that suggests that vapers actually use the products in the conditions in which *Jensen et al* tested the devices, made their calculation, drew their comparison with smoking and reported their results.

4. *It seems plausible that toxicant formation can occur without a particularly bad taste, especially given the known taste-masking effects of high levels of flavor chemicals in many vaping liquids*. That this "seems plausible" is not a reliable basis for the *Jensen et al* cancer risk calculation, especially as dry puff conditions are a well understood and recognised phenomenon and that, to most experts, the operating conditions used are implausible for human use. Dry puff conditions do not just produce a bad taste, they also create a nasty burning sensation and this is something that all users avoid. *Jensen et al* cannot justify their method and unqualified conclusions on this basis – including by citing another speculative paper about flavours in *combustible tobacco products* that has no relevance here. *Jensen et al* were responsible for ensuring their calculation of cancer risk was based on realistic conditions for humans – saying that it is *plausible* that they might be, is not an adequate validation of the applicability of the findings to human health, especially as it is not actually very plausible.

5. *Beyond this, we are finding that even some units without any user controls can produce considerable levels of formaldehyde hemiacetals*. This suggests that the authors still do not recognise the nature of their basic error. That error is to neglect the human control feedback that prevents human exposure to high-temperature operating conditions through a behavioural response to the harsh taste and burning sensation created by vaping at high temperatures. Even where there are no user settings on the device, the users exercise control over operating conditions by moderating their rate and depth of puffing, or as necessary, adding liquid or wetting the coil in response to the harsh taste and burning sensation.

The key point is that *Jensen et al* published a calculation of cancer risk without any assurance that human subjects would ever experience this exposure, and they have not provided any in response to the critical letter published about this research. They could have checked for the reality of their operating regime by asking one or more vapers to simulate their puffing regime with the chosen settings. They still could perform this check if they did wish to validate the reliability, or otherwise, of their work.

3.3 The responsibility of a leading journal to act ethically and decisively

Without retraction a flawed study would stand and continue to be cited and the "*integrity of the academic record*" would remain compromised in breach of the COPE code.

The errors in the methodology invalidate the letter completely and its calculations of formaldehyde

[13] Farsalinos KE., Voudris V., Poulas K. E-cigarettes generate high levels of aldehydes only in "dry puff" conditions. *Addiction*, in press, April 2015.

exposure and related cancer risk in their entirety. For that reason it should be retracted, not merely corrected or challenged with a short letter expressing a contrary view. This is not a matter of debate or legitimate but opposing interpretations of the findings, but a crude experimental flaw underpinning an erroneous calculation leading to widespread misrepresentation of risk.

It is also important that prestigious journals signal to authors and peer reviewers that they have responsibilities to produce high quality work and should not expect journals to shelter them when substantial mistakes are uncovered. Finally, a retraction is a mark of intellectual confidence on the part of the journal itself – a success not a failure. *Not retracting* such a flawed letter would be the weaker course. When the historical record is reviewed, there is no doubt that this letter will be counted as unreliable research that contributed to widespread misperception of risk about these products. It is better to be on record as the journal that recognized the flaws and retracted it in time to correct the integrity of the scientific record, rather than the journal that let it stand and continue to mislead.

4 Other flaws in the letter and further arguments for retraction

The case for retraction is sufficiently made by the combination of unrealistic operating conditions for humans and a calculation of cancer risk based on the machine exposures created under these conditions – as discussed in section 2 and 3 above. However, there are several further flaws in the letter that add to the case for retraction, and these are discussed in this section.

4.1 Use of formaldehyde-releasing compounds as a proxy for risk of formaldehyde

The authors measure formaldehyde hemiacetal and not formaldehyde in free form. This means that formaldehyde is bound to the glycols present in the e-cigarette liquid. It is likely that binding of formaldehyde to glycols will *protect* the nasopharyngeal and respiratory epithelium from exposure to formaldehyde. However, the authors chose to characterise the cancer risk associated with formaldehyde hemiacetal inhalation as being the same as for formaldehyde. This equivalence is an assumption, which is correctly stated but for which no justification is provided, yet the whole calculation of cancer risk depends on this assumption. As the authors rightly state: *How formaldehyde-releasing agents behave in the respiratory tract is unknown, but formaldehyde is an International Agency for Research on Cancer group 1 carcinogen*. It is quite possible that these agents would be mostly exhaled before releasing formaldehyde or might actually be protective. This error is sufficiently misleading in its own right to justify retraction.

4.2 Earlier studies show much lower formaldehyde levels in e-cigarette vapour

Previous studies of carbonyls in e-cigarette vapour found much lower levels of formaldehyde than in cigarette smoke, when used in normal operating condition. For example*, Kosminder et al (2014*)[14] found formaldehyde levels on average 13-fold lower than cigarettes on average – though it is likely that they also made some measurements in dry puff conditions at higher voltages. Goniewicz et al (2014)[15] found formaldehyde levels nine-fold lower. A Japanese team, *Bekki et al (2014*)[16] found

[14] Kosmider, L., Sobczak, A., Fik, M., Knysak, J., Zaciera, M.; Kurek, J., Goniewicz, M.L. Carbonyl compounds in electronic cigarette vapors-effects of nicotine solvent and battery output voltage. *Nicotine Tobacco Res*. 2014.

[15] Goniewicz, M.L., Knysak, J.; Gawron, M.; Kosmider, L.; Sobczak, A.; Kurek, J.; Prokopowicz, A.; Jablonska-Czapla, M.; Rosik-Dulewska, C., Havel, C., et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob. Control* 2014, **23**, 133–139.

from 0 to 34 micrograms of formaldehyde from 10 puffs of e-cigarettes In contrast, 10 puffs of a cigarette deliver around 150-250 micrograms or over 500 when smoked in a more intensive regime[17]. The consensus in the literature to date was that, in the case of formaldehyde, emissions from e-cigarettes were *one order of magnitude lower than for tobacco smoke* under normal conditions. *Jensen et al* measured what they describe as 'hidden formaldehyde' (formaldehyde hemiacetal) but if their theory rests on these 'formaldehyde-releasing agents' decomposing to release formaldehyde, which would have been detected in the other studies. It is unclear why *Jensen et al* did not measure formaldehyde as well or why they did not recognise that much of what was measured as formaldehyde hemiacetal would be exhaled prior to decomposition to formaldehyde.

Jensen et al should have been especially alert for experimental flaws given that previous studies had found low levels of formaldehyde in the gas phase (not measured in *Jensen et al*), and taken particular care to interpret their results in that light. If formaldehyde hemiacetals (not measured in other studies cited) are releasing formaldehyde then it should be expected this would appear when formaldehyde is measured. *Jensen et al* should have placed their findings in context and noted the limitations of assuming equivalence of formaldehyde and formaldehyde hemicactel.

Lessons from the publicity arising from Japanese research and careless statements. Although, the Japanese study (Bekki et al) mentioned above showed much lower levels of formaldehyde in the published research, one of the research team, Naoki Kunugita, publicised a single unpublished anomalous result, which found formaldehyde levels very much higher (1,600 micrograms – up to ten times the level for smoking). This achieved worldwide but highly misleading press coverage that was easily challenged by experts[18]. It was clear that this result had been obtained in uncontrolled dry puff conditions.

Jensen et al should have been aware of the extensive publicity received by Kunugita's remarks to the media, *and the subsequent critical analysis of this finding*, and should have taken steps to avoid misleading the media and public in the same way.

4.3 Misleading presentation of cancer risk calculations

The communication of calculated cancer risk in this letter is phrased in a way that is certain to mislead many of the audiences with an interest in these findings:

> *long-term vaping is associated with an incremental lifetime cancer risk of 4.2×10^{-3}. This risk is 5 times as high (as compared with the risk based on the calculation of Miyake and Shibamoto shown in Figure 1), or even 15 times as high (as compared with the risk based on the calculation of Counts et al. shown in Figure 1) as the risk associated with long-term smoking.*

While this may not be a technically inaccurate way of describing the authors' (flawed) calculation, it is certainly confusing and opaque. For many readers it will not be clear that:

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[16] Bekki K, Uchiyama S, Ohta K, Inaba Y, Nakagome H, Kunugita N. Carbonyl Compounds Generated from Electronic Cigarettes. *Int J Environ Res Public Health* 2014; **11**: 11192–200.

[17] Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol* 2008;**21**:494–502. doi:10.1021/tx700275p

[18] See Farsalinos K, E-cigarette aerosol contains 6 times LESS formaldehyde than tobacco cigarette smoke, E-cigarette Research blog 27 November 2014

- these comparisons refer *only* to formaldehyde-attributable cancer risk;
- that this risk is *low* in absolute terms;
- this risk amounts to a small fraction of the total cancer risk attributable to smoking;
- that e-cigarettes do not create 5-15 times the cancer risk of cigarettes.

It is no surprise that this statement was widely interpreted by the public and media as meaning that e-cigarettes carry a cancer risk that is comparable to or greater than smoking or that formaldehyde related risks are significant – a review of press coverage and social media will confirm that. See Appendix 1 with links to some examples.

Jensen et al should have taken much greater care to present these calculations of risk in a way that was not so prone to an exaggerated interpretation and would not be so easy to misunderstand by the media, public and non-specialists.

4.4 Findings that should reassure users rather than alarm them were ignored

The *Jensen et al* experiment contains data showing that under normal operating conditions *there were no formaldehyde or formaldehyde-releasing compounds detected*, and hence no cancer risk from formaldehyde when used under normal operating conditions – yet this forms no part of the discussion, analysis of cancer risk, conclusions or media communications. The part of the experiment that simulated realistic operating conditions (i.e. at lower voltage / temperature) should have provided a measure of reassurance to users. However, the focus was placed entirely on the flawed measurements and calculations and the exact opposite impression was conveyed to the media and public by the article and related public relations[19].

4.5 Excessive certainty about attribution of cancer risks

It should be understood that formaldehyde is present in the ambient atmosphere and in the body and that exposures can come from many sources[20]. *Jensen et al* do not put formaldehyde exposure from e-cigarettes into context with ambient exposure and other environmental exposures. In calculating an exposure to cancer risk, the letter provides a precise view of the contribution of formaldehyde to cancer from vaping and smoking. However, authorities such as the Surgeon General of the United States do not go as far as quantitatively attributing smoking-related cancer risks to specific carcinogens, and nor do they list formaldehyde as among the more significant hazards in tobacco smoke. Summarising the evidence in 2010, the Surgeon General of the United States stated[21]:

> *Fowles and Dybing (2003) […] considered the risk for cancer, cardiovascular disease, and heart disease. Using this approach, these investigators found that 1,3-butadiene presented by far the most significant cancer risk; acrolein and acetaldehyde had the greatest potential to be respiratory irritants; and cyanide, arsenic, and the cresols were the primary sources of cardiovascular risk. Other chemical classes of concern include other metals, N-nitrosamines,*

[19] See Portland State University press release: PSU researchers uncover high levels of hidden formaldehyde in e-cigarette vapor, 22 January 2015.

[20] Kaden DA, Mandin C, Nielsen GD, Wolkoff P. WHO Guidelines for Indoor Air Quality: Selected Pollutants. Formaldehyde. 2010.

[21] Surgeon General of the United States. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease. 2010. [link]

and polycyclic aromatic hydrocarbons (PAHs).

The use of simplistic models to attribute cancer risk for formaldehyde exposure remains, at best, controversial[22].

4.6 Misleading presentation of variance

In Figure 1 in the letter, the authors draw error bars for the measurements in a contrived and misleading way. According to the letter, the "*two bars on the left [cigarette smoke] indicate standard deviations, and the bar on the right [e-cigarette vapour] indicates the standard error*". The standard deviation expresses how much the individual data points vary; the standard error expresses how much the mean of all the data points would vary. Standard error (SE) and standard deviation (SD) are related ($SE = SD/\sqrt{n}$ - where n is the number of observations) and the standard error is thus always smaller. Whether or not it was the aim, the effect is visually to imply greater confidence in the e-cigarette tests than is justified in comparison to the cigarette test results. There was no need to do this: the authors could have plotted standard deviation for their own results, though the error bars would then cross zero, with visually obvious consequences for the reliability of the results.

5 Harmful consequences of miscommunication of risk

There is a broad expert consensus that e-cigarettes pose 1-2 orders of magnitude (at least 20 times) lower risk to health than smoking[23]. However, among smokers, the people at greatest risk, a large and increasing proportion believe e-cigarettes to be no less risky than cigarettes. For example, *Kaufman et al* (2015)[24] report that only 39.1% of adults and 59.7% of smokers believe e-cigarettes are less harmful than smoking at all. As a further example, *Tan & Bigman* (2014)[25] report that for US smokers:

> *In 2010, 84.7% of smokers surveyed believed e-cigarettes were less harmful than traditional cigarettes, but according to this new study in 2013, that number dropped to just 65%.*

There are similar findings in surveys of British smokers and even among those who believe the risks to be lower there are many who greatly overstate the risk *relative* to smoking. In Britain just 54% of adults perceive vaping to be less risky than smoking, but only 17% of adults correctly perceive vaping to be "much less risky than smoking"[26]. This perceived loss of a significant benefit (much lower risk than smoking) means that smokers will be less likely to try to switch and more likely to relapse – with more smoking and more disease and premature death than would otherwise be the case. Unlike much academic publishing, this is a situation where a misleading article can contribute to public misperceptions of risks, and these can have can have mortal consequences if they adversely influence smoking behaviour. It is essential that respected journals take the greatest possible care in

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[22] National Research Council. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde. Washington, DC: The National Academies Press, 2011 [link]

[23] West R, Brown J. Electronic cigarettes: fact and faction. *Br J Gen Pract* 2014; **64**: 442–3.[link]

[24] 1 Kaufman AR, Finney Rutten LJ, Parascandola M, et al. Food and Drug Administration Tobacco Regulation and Product Judgments. Am J Prev Med 2015;**48**:445–51. doi:10.1016/j.amepre.2014.10.026.

[25] Tan ASL, Bigman CA. E-cigarette awareness and perceived harmfulness: prevalence and associations with smoking-cessation outcomes. *Am J Prev Med* 2014; **47**: 141–9.

[26] Action on Smoking and Health, Smokefree Britain Survey, 2014. Total sample size was 12269 British adults (aged 18+). Fieldwork was undertaken by YouGov between 5th to 14th March 2014. The figures have been weighted.

the communication of risks associated with different choices that ordinary members of the public take, and put right any misleading statements as quickly as possible.

Given that real lives are at stake, is important that the New England Journal of Medicine takes its commitments under the Committee on Publication Ethics codes especially seriously in this case.

6 Complaint-handling mechanism

The COPE Code of Conduct states at Section 15:

> ***15. Complaints***
> *15.1. Editors should respond promptly to complaints and should ensure there is a way for dissatisfied complainants to take complaints further. This mechanism should be made clear in the journal and should include information on how to refer unresolved matters to COPE.*

This communication is intended as a complaint made under these guidelines and therefore it should be handled within the NEJM's complaint mechanism as referred to in this section of the Code. We would be grateful for further information on how this complaint will be addressed.

7 Conclusion – the findings are unreliable and should be retracted

The clear message readers were intended to take from the letter is that usage of e-cigarettes can cause more formaldehyde exposure, and related cancer risk, than smoking cigarettes. But this is flatly contrary to substantial existing evidence, and the authors' unrealistic test does not support this claim. The findings of this letter are unambiguously inaccurate, misleading and wholly unreliable. For that reason the letter should be retracted under the principles established by the Committee on Publication Ethics.

The errors made were foreseeable and diligent researchers familiar with their field should have avoided them. Such studies can adversely affect public risk perceptions in a way that can lead to additional ill-health as people who are at risk respond to reports about the research in the media. It is therefore particularly important that great care is taken in conducting and reporting on such research and that academic journals take a robustly ethical approach when such research is found to be fundamentally flawed.

Appendix 1: sample of press coverage generated

The headlines below (included as hyperlinks to the articles) illustrate the tone of the press coverage. Without exception they imply the findings represent an increased risk of cancer.

- Reuters: Ramping up e-cigarette voltage produces more formaldehyde -study
- LA Times E-cigarettes can produce more formaldehyde than regular cigarettes, study says
- NPR: E-Cigarettes Can Churn Out High Levels Of Formaldehyde
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