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EDITORIAL

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Special issue on electronic cigarettes

The recent rise in public interest in electronic nicotine delivery systems (ENDS) such as electronic cigarettes (e-cigarettes) has attracted significant attention from health practitioners, policy makers and regulatory authorities, investigative researchers, and the private industry. Tobacco use is clearly preventable, and according to health authorities at regulatory agencies is the single largest preventable cause of disease and death in the United States (FDA, 2016). E-cigarettes have been developed in recent years and predicated as an alternative to combustible cigarettes in a harm-reduction strategy. However, there are many outstanding questions regarding the role and impact of electronic cigarettes in public health, and many of these have been brought forth in both scientific and medical publications as well as government reports (DHHS, 2014; Grana et al., 2014; Kosmider et al., 2014; McNeill et al., 2015; Nelson, 2014). Long-term adverse health effects of e-cigarettes or ENDS remain poorly understood. Unlike combustible cigarettes or other smoked tobacco products, it is believed that e-cigarettes have less toxic and carcinogenic byproducts. However, recent data indicate that many e-cigarettes seemed to have significant amounts of formaldehyde, acetaldehyde and heavy metals, including nickel and chromium. Additionally, continuous exposure to ENDS has resulted in increased airway resistance with increased bacterial colonization and adverse vascular hemodynamics. A current view is that there are limited data and a need for new knowledge regarding enhancing our current understanding of the potential human health effects and risks of electronic cigarettes (Callahan-Lyon, 2014). Moreover, there is a need for description of toxicological methods and monitoring for biomarkers, a better understanding of potential beneficial effects, further hazard characterization of e-liquid, and development of frameworks for assessing the risks of these new and emerging tobacco products as well as many other areas in clinical science, non-clinical science, and social science. In an effort to stimulate and increase new scientific knowledge on the toxicological aspects and methods for assessing health effects of electronic cigarettes, *Toxicology Mechanisms and Methods*, presents its Special Issue on Electronic Cigarettes. A brief summary of the content in this Special Issue follows.

One of the components of ENDS that are often of focus by consumers is new e-liquids. E-liquids are known to contain flavors and have been shown to play an important role in the overall experience of electronic cigarettes (Costigan and Meredith, 2015). Consequently, having a framework for assessing the toxicology of e-liquids is important. In this issue, a research article appears which describes a framework using an *in vitro* systems toxicology assessment of e-liquids (Iskandar et al., 2016). The proposed framework utilizes a standard battery of toxicity assessments (e.g., genetic toxicity assays) and attempts to take into account variability between ENDS devices as well as using modern approaches such as high-throughput screening of e-liquids, and mechanistic considerations at a biological systems level. What makes the article interesting beyond the new proposed framework is the thought-provoking case examples to evaluate and demonstrate its utility in identifying potential long-term health risks.

As mentioned previously, further studies on hazard characterization of the e-liquid component of electronic cigarettes is needed. There are three articles in this special issue by El Golli and colleagues: one on the impact of e-liquid refill on rat testis and another on a neurobehavioral assessment of e-liquid exposure in a rat model (El Golli et al., 2016a, 2016c). These non-clinical studies in rodents provide new evidence in understanding the toxicological potential of e-liquid. In the first study, histological evidence of alternations in rat testis tissue with or without nicotine is provided. The data also show statistically significant decreases in plasma testosterone concentrations in response to e-liquid treatment. In addition, a mechanistic evaluation is provided in the study demonstrating treatment-related oxidative stress using a battery of classical enzymatic assays (El Golli et al., 2016c). In the second study, the effect of e-liquid on neurobehavior in a rat model is reported using various methodologies (El Golli et al., 2016a). A complexity of effects was found when comparing e-liquid with and without nicotine. For example, without nicotine, there were significant decreases in hippocampal cell viability, but not cortical cells. The hippocampal area of the brain is well known to be important for memory. The authors reported that e-liquid with nicotine had no modification of cognition or motor function. This research on e-liquid is pioneering given there are limited non-clinical studies of e-liquid on the neurological system. This work clearly points to further investigations on characterizing the biological effects of e-liquids (with and without nicotine) on the nervous system, especially at macro neurobehavioral and cellular levels. A third article evaluated the effect of e-liquid on liver function in the presence and absence of nicotine (El Golli et al., 2016b). The study showed evidence that e-liquid containing nicotine resulted in histopathological changes of the liver that were of greater significance than e-liquid without nicotine. The authors corroborated the liver histological changes with biochemical indices of oxidative stress showing e-liquid with nicotine having synergistic effects.

By virtue of the aims and scope of the journal, *Toxicology Mechanisms and Methods* is devoted to mechanistic studies to help describe pathways to toxicity. As such, the article by Dr. Andreas Flouris and associates is of interest from a mechanistic standpoint. The article focuses on the measurement of oxidative stress markers in a human clinical study comparing smoking conventional cigarettes to e-cigarette smoking under acute exposure conditions. Blood catalase, glutathione, and total antioxidant capacity were measured in human

subject volunteers prior to, immediately after, and 1-hour post exposure, and the authors report that the e-cigarette or conventional cigarette testing did not alter the response of the antioxidant systems. This study suggests no distinctions between these two types of products for the selected antioxidant indicators.

A recent public workshop held by the US FDA examined the need to identify and implement the use of biomarkers of exposure for tobacco products (FDA, 2015). The workshop underscored the importance of biomarkers to facilitate product regulation. The FDA is providing strong leadership in tobacco product control, knowledge development, and regulation. The article by Göney *et al.* (2016) in this special issue provides a seminal study in biomarkers of tobacco product exposure as it examines urinary cotinine levels in users after their exposure to electronic cigarettes. Cotinine is a well-known metabolite of nicotine and is used as a biomarker of exposure. The study compared cotinine levels in urine of e-cigarette human subjects and smokers of conventional cigarettes. Healthy non-smoking subjects served as controls and passive smokers were also measured. The study determined the cotinine levels using gas chromatography–mass spectrometry. Interestingly, the authors reported that there were no statistically significant differences in the biomarker between e-cigarette users and cigarette smokers and concluded that e-cigarette smokers were exposed to as much nicotine as cigarette smokers. This study would be of interest to readers from the standpoint of e-cigarette addiction liability.

Hazardous and potentially hazardous constituents (HPHCs) of tobacco products have been described by the U.S. Food and Drug Administration (FDA, 2016). HPHCs can be useful to monitor as biomarkers of harm and exposure to tobacco products. In this issue, O'Connell et al. (2016) present a clinical study describing levels of HPHCs following use of combustible cigarettes and electronic cigarettes. Based on the changes of 15 urine, blood and exhaled breath HPHC biomarkers, the authors conclude that smokers who completely or partially substituted conventional cigarettes with e-cigarettes over a period of just five days, experienced reduction in the levels of the measured HPHCs. Thus, this study may be of interest to those investigating e-cigarettes as a harm-reduction strategy compared to exposure and risks from conventional combustible cigarettes.

An *in vitro* study by Taylor et al. (2016) uses human bronchial epithelial cells to evaluate cellular stress responses after treatment by aqueous extracts of conventional cigarette smoke and e-cigarette aerosols. Apoptotic and necrotic responses were measured and the authors concluded that no cellular stress responses were detected in their model after e-cigarette aerosol exposure. This study is very detailed and represents a novel method development effort as well as a mechanistic investigation to provide new data for informing comparative risk between these tobacco product types.

The study by Azzopardi et al. (2016) provides a novel *in vitro* investigation on the cytotoxicity of aerosols from e-cigarettes compared to aerosol dilutions from the conventional research cigarette (Kentucky 3R4F). An exposure machine system normally used for conventional cigarettes was adapted for use with e-cigarettes to expose human lung epithelial cells to e-cigarette aerosol. The authors report that an e-cigarette aerosol induced 97%, 94% and 70% less cytotoxicity than the smoke from the 3R4F conventional (Azzopardi et al., 2016). This study provides ground work in the area of *in vitro* toxicity and development methods in e-cigarette exposure assessment. The study helps to clarify where further research is needed to evaluate risks and toxic responses of cellular tissues exposed to toxicants emitted from e-cigarettes.

The editor sincerely thanks all contributors, peer-reviewers, and editorial staff at Taylor & Francis for their valuable time and commitment for creating this first of its kind issue in a toxicology journal. To our knowledge, no other journal in the toxicological sciences has yet developed an entire Special Issue dedicated to the toxicological assessment of electronic cigarettes. It is anticipated this special issue will be widely read and cited by a wide audience. As new information arises on electronic cigarettes, the papers in this issue will prove to be valuable towards the evaluation, further testing, and understanding of these alternative tobacco products which are currently of high public interest.

Disclosure statement

The authors report no conflicts of interest.

References

Azzopardi D, Jaunky T, Santopietro S, et al. (2016). Electronic cigarette aerosol induces significantly less cytotoxicity than tobacco smoke. Toxicol Mechanisms Methods 26:477–491

Callahan-Lyon P. (2014). Electronic cigarettes: human health effects. Tobacco Control 23:ii36–40.

Costigan S, Meredith C. (2015). An approach to ingredient screening and toxicological risk assessment of flavors in e-liquids. Regulatory Toxicol Pharmacol 72:361–9.

DHHS. (2014). The health consequences of smoking – 50 years of progress. Rockville, MD: Public Health Service.

El Golli E, Dallagi Y, Rahali D, et al. (2016a). Neurobehavioral assessment following e-cigarette refill liquid exposure in adult rats. Toxicol Mechanisms Methods 26:425–432.

El Golli N, Jrad-Lamine A, Neffati H, et al. (2016b). Impact of e-cigarette refill liquid with or without nicotine on liver function in adult rats. Toxicol Mechanisms Methods 26:433–440.

El Golli N, Rahali D, Jrad-Lamine A, et al. (2016c). Impact of electronic-cigarette refill liquid on rat testis. Toxicol Mechanisms Methods 26:417–424.

FDA. (2015). Biomarkers of tobacco exposure – a public workshop. FDA CTP Public Workshop on Biomarkers of Tobacco Exposure. Silver Spring, MD: U.S. Food and Drug Administration.

FDA. (2016). Tobacco products. Products, ingredients, & components. US Food and Drug Administration. Available from: http://www.fda.gov/TobaccoProducts/Labeling/ProductsIngredientsComponents/default.htm [last accessed 5 July 2016].

Göney G, Çok İ, Tamer U, et al. (2016). Urinary cotinine levels of electronic cigarette (e-cigarette) users. Toxicol Mechanisms Methods 26:441–445.

Grana R, Benowitz N, Glantz SA. (2014). E-cigarettes. Scientific Rev 129:1972–86.

Iskandar AR, Gonzalez-Suarez I, Majeed S, et al. (2016). A framework for in vitro systems toxicology assessment of e-liquids. Toxicol Mechanisms Methods 26:392–416.

Kosmider L, Sobczak A, Fik M, et al. (2014). Carbonyl compounds in electronic cigarette vapors—effects of nicotine solvent and battery output voltage. Nicotine Tobacco Res 16:1319–1326.

McNeill A, Calder R, Hitchman S, et al. (2015). E-cigarettes: an evidence update. London, UK: Wellington House.
Nelson N. (2014). More questions than answers surrounding e-cigarette debate. J Natl Cancer Institute 1–9. doi: 10.1093/jnci/dju101.
O'Connell G, Graff DW, D'ruiz CD. (2016). Reductions in biomarkers of exposure (BoE) to harmful or potentially harmful constituents (HPHCs) following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. Toxicol Mechanisms Methods 26:453–464.
Taylor M, Oke O, Jaunky T, et al. (2016). E-cigarette aerosols induce lower oxidative stress in vitro when compared to tobacco smoke. Toxicol Mechanisms Methods 26:465–476.

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