Review of: "Carcinogenic and non-carcinogenic health risk assessment of organic compounds and heavy metals in electronic cigarettes"

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Criticism of a recently published article on a toxicological risk analysis of e-cigarettes

Abstract. We criticize a recently published article (Zhao et al., "*Carcinogenic and non-carcinogenic health risk assessment of organic compounds and heavy metals in electronic cigarettes*" [1]). This study presents a toxicological risk analysis of e-cigarettes (e-liquids and aerosols), with exposure data obtained from 28 studies listed in one of their supplementary files on toxic byproducts (metals and organic) in aerosol emissions and e-liquids. However, the usage of this data weakens the results of the risk analysis since a significant number of these studies are methodologically flawed, thus reporting overexposures and/or exposures from devices that are currently obsolete.

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The problem with the study by Zhao et al. is not its methodology. The authors compute risk evaluations from standard toxicological models. The article has several problems, for example, citing selectively studies that have detected high toxicant contents in emissions and biomarkers, ignoring contrary evidence. They did not cite the extensive review by the OHID [2] and reviews by Soulet and Sussman [3][4] on the literature on metals and organic byproducts.

However, the main problem and truly weak point of this article is in the data needed for the toxicological models to estimate exposure from metals and organic byproducts in e-cigarette aerosols (toxicity in e-liquids is a secondary issue). The authors place values of doses in their tables 4, 6, and 8 that are crucial for the toxicological analysis, values that are bound to be overestimations if they are based on flawed studies. They describe the collection of data sources in their methods section:

> *"This study retrieved articles from PubMed and CNKI databases... The years 2003.1.1-2023.1.1 were set as the start and end of the search for this study. We searched... "e-cigarettes" and obtained 9416 results, and then conducted advanced searches with keywords such as "e-cigarettes," "liquid tobacco," "aerosols," "heavy metals," and "chemical substances," … finally identified 28 articles with four organic compounds (formaldehyde, acetaldehyde, acrolein, and acetone) and seven heavy metal elements (arsenic, chromium, manganese, copper, lead, nickel, and cadmium) for data collection and processing."*

The 28 articles used as a basis for collecting exposure data for the toxicological analysis are listed in one of their supplementary files. The references below will refer to those in this file. A revision of these studies reveals that:

- 8 studies were published between 2012 and 2015, thus they examined emissions from first and second-generation devices, which are now obsolete. Outcomes from such studies are no longer reliable and relevant to assess emissions from current devices. A RIVM report elaborated in 2015 is profusely cited as source (reference 1), but it examined devices that are currently obsolete.
- Soulet and Sussman [3][4] reviewed 6 of the 28 studies, of which 4 reported excessive metal contents but had severe methodological flaws. These are their references 11, 13, 15, and 17. This is important because these studies reported high metal contents, which lead to overestimation of doses in tables 4, 6, and 8.
- One study (reference 25, Williams et al. 2014) was criticized by Farsalinos[4]. Another one (reference 26, Olmedo et al. 2021) was incorrectly cited; it deals with biomarkers, not with emissions. The one by the same authors dealing with emissions (reference 19 of the main manuscript) was criticized in the metals review by Soulet and Sussman [3].
- Some of the references are either unavailable (16, Chen et al; 18, PanLi Ning; 21, LI Q-Q) or only available in Chinese (12, Lu Yifeng).

The following paragraphs show the tendency of Zhao et al. for selectively citing background material in the main manuscript (their comments are in block quotes, and reference numbers are references of the main manuscript).

They cite a study (reference 21)

- [21] Kankanamage, R. N. T. et al. Metabolites of tobacco- and E-cigarette-related nitrosamines can drive Cu2+-mediated DNA oxidation. Chem. Res. Toxicol. 33(8), 2072-2086. https://doi.org/10.1021/acs.chemrestox.0c00027 (2020)

claiming that vaping causes DNA damage that can lead to genotoxicity from nitrosamine biomarkers in the urine of vapers who have never smoked. Unfortunately, Zhao et al. ignore the massive evidence on biomarkers contained in the 1300 pages of the OHID report [2], all this besides the fact that vapers who have never smoked are very hard to find (thus, results very likely rely on a very small sample).

An incorrect citation:

> - *"Jefferson et al.30 studied the carcinogenic and non-carcinogenic risks of heavy metals contained in e-cigarette*

> *liquids and aerosols by collecting data and organizing the organs on which these heavy metals acted, and calculating the total possible risk to different organs. The results showed that the carcinogenic risk for Cr exceeded the acceptable range even at low exposure concentrations, and the non-carcinogenic risk for Ni was the highest, with an average HI of 14.5."*

The correct cited reference 30 is a toxicological risk analysis on metals by Fowles et al. (see below), which was criticized by Soulet and Sussman [3]. Fowles et al. simply took at face value the results of a literature of metal studies that were found exhibiting serious methodological flaws. Therefore, the toxicological analysis of Fowles et al. is based on an enormous overestimation of doses.

- [30] Fowles, J., Barreau, T. & Wu, N. Cancer and non-cancer risk concerns from metals in electronic cigarette liquids and aerosols. Int. J. Environ. Res. Public Health. 17(6), 2146. https://doi.org/10.3390/ijerph17062146. PMID: 32213824; PMCID: PMC7142621 (2020).

Citation of results not applicable to current e-cigarette devices:

> - *"The non-carcinogenic risk caused by heavy metal exposure in the inhalation route is mainly derived from manganese, copper, and nickel, which may also be related to the migration of heavy metals from e-cigarettes, as mentioned above. This is because e-cigarette heating wires are made of different materials. The heating wire of the e-cigarette system used by Williams et al. 50 in their study was a nickel-chromium wire connected to a thicker silver-plated copper wire. They found green deposits containing copper in the fibers of both dust collectors and aerosols containing heavy metal particles with a diameter of 1 mm. The hazards associated with these particles entering alveolar cells are much greater than those caused by direct human contact with e-liquids."*

The cited article by Williams et al. was published in 2014.

- [50] Williams, M., Villarreal, A., Bozhilov, K., Lin, S. & Talbot, P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. PLoS ONE 8(3), e57987. https://doi.org/10.1371/journal.pone.0057987 (2013).

It deals with first and second-generation devices that are now obsolete and of marginal usage. Technology has advanced and corrected leaking effects from heating wires possibly in contact with the e-liquid. In spite of the scandal, Farsalinos [5] showed that Williams et al. did not detect metals in worrying concentrations but well below toxicological standards.

Another incorrect citation:

> - *"The amount of chemicals in the aerosols produced by e-cigarettes is highly variable and is related to many factors. In their study, Olmedo et al. 51 evaluated the effects of e-cigarette power, resistance, and frequency of*

> *coil replacement on the variation of heavy metal content in aerosols, showing that the Al, Co, Pb, and Zn content decreased with increasing power, while Cu, Mn, Ni, Sb, and Sn content were highest at medium power."*

The cited study in reference [50] by Olmedo et al. The citation is incorrect since that reference looks at metal biomarkers in vapers and found them to be indistinguishable from those of users. They probably referred to the emission study by Olmedo et al (reference 19), a deeply flawed study whose evaluation of exposure doses was criticized by Farsalinos and Rodu [6] and Soulet and Sussman [3].

Ignoring the recommendations of an excellent emissions study by Gillman et al. (2016):

> - *"The higher the output voltage of the battery, the higher the carbonyl content of the vapor. Gillman et al.18 investigated the effect of variable power levels on total aerosol mass production and aldehyde formation in e-cigarettes, and the results obtained showed that the total mass of aerosol produced by e-cigarettes gradually increased with increasing voltage, which was also accompanied by more aldehyde production. The above findings suggest that we should also consider factors such as device power and liquid composition when assessing the health risks of e-cigarettes, but they also show that the level of chemical hazards produced by e-cigarette products is controllable."*

This paragraph is correct; the cited reference by Gillman et al. is one of the best emission studies. However, it is not evident that Zhao et al. noticed that the exposure data used in their toxicological analysis comes from studies that tested aerosols generated under the abnormal conditions that Gillman et al. precisely identify as prone to generate large yields of carbonyls (too high voltage/power).

References

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3. a, b, c, d, e *Soulet, S.; Sussman, R.A. A Critical Review of Recent Literature on Metal Contents in E-Cigarette Aerosol. Toxics 2022, 10, 510. https://doi.org/10.3390/toxics10090510*
4. a, b, c *Soulet, S.; Sussman, R.A. Critical Review of the Recent Literature on Organic Byproducts in E-Cigarette Aerosol Emissions. Toxics 2022, 10, 714. https://doi.org/10.3390/toxics10120714*
5. ^ *Farsalinos KE, Voudris V, Poulas K. (2015). Are metals emitted from electronic cigarettes a reason for health concern? A risk-assessment analysis of currently available literature. Int J Environ Res Public Health 12:5215-32. https://doi.org/10.1080/08958378.2018.1523262*

6. ^*Farsalinos, K.E.; Rodu, B. Metal emissions from e-cigarettes: A risk assessment analysis of a recently-published study. Inhal. Toxicol. 2018, 30, 321-326.*