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Interplay of metals and organics in e-cigarette aerosols enhances the production of reactive oxygen species within ultrafine particles: Implications for passive vaping exposures

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Abstract

Recent work has shown that the atmospheric aging of vaping emissions in indoor environments produces organic hydroperoxides via ozonolysis of terpene flavoring chemicals. These peroxide species decompose to form radicals upon aqueous dissolution. While the mechanism responsible for producing these radicals has yet to be fully elucidated, one prevailing hypothesis to support this phenomenon is Fenton-like reactions between redox-active metals and peroxides. Vaping emits various redox-active metals, which may play an important role in mediating these types of aqueous reactions. Here, we observed that the production of radicals resulting from the aqueous decomposition of aged e-cigarette aerosols was found to be highly dependent on the presence of redox-active metals, indicating the reliance of Fenton-like reactions on mediating the formation of radicals. Additionally, we observed that peroxides and metals are enriched within the ultrafine particles (UFPs) of aged vaping emissions, which leads to a drastic enhancement of their ability to generate radicals. This work provides a mechanistic perspective regarding the oxidative ability of aged e-cigarette aerosols as well as potential negative implications associated with their inhalation and subsequent deposition in aqueous regions of the lungs.

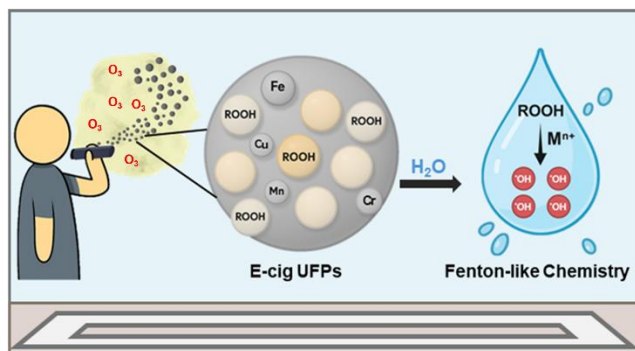
KEYWORDS

secondhand vaping, peroxides, redox-active metals, Fenton-like reactions, radicals, metal nanoparticle

35 **Synopsis**

36 The interactions between metals and organic peroxides in the ultrafine particle fraction of aged e-
37 cigarette aerosols produce elevated levels of reactive radical species, which may lead to oxidative
38 damage upon inhalation.

39 TOC Graphic



40

1. Introduction

Ever since the introduction of e-cigarettes to the U.S. market in 2007, their use has been steadily increasing and eventually exceeded traditional tobacco cigarette usage.¹⁻³ Like cigarette smokers of the past, users of e-cigarettes commonly vape indoors. Emissions of volatile organic compounds (VOCs) and particulate matter (PM) during a vaping session can greatly exceed the amounts released during cigarette smoking, and once in the air, these emissions can be inhaled by others through secondhand exposure.⁴ Prior to exposure, these emissions can undergo aging processes in indoor environments where ground-level oxidants, such as O₃, can chemically transform vaping emissions to form new compounds that exhibit greater toxic potential than the unaged, fresh emissions.^{5,6} Previous work has shown that the indoor aging of e-cigarette aerosols containing terpene flavor additives leads to the generation of particle-bound reactive oxygen species (ROS) that are comprised of peroxide functional groups, such as hydroxy hydroperoxides, hydroxyalkyl hydroperoxides, and diperoxides.^{5,7,8} These peroxide species tend to decompose in water to form reactive hydroxyl (OH) and organic radicals, which have negative implications regarding their inhalation and subsequent deposition in the aqueous lung lining fluid (LLF) that resides all throughout the respiratory tract.^{9,10}

The generation of radicals from the aqueous decomposition of these peroxides is considered to be a spontaneous process,⁹ but it has been proposed that certain metal-organic interactions, such as Fenton-like reactions, may play a role in this process.^{9,11} Many recent studies have reported the presence of metals in vaping emissions.¹²⁻¹⁴ The release of these metals has been linked to specific components that make up the e-cigarette device, such as the heating coil. These metals are often released as ultrafine particles (UFPs) with a diameter less than 100 nm.¹⁵ Some of the metals that are released from the device are heavy metals, such as Pb, Cd, and As, whose discovery led to

increased public concern regarding vaping.¹⁶ However, the presence of these heavy metals has always been reported in trace quantities, and less attention has been given to the other metal species present in vaping emissions. Most metals that are found in vaping emissions have been reported to be redox-active transition metals such as Cr, Fe, and Cu, as well as non-redox-active transition metal species such as Al and Zn.¹³ Similarly to the Fenton reaction, Fenton-like reactions can utilize a redox-active metal to facilitate the heterolytic cleavage of O-O bonds in peroxide compounds to form reactive radicals.^{17,18} Therefore, the presence of these redox-active metals in aged e-cigarette aerosols presents the possibility for Fenton-like reactions to take place in aqueous conditions to enhance the ability of e-cigarette aerosols to generate radicals.

While the presence of redox-active metals and organic peroxides in e-cigarette aerosols has been previously established, current studies have largely examined these components in isolation. The combined effects of metal-organic interactions, particularly within size-resolved aerosol fractions that more realistically represent the particles inhaled during passive exposure, remain poorly understood. Moreover, little is known about how atmospheric aging processes, such as ozonolysis, alter the spatial distribution and co-localization of metals and peroxides with UFPs. Changes in these conditions could drastically alter the oxidative potential of these UFPs once dissolved in lung lining fluid. To address these limitations, this study investigates the coupled role of redox-active metals and organic peroxides in mediating Fenton-like radical generation within aged e-cigarette aerosols. By linking chemical composition, particle size distribution, and radical production, we provide a mechanistic framework that connects atmospheric transformation chemistry with inhalation toxicology. This approach clarifies how indoor aging enhances the oxidative reactivity of vaping emissions and identifies the physicochemical factors that drive radical formation upon aqueous deposition.

2. Materials and Methods

2.1 Chemicals

1,2-Propanediol (PG, >99%, P0485) and *tert*-butyl hydroperoxide solution (TBHP, 70% in H₂O, B3153) were purchased from TCI America. Glycerol (VG, Certified ACS, G33-500) and KCl/HCl buffer solution (pH 2.00, SB96-500) were purchased from Fisher Chemical. Linalool (99%, AC125151000) was purchased from Acros Organics. Potassium iodide (KI, 99%, A12704.18) was purchased from Thermo Scientific. 5-*tert*-Butoxycarbonyl-5-methyl-1-pyrroline-N-oxide (BMPO, >98%, 14958) was purchased from Cayman Chemical Company. 1-Hydroxy-2,2,6,6-tetramethyl-4-oxopiperidine (TEMPONE-H, 99%, ST00D06H) was purchased from 1st Scientific. Nitric acid (TraceMetal™ Grade, A509P500) was purchased from Fisher Scientific. For all aqueous sample preparations, Milli-Q water (18.2 MΩ·cm) obtained from the Environmental Science Research Laboratory (ESRL) was used.

2.2 E-liquids and e-cigarette device

To establish a reliable baseline and reduce variability inherent to commercial e-liquids, the e-liquids utilized in this study were made in-house and composed of a 30% PG and 70% VG mixture. While a PG/VG ratio of 50:50 is common, a 30:70 PG/VG blend is also highly prevalent^{19,20} on the vape product market for users who prefer enhanced cloud production and direct-to-lung (DTL) inhalation, because the high VG content is directly responsible for generating large and dense aerosol clouds.²¹ Additionally, the choice of a PG/VG ratio of 30:70 was also to align with previous research⁵ that used the 30:70 for studying high aerosol output and exposure as benchmarks. Linalool was added to the PG/VG mixture to achieve a terpene concentration of 3% by volume. Prior tests that compare the concentration of metals in e-cig aerosols with and without the addition of terpenes were performed and as shown in Figure S1, there were no significant differences observed in the abundance of metals ($p>0.05$), indicating that terpene flavor additives do not have much influence on the release

of metals during vaping. The e-cigarette device was composed of a variable voltage battery (Vari-Vape®, O2Vape) that operated at 4.8V. To generate e-cigarette aerosols with varying concentrations of metals, two types of 510-threaded cartridges were used in this study (Figure S2), including (1) the CCELL borosilicate glass cartridges (TH2) and (2) the O2Vape all glass 510 vape cartridges (O2V-GC). Before each chamber experiment, the cartridges were filled with 450 μ L of our e-liquid mixtures and preconditioned by taking three puffs before injection into the chamber.

2.3 Chamber experiments to simulate aging

E-cigarette aerosols underwent O₃-mediated aging as previously described.^{5,6} A 2 m³ chamber made of fluorinated ethylene propylene (FEP) was filled with 100 ppbv of O₃ produced by a laboratory benchtop O₃ generator (A2Z Ozone 3 GLAB) using pure O₂ (Airgas). Real-time measurements of O₃ concentrations were taken with a photometric O₃ analyzer (Advanced Pollution Instrumentation, model 400A) with a time resolution of 1 minute. E-cigarette aerosols were injected into the chamber using an e-cigarette puffing machine (CSM-eSTEP, CH Technologies), and the puffing topography followed the CORESTA recommended protocol with a puff period of 3 s, a puff interval of 30 s, and a puff volume of 55 mL.²² The size distribution of e-cigarette aerosols with and without the presence of O₃ was monitored in real time with a scanning electrical mobility spectrometer (SEMS, Brechtel) for a period of 90 minutes throughout the chamber experiments. The SEMS was set to scan from 10 to 800 nm, with 140 size bins. After aging, the size-integrated aged aerosols generated from both CCELL-TH2 and O2V-GC cartridges were collected onto 25- and 47-mm polytetrafluoroethylene (PTFE) filters (Zefluor, Pall Laboratory, 1 μ m pore size) for 5 and 10 minutes, respectively, at a flow rate of 20 LPM for further offline analysis. To investigate the size dependence on aerosol composition, size-separated aged aerosols generated from the CCELL-TH2 cartridges were collected onto 47-mm PTFE filters using

a Micro-Orifice Uniform Deposit Impactor (MOUDI 110NR, TSI) at the cut sizes ranging from 0.056 to 1.8 μm . MOUDI samples were collected with a flow rate of 30 LPM for 50 minutes. The relative humidity (RH) inside the chamber was kept below 20% throughout both aging and sampling processes (Figure S3). The aerosol mass loading on each filter was determined gravimetrically by weighing the filters before and after aerosol sampling. After aerosol collection, the filter samples were stored at -20 °C until further analysis.

2.4 Elemental analysis of device components

The CCELL-TH2 and O2V-GC cartridges were disassembled and dissected by removing their respective heating coils, wire connections between the heating coils and power source, and the ceramic cores that encase the heating coils. The metal housing surrounding the ceramic core and heating coil in the CCELL-TH2 cartridge was also removed and analyzed. Portions of each component were placed onto 12.7 mm sample stubs (Ted Pella). The elemental composition of the individual device components was analyzed with a scanning electron microscope (SEM, TESCAN, Vega3 SBH) coupled with energy dispersive X-ray spectroscopy (EDS, Bruker, XFlash7T).

2.5 Metal analysis of aged e-cigarette aerosols

For metal analysis, aerosol samples collected onto 47 mm PTFE filters were stored in 7 mL polyethylene scintillation vials and extracted with 1% HNO_3 and sonication for 60 minutes. The subsequent extracts were passed through syringe filters (Agilent Captiva, PTFE, 0.2 μm pore size) and transferred to 15 mL polypropylene conical tubes (Basix). Aerosol extracts were analyzed using single quadrupole, inductively coupled plasma mass-spectrometry (ICP-MS), following standard methods using an Agilent 7900 ICP-MS. Metal concentrations (Al, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Sr, Mo, Sn, and Pb) were quantified relative to matrix matched standards prepared in-

house. Analysis of NIST SRM 1640a (Trace Elements in Natural Water) and two additional in-house reference materials repeatedly throughout multiple runs ensured accuracy of measurement. Repeat analyses of sample solutions, both within runs and between multiple runs, suggest a very high precision (generally less than $\pm 1\%$ on all elements). However, long-term in-house instrument stability monitoring suggests that a more conservative $\pm 5\%$ for major elements and $\pm 10\%$ for trace elements should be used. Instrument detection limits for all listed elements were in the low parts per trillion range (1-100 ppt).

2.6 Iodometric quantification of peroxides

Peroxides in the aged e-cigarette aerosol samples were quantified with iodometry. A 60 mM KI solution was prepared by dissolving KI in a pH 2.00 KCl/HCl buffer solution. Aged CCELL-TH2 and O2V-GC emissions that were collected onto 25 mm PTFE filters were transferred into 1.7 mL microcentrifuge tubes. Depending on the aerosol mass loading of each sample, a corresponding volume of KI solution was added to achieve a final aerosol concentration of 1 mg mL^{-1} , and extraction was performed by vigorously vortexing the filters for 10 minutes. The extract was then allowed to incubate in the dark at room temperature for 1 hour. After incubation, 100 μL of sample was pipetted into a 96-well, flat, clear-bottom plate (Corning), and its absorbance at 350 nm was measured with a SpectraMax iD5 plate reader. A calibration curve of $1 \text{ }\mu\text{M}$ to 1 mM of *tert*-butyl hydroperoxide (TBHP) was made for each run, and it was utilized to calculate the concentration of total peroxides as TBHP equivalences in each sample (Figure S4). MOUDI samples collected onto 47 mm PTFE filters were extracted and analyzed in a similar manner except all samples were extracted with 500 μL of the prepared KI solution and peroxide concentrations were normalized by their mass loading.

2.7 Electron paramagnetic resonance (EPR) spin trapping

For EPR analysis, aerosol samples collected onto 25 mm PTFE filters were transferred into 500 μ L microcentrifuge tubes (Fisher Scientific). For radical speciation, a 20 mM solution of 5-*tert*-butoxycarbonyl-5-methyl-1-pyrroline-*N*-oxide (BMPO) was prepared before analysis by dissolving 2 mg of BMPO into 500 μ L of Milli-Q water. 150 μ L of the BMPO solution was added to the sample, and the aerosols were extracted by vortexing for 10 minutes. The extract was collected into a 50 μ L capillary tube and placed into the sample cavity of an ESR5000 (Magnettech). EPR spectra were acquired with a field range of 333–340.5 mT, a sweep time of 22 s, a modulation amplitude of 0.1 mT, a modulation frequency of 100 kHz, a microwave power of 20 mW, and 25 accumulations. Spectral simulations were performed with the MATLAB package, EasySpin.²³ Simulations were performed with the “garlic” function, and hyperfine splitting parameters were adopted from a previous study (Table S1).^{5,24}

For radical quantification, a 1 mM solution of 1-hydroxy-2,2,6,6-tetramethyl-4-oxopiperidine (TEMPONE-H) was prepared immediately before analysis by dissolving 2 mg of TEMPONE-H in 10 mL of Milli-Q water. 150 μ L of the TEMPONE-H solution was added to the filter samples and extracted in the same manner as the method for radical speciation. The TEMPONE spectra were acquired with a field range of 334–340 mT, a sweep time of 60 s, a modulation amplitude of 0.1 mT, a modulation frequency of 100 kHz, a microwave power of 20 mW, and 1 accumulation. Experimental spectra were double integrated to calculate their area, and total radical abundance was calculated with a TEMPONE calibration curve (Figure S5).

2.8 Data Analysis

Data is reported as the mean $\pm$ the standard error of the mean (SEM) from replicate experiments. Statistical significance in Section 3.2 was determined by an unpaired two-sample t-test with $p < 0.05$ being determined as significant. The linear regression analysis was performed in Section 3.3 to

determine the Pearson correlation coefficients (R) between aerosol mass-normalized metal concentrations and radical production, with strong associations being defined as $R > 0.8$.

3. Results and Discussion

3.1 Abundance of redox-active metals in aged vaping emissions

The aged e-cigarette aerosols generated from both CCELL-TH2 and O2V-GC cartridges contained a variety of metals, many of which are redox-active, such as Fe, Mn, Cu, and Cr.^{25,26} Yet, for each metal tested other than As, CCELL-TH2 emissions contained 2-5 times more metals per mg of aerosol compared to its O2V-GC counterpart (Figure 1A). The most abundant metal present for both emission sources was Fe, with concentrations of $201.89 \pm 43.84 \text{ ng mg}^{-1}$ and $88.33 \pm 54.69 \text{ ng mg}^{-1}$ for the CCELL-TH2 and O2V-GC emissions, respectively. Since these devices were operated at the same coil temperature (Figure S6), the differences in metal abundance within the two types of emissions are likely attributable to differences in the bulk composition of their individual device components (Figure S7). The EDS analysis of individual device components showed that the heating coils for both devices were mainly composed of Ni and Cr (Figure S7), but the abundances of these two metal species within the aerosols were lower than for Fe, Al, and Zn. This observation indicates that most of the metal species within the aged e-cigarette aerosols originate from other device components that come into contact with the e-liquids or aerosols. Nonetheless, both devices emit significant amounts of metals that are not only redox-active but also toxic.²⁷

Like past reports,^{12,13} we detected the presence of heavy metals in our aged e-cigarette aerosols, such as Pb, As, and Sn. However, these heavy metals were only present in trace quantities and are not major components of the total metal distribution within e-cigarette aerosols. As shown

226 in Figure 1B, many of the metals that are in the aged e-cigarette aerosols are redox-active, with Fe
227 making up greater than 50% of the distribution for both CCELL-TH2 and O2V-GC emissions. A
228 large portion of the metal distribution is also taken up by Al and Zn, which are likely present in
229 their trivalent and divalent forms, respectively, and therefore are not redox-active.^{28,29} In CCELL-
230 TH2 emissions, Al made up 18.1% of the metal distribution and Zn was 11.4%. The distribution
231 for Al and Zn in O2V-GC emissions was 7.4% and 7.2%, respectively. Besides Fe, both types of
232 aged aerosols contained significant amounts of other redox-active metals. Chromium made up
233 roughly 3.2% of the distribution in the CCELL-TH2 emissions and 4% in the O2V-GC emissions.
234 Copper made up about 3.8% of the distribution in the CCELL-TH2 emissions and around 3.5% in
235 the O2V-GC emissions. Manganese was present in low abundance and made up only 1% of the
236 total metal distribution in both emission types. Lead, As, and Sn were present in trace quantities
237 and only accounted for less than 2% of the total metal distribution. Heavy metals, such as Pb and
238 As, were not detected in the device components with EDS, but they are likely present as trace
239 impurities within the metallic components that make up the CCELL-TH2 and O2V-GC cartridges.

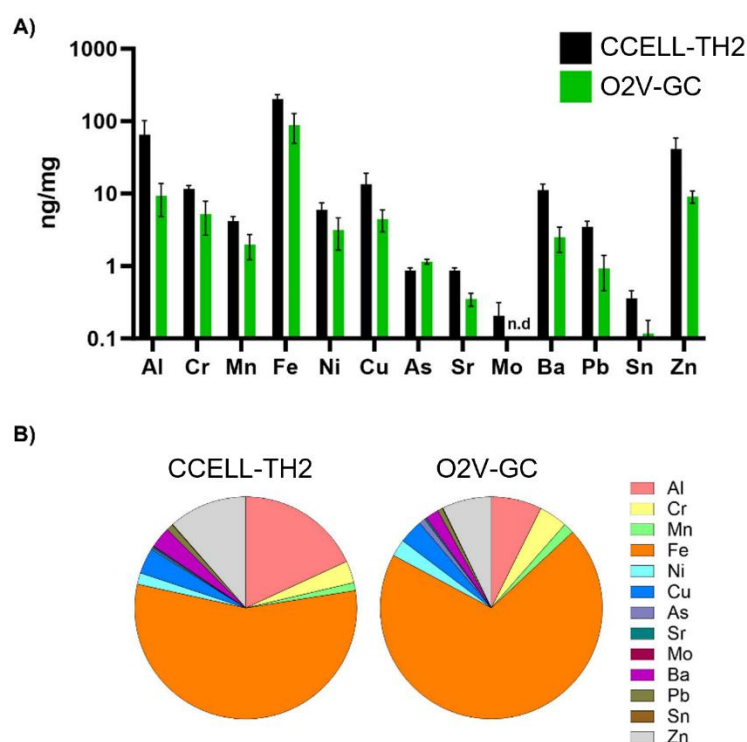


Figure 1. ICP-MS analysis of metals in aged vaping emissions produced by the CCELL-TH2 and O2V-GC e-cigarette devices: (A) Metal abundance per mg of collected aerosols and (B) Distribution of metals in aged vaping emissions. The data is expressed as the means of 6 replicate experiments (n=6) $\pm$ the standard error of the mean (SEM).

3.2 Influence of device components on peroxide decomposition and radical production

As described previously^{5,9,24}, once in aqueous conditions, the peroxides that are formed from the ozonolysis of terpenes can decompose to produce hydroxyl (OH) and alkyl (R) radicals. From the ozonolysis of linalool within e-cigarette aerosols, we observed this same effect, where our aged aerosols generated from both devices produced OH and R radicals in aqueous conditions (Figure 2A). By utilizing EPR spin trapping, we observed the formation of the respective BMPO spin adducts for OH and R radicals, with hyperfine splitting constants of $\alpha_N = 14.4$ G, $\alpha_{H\beta} = 14.9$ G, and $\alpha_{H\gamma} = 0.76$ G for BMPO-OH, and $\alpha_N = 15.1$ G and $\alpha_{H\beta} = 21.1$ G for BMPO-R. Once normalized by aerosol mass loading, the aged CCELL-TH2 emissions exhibited greater signal intensity than

the O2V-GC emissions, indicating a greater abundance of BMPO-OH and BMPO-R spin adducts. As shown in Figure 2B, once in aqueous conditions, aged CCELL-TH2 emissions produced 6.03 ± 1.14 nmol of radicals per mg of aerosol, while the aged O2V-GC emissions produced 3.71 ± 1.31 nmol mg^{-1} of radicals. Total radical quantification with the spin trap, TEMPONE-H, corresponded well with the observed signal intensities of BMPO spin adducts.

The enhanced production of radicals attributed to the aged CCELL-TH2 emissions compared to their O2V-GC counterpart may be explained by greater amounts of organic peroxides in the aged aerosols produced by the CCELL-TH2 device. Previous studies have shown that the magnitude of radical formation from the aqueous decomposition of atmospheric secondary organic aerosols (SOAs) is positively associated with organic peroxide concentrations in the aerosol phase.^{30,31} However, Figure 2C shows that at the same aerosol mass concentrations, aged CCELL-TH2 emissions contain similar amounts of peroxides as the aged O2V-GC emissions. Control experiments revealed that the presence of redox-active metals may introduce analytical artifacts during the iodometry assay, causing an overestimation of peroxide concentrations (Figure S8). However, it was determined that the e-cig aerosols generated in this study do not have a large influence on the accuracy of this assay (Figure S8). Additionally, during the aging process, both CCELL-TH2 and O2V-GC emissions exhibited similar O_3 consumption rates (Figure S9), indicating that both emission types undergo aging in a similar manner regardless of differing device components and metal concentrations. The rate of peroxide decomposition and radical formation is also metal-dependent due to the existence of Fenton and Fenton-like reactions.^{17,32,33} Furthermore, Fenton-like reactions are pH dependent and exhibit greater rates in acidic conditions^{17,34-36}; however, the pH of the aqueous extracts of both CCELL-TH2 and O2V-GC emissions were measured to be 6.3-6.5 (Figure S10). Therefore, it is likely that the enhanced

radical production associated with the aged CCELL-TH2 emissions is attributed to the greater abundance of redox-active metals and Fenton-like reactions that catalyze the decomposition of organic peroxides and the subsequent production of radicals. This brings forward the hypothesis that aged e-cigarette aerosols are Fenton-like systems, and their inhalation and deposition into aqueous lung lining fluid presents the risk of oxidative damage to the respiratory epithelium from the interactions between radicals and biomolecules.^{31,37}

In interpreting these findings, it is important to consider the role of the simplified e-liquid formulation used in this study. The e-liquid prepared in our laboratory was intentionally less complex than commercial products and did not contain nicotine, reflecting our specific interest in peroxide formation from linalool ozonolysis. Using a simple, chemically defined e-liquid enabled us to establish a reliable and reproducible baseline for evaluating metal–organic interactions while minimizing variability introduced by commercial formulations. While the e-liquid was simplified for experimental rigor, the delivery systems employed in this work maintain real-world relevance. The two cartridge types and variable-voltage batteries used here are commercially available vape pens with refillable tanks. Thus, although our formulation was simplified to enable mechanistic clarity, the vaping emissions and their associated metal release profiles reflect those of commonly used vaping products.

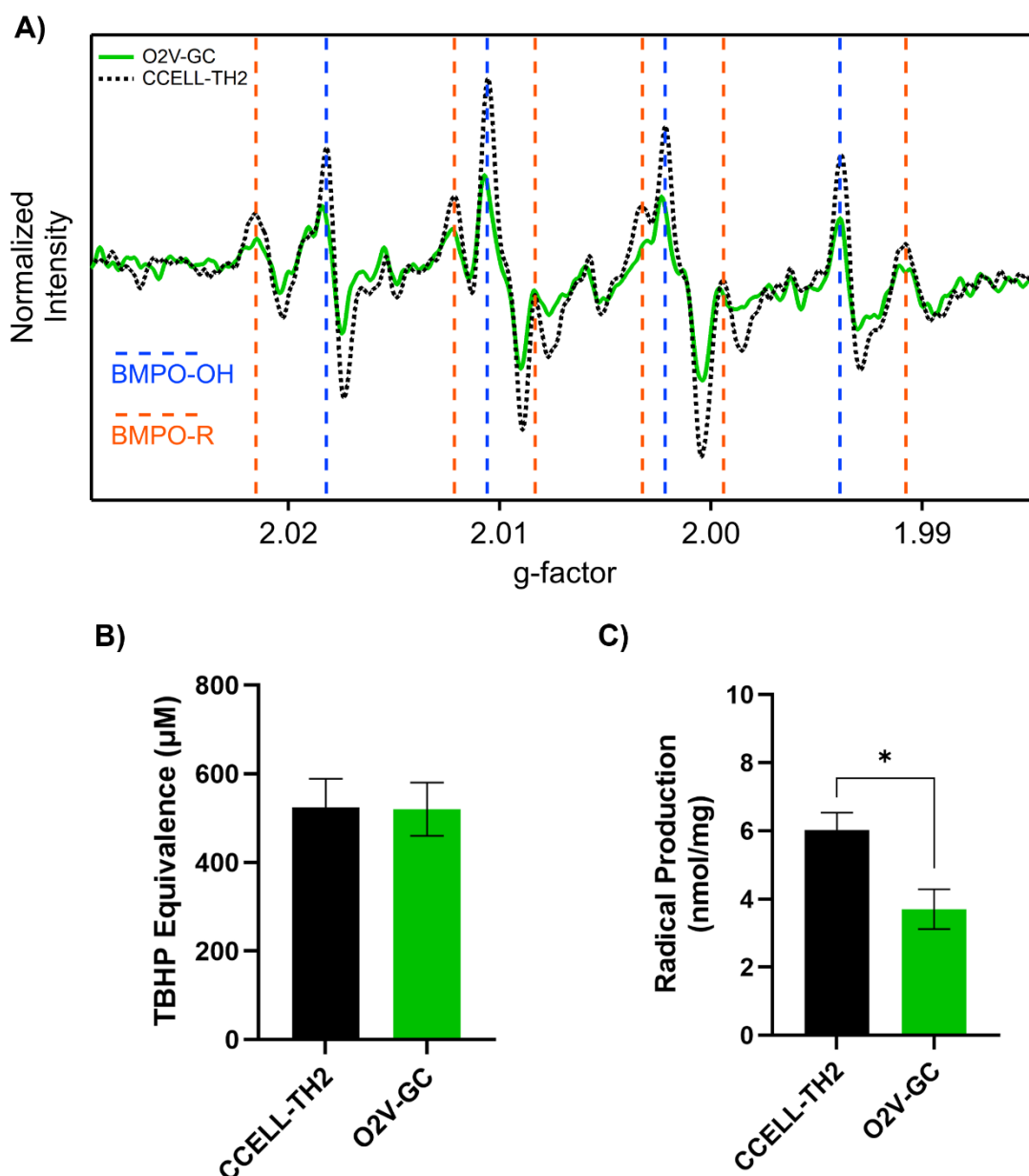


Figure 2. (A) Radical speciation, (B) radical abundance, and (C) peroxide abundance of aged e-cigarette aerosols produced by the CCELL-TH2 and O2V-GC e-cigarette devices. EPR spectra of BMPO spin adducts are observed signals whose intensities were normalized by their mass loading on their respective filters. The data for radical abundance and peroxide abundance is expressed as the mean of 6 replicate experiments ($n=6$) $\pm$ the standard error of mean (SEM). An unpaired two-sample t-test was used to determine statistical significance, and * indicates $p < 0.05$.

3.3 Enhanced radical production from increasing metal concentrations

Previous chamber studies involving terpene oxidation have shown that organic peroxides formed from the ozonolysis of terpenes can spontaneously decompose in aqueous conditions to form OH and organic radicals.^{38,39} However, it has been hypothesized that these organic peroxide species bear similar characteristics to simpler peroxides such as H₂O₂, and thus can undergo Fenton and Fenton-like processes when redox-active metals are present.¹¹ Additionally, it has previously been reported that the rate of Fenton and Fenton-like reactions is dependent on the concentration of metals in solution, where higher concentrations of Fe²⁺ lead to quicker decomposition of H₂O₂ and greater production of OH radicals.⁴⁰ Therefore, we presumed that the aged e-cigarette aerosols containing greater amounts of redox-active metals would have an enhanced capability to produce more radicals in aqueous conditions.

As shown in Figure 3, by utilizing TEMPONE-H spin trapping, we observed that as metal concentrations within aged e-cigarette aerosols increase, greater amounts of radicals are produced from aerosol-water interactions. This indicates a synergistic role that metals have with peroxides within aged e-cigarette aerosols, which corresponds well with other Fenton-like systems that have been described in past literature.^{9,41,42} Figures 3A to 3F highlight the positive linear relationship between metal abundance in the aerosol phase and total radical production once these aerosols are in aqueous conditions. Iron abundance shows a strong association with radical production (R=0.8328), which corresponds well with what is already known regarding Fe's ability to facilitate Fenton-like reactions.⁴¹⁻⁴³ The strongest association was observed between the addition of Fe, Cu, Cr, and Mn concentrations with radical production (R=0.8447), potentially hinting at the possibility of redox coupling and synergism between metals during Fenton-like reactions.^{44,45}

There is large variation in the magnitude of metal emissions across different e-cigarette devices, with some devices being considered as super-emitters of metals.^{46,47} These results predict

that these metal super-emitters have the potential to produce aged e-cigarette aerosols that can generate even more aqueous radicals than the ones in this study. Additionally, the results in this study do not consider the presence of background metal concentrations in ambient air and thus may be underestimating the full extent of radical production that aged e-cigarette aerosols can undergo in a realistic exposure scenario.

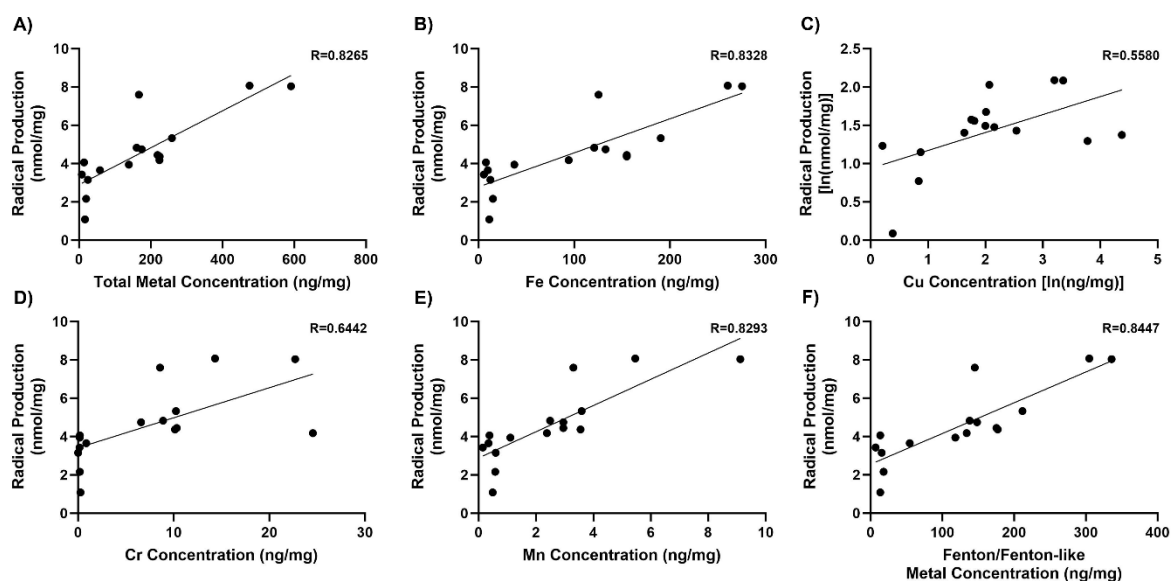


Figure 3. Correlations of aqueous radical production by aged e-cigarette aerosols produced by the CCELL-TH2 device with mass concentrations of (A) all metals, (B) Fe, (C) Cu, (D) Cr, (E) Mn, and (F) all Fenton-like metals.

3.4 Generation of ultrafine particles during the aging process

During the aging process of e-cigarette aerosols, we observed the formation of UFPs (Figure 4). When O_3 was not present, UFPs were detected directly after the injection of e-cigarette aerosols into the chamber. These UFPs are likely to be emitted directly from the e-cigarette device during vaping, but over time, we observed a steady decrease in their concentration (Figure 4A). During these fresh conditions, UFPs are likely aggregating into larger particles or experiencing wall loss to the experimental chamber.⁴⁸ However, as shown in Figure 4B, when O_3 is present, UFPs are constantly being generated during the aging process, which is indicative of new particle formation

from the oxidation of constituents within the aerosol and gas phase.⁴⁹ Oxidation products of linalool and other terpenes have been characterized by their low volatility due to their large degree of oxygenation, which would allow for their condensation to form new particles.⁵⁰ Therefore, the organic peroxides generated during the aging process, along with other highly oxygenated products, are likely condensing to form new particles ranging from 10 to 100 nm in diameter. This phenomenon would then suggest that UFPs in aged vaping emissions are enriched with organic peroxides, and they could be the greatest contributors to the oxidative ability of aged e-cigarette aerosols.

While the controlled laboratory studies presented here provide essential insights for establishing the definitive mechanistic pathways of reactive chemical formation (i.e., metals, peroxides, and radicals), cautious extrapolation of our mechanistic findings to real-world exposure scenarios is warranted, as real-world conditions during actual e-cigarette use are inherently more complex and variable. Despite these limitations, the evidence regarding the composition and potential toxicity of UFPs found in aged e-cig aerosols is critical. These UFPs carry an undeniable risk during secondhand exposure. Even though cases of secondhand exposure are characterized by a lesser aerosol exposure concentration than primary users of e-cigarettes, chronic exposure to these UFPs could have detrimental effects on respiratory health, especially for vulnerable populations with increased sensitivity to PM inhalation.⁵¹ Aerosol deposition in the lungs is size-dependent; as particle size decreases, there is preferential deposition into distal regions of the respiratory tract.⁵² It has been reported that UFPs mainly deposit in the alveolar region where the majority of gas exchange takes place.⁵³ Therefore, there may be a risk that the UFPs in aged vaping emissions will interact with lung alveoli and induce oxidative damage to biological components within the alveolar region. Oxidative damage to alveolar epithelial cells has been shown to inhibit

efficient gas exchange and respiratory function, but there may also be interactions with resident macrophages and antimicrobial peptides that are responsible for maintaining the immunological barrier within lung alveoli.^{54–56} Overall, the UFPs present in aged vaping emissions raise public health concerns regarding their inhalation, and further studies should be employed to determine the true extent of their ability to induce respiratory damage *in vivo*.

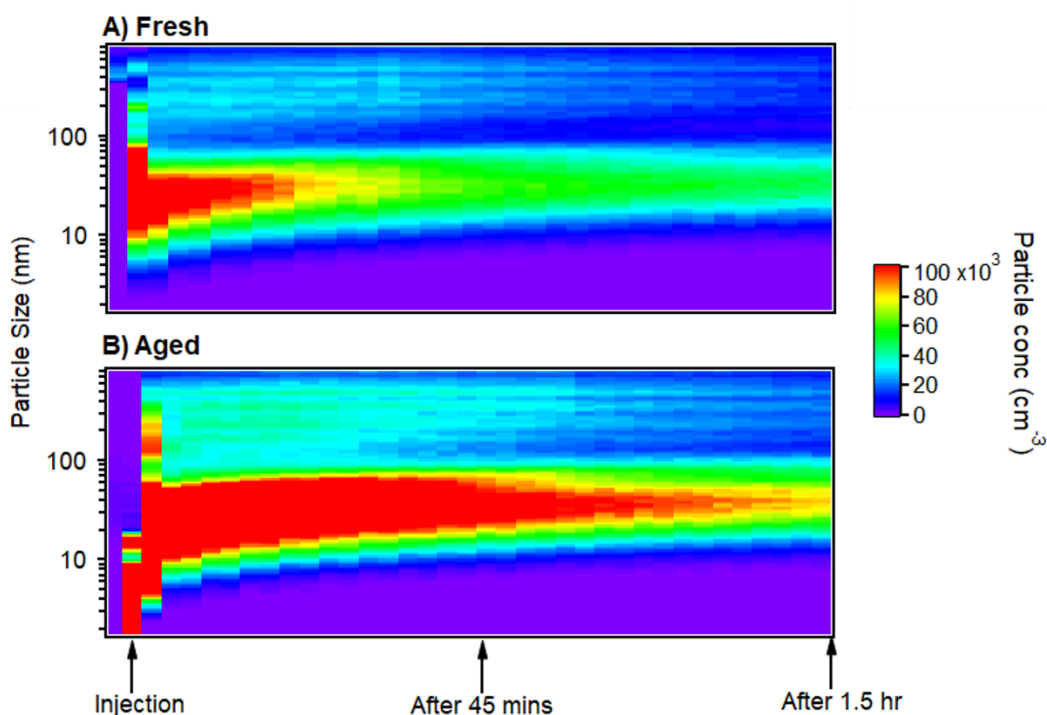


Figure 4. Particle size distribution of e-cigarette aerosols (A) during fresh conditions and (B) during O₃-mediated aging. Particle sizes are expressed as their aerodynamic diameter in nm and their concentrations are expressed as the number of particles per cm³.

3.5 Enrichment of redox-active metals and peroxides within ultrafine particles

As described in past reports, metals in e-cigarette emissions are commonly found as nanoparticles.¹² In Figure 5A, we report that metals can be found as particles larger than 1.0 μm , but the majority of the metals in our aged e-cigarette emissions are nanoparticles that are less than 1.0 μm in diameter. Within our non-normalized data, we also observed that most of the metals are

found within the smallest size fraction of 0.056-0.10 μm and exist as UFPs. Figure 5B shows the enrichment of peroxides within smaller size fractions. As particle size decreases within our aged e-cigarette aerosols, we observed a greater abundance of peroxides per unit mass of aerosol. Per unit mass of aerosol, UFPs between 0.056-0.10 μm contained roughly 8.4-fold more peroxides than the aged aerosols between 1.0-1.8 μm in diameter. This data presented in Figure 5B, along with the data presented in Figure 4, provides evidence that the peroxides formed from the aging of vaping emissions are contributing to new particle formation and are subsequently enriched in smaller particle sizes.

Based on the data from Figures 5A and 5B, we can presume that the smaller particle sizes within the aged vaping emissions are the most important contributors to the observed radical formation in Figures 2A and 2B, as these particles are enriched with peroxide and metals, allowing for a greater extent of Fenton-like reactions to occur in solution. This prediction is supported by the data in Figure 5C, where we show that as the particle size decreases, there are drastic increases in their ability to produce radicals in aqueous conditions. Following a similar trend as Figure 5B, we see that per unit mass of aerosol, UFPs between 0.056-0.10 μm produced 100-fold more radicals than the aerosols between 1.0-1.8 μm in diameter. These findings make it evident that the greater abundance of metals within the UFPs of aged vaping emissions in combination with greater peroxide abundance plays a major role in facilitating the oxidative ability of aged e-cigarette aerosols.

As mentioned in Section 3.4, UFPs are preferentially deposited in the alveolar region of the lung. Therefore, inhalation of UFPs in aged vaping emissions allow for the co-localization of redox-active metals and peroxides within the alveolar region. As discussed in previous sections, this co-localization and deposition of aged e-cigarette UFPs in alveolar fluid may produce radicals

via Fenton-like reactions. The resulting radicals that are formed from this process could pose a risk of causing oxidative damage to the alveolar epithelium. Individuals with compromised respiratory symptoms, such as those with asthma and chronic obstructive pulmonary disease (COPD), are already susceptible to experiencing respiratory damage from inhaling oxidative particulate matter.⁵⁷ Therefore, it would be worrisome for these individuals to experience chronic exposure to these UFPs, which would only add to their overall respiratory toxicant burden throughout the course of their lives.^{51,52}

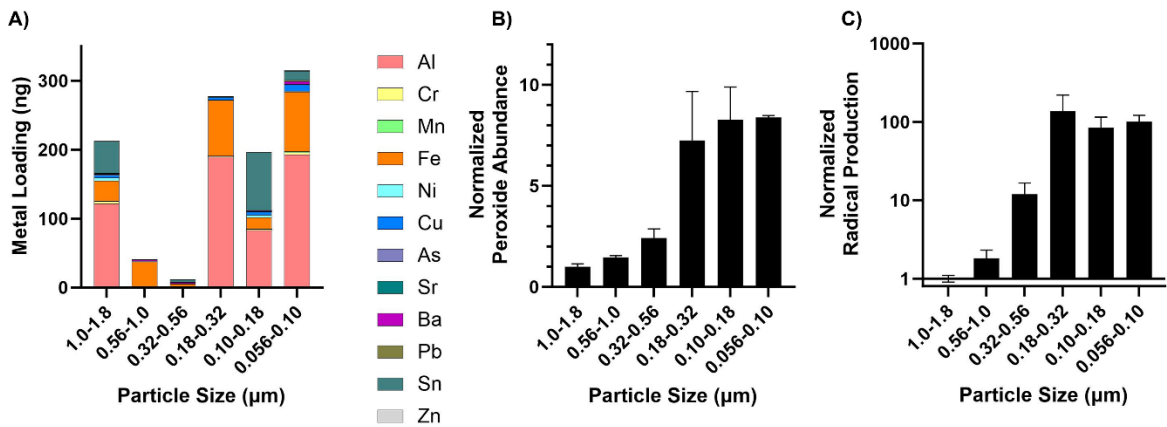


Figure 5. Differences in A) metal abundance, B) peroxide abundance, and C) aqueous radical production across 6 separate aerosol size fractions between 0.056-1.8 μm . Data is expressed as either A) the mean of 3 replicate experiments (n=3) or B,C) the mean of 3 replicate experiments (n=3) normalized by their mass loadings relative to the mean values of the 1.0-1.8 μm size fractions $\pm$ the standard error of mean (SEM).

4. Implications

This study tested the hypothesis that redox-active metals mediate Fenton-like reactions that enhance radical formation upon the aqueous dissolution of aged vaping emissions. Our results support this hypothesis, with radical production increasing linearly with metal abundance, particularly with Fe, Cu, Cr, and Mn, indicating that the oxidative potential of aged e-cigarette aerosols arises from metal-organic interactions. These findings build upon recent work on

atmospheric aqueous-phase chemistry and secondary organic aerosol (SOA) reactivity, where organic hydroperoxides derived from terpene ozonolysis have been shown to decompose via Fenton-like mechanisms in the presence of transition metals.^{11,30,31} The observed synergy between peroxides and redox-active metals in aged e-cigarette aerosols mirrors reactions described by Fang et al. and Wei et al., who demonstrated that Fe ions catalyze the decomposition of terpene-derived hydroperoxides in surrogate lung fluid to generate hydroxyl radicals.^{11,31} Our findings also expand upon earlier work by Woo et al. and Tian et al., which established that terpene flavorants in e-liquids can form highly oxygenated compounds, including hydroperoxides, upon ozonolysis.^{5,6} Here, we show that these peroxides do not act in isolation. Instead, their decomposition is amplified by co-emitted redox-active metals, most notably Fe. The combination of organic peroxides and metal nanoparticles creates a Fenton-like microenvironment within UFPs. This mechanistic coupling provides a more comprehensive understanding of the oxidative reactivity of aged e-cigarette aerosols.

The enrichment of both metals and peroxides within the UFP fraction further reinforces that smaller particles exhibit disproportionately high oxidative potential. The observed enhancement of radical production by UFPs aligns with previous literature on highly oxygenated molecules, which contribute to new particle formation and condensed-phase radical chemistry.⁵⁰ In the context of aerosol exposure, this enrichment is particularly concerning because UFPs efficiently deposit in the alveolar region, where they can interact with epithelial cells and the lung lining fluid.^{52–54} Similar to SOA and combustion-derived nanoparticles, these aged e-cigarette UFPs may serve as carriers for both redox-active metals and organic oxidants, leading to persistent ROS generation in the respiratory tract.^{37,55}

Together, these findings suggest that the oxidative ability of aged e-cigarette aerosols results from the interplay between atmospheric transformation processes and device-derived metals. The production of radicals through Fenton-like chemistry bridges atmospheric aerosol mechanisms with emerging concerns in inhalation toxicology. This work highlights the need to consider the indoor aging of vaping emissions not just as a compositional transformation but as a process that creates chemically reactive, metal-enriched particles with potential to cause oxidative damage in the lung. Future *in vitro* and *in vivo* studies examining oxidative injury and cellular responses to these aged aerosols would provide critical insight into their toxicological relevance and inform risk assessments for secondhand vaping exposures.

ASSOCIATED CONTENT

Supporting Information

Hyperfine splitting constants of BMPO adducts (**Table S1**); Influence of terpenes on the release of metals during vaping (**Figure S1**); 510-threaded cartridges used for e-cigarette aerosol generation (**Figure S2**); Relative humidity measurements throughout the aging process (**Figure S3**); Calibration curve used for iodometric quantification of peroxides (**Figure S4**); TEMPONE calibration curve used for quantification of radicals (**Figure S5**); Temperatures of CCELL-TH2 and O2V-GC coils at differing operating voltages (**Figure S6**); Elemental analysis of individual device components in CCELL-TH2 and O2V-GC cartridges (**Figure S7**); Influence of redox-active metals on peroxide quantification (**Figure S8**); Ozone consumption during the aging of CCELL-TH2 and O2V-GC emissions (**Figure S9**); pH measurements of CCELL-TH2 and O2V-GC aerosol extracts (**Figure S10**).

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494 **ABBREVIATIONS**

495 ROS – Reactive Oxygen Species

496 UFP – Ultrafine Particle

497 PG – Propylene Glycol

498 VG – Glycerol

499 RH – Relative Humidity

500 BMPO – 5- *tert*-Butoxycarbonyl-5-methyl-1-pyrroline-N-oxide

501 TEMPONE-H – 1- Hydroxy-2,2,6,6-tetramethyl-4-oxopiperidine

502 MOUDI – Micro-Orifice Uniform Deposit Impactor

503 ICP-MS – Inductively Coupled Plasma Mass Spectrometer

504 EDS – Energy-Dispersive X-Ray Spectroscopy

505 EPR – Electron Paramagnetic Resonance

506 SOA – Secondary Organic Aerosol

507 COPD – Chronic Obstructive Pulmonary Disease

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