E-cigarettes are becoming an increasingly popular alternative to conventional tobacco cigarettes among smokers worldwide.

The concentration of toxicants (including many Harmful and Potentially Harmful Constituents (HPHCs)) in e-cigarettes has been found to be generally tens to thousands of times lower than in tobacco smoke; many toxicants are simply not present in e-cigarette aerosol at detectable levels (e.g. Fig. 1). As a result, e-cigarette aerosol elicits minimal biological responses in comparison to tobacco smoke aerosol, which toxicity assays compared to conventional cigarettes (e.g. Fig. 2). While such findings are consistent with observed reductions in biomarkers (e.g. conventional cigarettes), they do not necessarily indicate a lack of potential health benefits or risks for all individuals. There is relatively little information available on consumer exposure to HPHCs resulting from the use of e-cigarettes compared to conventional cigarettes. To that end, the objective of this study was to compare changes in selected urine, blood and exhaled breath markers of exposure to HPHCs among different user groups following a 5-day forced-switch from usual conventional cigarette brand to:

- (i) exclusive use of a commercially available blu® e-cigarette;
- (ii) dual use of a commercially available blu® e-cigarette and the subject's usual conventional cigarette brand; or
- (iii) discontinuous use of all tobacco or nicotine products.

The biomarkers of exposure to the HPHCs selected included a number of cigarette smoke constituents representing classes of compounds believed to be the most significant contributors to smoking-associated disease risks as reported by the FDA.

3. Reductions in Blood and Urine Biomarkers of HPHC Exposure from Day -1 to Day 5

- Reducing consumption of conventional cigarettes over 5 days according to the requirements of the study resulted in a steady decrease in exposure to a number of HPHCs (Figs. 4 and 5).
- Smoking cessation leads to a 60% to 90% reduction in excretion of the biomarkers of exposure in the urine of the subjects (Figs. 5) as compared to conventional cigarette smokers (Figs. 3). The reduction in exposure was seen in urine, which has the longest half-life of the individual biomarkers listed [6]. Prominent decreases were also observed in the C6H6, nicotine, and the nicotine metabolite cotinine, as the cessation period had no exposure to CO or nicotine (Fig. 4).
- The reduction in biomarker exposure to HPHCs observed in the exclusive cigarette e-cigarette use group were mostly comparable to those seen in the cessation group (Fig. 4). The reduction in exposure for the subjects who continued to smoke did not approach baseline as compared to the nicotine group (Fig. 4).
- Dual users smoked 52% lower conventional cigarettes compared to smoking 25% lower compared to day 1). Dual users of cigarette and e-cigarette smoked reported daily cigarette consumption with the e-cigarette exhibited reduced biomarker levels that were broadly proportional to the reduced number of cigarettes smoked. Reductions were also observed for the nicotine metabolite cotinine, with a statistically significant decrease in blood of the end of the exposure study (Fig. 4).
- Overall, measurable nicotine and cotinine were present in the samples from exclusive e-cigarette users in the e-cigarette group for all biomarkers that were significantly lower and many were indistinguishable, from those who had ceased to use any nicotine product (Figs. 4 and 5). The excretion and concentration of all exposure biomarkers evaluated in this study were higher in the dual use group at Day 5 compared to the cessation group (Figs. 4 and 5).

4. Changes in Exhaled CO and NO Levels

- Physiological changes associated with smoking reductions were noted in both carbon monoxide (CO) and nitric oxide (NO) endpoints. CO exposure is often estimated as the area under the curve of CO concentrations in exhaled breath from CO bound to haemoglobin (Fig. 4).
- All groups experienced decreases in exhaled CO at Day 5 compared to Day -1, with decreases in the cessation and exclusive e-cigarette user groups at around 90% and 31% in the dual use group (Fig. 6). Further, there were no differences between the cessation and exclusive use group measurements on Day 5 whereas the dual use group had higher exhaled CO compared to cessation, as expected since this group still consumed conventional cigarettes.
- Smoking has been reported to decrease NO production but the mechanism remains incompletely understood. Exhaled NO is used as a noninvasive biomarker of inflammation in the airways, and can be detected in exhaled breath. In this study, exhaled NO was observed to increase from Day -1 to Day 5 in the cessation (49%) and exclusive e-cigarette use groups (76%), whereas the dual use group experienced reductions in exhaled NO from 26% and 45% from baseline to Day 5.
- The findings associated with exhaled breath biomarkers in the cessation and exclusive e-cigarette use groups are consistent with other research findings associated with reductions in exhaled CO and increase in exhaled NO following smoking cessation (e.g. 7.6.8).

5. Conclusions

- The data presented here demonstrate that smokers who completely switched conventional cigarettes with e-cigarettes over a short period of time (5 days) experienced reductions in exposure to a number of HPHCs as measured by urine, blood, and exhaled biomarkers of exposure. Moreover, the data show that users who switched exclusively also experienced significantly reduced HPHC exposures after partially replacing consumption with the blu® e-cigarette product, albeit to a lesser extent. The data are consistent with the findings of other investigations which have demonstrated that e-cigarette use results in a decrease in biomarkers of tobacco exposure (e.g. 9,10,11)
- This current study extends the findings of [1] (summarised in Fig. 1), which showed the e-cigarette aerosol levels of HPHCs such as carbonyl compounds, tobacco-specific nitrosamines, polyaromatic hydrocarbons, and other constituents are at least 1000 times lower than those found in the smoke of conventional tobacco cigarettes (i.e., <2 µg/g vs. >3.0µg/g), with the observation that the blu® closed-system e-cigarette produced markedly lower levels of exposure biomarkers when used by smokers in lieu of their usual cigarette brand style for a period of 5 days.
- It has been suggested that dual use may be a public health concern because of a possibility that it exposes smokers to greater risk than those encouraged by smoking conventional cigarettes alone [12]. Furthermore, a recent study reported that dual use of e-cigarettes while continuing to smoke did not result in reduced exposure to known carcinogens and toxicants [13]. The study presented here has shown a reduction in daily cigarette smoking on the dual use group as an initial examination of the reversibility of the measured HPHC exposure biomarkers to more completely reduced smoking combined with unlimited all blu® usage of e-cigarettes. Under these conditions, the data show that dual users experienced significant reductions in all of the urine biomarkers assessed. It appears there may also be a relationship between the magnitude of reduction in biomarkers of exposure to HPHCs in this group and the reduction in conventional cigarette smoking. The impact of longer term exclusive and dual cigarette use on biomarkers of exposure to HPHCs remains an area of ongoing concern.
- Whether the reductions in toxic and carcinogenic constituent exposures such as those observed here may have the potential to reduce risks for chronic, smoking-caused diseases for long-term e-cigarette users who partially or completely abstain from conventional cigarettes has yet to be determined.
- Overall, the present study shows the great potential that the blu® closed-system e-cigarette may provide for smokers seeking an alternative to tobacco products; the role that biomarkers of exposure may play in assessing and comparing exposure to HPHCs across different product categories, and supports the case for regulating e-cigarettes differently from tobacco-containing products.

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Further research is needed to fully understand the health implications of dual use as well as the long-term effects on biomarkers of exposure to HPHCs in this group and the reduction in conventional cigarette smoking. The impact of longer term exclusive and dual cigarette use on biomarkers of exposure to HPHCs remains an area of ongoing concern.

- Whether the reductions in toxic and carcinogenic constituent exposures such as those observed here may have the potential to reduce risks for chronic, smoking-caused diseases for long-term e-cigarette users who partially or completely abstain from conventional cigarettes has yet to be determined.
- Overall, the present study shows the great potential that the blu® closed-system e-cigarette may provide for smokers seeking an alternative to tobacco products; the role that biomarkers of exposure may play in assessing and comparing exposure to HPHCs across different product categories, and supports the case for regulating e-cigarettes differently from tobacco-containing products.

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