Public Health Aspects of Vaping Toxicology

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Determinants of toxicity related to vaping

Ingredients

- Delivery solvents (e.g., propylene glycol, PG; vegetable glycerin VG)
- Medium chain triglycerides
- Flavors*
- Other

Coil age, condition, and temperature

Delivery system design

Exposure route and concentration:

- Not everything safe for ingestion or inhalation is safe when heated or burned

* In one study, only 1% of users reported preference for unflavored vape products (Dawkins et al., 2013)

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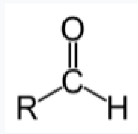
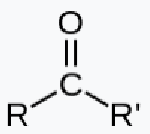
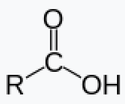
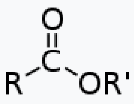
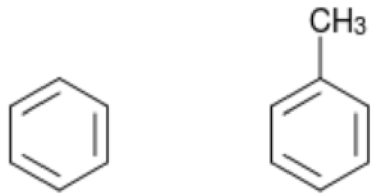
Potentially toxic agents in vape aerosol

- Particulate matter
- Carbonyls and volatile organic compounds (e.g., acrolein, diacetyl, formaldehyde, benzene, toluene, styrene)
- Furans (e.g., furfural, hydroxymethylfurfural)
- Reactive oxygen species (ROS) and free radicals
- Trace elements (e.g., arsenic, cadmium, chromium)
- Terpenes (e.g., squalene, linalool, citral, dipentene)
- Other

Carbonyls and VOCs

Aldehyde	Ketone	Carboxylic acid	Carboxylate Ester
			
RCHO	RCOR'	RCOOH	RCOOR'



benzene toluene

- Factors that increase carbonyl generation
  - Higher operating power
  - Higher device temperature
  - Higher heating coil resistance (sub-ohm vs supra-ohm)
  - Dry puff operation (insufficient amount of e-liquid) (sometimes more than conventional cigarettes)
  - Inadequate wick saturation
  - Top vs bottom coil atomizers
  - Horizontal vs vertical coils

Carbonyls and VOCs can be harmful to many body systems (e.g., heart, lung, leukemia)

Carbonyl generation varies by temperature and solvent

Carbonyls generated at 270 and 318°C from different e-liquids. μg/mg-liquid

E-liquid	Carbonyls generated at 270°C		
	Formaldehyde	Acetaldehyde	Acrolein
PG	0.29 ± 0.11	0.30 ± 0.10	ND
GL	7.97 ± 1.08	1.70 ± 1.06	0.05 ± 0.02
PG/GL (1:1)	0.96 ± 0.35	0.30 ± 0.12	0.03 ± 0.02
E-liquid #1	0.97 ± 0.87	0.20 ± 0.15	0.05 ± 0.04
E-liquid #2	0.73 ± 0.28	0.22 ± 0.09	0.02 ± 0.00
	Carbonyls generated at 318°C		
PG	2.03 ± 0.80	2.35 ± 0.87	ND
GL	21.1 ± 3.80	2.4 ± 0.99	0.8 ± 0.5
PG/GL (1:1)	5.47 ± 0.72	1.76 ± 0.52	0.41 ± 0.05
E-liquid #1	5.99 ± 5.46	0.97 ± 0.87	0.05 ± 0.04
E-liquid #2	5.22 ± 4.35	1.37 ± 0.84	0.26 ± 0.13

Wang et al. (2017) A Device-Independent Evaluation of Carbonyl Emissions from Heated Electronic Cigarette Solvents. PLoS ONE 12(1)

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Cannabis dabbing and vaping can produce carbonyls and VOCs

Measured gas-phase components of dabbing emissions of THC and 9:1 THC+terpene mix and vaping emissions of the latter*

- Calculated cancer and noncancer risk of exposure to gas phase components

- All experiments generated carbonyls and VOCs
  - Terpenes generated more gas-phase components than THC
  - Gas phase component concentrations increased with voltage
- Authors' calculated health risks were not of public health significance
- Additional components, experimental conditions, device types might produce different results
- Authors did not report particle phase emissions
  - Jacques et al. found very high particle concentrations associated with dabbing (400-700 µg/m^3) and vaping THC (200-300 µg/m^3)

*Meehan-Atrash et al., 2019

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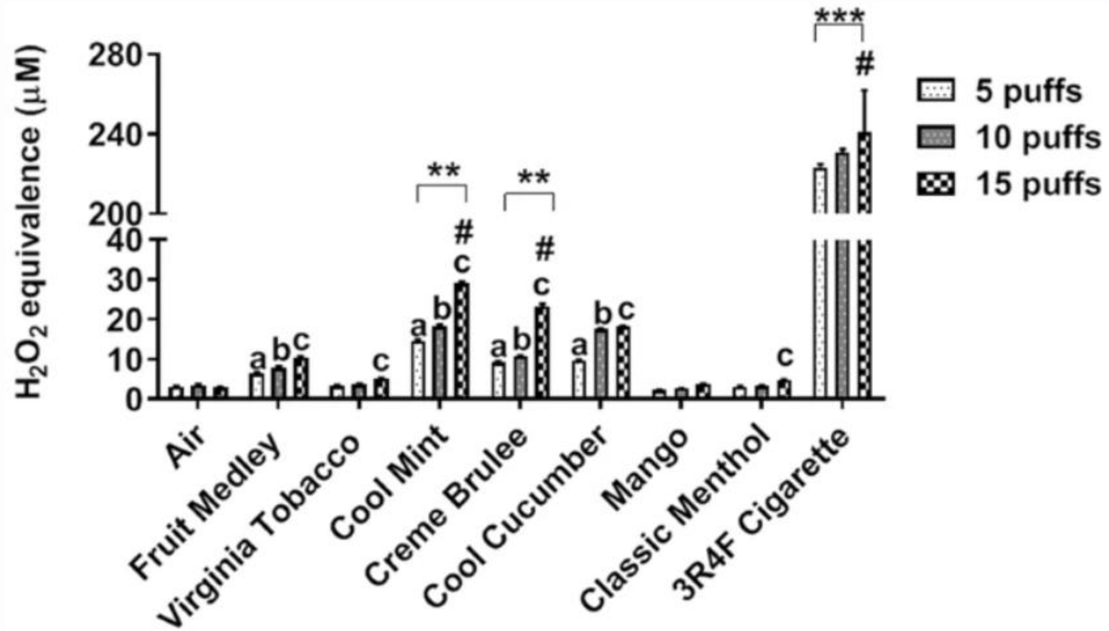
ROS and free radical formation

Factors that favor increase in oxidative potential

- Higher coil temperature and device power
- E-liquid composition
  - Increasing glycerol and glycerol:PG
  - Flavor type



Muthumalage et al. *Sci Rep* **9,** 19035 (2019)

Reactive oxygen species can damage cells and membranes in the body and they are implicated in contributing to disease

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Flavor type modulates inflammation and lipid peroxidation potential of e-liquid aerosols

- ROS react with cell lipids resulting in peroxidation, damaging cells
- Flavor type effect on lipid peroxidation (Bitzer et al. 2018)
  - Increased: δ-tetradecalactone, linalool, dipentene, piperonal, ethyl maltol, citral, γ-decalactone
  - Decreased: ethyl vanillin

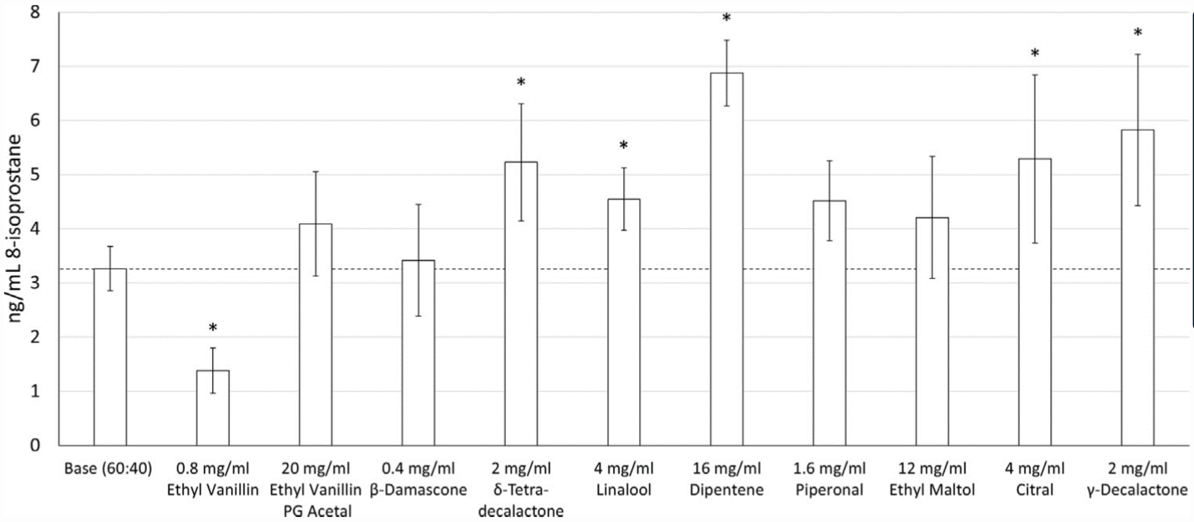
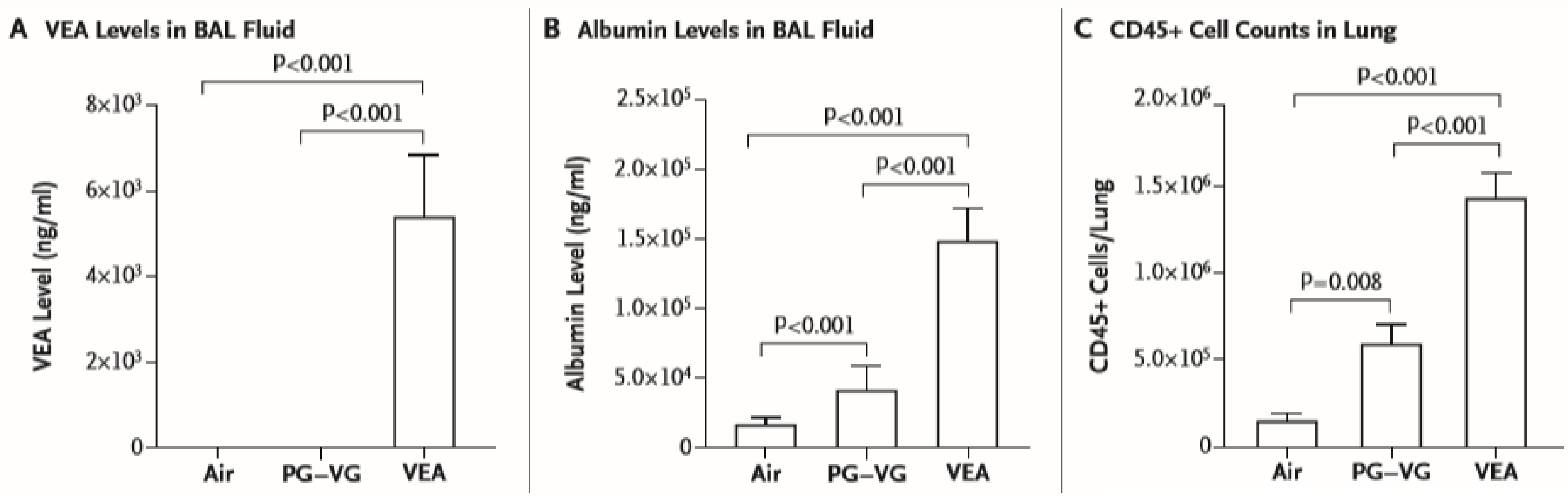


Figure adapted from Bitzer et al., 2018

Some flavor additives showed potential for increased proinflammatory mediator release in mice exposed to aerosol (Lerner et al., 2015)

Select animal studies

1. Mouse inhalation exposure to aerosol from tobacco flavor e-cigarettes (e-cigs) for 3 days (Lerner et al., 2015)
   - increased lung proinflammatory response (interleukins)
   - decreased antiinflammation indicators (glutathione)
2. Mouse inhalation exposure to air, PG:VG mix, or Vitamin E Acetate (VEA) aerosols (Bhat et al., 2020)
   - Comparable doses
   - Lipid-laden macrophages
   - Epithelial damage



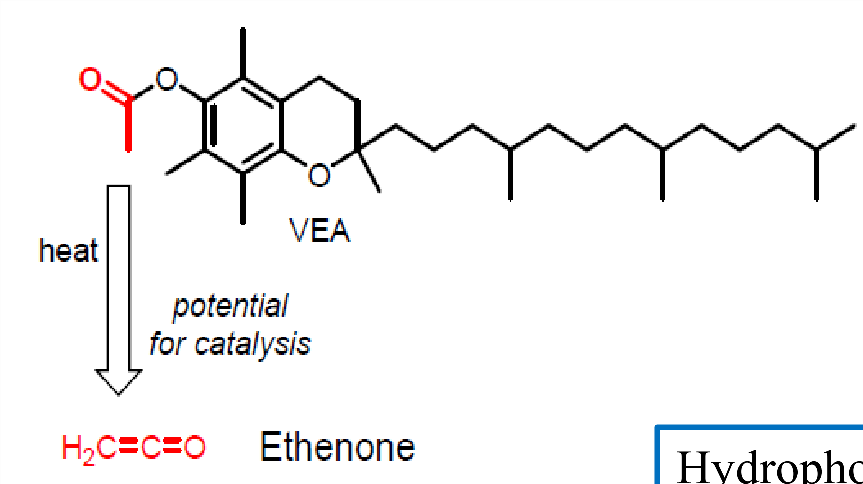
VEA accumulation in lung | Lung epithelial damage | White blood cell infiltration

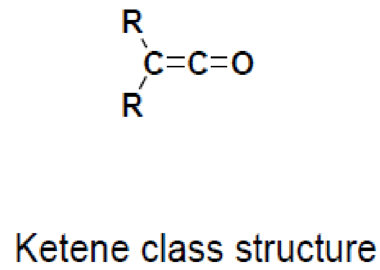
Inhaled oils

- Vitamin E acetate (VEA), squalene (a terpene), and other oils have been found in e-liquids associated with morbidity and mortality in vapers
- Inhalation of oil mists has been associated with lipoid pneumonia, chemical pneumonitis, and pulmonary fibrosis
  - Evidence mostly from occupational settings

Unknown and untested additives can have acute and visible health effects

- Clinical case studies pre-VALI indicate severe pulmonary reactions in some e-cig users (Viswam et al., 2018; Sommerfeld et al., 2018; Khan et al., 2018)





Attfield et al., 2020

Hydrophobic conditions in the presence of a metal or ceramic catalyst under heat (vaping pen)

Ethenone as an example of ketenes

- Highly reactive
- Can be highly toxic following relatively short exposures
  - Acute pulmonary congestion and alveolar edema, respiratory effects, lethargy, death, (monkeys, guinea pigs, rats, mice) occurred at 12+ ppm*
  - Rapidly progressing acute respiratory distress syndrome, hypoxic respiratory failure and diffuse ground glass opacities in lung of male worker exposed to ethenone and crotonaldehyde mixture (Huang et al., 2015)
- Similar effects and mode of action to phosgene (chemical warfare agent)*
  - Damages proteins and other molecules in the lung
  - Disrupts blood-air membranes affecting breathing

* Reviewed in NRC, 2014. AEGLs for selected airborne chemicals: Vol. 16

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Sample health benchmark comparisons

Vape aerosol component	Detection in aerosol	Public health exposure limit	Occupational exposure limit	Sources
Propylene Glycol	700 ppb	9 ppb (intermediate)	10,000 ppb 8-h TWA	Getts et al., 2014; ATSDR; AIHA
Formaldehyde	510 ppb	40 ppb (acute) 8 ppb (chronic)	16 ppb 8-h TWA	Klager et al., 2017; ATSDR; NIOSH
Diacetyl	239 µg/e-cig		18 $\mu g/m^3$ 8-hour TWA; 88 $\mu g/m^3$ STEL 15 min	Allen et al., 2016; NIOSH
Cadmium	140 $\mu g/m^3$	0.03 $\mu g/m^3$ (acute) 0.01 $\mu g/m^3$ (chronic)	5 $\mu g/m^3$	Beauval et al., 2017; ATSDR; OSHA

*STEL = Short Term Exposure Limit; TWA = Time Weighted Average

Public health perspective

- Benefits as a conventional cigarette quitting aid unclear and large numbers of nonsmokers are adopting e-cigs.
- Conventional cigarettes generate many more toxicants than e-cigs, but some components are at comparable concentrations in e-cigs.
- Humans do not always sense harmful substances in air, food, or water. Some are odorless and others are toxic below or above odor threshold.
- Need for standardization of devices and e-liquids to facilitate meaningful exposure and health studies
  - Rapidly changing industry and technology might make current scientific findings irrelevant with time
  - Adequate information on toxicity of additives is unavailable.
- Need for engineering controls for devices and e-liquids to minimize generation of toxicants
  - coil location, wick material, resistance (sub-ohm), PE/VG ratio, additives, coil make-up and quality, etc.
- Some e-liquid ingredients might be considered as safe in food but not to be inhaled or heated and inhaled.

Oregon's VALI investigation

- In Oregon, 23 cases of vaping-associated lung injury were reported between June and December 2019
- 2 cases were fatal
- Oregon cases involved cannabis-only vaping, nicotine-only vaping, and a combination of both
  - 14 people (61%) reported vaping a cannabis product
  - 16 people (70%) reported vaping a nicotine product
  - 14 people (61%) reported vaping a flavored product
  - Both people who died reported vaping a flavored THC product and did not report vaping nicotine products

Oregon’s VALI investigation

- Products tested by the US FDA Forensic Chemistry Center and by CDC
- FDA tested liquids of products from 3 Oregon cases
  - Cannabinoids, terpenes, squalene, chloroform, cobalt, zinc found in cannabis products
  - PG, glycerol, nicotine, triethyl citrate (used to “emulsify” aerosol) found in nicotine product
- CDC tested aerosols from 7 cannabis and 4 nicotine vaping products from Oregon cases
  - Squalene in all the cannabis product aerosols
  - PG, glycerol, nicotine found in all the nicotine product aerosols
  - Menthol in several nicotine product aerosols

- PG and glycerol used in large number of nicotine e-cigarette products to date
- Squalene is potentially concerning, and it was found in one of our liquids tested by FDA previously
- Vitamin E acetate was not found in any of the products used by people with VALI in Oregon

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