Editorial: Alternative tobacco products: Toxicology and health issues

Demetrios Kouretas, Konstantinos Poulas

PII: S0278-6915(18)30356-9
DOI: 10.1016/j.fct.2018.05.056
Reference: FCT 9811

To appear in: Food and Chemical Toxicology

Please cite this article as: Kouretas, D., Poulas, K., Alternative tobacco products: Toxicology and health issues, Food and Chemical Toxicology (2018), doi: 10.1016/j.fct.2018.05.056.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Alternative tobacco products: Toxicology and health issues

Demetrios Kouretas\textsuperscript{1} and Konstantinos Poulas\textsuperscript{2}

\textsuperscript{1}Department of Biochemistry-Biotechnology, School of Health Sciences, University of Thessaly, Viopolis, Larissa, 41500, Greece

\textsuperscript{2}Department of Pharmacy, University of Patras, Rio-Patras, 26500, Greece

Smoking cigarettes and any other combustible tobacco products causes adverse health outcomes, especially cancer and cardiovascular and pulmonary diseases. On the other hand, research is showing that all the non-combustible nicotine delivery vehicles are substantially less dangerous than combustible tobacco products. Over the past ten years, smokers have begun using e-cigarettes at a markedly increasing rate. The following main concerns about the use of these products should be noted: a. These products contain nicotine, the "drug" found in cigarettes, b. The emissions can harm the body, c. Flavorings can attract the youngers, d. Some of these products can cause injuries. The current issue is attempting to clarify some of these very important research questions, continuing the dialogue and adding evidence.

Carbonyls are some of the main toxicants in tobacco cigarette smoke, thus there is a lot of interest in evaluating such emissions in tobacco harm reduction products. Mubarak et al developed and validated a new methodology for simultaneous quantitative analysis of aldehydes in base liquids. This method was used for the quantification of aldehydes emitted by different base liquids and according to the study vegetable glycerin produces the highest percentage of aldehydes after thermal decomposition compared to propylene glycerol. The current issue is presenting 2 studies evaluating carbonyl emissions from e-cigarettes. While several studies have been published in recent years on the subject, these two studies are unique in that they replicated previous publications using the same device equipment and liquids (Farsalinos et al, 2018a, 2018b). The original studies have found very high levels of carbonyls emitted from e-cigarettes, which in many cases exceeded the levels found in cigarette smoke (A. Khlystov and V. Samburova, 2016; M. Sleiman et al, 2016). One of them identified flavorings as being the main source for carbonyl emissions from e-cigarettes, with up to 10,000-fold higher levels of formaldehyde detected in the aerosol of flavored vs unflavored e-cigarette liquid. This could have important implications since the vast majority of e-cigarette users use flavored liquids. The replication studies failed to verify the previous findings. Substantially lower levels of carbonyls emitted from e-cigarettes were reported. For the first study, the authors identified overheating and dry puff conditions, which represent unrealistic exposure in the clinical setting. However, even under normal conditions the
levels of carbonyls detected were much lower than in the original report. For the second study, flavorings were found to have minimal effect on carbonyl emissions, with levels being overall very low and lower than environmental levels and safety limits. Recently, a systematic review on carbonyl emissions from e-cigarettes also presented the issue of conflicting results and potential methodological issues in many of the studies (Farsalinos and Gillman, 2018). As an abstract of the findings, the e-cigarettes tested were shown to emit very low levels of aldehydes, up to 589-fold compared to the previous report, with these emissions being 79–99.8% lower than smoking and lower than commonly measured indoor levels and occupational and indoor safety limits. Some flavorings may contribute to aldehyde emissions, but the overall absolute levels were minimal. It was concluded that validated methods should be used when analyzing e-cigarette emissions.

Given the complexity of cigarette smoke, as a mixture of chemicals, a review investigating tobacco-specific nitrosamines (TSNA) is published (Konstantinou et al, 2018). Considerable pieces of evidence support the role of TSNA as an important causative factor for cancers of the lung, pancreas, esophagus, and oral cavity, concerning people that use tobacco products. Tobacco harm reduction products, such as e-cigarettes, according to several studies, still contain TSNA in replacement liquids and vapor, yet the levels are considerably lower than the tobacco cigarettes’ levels, where TSNA was formed both during the post-harvest period and during the burning of the cigarette. The FDA recently announced its intention to regulate TSNA in e-cigarettes, cigar tobacco and pipe tobacco and in combination with the rise of new technologies for the reduction of exposure to harmful chemicals (such as e-cigarettes) pave the way for the researchers’ monitoring of levels of TSNA in the body as a result of the use of these devices.

Studies have found that metals are emitted to the electronic cigarette aerosol. However, the potential health impact of exposure to such metals has not been adequately defined. The study by Kamilari et al is developing a methodology for the detection and quantitative analysis of heavy metals (cadmium, lead, nickel, copper, arsenic and chromium), which may enter the refill liquid of e-cigarettes, disputing their characterization as healthier alternatives. Total Reflection X-Ray Fluorescence Spectroscopy (TXRF) was used, due to a number of strengths, such as short analysis time, simultaneous multi-element analysis capability and minimum sample preparation, against alternative technique of ICP-MS or ICP-OES was applied to a large number of electronic cigarette liquids, as well as their constituents, in order to evaluate their safety. The e-liquids tested were found to be below the limits defined by regulatory authorities for inhalational medicines, while the metals measured in the concentrated constituents of e-liquids (nicotine, flavoring agents) surpassed the limits, showing that TXRF may be a valuable tool for probing heavy metals in electronic cigarette refill liquids to serve for the protection of human health.
Since most of e-cigarette liquids contain two primary solvents: propylene glycol (PG) and vegetable glycerin (VG), the primary aim of the study by Kosmider et al was to examine the extent to which PG and VG composition and device power interact with each other to influence e-cigarette nicotine emissions. Nicotine yield was measured in aerosols, via gas chromatography, produced from three solutions containing three distinct solvent compositions and power settings. At the lowest power setting, nicotine yield increased as PG concentration increased. Nevertheless, as device power was increased, differences in nicotine yield across liquids became less pronounced, while at the highest power setting, nicotine yields did not differ across the three liquids examined. The study, hence, demonstrated that e-cigarette liquid PG and VG compositions do influence the nicotine emissions, depending on the device power, to a greater degree relative to solvent concentrations.

Based on the fact that well-mixed models do estimate the room average concentration of constituents from sources, yet do not inform on firstly, how far and how fast the emitted chemicals travel in the indoor space and secondly, how the concentration changes as a function of distance from the emission source, the study by Rostami et al developed an alternative distributed model. It used computational fluid dynamics and thermodynamics principles to estimate air levels of constituents in exhaled aerosol from e-vapor use, leading to the estimation of concentrations of selected constituents in a confined space, which are relevant to second hand exposure. The accurate results of the comparison of the model predictions with experimental data from literature, along with its estimation of spatial and temporal distributions of constituents in indoor air under different condition render this model promising for further use.

Dosimetry models can be used to predict the dose of inhaled material, requiring, though several parameters including particle size distribution. However, the reported particle size distributions for aerosols from electronic nicotine delivery system (ENDS) products vary widely and do not always identify a specific product. The study by Oldham et al pursued the determination of the particle size distribution [mass median aerodynamic diameter (MMAD); geometric standard deviation (GSD)] from 20 different cartridge based ENDS products through the use of a low-flow cascade impactor. The experiments, comparing the collected mass in the impactor to the difference in ENDS product mass, showed no consistent pattern of change in the MMAD and GSD as a function of number of puffs (cartridge life), while the collection efficiency indicated that 9%–26% of the generated mass was deposited in the collection system or was in the vapor phase. It was therefore, suggested that particle size distribution data are suitable for use in aerosol dosimetry programs.

Mitochondrial dysfunction caused by cigarette smoke is involved in the oxidative stress-induced pathology of airway diseases. Reducing the levels of harmful and
potentially harmful constituents by heating rather than combusting tobacco may reduce mitochondrial changes that contribute to oxidative stress and cell damage. As a result, Malinska et al evaluated mitochondrial function and oxidative stress in human bronchial epithelial cells (BEAS 2B) following 1- and 12-week exposures to total particulate matter (TPM) from the aerosol of a novel candidate modified-risk tobacco product, the Tobacco Heating System 2.2 (THS2.2) (novel product under investigation by PMI), in comparison with TPM from the 3R4F reference cigarette. The findings suggest that 3R4F TPM had a stronger effect on oxidative phosphorylation, gene expression and proteins involved in oxidative stress than TPM from the candidate modified-risk tobacco product THS2.2.

Within the framework of a systems toxicology approach, the inhalation toxicity of aerosol from another novel tobacco-heating potentially modified risk tobacco product, the carbon-heated tobacco product (CHTP) 1.2, was characterized and compared by Phillips et al with that of mainstream smoke (CS) from the 3R4F reference cigarette in a 90-day nose-only rat inhalation study. The CHTP1.2 is a potential MRTP that uses a pressed carbon heat source to generate an aerosol by heating tobacco. The lower uptake of harmful constituents from inhaled CHTP1.2 aerosol than from CS at comparable nicotine level was contrasted by the upper airway effects of CHTP1.2 aerosol, which were less severe and fully reversible in contrast to CS effects. Minimal lung inflammation effects of CHTP1.2 aerosol compared to moderate inflammation caused by CS, suggesting that similar weak systemic effects of CHTP1.2 aerosol and CS attributable to tube restraint stress and nicotine content. The study by Titz et al also used the systems toxicology of a 90-day rat inhalation study to assess the effects of CHTP1.2 aerosol compared with CS. Transcriptomics, proteomics, and lipidomics analyses complemented the standard endpoints in the assessment of exposure effects, while molecular analyses complemented apical endpoints, e.g. for inflammation and cell stress. Overall, this systems toxicology analysis complements and confirms the results from classical toxicological endpoints and further suggests potentially reduced respiratory health risks of CHTP1.2. The study by Zanetti et al showed an absence of cytotoxicity, reduction in pathophysiological alterations, toxicological marker proteins, and inflammatory mediators following exposure to CHTP1.2 aerosol compared with 3R4F CS, while the regulatory role of miRNAs in several smoke/disease-relevant biological processes induced by 3R4F CS was suggested. The same novel product was assessed in vitro, by Iskandar et al, using human small airway and nasal epithelial models, against 3R4F cigarette smoke at similar nicotine concentrations. The biological impacts, determined based on a collection of endpoints including morphology, cytotoxicity, proinflammatory mediator profiles, cytochrome P450 1A1/1B1 activity, global mRNA and microRNA changes and proteome profiles, showed that the impact of 3R4F smoke exposure persisted long post-exposure and greater than CHTP1.2 aerosol, while morphological changes were observed only in cultures exposed
to 3R4F smoke. It was eventually observed that the reduced impact of heated tobacco aerosols on small airway was similar with that on nasal epithelial cultures.

Food and Chemical Toxicology is publishing a Special Issue, entitled Alternative tobacco products: Toxicology and health issues, to provide up-to-date information on non-combustible nicotine delivery product, for the benefit of its readers. It is our honor to serve as the guest editor of this special issue. We hope that it will provide a source of evidence in this area of research.

References


Mohamed A. El Mubaraka, Charikleia Danika, Nikolaos S. Vlachos, Konstantinos Farsalinos, Konstantinos Poulas, Gregory Sivolapenko. Development and validation of analytical methodology for the quantification of aldehydes in e-cigarette aerosols using UHPLC-UV


Konstantinos E. Farsalinos and Vassilis Voudris. Do flavouring compounds contribute to aldehyde emissions in e-cigarettes?


Eleni Kamilari, Konstantinos Farsalinos, Konstantinos Poulas, Christos G. Kontoyannis Malvina G. Orkoula. Detection and quantitative determination of heavy
metals in electronic cigarette refill liquids using Total Reflection X-ray Fluorescence Spectrometry

Leon Kosmider, Tory R.Spindle, Michal Gawron, Andrzejsobczak, Maciej Lukasz Goniewicz. Nicotine emissions from electronic cigarettes: Individual and interactive effects of propylene glycol to vegetable glycerin composition and device power output

Ali A.Rostami, Samuel Agyemang, Yezdi B. Pithawalla. A distributed computational model for estimating room air level of constituents due to aerosol emission from e-vapor product use

Michael J.Oldham, Jingjie Zhang, Mark J. Rusyniak, David B.Kane, William P. Gardner. Particle size distribution of selected electronic nicotine delivery system products

Dominika Malinska, Jędrzej Szymański, Paulina Patalas-Krawczyk, Bernadeta Michalska, Aleksandra Wojtala, Monika Prill, Małgorzata Partyka, Karolina Drabik, Jarosław Walczak, Alain Sewer, Stephanie Johne, Karsta Luetich, Manuel C.Peitsch, Julia Hoeng, Jerzy Duszynski, Joanna Szczepanowska, Marcovan der Toorn, Mariusz R.Wieckowski. Assessment of mitochondrial function following short- and long-term exposure of human bronchial epithelial cells to total particulate matter from a candidate modified-risk tobacco product and reference cigarettes

Blaine W.Phillips, Walter K.Schlage, Bjoern Titz, Ulrike Kogel, Davide Sciuscio, Florian Martin, Patrice Leroy, Gregory Vuillaume, Subash Krishnan, Tom Lee, Emilija Veljkovic, Ashraf Elamin, Celine Merg, Nikolai V.Ivanov, Manuel C.Peitsch, Julia Hoeng, Patrick Vanscheeuwijck. A 90-day OECD TG 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of the aerosol from the carbon heated tobacco product version 1.2 (CHTP1.2) compared with cigarette smoke. I. Inhalation exposure, clinical pathology and histopathology

Bjoern Titz, Ulrike Kogel, Florian Martin, Walter K.Schlage, Yang Xiang, Catherine Nury, Sophie Dijon, Karine Baumer, Dariusz Peric, David Bornand, Remi Dulize, Blaine Phillips, Patrice Leroy, Gregory Vuillaume, Stefan Lebrun, Ashraf Elamin, Emmanuel Guedj, Keyur Trivedi, Julia Hoeng. A 90-day OECD TG 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of the aerosol from the carbon heated tobacco product version 1.2 (CHTP1.2) compared with cigarette smoke. II. Systems toxicology assessment

Filippo Zanetti, Alain Sewer, Elena Scotti, Bjoern Titz, Walter K. Schlage, Patrice Leroy, Athanasios Kondylis, Gregory Vuillaume, Anita R.Iskandar, Emmanuel Guedj, Keyur Trivedi, Thomas Schneider, Ashraf Elamin, Florian Martin, Stefan Frentzel, Nikolai V. Ivanov, Manuel C.Peitsch, Julia Hoeng. Assessment of the impact of aerosol
from a potential modified risk tobacco product compared with cigarette smoke on human organotypic oral epithelial cultures under different exposure regimens