Webinar Q&A Report

Assessing Toxicity and Health Risks of E-cigarettes: How to Take Aim at a Moving Target

Questions in this Q&A Report were submitted during the live webinar, Assessing Toxicity and Health Risks of E-cigarettes: How to Take Aim at a Moving Target.

How were nasal samples collected and analyzed?

In collaboration with our colleagues at UNC, we use modified Leukosorb strips to collect biomarkers of inflammation present at the nasal mucosal surface[1]. We then quantified ten cytokine proteins from each sample using the V-Plex Proinflammatory Panel 1 (human) kit (Meso-Scale Discovery).

To what extent do comprehensive versus weaker smoking restriction laws affect second-hand smoke (SHS) exposure and public health?

The American Lung Association published a map grouping states by the strength of their smokefree air laws and state that 22 states still lack comprehensive laws to sufficiently protect the public from passive exposure to environmental tobacco smoke in public/occupational places (https://www.lung.org/policy-advocacy/tobacco/smokefree-environments/smokefree-air-laws). Given that no amount of SHS exposure is considered safe, there's concern that individuals in these states are at greater risk for SHS-related adverse health risks. For a detailed state-by-state breakdown of SHS-restrictions by location: https://www.lung.org/policy-advocacy/tobacco/slati/appendix-b

Can you go into more detail about what information SDNN provides that SDANN and rMSSD do not?

In simple terms, HRV encompasses how heartbeat duration varies (or changes) over a range of time scales. Changes in HRV are normal and represent an important homeostatic mechanism for maintaining physiological equilibrium when cardiovascular demands shift. Within the umbrella of HRV parameters, variance can be calculated several different ways:

- Short-term—or instantaneous—HRV (rMSSD) reflects beat-to-beat variation between adjacent heartbeats. This parameter is most highly associated with parasympathetic, or vagal, regulation of heart rate.

- Intermediate HRV measures (e.g., SDANN) can be calculated by looking at the range of variation over somewhat longer periods (on the scale of minutes). This provides information on the balance between parasympathetic and sympathetic control of the autonomic nervous system's cardiac regulation.
- Overall HRV (SDNN) evaluates heartbeat variation over longer periods of time (hours to days). Overall HRV is not only reflective of cardiac autonomic regulation, but also is influenced by circadian rhythm, age, activity level, hormones, and disease.

Reduced HRV is associated with myriad pathologies, including depression, diabetes, heart failure and hypertension. A prevailing clinical assumption of attenuated HRV is that autonomic imbalance (i.e. reduced vagal and/or increased sympathetic modulation) favors the cardiac instability that underlies associated pathological conditions[2,3]. However, emerging data suggest that the relationship between neural projections and cardiac (sino-nodal) responsiveness may not be truly linear; rather, the delicate balance controlling HRV appears to reflect a complex integration of both neural and non-neural mechanisms[2,4]. Notwithstanding the relative contributions of underlying mechanisms dictating regulation of HRV, attenuated HRV is still a reliable prognostic tool for identifying people at greater risk of cardiovascular morbidity and mortality in the clinic[5,6].

For the air quality data, given that you are in NYC with most of the population in multi-unit dwellings, have you assessed the neighbors' smoking habits? Have you looked for thirdhand smoke residue?

This is an important question, but a logistically challenging one to obtain. First, we would likely only be able to measure nicotine/cotinine as a proxy for any thirdhand tobacco residues as it is the most economical/least difficult way to confirm the presence of tobacco emissions. However, it would not provide any information about what specific products were used, nor could we determine anything about the temporality of those residues. Second, we assumed that any second-hand residues in the homes related to residential tobacco use would exceed any meaningful contribution of thirdhand exposures originating from outside of the home, so we chose to limit our analysis to that inside the home itself. Lastly, we have no reason to believe that thirdhand tobacco residues are higher in multi-unit dwellings where recruited tobacco users live compared to our non-smoking participants. Therefore, any potential effect of thirdhand exposures should be captured in the biological signals of our non-smoking "controls".

Considering the fact that vaping increases nasal inflammation (high levels of cytokines) compared to cigarettes, has anyone found any association between sinus or nasal polyposis and vaping?

No studies are published characterizing the nasal health of e-cigarette vapers or potential mechanisms through which vaping may lead to—or worsen—nasal health explicitly. However, a couple case studies have implicated e-cigarettes as the probable cause of nasal polyps and damage in vaping patients[7,8]. And more recently, a potential nicotine-dependent attenuation of nasal inspiratory flow was detected in a cohort of vapers with no nasal structural irregularities[9].

Are you aware of any correlation between vaping and allergy?

A growing number of studies are examining how vaping changes allergy response and risk, and the results appear to be dependent on the asthmatic and smoking status of the population. For example, in a cohort of asthmatic smokers, vaping acutely impaired pulmonary function and increased inflammation[10]. By contrast, another study found that a majority of former smokers who had completely switched to vaping did not report a worsening of their asthmatic symptoms[11]. However, among tobacco-naïve children and adolescents, studies have consistently identified an association between vaping and elevated risk of asthma, cough, and bronchitis[12-14].

What is the issue with menthol flavor? Is this a radially based issue?

Potentially. We know that vapers overwhelmingly prefer flavored e-liquids—and menthol has been shown to facilitate initiation of vaping. In fact, menthol was the most popular e-cigarette flavor used by adults in 2015[15]. Menthol can also mask the bitter taste of nicotine, so people that vape menthol-flavored e-cigarettes have been found to tolerate higher concentrations of nicotine in their e-liquids[16]. Not only can menthol disrupt cellular processes respiratory tissues[17], but a recent study found that a majority of menthol-flavored e-liquids (indicated by "Kool/Cool" or "Ice" in the name) contained synthetic cooling agents in concentrations greater than established safety thresholds[18]. Currently, menthol-flavored e-cigarettes are not included in the FDA's flavor ban. However, a 2018 study found that roughly 1/3 of high school students cited flavored e-cigarettes (including mint and menthol) as their reason for vaping[19], which suggests that the popularity of menthol-flavored e-cigarettes may rise as other flavor options are restricted.

Could you comment on risks of non-nicotine vaping?

Several studies have found evidence of molecular and cellular respiratory toxicity associated with nicotine-free e-liquids and aerosols[20,21]. It is worth noting that it is now possible to vape a growing number of nicotine-free materials, including cannabis extracts (CBD and/or THC), essential oils, and even caffeine. In the absence of regulatory oversight, product transparency often suffers. As a result, we cannot confidently know what is in these products beyond the advertised "active" ingredient(s), which complicates any evaluation of potential risk to consumers. For example, the EVALI (E-Cigarette, or Vaping-Product, Use Associated Lung Injury) outbreak of 2019 was linked to Vitamin E Acetate in unregulated products (counterfeit/cannabis e-liquids).

What about additives to the vaping mixture?

Most chemicals in e-liquids are there to enhance flavor. While the FDA has given these flavoring chemicals—or flavorants—a GRAS (generally regarded as safe) rating, this designation refers only to their safety when *ingested*. Because route of exposure is a strong driver of subsequent toxicity (based on tissue-specific susceptibilities, delivered dose and metabolism), it's difficult to know how inhaling these chemicals will affect health outcomes. However, several studies have found that common e-liquid carrier solvents (propylene glycol and vegetable glycerin)[22] and

flavorants (cinnamaldehyde, menthol, vanillin)[23,24] can cause respiratory irritation. Moreover, in a study that evaluated more than 120 different e-liquids, 100% of all samples contained at least one chemical that was known to cause "some level" of danger/risk[25].

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