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Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study

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Abstract

Introduction: Electronic cigarettes (e-cigarettes) are purported to deliver nicotine aerosol without any toxic combustion products present in tobacco smoke. In this longitudinal within-subjects observational study, we evaluated the effects of e-cigarettes on nicotine delivery and exposure to selected carcinogens and toxicants.

Methods: We measured seven nicotine metabolites and 17 tobacco smoke exposure biomarkers in the urine samples of 20 smokers collected before and after switching to pen-style M201 e-cigarettes for 2 weeks. Biomarkers were metabolites of 13 major carcinogens and toxicants in cigarette smoke: one tobacco-specific nitrosamine (NNK), eight volatile organic compounds (1,3-butadiene, crotonaldehyde, acrolein, benzene, acrylamide, acrylonitrile, ethylene oxide, and propylene oxide), and four polycyclic aromatic hydrocarbons (naphthalene, fluorene, phenanthrene, and pyrene). Changes in urine biomarkers concentration were tested using repeated measures analysis of variance.

Results: In total, 45% of participants reported complete abstinence from cigarette smoking at 2 weeks, while 55% reported continued smoking. Levels of total nicotine and some polycyclic aromatic hydrocarbon metabolites did not change after switching from tobacco to e-cigarettes. All other biomarkers significantly decreased after 1 week of using e-cigarettes ($p < .05$). After 1 week, the greatest percentage reductions in biomarkers levels were observed for metabolites of 1,3-butadiene, benzene, and acrylonitrile. Total NNAL, a metabolite of NNK, declined by 57% and 64% after 1 and 2 weeks, respectively, while 3-hydroxyfluorene levels declined by 46% at week 1, and 34% at week 2.

Conclusions: After switching from tobacco to e-cigarettes, nicotine exposure remains unchanged, while exposure to selected carcinogens and toxicants is substantially reduced.

Implications: To our knowledge, this is the first study that demonstrates that substituting tobacco cigarettes with an e-cigarette may reduce user exposure to numerous toxicants and carcinogens otherwise present in tobacco cigarettes. Data on reduced exposure to harmful constituents that are present in tobacco cigarettes and e-cigarettes can aid in evaluating e-cigarettes as a potential harm reduction device.

Introduction

Each year, cigarette smoking is responsible for approximately one in five deaths from all causes in the United States.[1] Despite the health risks associated with use of these products, nearly 42 million US adults continue to smoke cigarettes, of whom 6.2% will successfully achieve complete smoking cessation within 1 year of quitting.[2] While smoking cessation remains the optimal method for reducing exposure to the numerous toxic and carcinogenic substances found in cigarette smoke,[1] the application of harm reduction strategies in continuing smokers could aid in further declines in smoking-attributable morbidity and mortality.[3]

Electronic cigarettes (e-cigarettes) represent a new prospect in harm reduction from tobacco use.[4,5] However, studies demonstrating the efficacy of e-cigarettes as harm reduction devices are lacking.[6,7] While several laboratory studies have shown that e-cigarette aerosol contains significant amounts of nicotine and reduced levels of toxicants compared to tobacco smoke,[8–10] laboratory machine yields do not necessarily reflect toxicant exposure in an individual smoker. Moreover, it remains unclear how effectively e-cigarettes deliver nicotine to the user.[8–13]

Very little research on observed toxicant levels in e-cigarette users has been conducted.[14,15] To help better inform whether or not e-cigarettes pose real utility as a harm reduction device, data are needed to assess levels of nicotine, carcinogenic substances, and other toxicants in cigarette smokers who switch to e-cigarettes. In this longitudinal within-subjects observational study, we evaluated the effects of e-cigarettes on nicotine delivery and exposure reduction to selected carcinogens and toxicants. We hypothesized that due to reduced exposure to tobacco combustion-derived toxins with use of e-cigarettes, we would observe a significant decrease of their biomarker levels in urine.

Methods

Participant Recruitment

This study was conducted at the Medical University of Silesia in Poland between March and June 2011. Subjects were recruited from the local metropolitan area using advertisements in the media, the internet, posted advertisements in clinics and offices, and by word of mouth. Advertisements used to recruit healthy adult daily smokers referred to the opportunity to reduce cigarette smoking by use of a modified risk tobacco product (MRTP). Subjects were screened for eligibility through a comprehensive physical examination. Subjects had to be aged 18 or older, current daily cigarette smokers (>5 cigarettes per day within the last 12 months), may have had interest in quitting smoking, in good health (per the clinic screening visit), able to communicate in Polish, and able to use an e-cigarette safely (all items were self-reported). Participants were excluded if they had been diagnosed as having asthma, chronic obstructive pulmonary disorder (COPD), hypertension, inhaled allergies, chronic heart disease, or cancer; were taking a cardiac medication, or were pregnant at the time of study. Subjects were not paid for participation in the study, but were able to keep their e-cigarettes after completing the study.

E-cigarette Product

At the baseline visit, subjects were provided with an e-cigarette (M201 Mild, Poland) with 20 tobacco-flavored cartridges per week containing 11.0 ± 1.5 mg of nicotine in a mixture of propylene glycol and vegetable glycerin (50:50) as determined in a previous study.[9] M201 was a commonly used pen style e-cigarette in Poland, measuring 153 mm in length and 9 mm in diameter.[8,9] It had an automatically-operated battery with an output power of 4.6 Volts (280 mAh) and the heating element resistance of 3.6–3.8 Ohms. In laboratory conditions, M201 generated aerosol with nicotine levels 8.4 ± 1.1 mg with 150 puffs.[9] Additionally, we screened this model for selected toxicants and found that it generated aerosol with significantly reduced yields of potential toxicants as compared to other similar e-cigarette models.[8]

Study Protocol

Figure 1 displays the process for inclusion in the study. Subjects who passed screening and provided written informed consent were asked to continue using their own brand of cigarettes prior to the first scheduled clinic visit. Subjects were required to attend three morning clinic visits on the same days of the week: during Day #1 (baseline), during Day #7 (Week 1), and during Day #14 (Week 2) of the study. During the first visit (baseline), subjects were encouraged to substitute their regular cigarettes with the e-cigarette for 2 weeks and refrain from smoking. Subjects recorded number of cigarettes smoked and use of the study product on daily basis. At each visit, a urine sample was collected from each participant for tobacco biomarker analysis (see below), and subjects completed questionnaires on health, withdrawal symptoms, and tobacco use. Expired carbon monoxide was also measured (MicroCO, Micro Direct, UK). Prior to data collection, the study protocol was reviewed and approved by the Institutional Review Board at the Medical University of Silesia, Poland. A waiver for registering the trial in a public registry was granted by the Office for Registration of Medicinal Products, Medical Devices and Biomedical Products, a government administrative authority, competent for matters concerning clinical trials in Poland.

Biomarkers of Exposure Analysis

We measured urine levels of seven nicotine metabolites and 17 biomarkers of exposure to important carcinogens and toxicants in cigarette

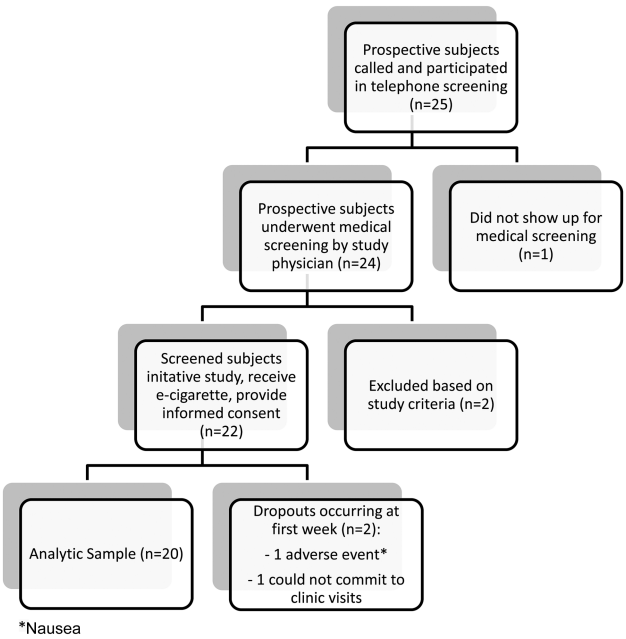

Figure 1. Participant flow chart.

smoke. The characteristics and significance of measured biomarkers and their precursors are presented in Supplementary Table 1.[16–27]

Urine total (free plus conjugated) concentrations of nicotine, cotinine, trans-3′-hydroxycotinine, and free nicotine N-oxide and cotinine N-oxide were measured by LC-MS/MS as described previously.[28,29] Urine nicotine equivalents (Nic Eq) was determined as the molar sum of nicotine, cotinine, trans-3′-hydroxycotinine and their respective glucuronides, and free nicotine N-oxide and cotinine N-oxide corrected for creatinine concentration. When measured at steady state, the sum of these metabolites accounts for on average 80%–90% of a daily dose of nicotine.[28]

Urine concentrations of total NNAL were measured by LC-MS/MS.[30] The following metabolites of volatile toxicants (derivates of mercapturic acid, MA) were determined using an LC-MS/MS method: 2-hydroxyethylmercapturic acid (HEMA), 2-hydroxy-3-buten-1-yl-mercapturic acid and isomers (MHBMA), 3-hydroxy-1-methyl propylmercapturic acid (HPMMA), 3-hydroxypropylmercapturic acid (3HPMA), *S*-phenylmercapturic acid (SPMA), 2-carbamoylethylmercapturic acid (acrylamide mercapturic acid (AAMA), 2-cyanoethylmercapturic acid (CNEMA), and 2-hydroxypropylmercapturic acid (2HPMA).[31] The following metabolites of polycyclic aromatic hydrocarbons (PAHs) (free plus conjugated) were determined using LC-MS/MS: 2-naphthol, 1-hydroxyfluorene, 2-hydroxyfluorene, 3-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3+4-hydroxyphenanthrene (sum); and 1-hydroxypyrene.[32] Methods and analytical runs were validated using established procedures.[33,34] Lower limits of quantitation are provided in Supplementary Table 2, and the details on quality control measures for the various assays are listed elsewhere.[30–32,35] Urine creatinine was measured in the San Francisco General Hospital clinical laboratory using a standard colorimetric assay.

Questionnaire Measures

At each visit, subjects were asked, "In the last week, have you experienced any of the following symptoms?", while providing a response of "never," "rarely," or "often" to the following list of health effects: daytime cough, difficulty concentrating, difficulty breathing during sleep, difficulty sleeping, dizziness, headache, irritability, nausea, nighttime cough, chest pain, phlegm, shortness of breath, tightness in chest, visual disturbances, and wheezing. Responses of "rarely" or "often" were combined to indicate presence of an adverse health effect. Assessment of current nicotine withdrawal was measured before and after each session using self-reported data from the revised Minnesota Nicotine Withdrawal Scale (MNWS-R)[36] using a 0–5 rating scale. Overall MNWS-R scores were calculated by summing scores for the first nine validated items in the scale (irritability, anxiety, depressed mood, desire or craving to smoke, difficulty concentrating, increased appetite, insomnia, restlessness, and impatience).

Statistical Analysis

Using historical biomarker data, we estimated a sample size based on anticipated reductions in urine levels of NNAL observed among smokers who quit smoking.[37] The probability was 80 percent that the study would detect a difference at a two-sided .050 significance level, if the true decrease in NNAL urine levels was 25 pg/mg creatinine (within-patient *SD* 50 pg/mg). Sample size calculations were carried out using an online sample size calculator for a two-sample parity *t* test.[38]

All analyses were performed using IBM SPSS Statistics version 21.0. Frequencies and Pearson-chi square tests were used to describe and explain associations between categorical data. To assess changes in biomarkers levels, we compared biomarker values at baseline with biomarker values at 1 and 2 weeks of using e-cigarettes. Using the General Linear Models (GLM) procedure, repeated measure analysis of variance was used to examine initial changes for each analyte from baseline to 7 days, and 14 days. Multiple comparisons of mean outcomes for a given analyte were adjusted by using Bonferroni's method. Repeated measures analysis of variance was used to assess changes in pre-session MNWS-R scores over the study period. All tests were two-sided, and *p* values <.050 were considered statistically significant.

Results

Demographic Characteristics

Twenty subjects completed the study. All subjects were Caucasian, 60% were females with an average age [mean (*SD*)] of 31.0 (9.7) (range: 20–52). Subjects smoked an average of 12.1 (7.5) years (range: 4–35); the mean level of nicotine dependence among subjects (as measured by the Fagerstrom Test for Cigarette Dependence [FTCD])[39] was 3.9 (2.7) (range: 0–9). At the time of screening, 95% of subjects (n = 19) reported planning to quit smoking, with 80% (n = 16) reporting that they have made at least one quit attempt prior to involvement in the study. All participants reported hearing of e-cigarettes prior to their involvement in the study.

Patterns of Tobacco Cigarette Consumption

At baseline, subjects reported smoking on average 16 (9) cigarettes per day. The average number of cigarettes smoked per day declined at week 1 to 0.8 (1.3) (p < .001) and at week 2 to 0.6 (1.2) (p < .001; Figure 2A).

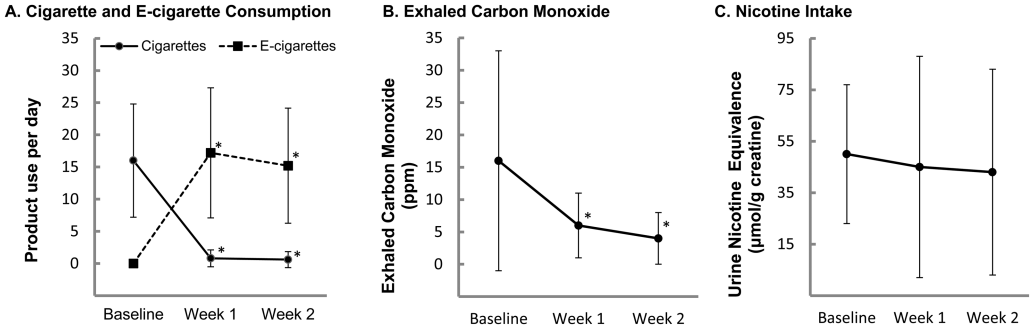

Figure 2. Changes in cigarette and electronic cigarette (e-cigarette) consumption (A; left) exhaled carbon monoxide (B; center), and nicotine intake (C; right) over 2 weeks of e-cigarette use among 20 cigarette smokers (mean ± *SD*). *Denotes statistically significant differences from baseline according to repeated measure analysis of variance (p < .05).

Nine participants (45%) reported no use of tobacco cigarettes at either week 1 or week 2 of the study period. Among those participants who continued to smoke throughout the study, the mean number of cigarettes smoked per day was 1.4 (1.6) at week 1 and 1.1 (1.5) at week 2. Self-reported smoking status was confirmed by the decline in exhaled CO levels in all subjects over the 2-week period of study (p = .007; Figure 2B).

Patterns of E-cigarette Use

At week 1, all participants reported using e-cigarettes every day; one participant initiated less frequent (every 2–3 day) use of e-cigarettes at the week 2 visit. On average, participants reported 17 (10) episodes of e-cigarette use per day at week 1, and 15 (9) episodes of e-cigarette use per day at week 2 (Figure 2A). Most study participants reported using at least one or two nicotine cartridges per day (55% at week 1, 50% at week 2), with the remaining subjects using three or more cartridges per day. The majority of subjects reported first daily use of e-cigarettes 30 minutes after waking (70% at week 1, 75% at week 2), with most subjects reporting heavier frequency of use outside of morning hours (85% at week 1, 75% at week 2). Most subjects reported puffing on e-cigarettes more frequently than tobacco cigarettes (45% at week 1, 40% at week 2); while 30% of subjects at week 1 reported puffing on e-cigarettes less frequently than tobacco cigarettes. At week 2, 25% of subjects reported puffing on e-cigarettes less frequently than tobacco cigarettes. Twenty-five percent of subjects at week 1 reported puffing on e-cigarettes and cigarettes about the same amount, which increased to 35% of subjects at week 2. No significant differences in these behaviors were observed between week 1 and week 2 of the study.

Nicotine Intake

Mean levels of various nicotine metabolites remained largely unchanged, with the exception of a slight decline in nornicotine levels (Table 1). Total nicotine equivalents did not significantly change over the study period (p = .53; Figure 2C). At week 1, four (20%) participants increased total nicotine equivalents by greater than 50%, while six (30%) experienced at least a 50% reduction in total nicotine equivalents. At week 2, only two subjects (10%) increased total nicotine equivalents by greater than 50%, while six (30%) experienced at least a 50% reduction in total nicotine equivalents.

Exposure to Carcinogens and Toxicants

Upon switching from tobacco cigarettes to e-cigarettes, statistically significant declines in 12 out of 17 measured biomarkers of exposure to toxicants were observed (Table 1). Figure 3 displays declines in biomarker urine levels of four toxicants classified by IARC as human carcinogens. At week 2, mean nitrosamine levels declined in all subjects by 64% (p < .001). Significant declines were also observed in biomarkers of volatile organic compounds, most notably for 1,3-butadiene, benzene, and acrylonitrile (all p < .050). Among biomarkers of exposure to PAHs, mean levels of 1-hydroxyflourene, 2-hydroxyflourene, and 3-hydroxyfluorene significantly declined (all p < .050), while no statistically significant changes in mean levels of 3-, 4-hydroxyphenanthrenes (p = .38), 1-hydroxypyrene (p = .32), 2-hydroxyphenanthrene (p = .126), 1-hydroxyphenanthrene (p = .076), or 2-naphthol (p = .095) were detected.

Stratified analyses suggest that complete substitution with an e-cigarette may have impacted observed trends in some PAH biomarkers and exhaled CO levels (Supplementary Table 3). For example, the overall decline in levels of 3-hydroxyfluorene were significant among those who were abstinent ("Quitters") at week 1 (n = 9, p = .004) and those who were abstinent at week 2 (n = 11, p = .001); while no statistically significant declines were observed among those who continued to use tobacco cigarettes ("Reducers") at weeks 1 or 2 (n = 11 and n = 9, respectively).

Health Effects

Significant improvements in chest tightness (35% baseline, 10% week 1, 5% week 2; p = .024) and visual disturbances (25% baseline, 5% week 1, 0% week 2; p = .020) were observed. Subjects reported non-significant improvement in daytime cough (80% baseline, 70% week 1, 65% week 2), difficulty concentrating (65% baseline, 35% weeks 1 and 2, respectively), irritability (60% baseline, 50% week 1, 40% week 2), and presence of phlegm (75% baseline, 65% week 1, 50% week 2).

Subjective Effects

On average, participants reported a decline in nicotine withdrawal symptoms over the course of the study. We observed an overall statistically significant decline in pre-session MNWS scores over the 2-week period (p = .005). The overall decline in MNWS scores over the 2-week time period was driven by significant declines in "desire or craving to smoke" (p = .002) and "restlessness" (p = .049).

Discussion

This study sought to better understand the effectiveness of e-cigarettes in nicotine delivery and exposure reduction to selected carcinogens. We previously reported high yields of nicotine and reduced levels of several toxicants in aerosol generated from e-cigarette when compared to tobacco smoke.[8] Consistent with our primary hypothesis that e-cigarettes deliver nicotine while reducing exposure to toxicants, we observed sustained nicotine intake and substantially reduced levels of several urine biomarkers of toxicant exposure among cigarette smokers who switched to e-cigarettes.

We found that virtually all nicotine metabolites in urine remained unchanged among the majority of study participants over the 2-week period, suggesting that nicotine intake in smokers who used e-cigarettes remained stable. This confirms previous findings from laboratory studies showing that e-cigarettes effectively deliver nicotine to blood.[12,13] There was a slight decrease in nornicotine during e-cigarette use, which is expected as nornicotine is both a nicotine metabolite and a minor alkaloid present in tobacco, and not present in e-liquids or present in lower concentrations (relative to nicotine) than in tobacco. While we observed no significant declines in urine cotinine levels in our participants, McRobbie et al.[15] noted a slight decline in cotinine levels over a period of 1 month. This may result from more effective nicotine delivery to e-cigarette users from the product used in our study. As nicotine is the substance in tobacco cigarettes that contributes to tobacco addiction, sustained levels of nicotine delivery have important implications for the potential effectiveness of e-cigarettes as a harm reduction device. Future studies should evaluate long-term effects of inhaled nicotine in regular established users of e-cigarettes.

Among smokers who switched to e-cigarettes in our study, we observed significant reduction in exposure to several tobacco-related human carcinogens, namely NNK, 1,3-butadiene and benzene. Previous cohort studies showed that exposure to NNK as quantified by urine NNAL is directly associated with lung cancer risk

Table 1. Mean Levels of Biomarkers in Smokers ($N = 20$) at Baseline, After 1 Week and 2 Weeks of Using Electronic Cigarettes (E-cigarettes)

Biomarker urine concentration (normalized per gram creatinine)	Toxicant	Baseline (tobacco cigarette)	Week 1 (e-cigarette)	Week 2 (e-cigarette)	*p*
		Mean ± *SD* (interquartile range)			
Nicotine metabolites					
3-Hydroxycotinine (μg/g)	Nicotine	4765 ± 3163 (2525–5151)	4472 ± 4315 (1590–5862)	4686 ± 4409 (1506–6576)	NS
Cotinine (μg/g)	Nicotine	2287 ± 1381 (1344–2941)	2048 ± 2102 (745–2211)	1927 ± 1728 (792–2590)	NS
Nicotine (μg/g)	Nicotine	1126 ± 821 (634–1578)	962 ± 1139 (202–1290)	584 ± 752 (112–734)	NS
Cotinine N-Oxide (μg/g)	Nicotine	392 ± 238 (280–466)	345 ± 276 (122–592)	349 ± 303 (95–543)	NS
Nicotine N-Oxide (μg/g)	Nicotine	335 ± 231 (235–415)	326 ± 399 (49–442)	223 ± 232 (36–395)	NS
Norcotinine (μg/g)	Nicotine	136 ± 91 (85–153)	101 ± 97 (30–146)	108 ± 131 (27–118)	NS
Nornicotine (μg/g)	Nicotine	73 ± 39 (47–105)	46 ± 45 (10–58)	38 ± 38 (8–50)[a]	.015
Nicotine equivalents (μmol/g)	Nicotine	50 ± 27 (35–66)	45 ± 43 (16–57)	43 ± 40 (27–59)	NS
Nitrosamines (TSNAs)					
NNAL (ng/g)	NNK	225 ± 165 (89–340)	97 ± 60 (45–147)[a]	80 ± 69 (32–120)[a]	<.001
Mercapturic acids (MAs)					
HEMA (ng/g)	Ethylene oxide	3821 ± 3120 (1790–5050)	1400 ± 864 (770–1790)[a]	1480 ± 1573 (460–1830)[a]	.001
MHBMA (ng/g)	1,3-Butadiene	1912 ± 1283 (830–2860)	300 ± 478 (0–430)[a]	305 ± 887 (0–140)[a]	<.001
HPMMA (μg/g)	Crotonaldehyde	1857 ± 1379 (936–2384)	632 ± 387 (312–856)[a]	616 ± 575 (331–706)[a]	<.001
3HPMA (μg/g)	Acrolein	937 ± 700 (433–1118)	492 ± 455 (162–680)[a]	410 ± 465 (127–462)[a]	.001
SPMA (ng/g)	Benzene	792 ± 674 (249–1203)	159 ± 193 (37–193)[a]	188 ± 481 (33–161)[a]	<.001
AAMA (μg/g)	Acrylamide	254 ± 148 (119–395)	163 ± 188 (66–211)	110 ± 97 (50–132)[a]	.005
CNEMA (μg/g)	Acrylonitrile	212 ± 178 (103–311)	51 ± 58 (20–48)[a]	45 ± 66 (13–42)[a]	<.001
2HPMA (μg/g)	Propylene Oxide	45 ± 24 (23–55)	24 ± 18 (15–28)[a]	21 ± 15 (12–23)[a]	<.001
Metabolites of polycyclic aromatic hydrocarbons					
1-Hydroxyfluorene (ng/g)	Fluorene	1414 ± 864 (674–2052)	441 ± 492 (44–768)[a]	592 ± 833 (48–1074)[a]	<.001
3-, 4-Hydroxyphenanthrenes (ng/g)	Phenanthrene	1314 ± 669 (808–1720)	1098 ± 544 (630–1464)	1410 ± 1262 (759–1429)	NS
2-Hydroxyfluorene (ng/g)	Fluorene	1029 ± 463 (609–1401)	738 ± 315 (417–1003)[a]	842 ± 495 (543–1078)	.048
1-Hydroxypyrene (ng/g)	Pyrene	778 ± 338 (556–1000)	606 ± 279 (378–817)	746 ± 627 (430–733)	NS
3-Hydroxyfluorene (ng/g)	Fluorene	679 ± 312 (407–878)	367 ± 192 (181–524)[a]	451 ± 349 (211–768)[a]	.001
2-Hydroxyphenanthrene (ng/g)	Phenanthrene	655 ± 333 (339–933)	755 ± 492 (375–947)	968 ± 800 (522–1026)	NS
1-Hydroxyphenanthrene (ng/g)	Phenanthrene	488 ± 211 (316–678)	407 ± 196 (235–561)	584 ± 415 (346–716)	NS
2-Naphthol (μg/g)	Naphthalene	24 ± 13 (12–34)	15 ± 8 (11–18)	19 ± 14 (8–30)	NS
Toxic gases					
Carbon monoxide (ppm, exhaled)	Carbon monoxide	16 ± 17 (8–18)	6 ± 5 (2–8)	4 ± 4 (2–6)[a]	.007

2HPMA = 2-hydroxypropyl mercapturic acid; 3HPMA = 3-hydroxypropyl mercapturic acid; AAMA = 2-carbamoylethylmercapturic acid; CNEMA = 2-cyanoethyl mercapturic acid; HEMA = 2-hydroxyethylmercapturic acid; HPMMA = 3-hydroxy-1-methylpropylmercapturic acid; MHBMA = 2-Hydroxy-3-buten-1-yl-mercapturic acid; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SPMA = S-phenylmercapturic acid.

[a]Denotes statistically significant difference in mean biomarker levels compared to baseline values, according to repeated measures analysis of variance (ANOVA) ($p < .05$). *p* value of "NS" denotes nonsignificant findings.

among smokers.[40] Regarding exposure to other toxicants, consistent with findings from McRobbie et al.[15] we also observed a decline in exposure to acrolein among smokers who switched to e-cigarettes. Moreover, the observed decline in various urine toxicant biomarker levels in our study was similar to decline among smokers who have quit smoking completely and did not substitute with any other product.[41] This observation suggests that e-cigarettes are not a significant source of exposure to those toxicants. Further evaluation should be undertaken on the impact of e-cigarettes on longer-term behaviors and effects of e-cigarettes that may contain low levels of toxicants. Such studies should include end points that assess the possible effects of toxicant reductions on health, including the impact of toxicant reductions on future disease risk.

Preliminary sensitivity analyses suggest that observed declines in some biomarkers of exposure (namely, PAHs) were mainly driven by participants who switched completely from tobacco cigarettes to e-cigarettes. Given that we did not collect information on potential background sources of exposure to PAH compounds, it is difficult to definitively conclude that all observed PAH reductions were fully attributable to switching to e-cigarettes. Yet our data show a significant decline in 1-hydroxyfluorene levels, which prior studies have demonstrated to be a highly specific marker of tobacco exposure,[42] along with markers for several of our measured volatile organic compounds (eg, toluene, benzene, acrolein).[1] While continued smokers may derive some harm reduction benefits from using e-cigarettes, a much greater level of risk minimization is likely to be derived if they were to completely substitute e-cigarettes for tobacco cigarettes. The health effects of concurrent tobacco smoking and e-cigarette use (so called "dual use") need to be evaluated in a larger population and in longitudinal observational studies.

The promise of using e-cigarettes as a harm reduction tactic could be strengthened by their appeal to cigarette smokers coupled with fewer negative health effects stemming from use. For example, participants who switched to e-cigarettes reported declines in overall nicotine withdrawal symptoms along with cigarette cravings. When switching to e-cigarettes, participants in our study reported significant improvements in chest tightness and visual disturbances, along with nonsignificant improvements in daytime cough, difficulty

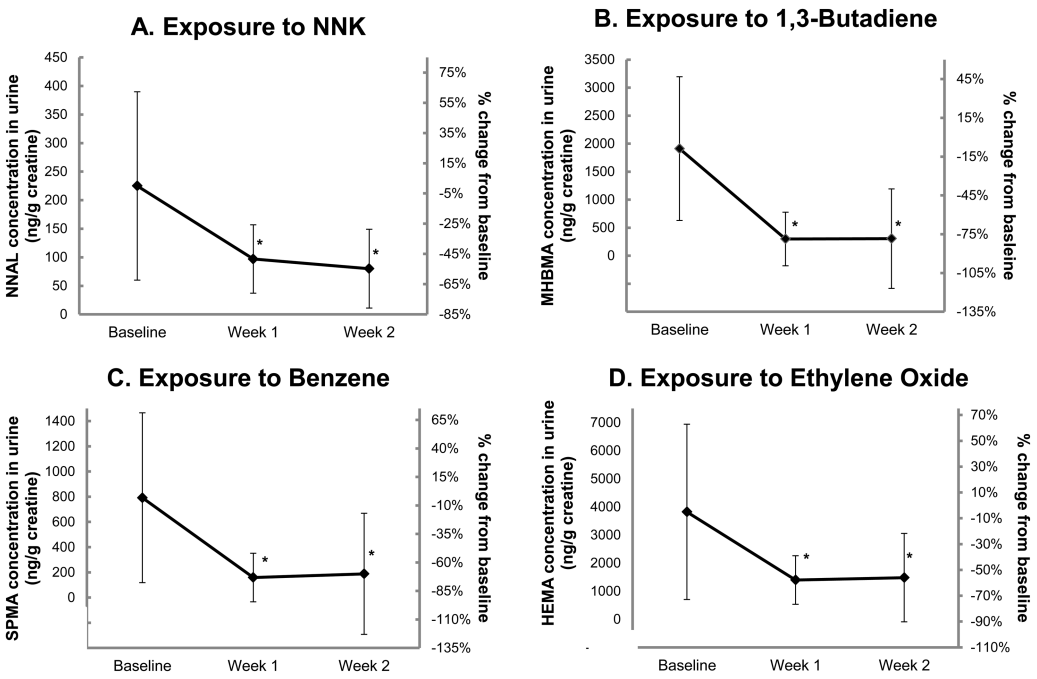

Figure 3. Changes in select carcinogen levels over 2 weeks of electronic cigarette (e-cigarette) use among 20 smokers (mean ± *SD*). *Denotes statistically significant differences from baseline according to repeated measure analysis of variance ($p < .05$).

concentrating, irritability, and presence of phlegm over the course of 2 weeks. One survey conducted among e-cigarette users suggest use of these products pose minimal side effects to users and can in fact improve reported health issues experienced when using tobacco cigarettes.[43]

Strengths and Limitations of the Study

To our knowledge, this is the first study showing substantial reductions in exposure to several toxicants among smokers who switched to e-cigarettes. However, relatively small sample size and laboratory settings limit the ability to generalize findings to the general population of e-cigarette users. The small sample size limited our ability to perform in depth analysis of effects among dual users, however our data suggest that there may be some patterns of change in metabolites that may differ based on whether or not an individual continues to smoke tobacco cigarettes or switches completely to e-cigarettes. Future studies should aim to assess variability of toxicant exposure among dual users and smokers who completely switch to e-cigarettes among larger sample of users. During our study, we did not monitor environmental and dietary exposure to carcinogens. There are several sources of exposure to those toxicants in addition to tobacco smoke, and there may have been a certain background exposure in our study group, in particular PAHs and many of the volatile organic compounds have dietary and environmental sources that lessen the difference seen in comparing users with tobacco smokers. We studied only one product, which we had previously determined to deliver adequate nicotine and low concentrations of toxic chemicals. While other studies have determined this to be a popular product in Poland[8,9] other devices may not be as effective in delivering nicotine and may deliver more of various toxic chemicals, including aldehydes such as acrolein. Given possible variability in exposures from emerging e-cigarette products (particularly, third generation e-cigarette models) future studies should expand measurement of toxicants and carcinogens to users of other types of e-cigarette products. Finally, we tested a selection of key toxic and carcinogenic substances for which adequate biomarkers of exposure were available. Yet there may be other toxicants delivered by e-cigarettes not measured in this study (eg, formaldehyde, harmful metals such as lead).

Conclusions

This study showed for the first time that after switching from tobacco to e-cigarettes, nicotine exposure remains unchanged, while exposure to selected carcinogens and toxicants is substantially reduced. These findings suggest that e-cigarettes may effectively reduce exposure to toxic and carcinogenic substances among smokers who switched to these products. Future research should assess the effects of e-cigarettes on reduction in disease risk among dual users, as well as smokers who substituted their regular cigarettes with these products.

Supplementary Material

Supplementary Tables 1–3 can be found online at http://www.ntr.oxfordjournals.org

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Declaration of Interests

MLG was a faculty member of the Medical University of Silesia, Poland during the study. He received a research grant from Pfizer, a pharmaceutical company

that markets smoking cessation medications. MLG and NLB have been consultants to pharmaceutical companies that market smoking cessation medications. NLB has been an expert witness in litigation against tobacco companies. The other authors declare no potential conflicts of interest.

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