

# Respiratory effects of e-cigarettes

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# Contents

- E-cigarettes (electronic cigarettes) vs. heated tobacco products
- Device
  - Battery: inhalation injury
  - Atomizer: silica and metal
  - E-liquid: VG, PG, flavoring components
- Spirometry
- Host defense
- E-cigarette, or vaping, product use-associated lung injury (EVALI)
- Challenges in e-cigarette study

# E-cigarettes vs. heated tobacco products

- E-cigarettes (2003)

- (액상형) 전자담배
- 액체 카트리지를 가열, 흡입
- 100~250°C

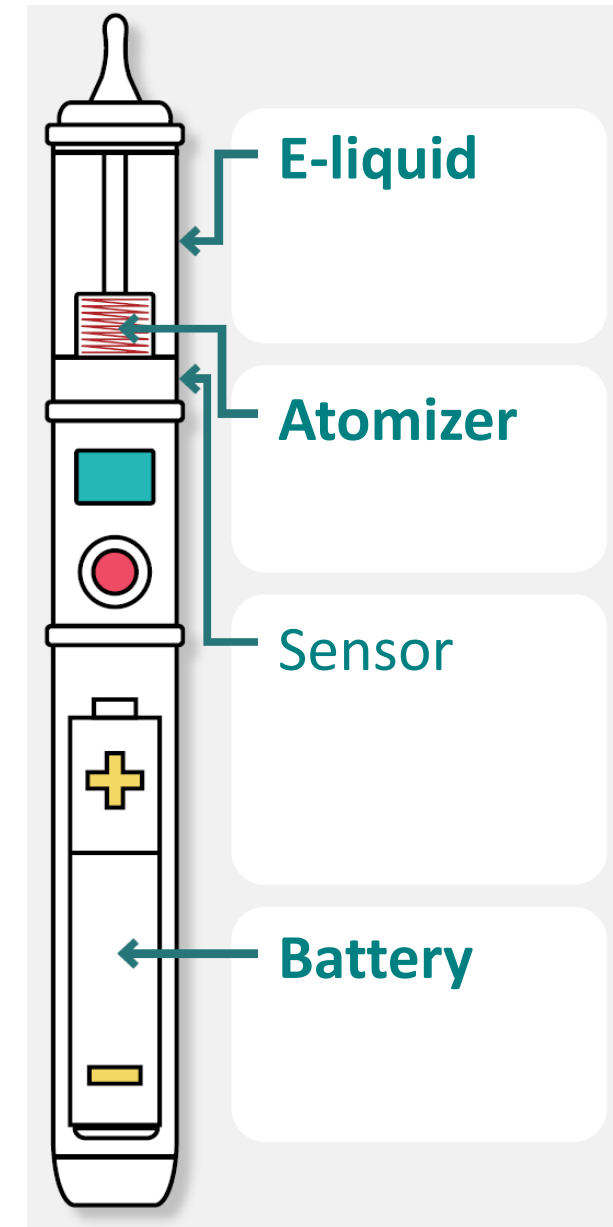
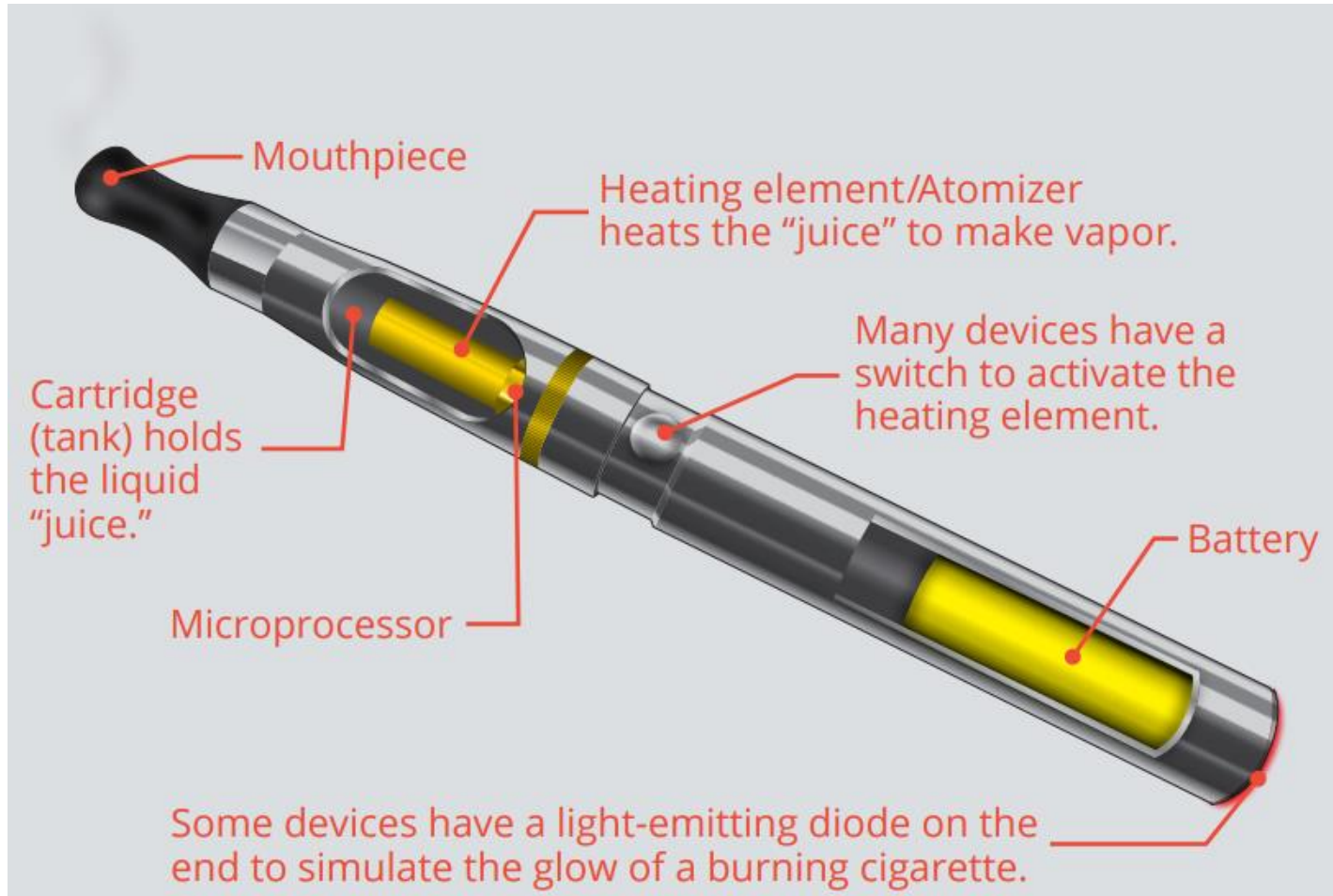


- Heated tobacco products (2014)

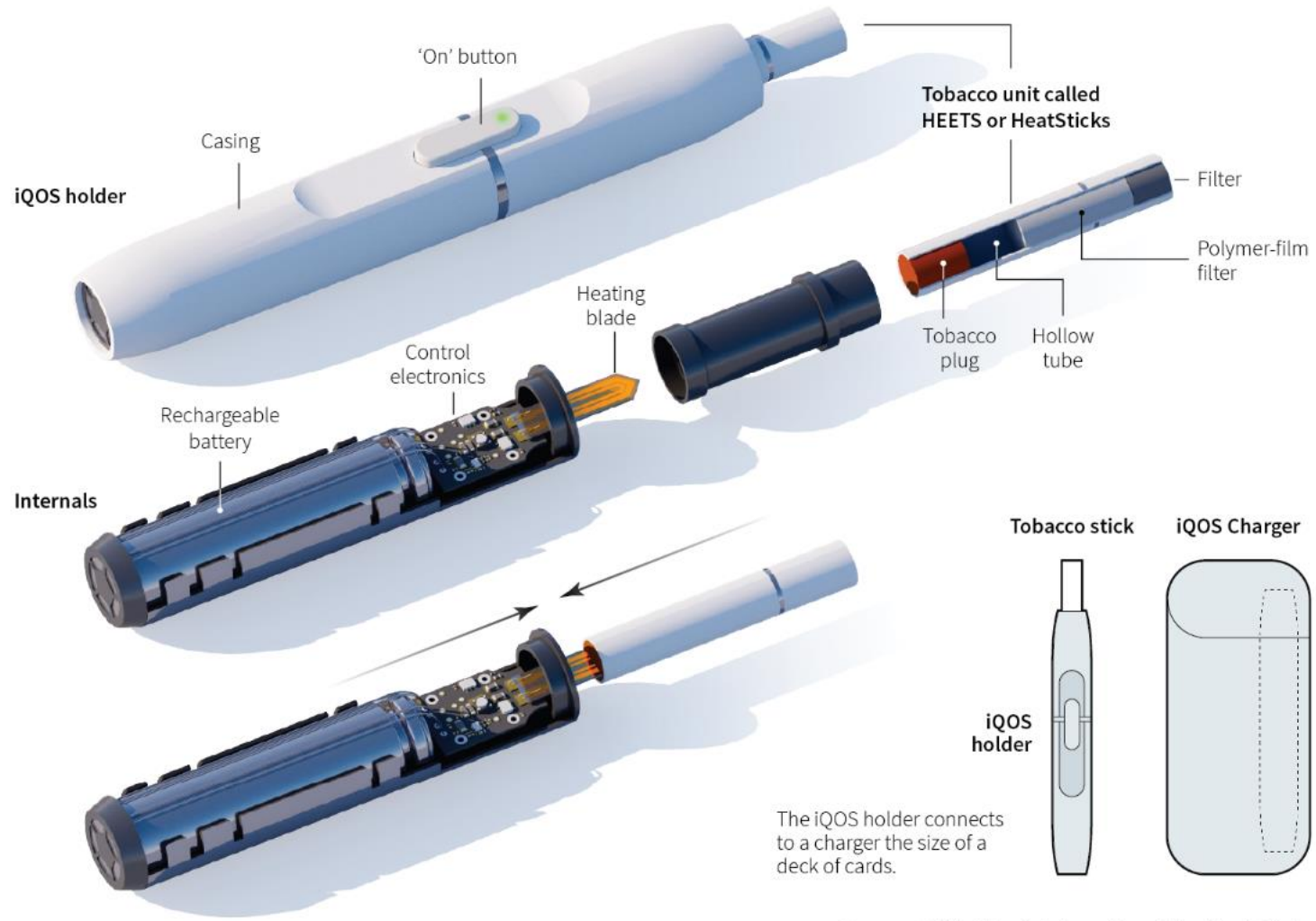
- 궤련형 전자담배, 가열담배, 찢 담배
- 궤련스틱을 가열, 흡입
- 300~350°C



# E-cigarettes



# Heated tobacco products

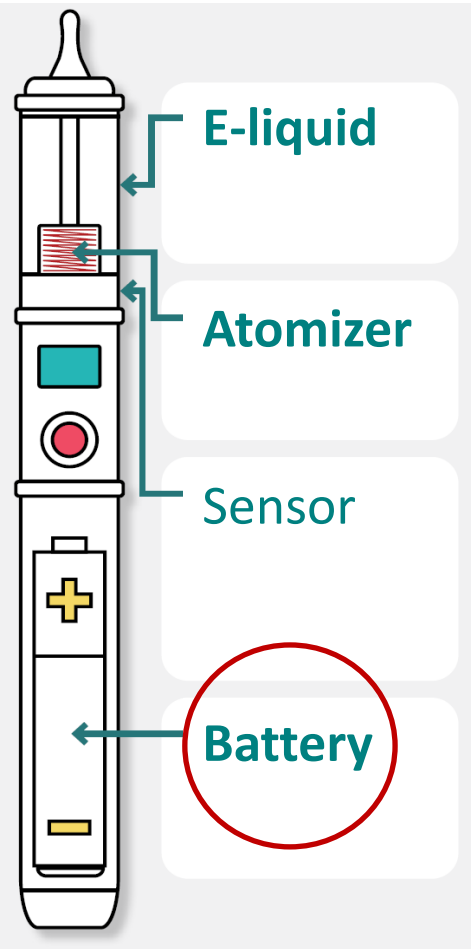


Sources: Philip Morris International; TechInsights Inc

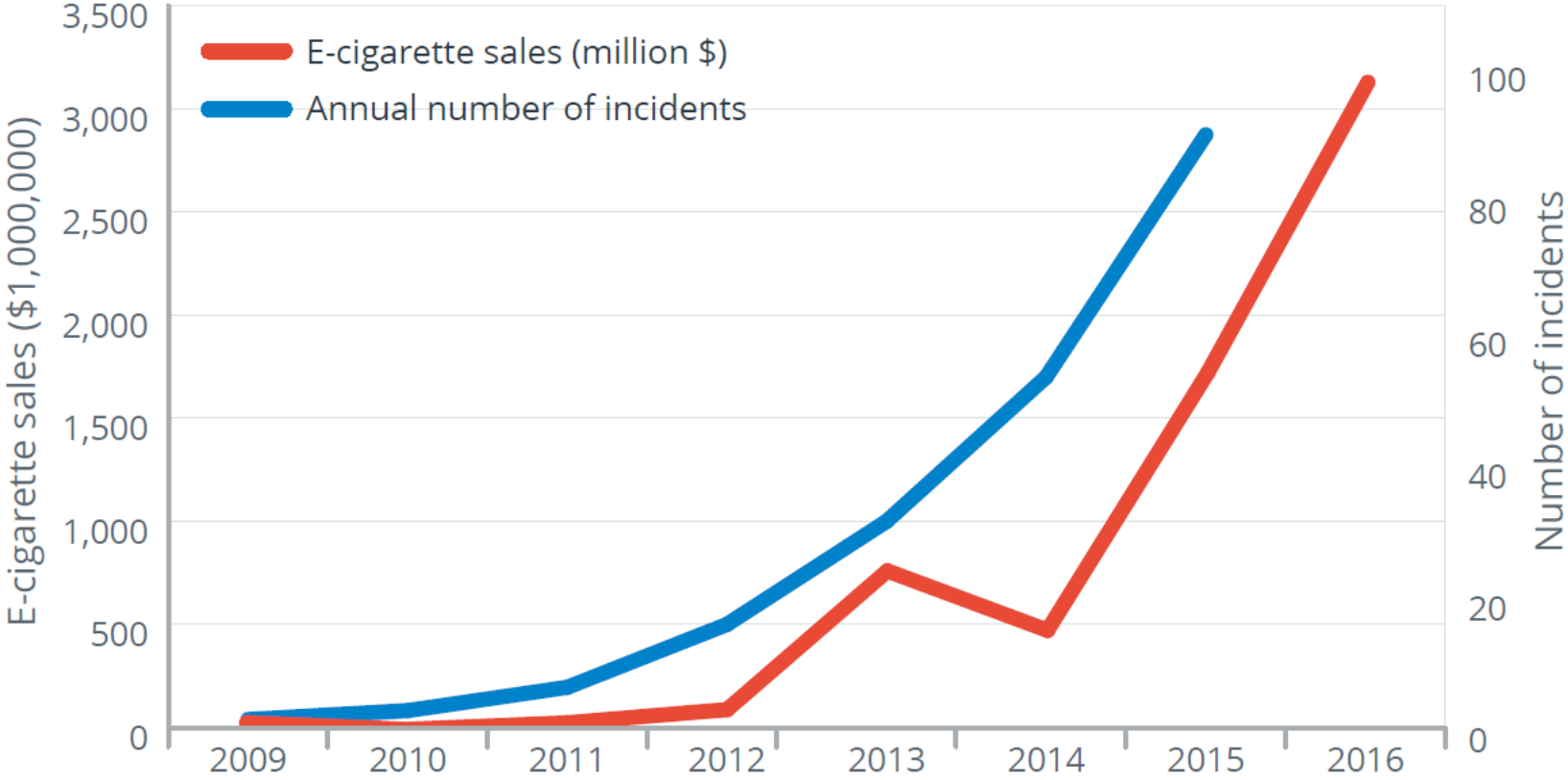
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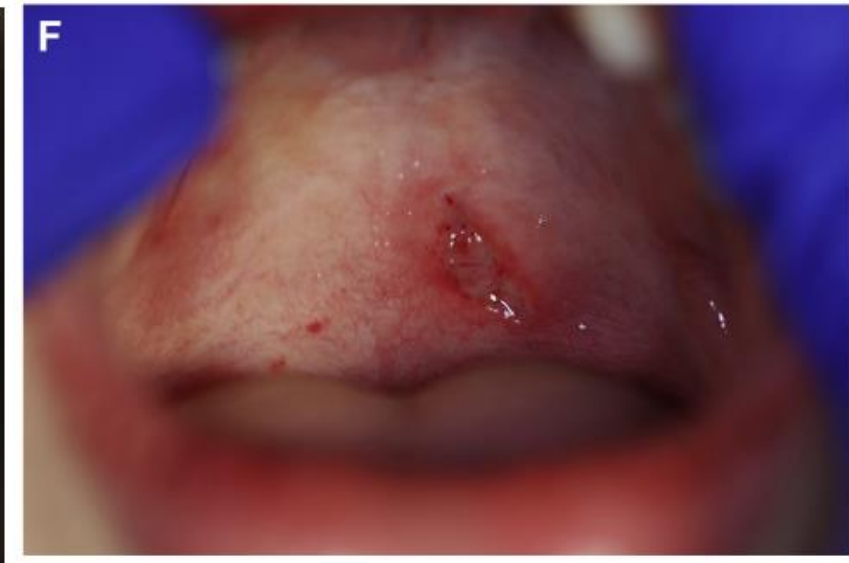
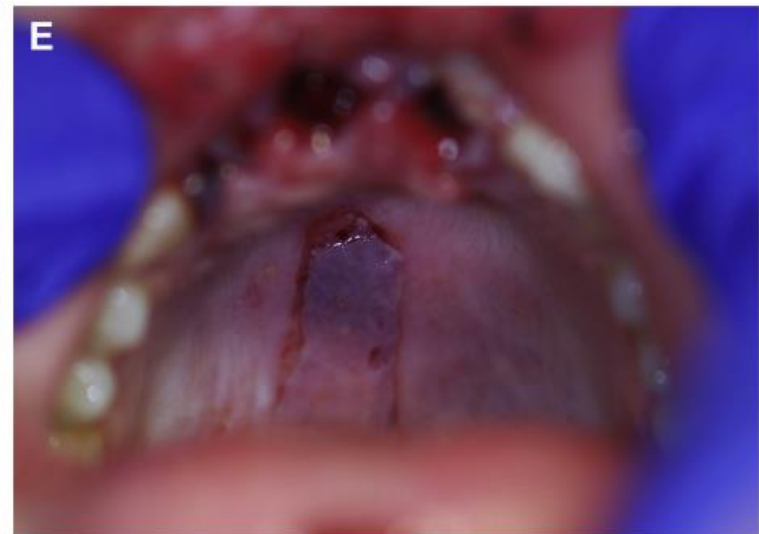
# E-cigarette battery and explosions in US



**Figure 8. E-Cigarette fires and explosions compared to sales.**



# Injuries from e-cigarette explosions



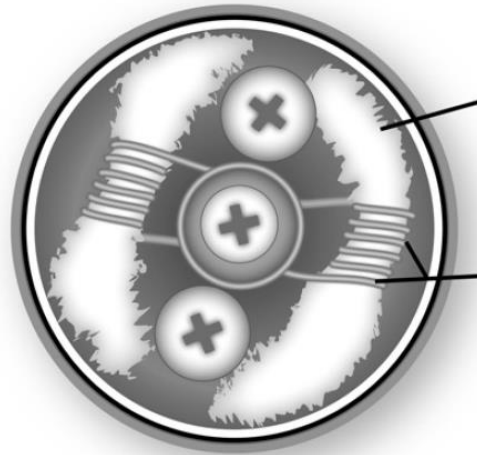
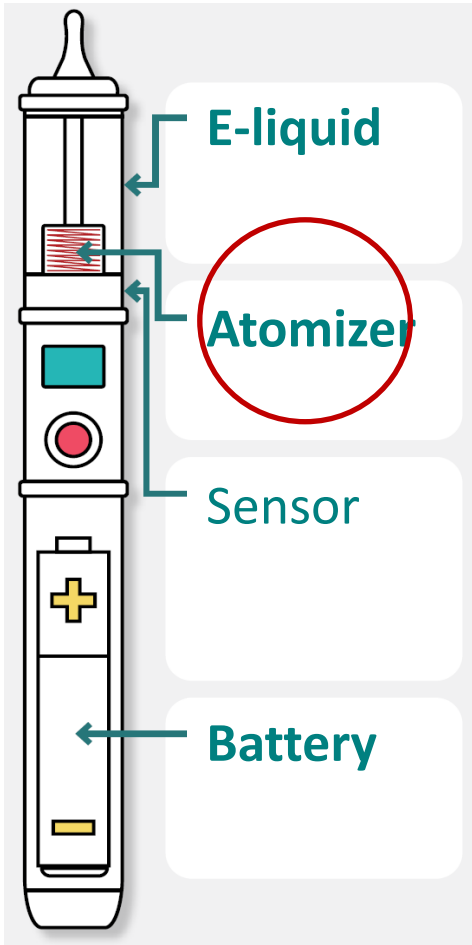
# Inhalation injury

**Table 2.** Proposed numerical classification of e-cigarette burns by mechanism

Direct vs Indirect	Injury Type	Definition	Cases (n = 26)	Education Prevention
Direct injury	Type 1	Hand injury	7	Potential for injury Fire resistant container to carry
	Type 2	Face injury	8	Preventing explosion
	Type 3	Waist/Groin injury	11	Hazards storing device in pockets
	Type 5a (inhalation)	Inhalation injury from using device	2	Potential for injury
Indirect injury	Type 4	House fire injury	7	Correct charger Avoiding charging around combustible material Using fire extinguishers
	Type 5b (inhalation)	Inhalation injury from fire started by the device	4	Same as type 4 Home sprinklers Fire detectors Home escape plans

Direct injury: from the e-cigarette device; indirect injury: from the e-cigarette device (fire, smoke).

# E-cigarette atomizer



**Wick:**  
cotton, silica, ceramic

**Coil:**  
NiChrome, kanthal, etc.

Material	Known Risks
Silica	Silicosis
Nickel	Carcinogenesis, lung injury, immune suppression
Chromium	Carcinogenesis, lung injury, immune suppression, reproductive toxicity

# E-cigarettes as a source of toxic metals

- Cartomizer liquid of five brands

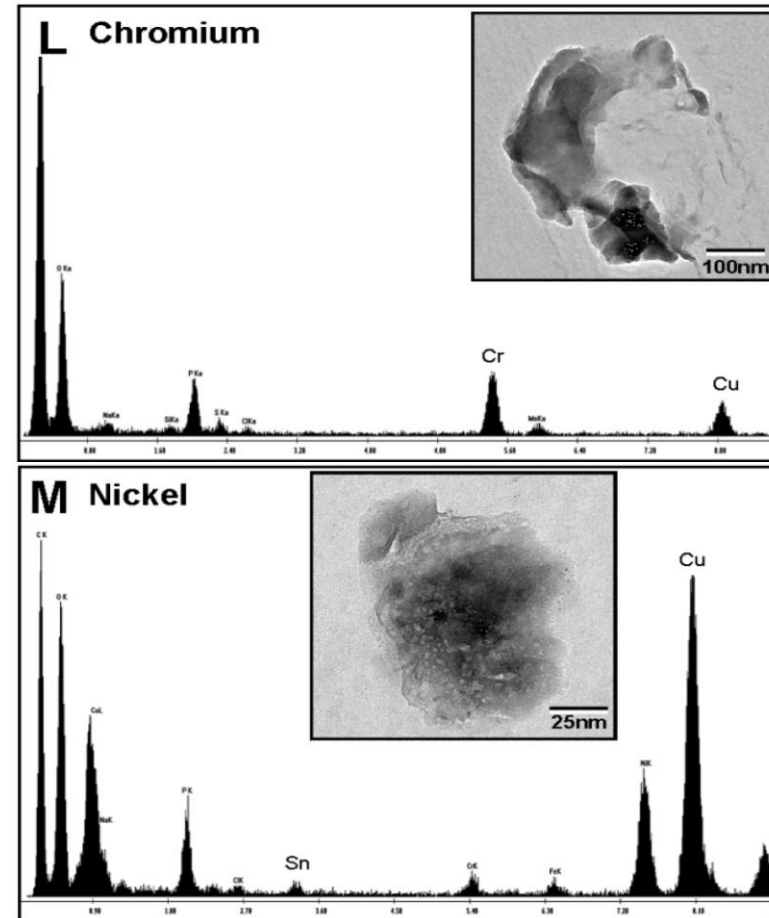
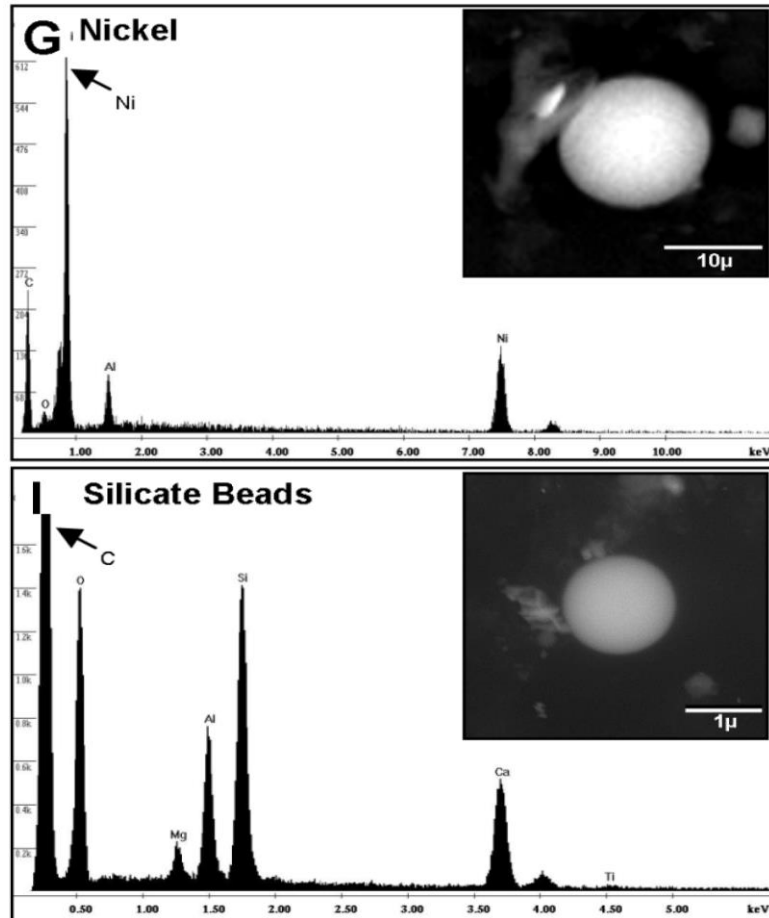
Metal concentrations in five commercial brands of cig-a-like e-cigarettes ( $\mu\text{g/L}$ ).

Brand	N	Cadmium			Chromium			Lead			Manganese			Nickel		
		Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Brand A ( $\mu\text{g/L}$ )	10	205 (318)	12.40	322–755	2110 (5220)	213	98.6– 16,900	1970 (1450)	1630	500–4870	6910 (12,200)	918	541– 31,500	22,600 (24,400)	15,400	2040– 72,700
Brand B ( $\mu\text{g/L}$ )	10	1.17 (1.09)	0.796	0.470–4.11	788 (284)	726	306– 1130	58.1 (79.4)	18.5	3.53–218	670 (283)	627	247– 1200	13,400 (4540)	13,100	4560– 20,500
Brand C ( $\mu\text{g/L}$ )	8	1.57 (1.30)	1.17	0.157–4.18	231 (71.6)	205	162– 381	5.83 (1.80)	5.15	4.50–9.82	200 (33.9)	187	154– 258	463 (132)	491	316– 652
Brand D ( $\mu\text{g/L}$ )	10	0.982 (0.802)	0.502	0.249–2.23	76.1 (11.0)	75.6	60.2– 92.7	4.89 (0.893)	4.98	3.17–5.89	41.50 (13.9)	44.4	11.8– 65.5	58.7 (22.4)	58.1	13.7– 85.4
Brand E ( $\mu\text{g/L}$ )	10	0.415 (0.38)	0.204	0.137–1.23	53.9 (6.95)	56.7	41.5– 60.79	93.4 (80.5)	69.3	7.94–233	28.7 (9.79)	26.1	15.5– 48.23	114 (49.3)	134	39.3– 175
LOD ( $\mu\text{g/L}$ ) <sup>*</sup>			0.04			0.1			0.02			0.08			0.1	
Intra-laboratory ICC	48×2		0.965			0.999			0.997			1.000			1.000	
Inter-laboratory ICC	4×2		0.997			0.993			0.997			0.988			0.988	

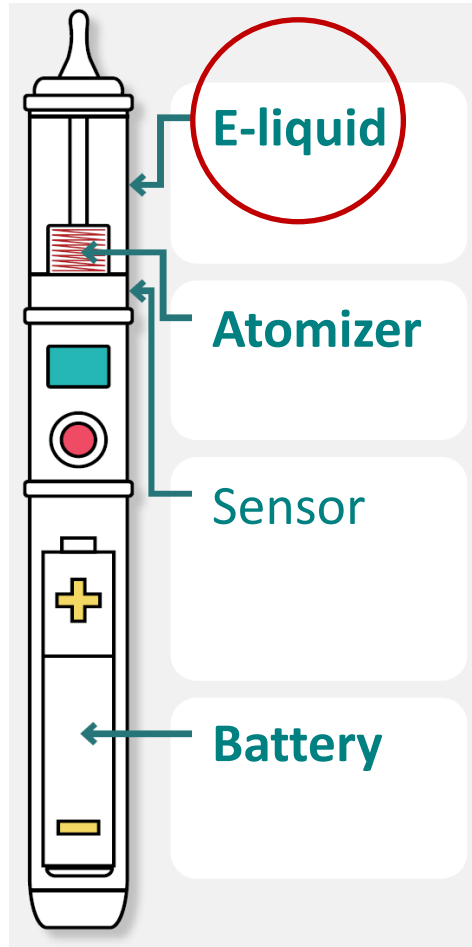
ICC: intraclass correlation coefficient. The intra-laboratory ICC was calculated from duplicate aliquots from the same e-cigarette liquid sample. Mean concentration was calculated by taking the mean of 2 duplicate samples from the same e-cigarette. The inter-laboratory ICC was calculated from duplicate analyses conducted in a subset of 4 e-cigarette liquid samples conducted at Graz University (Graz, Austria). \*LOD are calculated to a 1:20 dilution factor.

# Metal and silicate particles in e-cigarette aerosol

- Analyze cartomizer aerosols using electron microscopy and spectroscopy



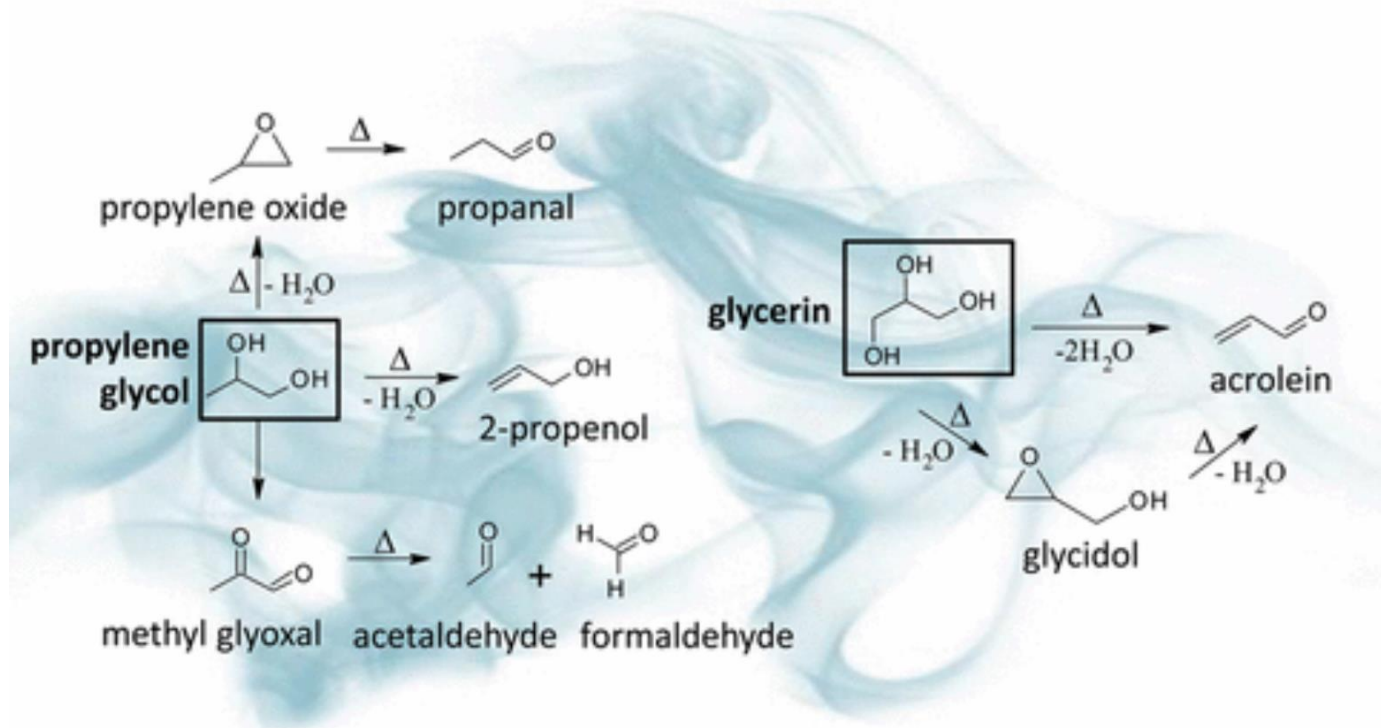
# E-liquid



- Nicotine
- Vegetable glycerin (VG)
- Propylene glycerol (PG)
- Flavoring agents

# Harmful chemicals from e-cigarettes

- Three different refill e-liquids
- E-liquid: PG, glycerin, nicotine, ethanol, acetol, and propylene oxide
- Aerosol: 31 compounds, including nicotine, formaldehyde, acetaldehyde, glycidol, acrolein, acetol, and diacetyl



# Safety evaluation of PG aerosol

- Inhalation exposure to aerosolized PG for 28-days (rat)

**Table 4**

Incidence of respiratory tract histopathology findings in male and female rats in the low, mid-1, mid-2 and high exposure groups following inhalation exposure to CAG-PG aerosol for 28-days.

Tissue	Exposure group									
	Males					Females				
Histopathology	Air	Low	Mid-1	Mid-2	High	Air	Low	Mid-1	Mid-2	High
Number evaluated=	10	10	10	10	10	10	10	10	10	10
Larynx										
Squamous										
Metaplasia	0	0	0	4	8 <sup>***</sup>	0	0	0	2	6 <sup>*</sup>
Hyperplasia	0	0	0	0	0	0	0	0	1	0
Trachea										
No anomaly	0	0	0	0	0	0	0	0	0	0
Lung										
Inflammatory cell										
Infiltrate										
Minimal	0	2	1	2	4	1	0	5	3	1
Mild	8	5	4	3	2 <sup>*</sup>	2	2	0	1	2
Moderate	0	1	2	2	1	0	1	0	0	0
Congestion/hemorrhage	4	1	1	1	2	0	0	0	0	1

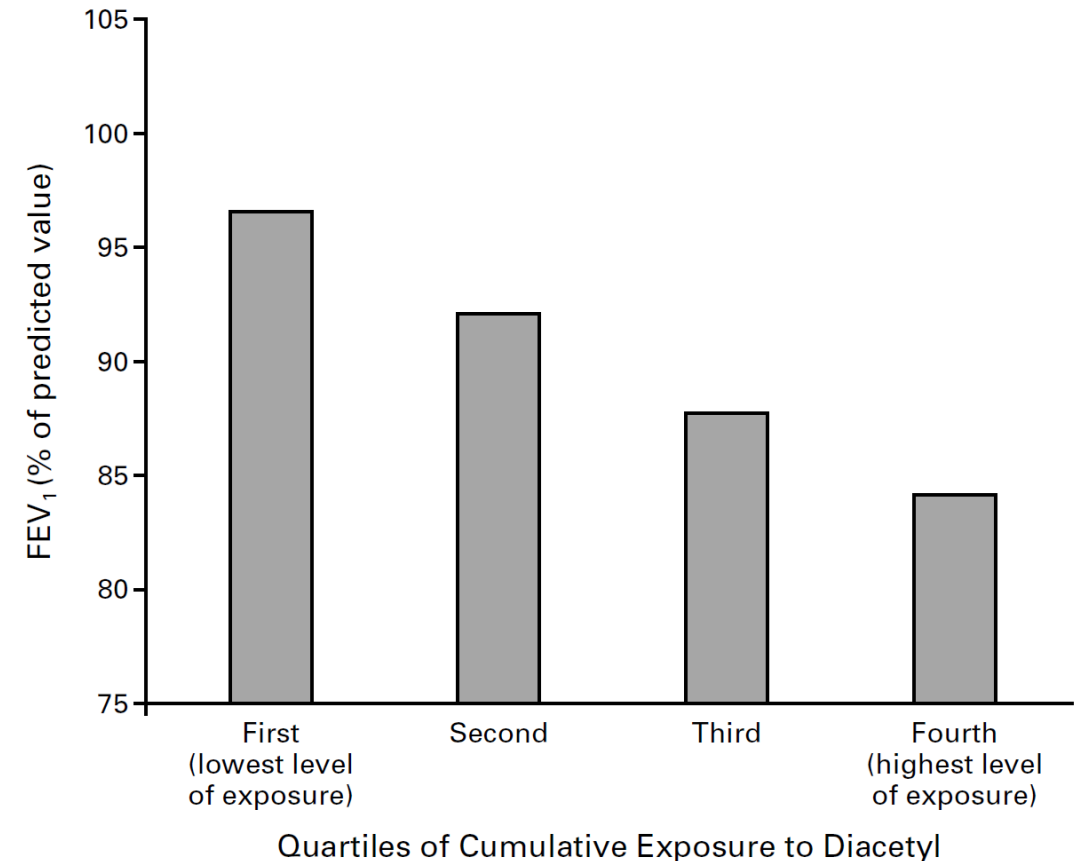
\* Statistically significant difference,  $p < 0.05$ .

\*\*\* Statistically significant difference,  $p < 0.001$ .

# Flavoring components – diacetyl

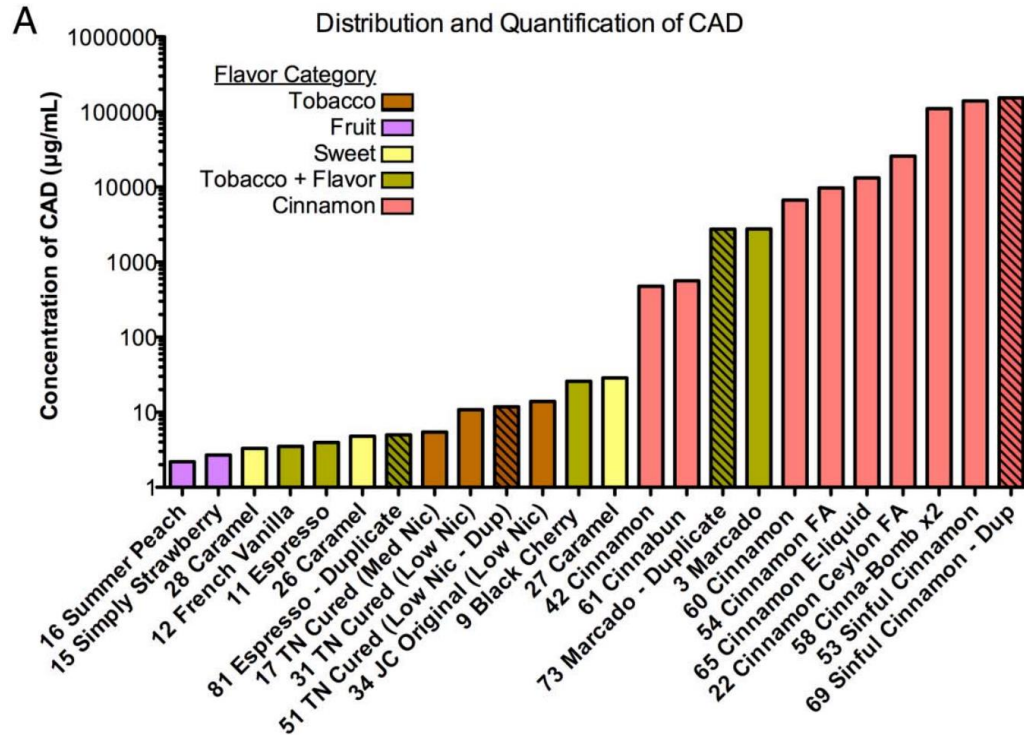
- Butter flavoring; 70% of sweet e-cigarettes
- In 2000, 8 persons formerly worked at a microwave-popcorn plant reported to have severe bronchiolitis obliterans
- 117 employees of the popcorn plant

WORK AREA	NO. OF SAMPLES	DIACETYL
		LEVEL
		ppm
Plain-popcorn packaging line, bag-printing areas, warehouse, offices, or outside	14	0.04 ( $\leq 0.25$ ) $\ddagger$
Quality control or maintenance	5	0.56 (0.33–0.89)
Microwave-popcorn packaging lines	22	1.88 (0.26–6.80)
Mixing room	12	32.27 (1.34–97.94)

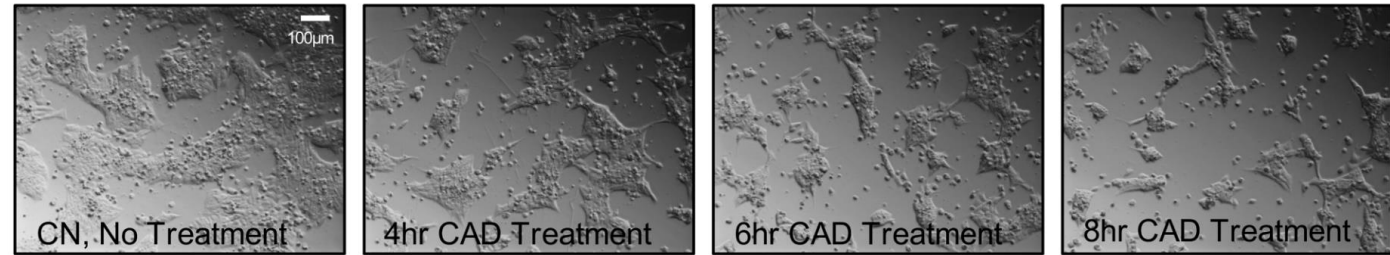


# Flavoring component – cinnamaldehyde

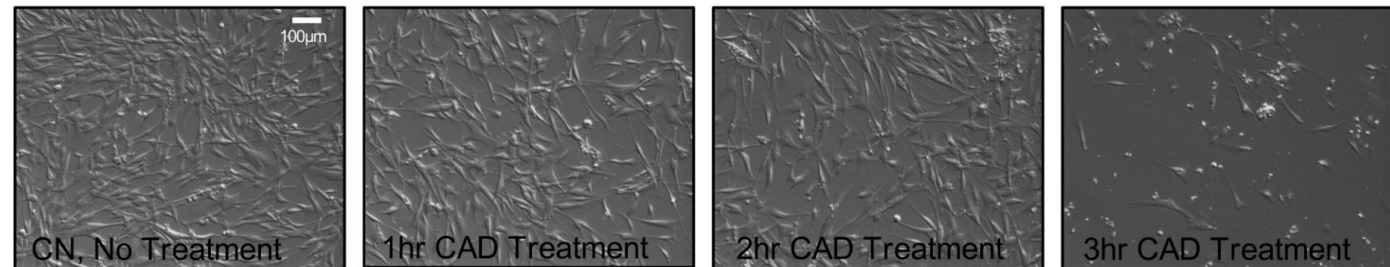
- 22 of the 39 e-cigarette refill fluids
- E-cigarette aerosol → solution → exposure → recovery



**A. hESC, T=48hr**



**B. hPF, T=48hr**



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# Short-term effects on PFT and FeNO

- 30 healthy smokers, effects of e-cigarette use for 5 minutes
- FeNO, spirometry, impulse oscillometry

Characteristics	Pre-Mean	Post-Mean	Mean Difference	95% CI of the Mean Difference, Lower - Upper	Pre vs Post P Value
Feno, ppb	13.02	10.89	22.14	2 3.53 to -0.74	.005
Flow resistance					
IOS Z5Hz, kPa/(L/s)	0.376	0.409	0.033	0.016 to 0.050	<.001
IOS R5Hz, kPa/(L/s)	0.367	0.397	0.031	0.014 to 0.048	.001
IOS R10Hz, kPa/(L/s)	0.325	0.353	0.029	0.013 to 0.045	.001
IOS R20Hz, kPa/(L/s)	0.299	0.329	0.030	0.010 to 0.050	.005

# Short-term effects on PFT and FeNO

- 30 healthy smokers, e-cigarette use for 5 min
- FeNO, spirometry, impulse oscillometry

**Table 3—Regression Analysis on the Effect of Using an e-Cigarette on FENO and Airway Flow Resistance (IOS), Controlling for the Participants' Baseline Measurements**

Variable	R <sup>2</sup>	β	95% CI	P Value <sup>a</sup>
FENO, ppb	0.950	−2.194	−4.038 to −0.350	.021 <sup>b</sup>
IOS Z5Hz, kPa/(L/s)	0.991	0.040	0.015 to 0.065	.003 <sup>b</sup>
IOS R5Hz, kPa/(L/s)	0.991	0.040	0.015 to 0.065	.003 <sup>b</sup>
IOS R10Hz, kPa/(L/s)	0.990	0.034	0.009 to 0.058	.008 <sup>b</sup>
IOS R20Hz, kPa/(L/s)	0.981	0.043	0.012 to 0.074	.007 <sup>b</sup>
IOS peripheral R, kPa/(L/s)	0.952	0.042	0.006 to 0.078	.024 <sup>b</sup>
IOS central R, kPa/(L/s)	0.934	0.034	−0.003 to 0.071	.069

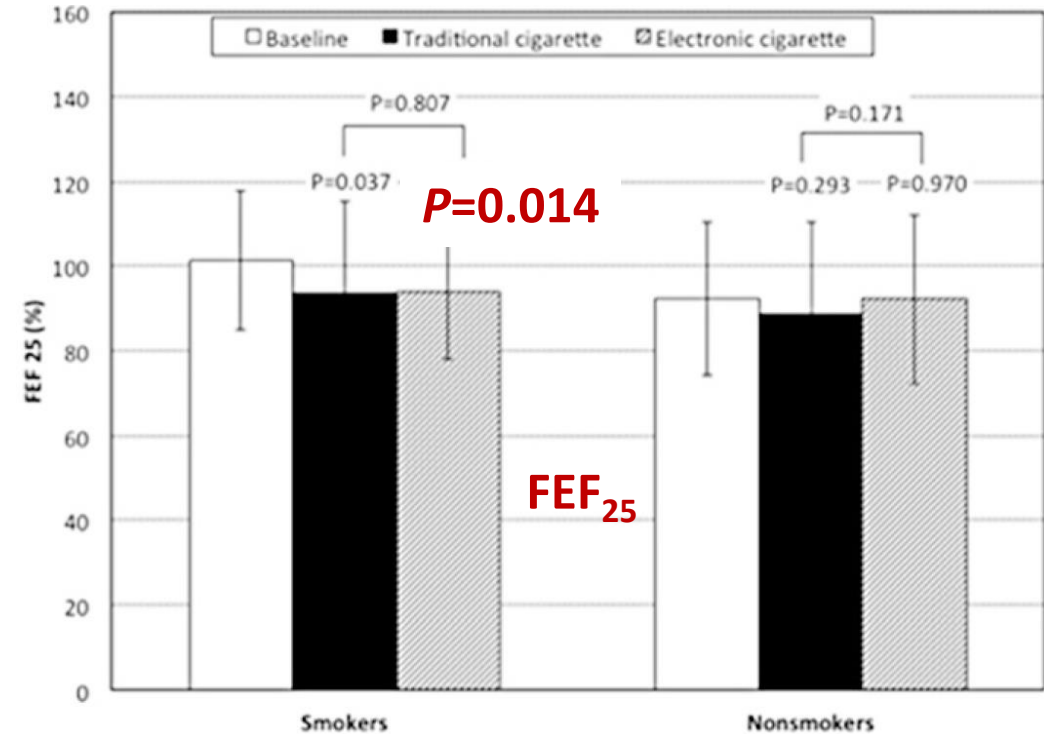
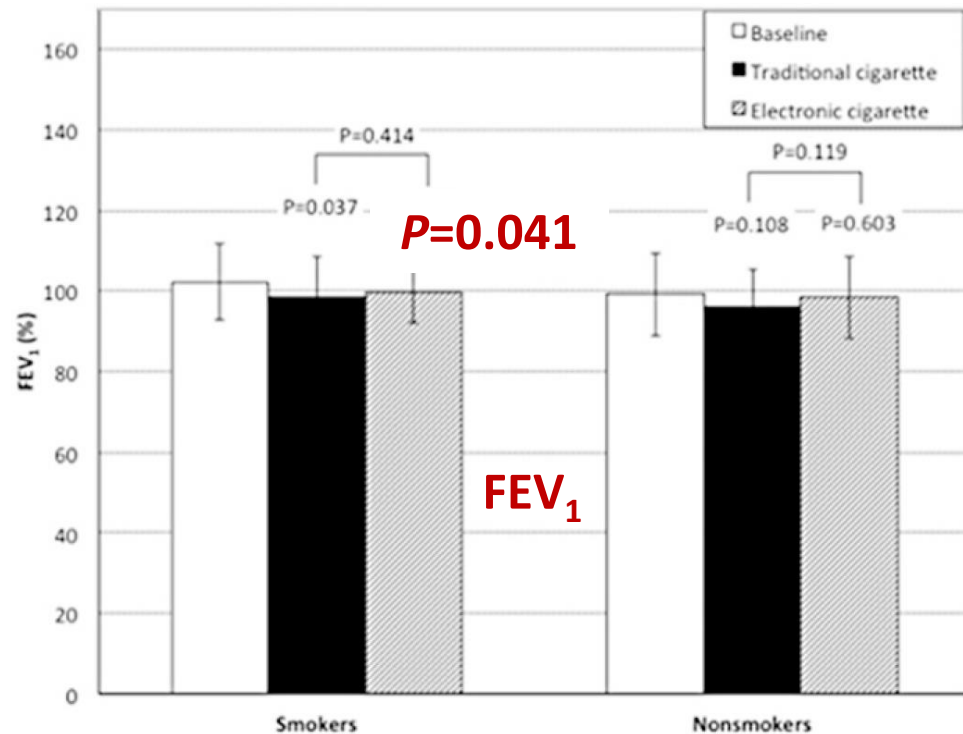
See Table 1 and 2 legends for expansion of abbreviations.

<sup>a</sup>Each value represents a separate linear regression model adjusting for the group (control vs experimental) and the relative baseline measurement (pre vs post).

<sup>b</sup>Significant.

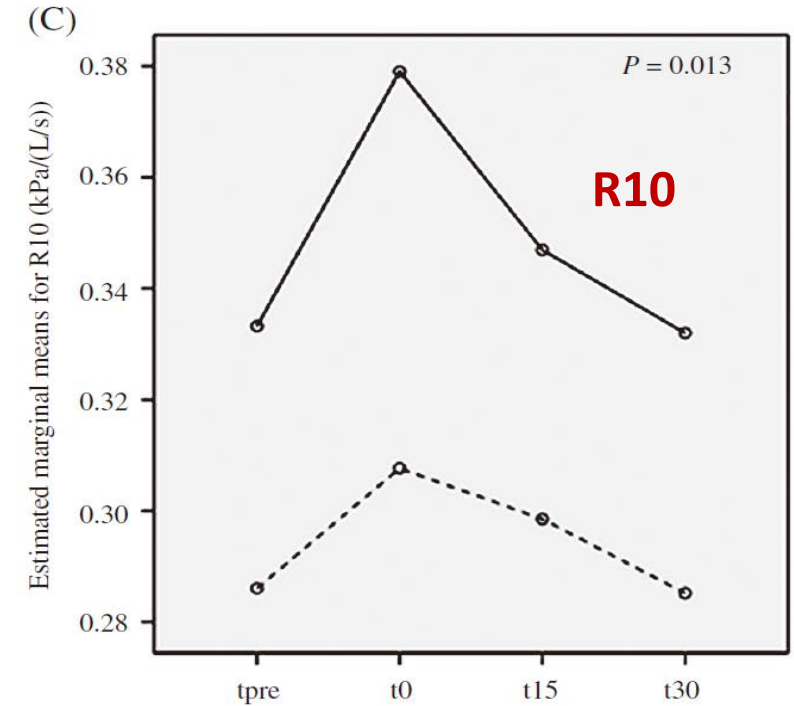
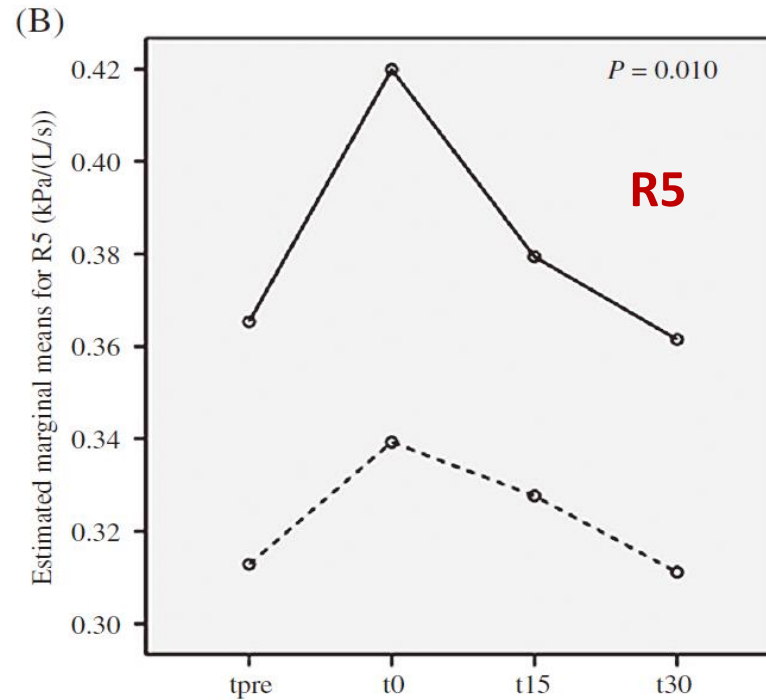
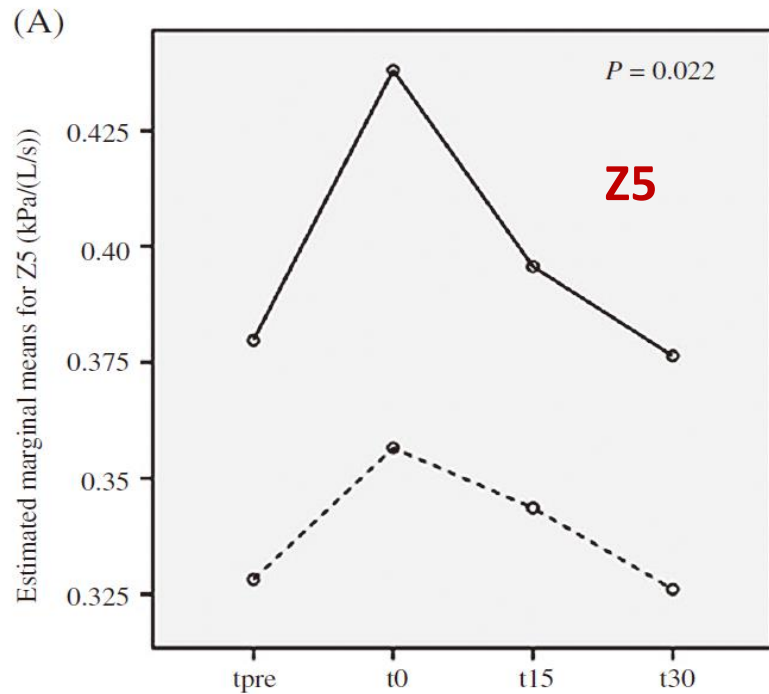
# Short-term effects of nicotine-free e-cigarettes

- 10 smokers and 10 non-smokers, nicotine-free e-cigarette use for 5 min
- Smokers: FEV<sub>1</sub> (102.2% vs 99.5%,  $P=0.041$ ), FEF<sub>25</sub> (103.4% vs 94.2%,  $P = 0.014$ )



# Short-term effects in smokers with asthma

- 27 healthy smokers and 27 smokers with mild asthma, e-cigarette use for 5 min

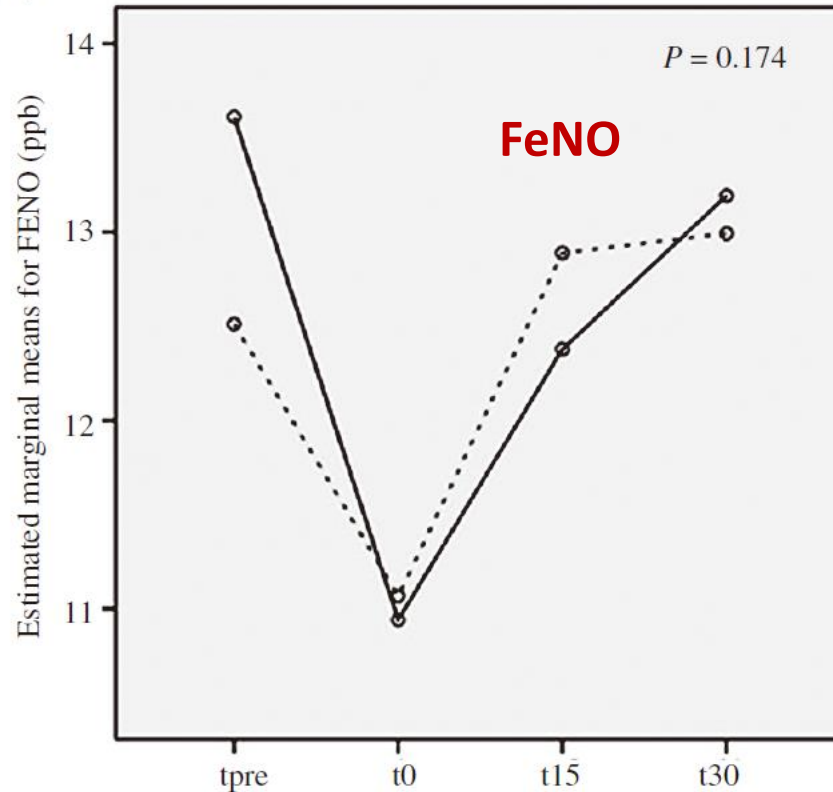


-----, Healthy smoker  
—, Smokers with mild asthma

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(D)



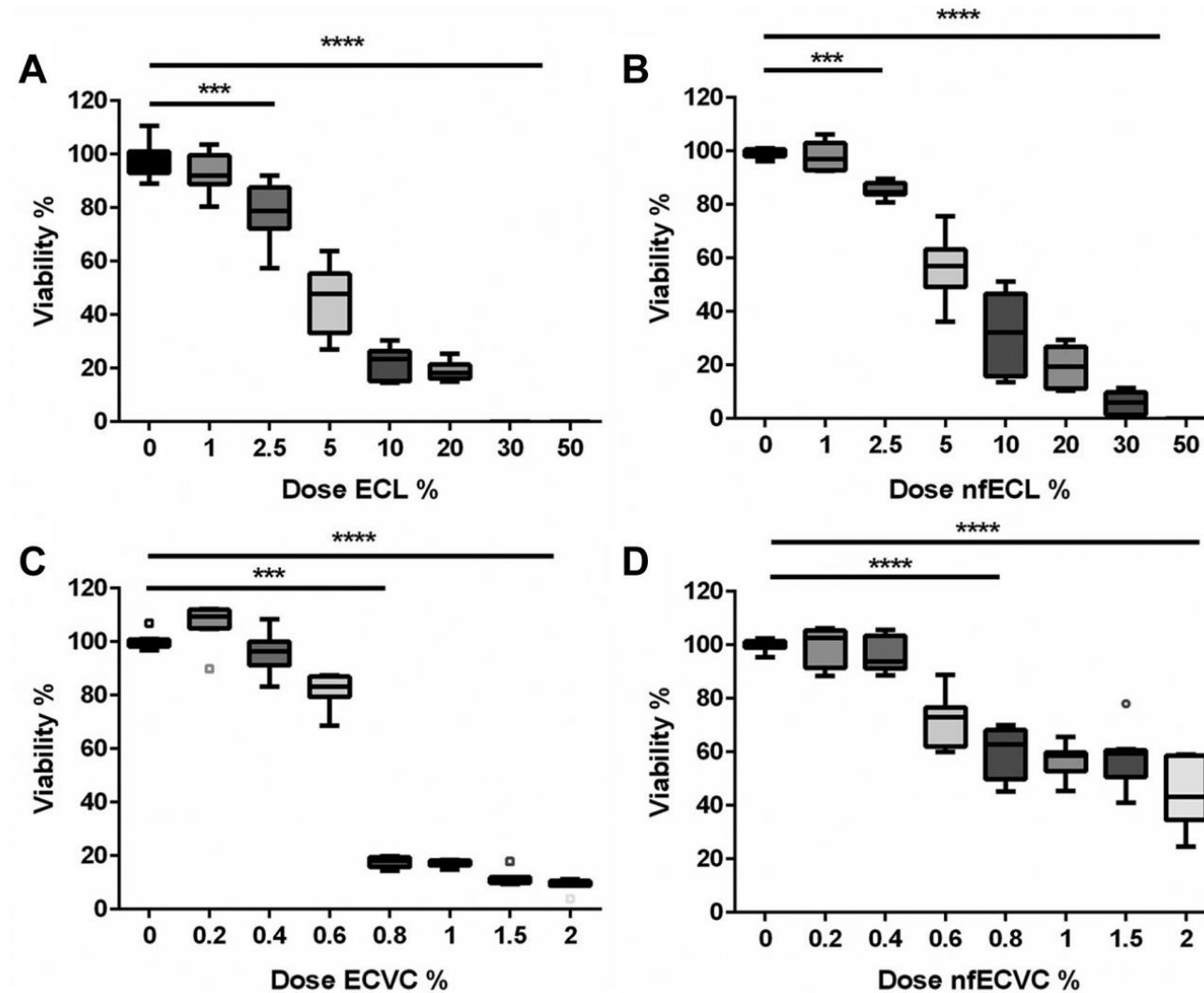
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# Pro-inflammatory effects of e-cigarette vapour condensate

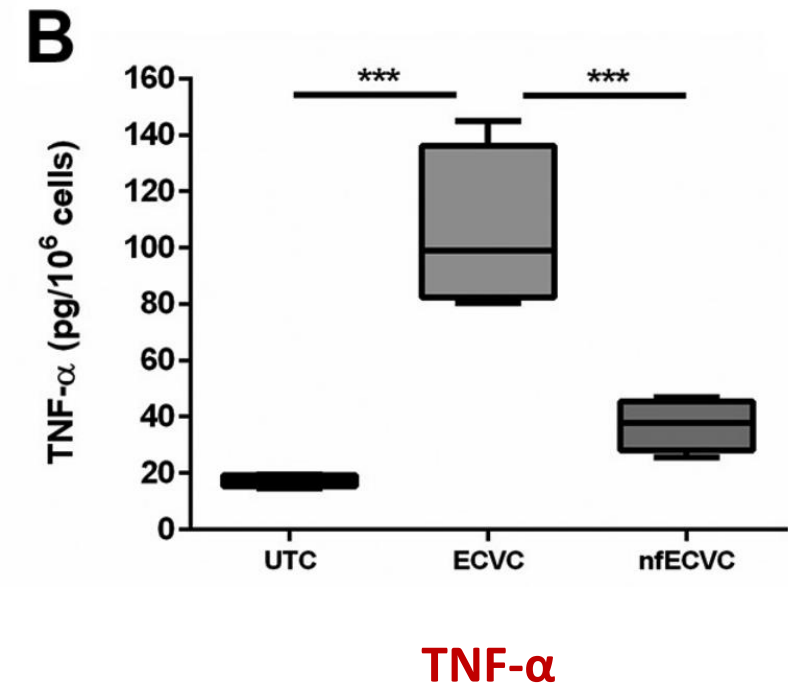
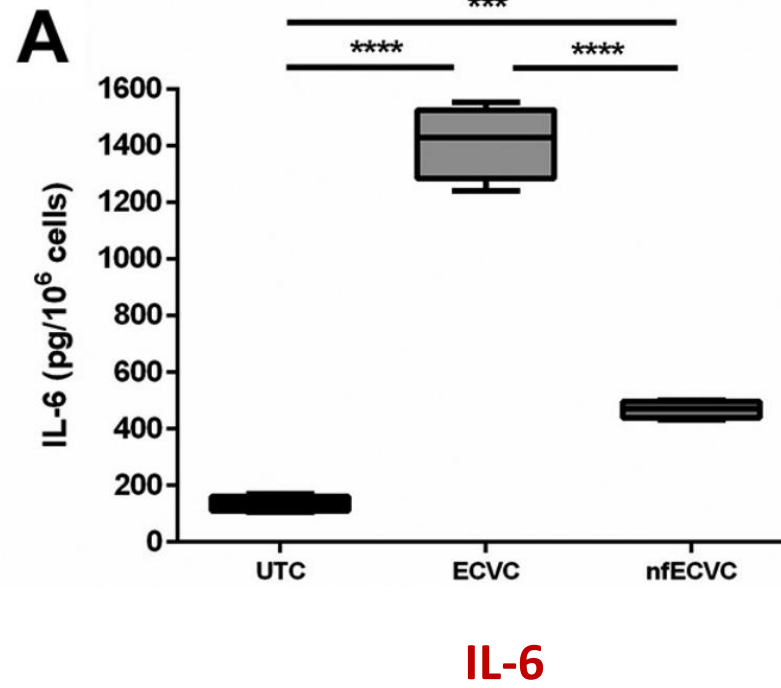
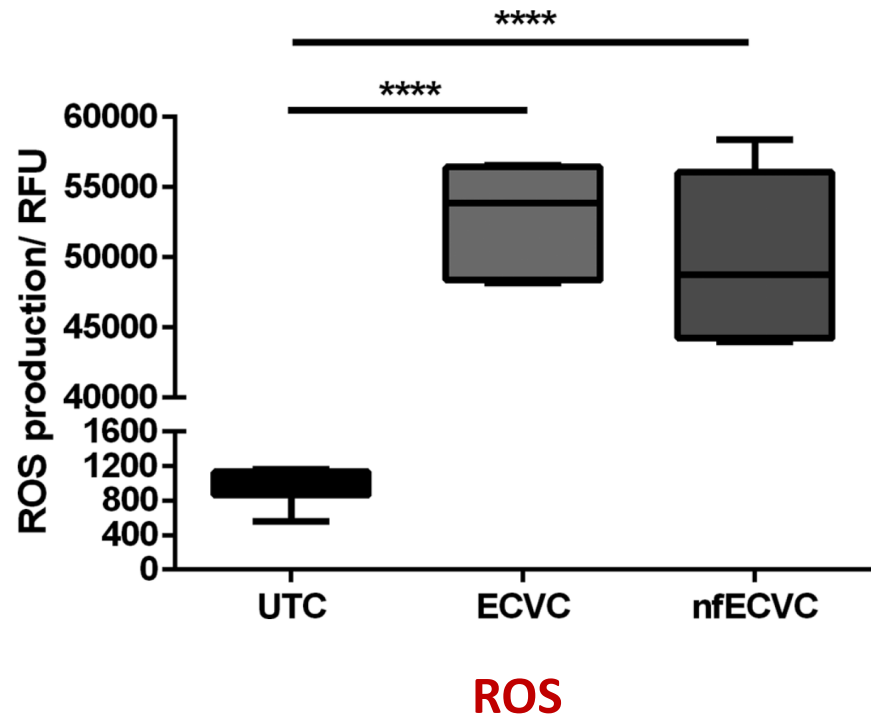
- Alveolar macrophage from 8 never smokers



ECL, E-cigarette liquid;  
ECVC, E-cigarette vapour  
condensate;  
nfECL, nicotine-free ECL;  
nfECVC, nicotine-free  
ECVC

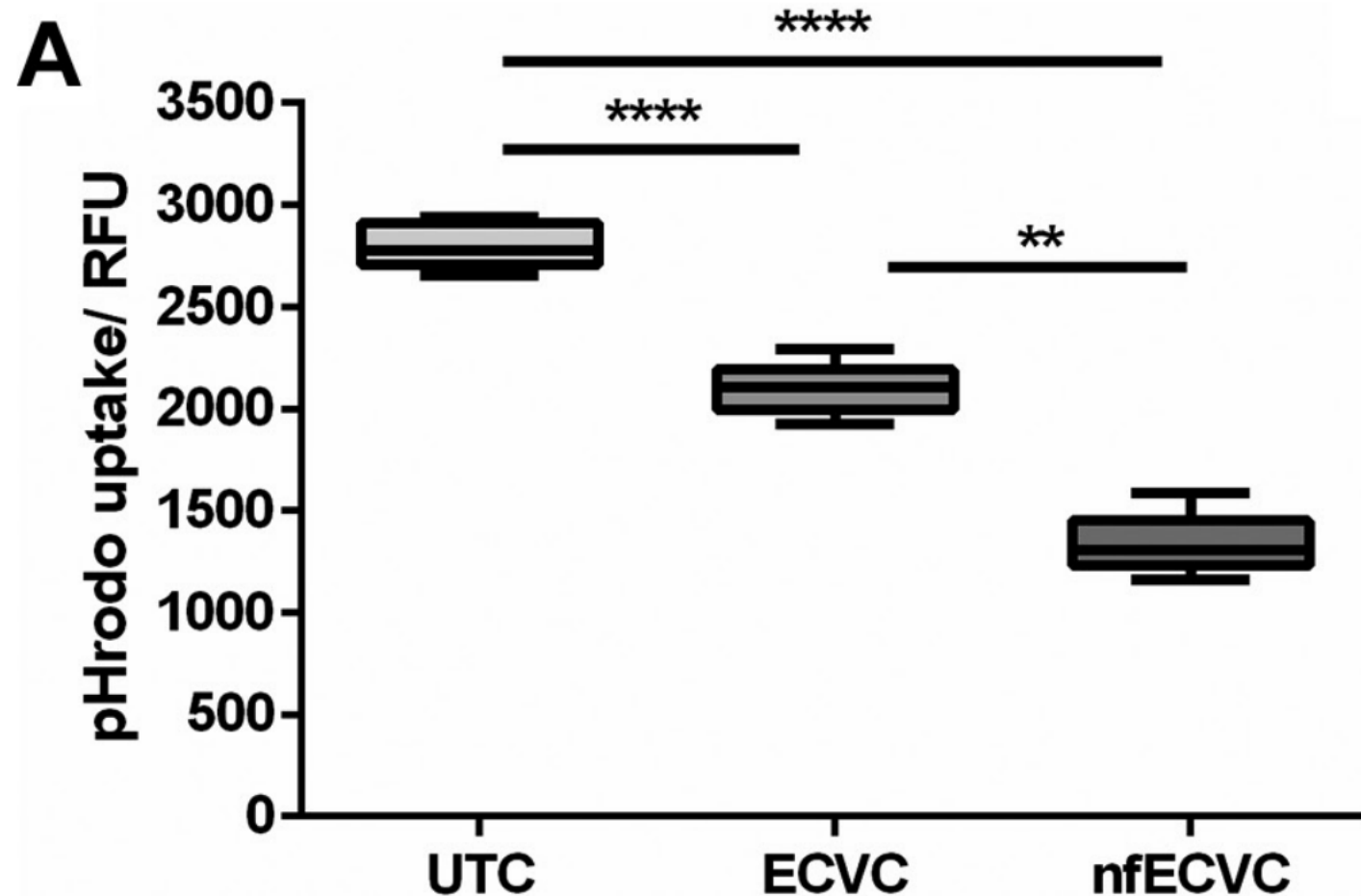
# Pro-inflammatory effects of e-cigarette vapour condensate

- Exposure to sub-lethal 0.5% ECVC/nfECVC



# Pro-inflammatory effects of e-cigarette vapour condensate

- Exposure to sub-lethal 0.5% ECVC/nfECVC

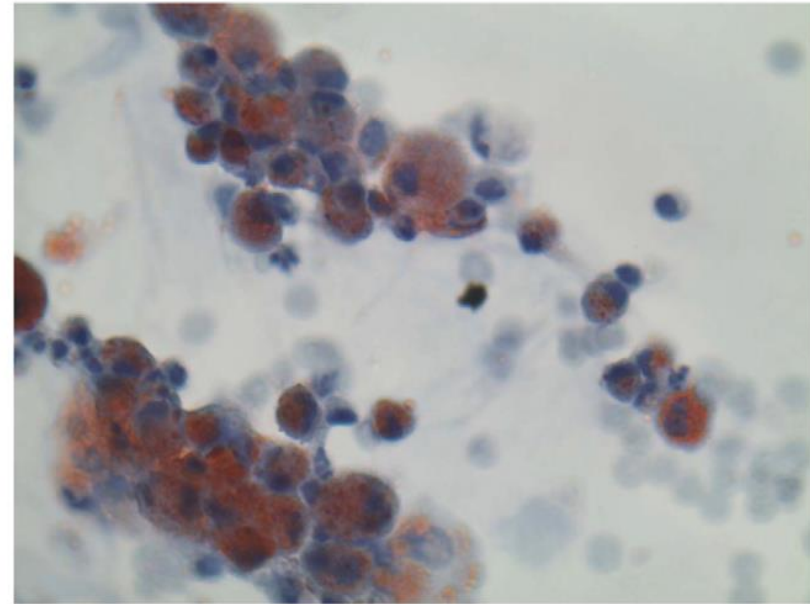
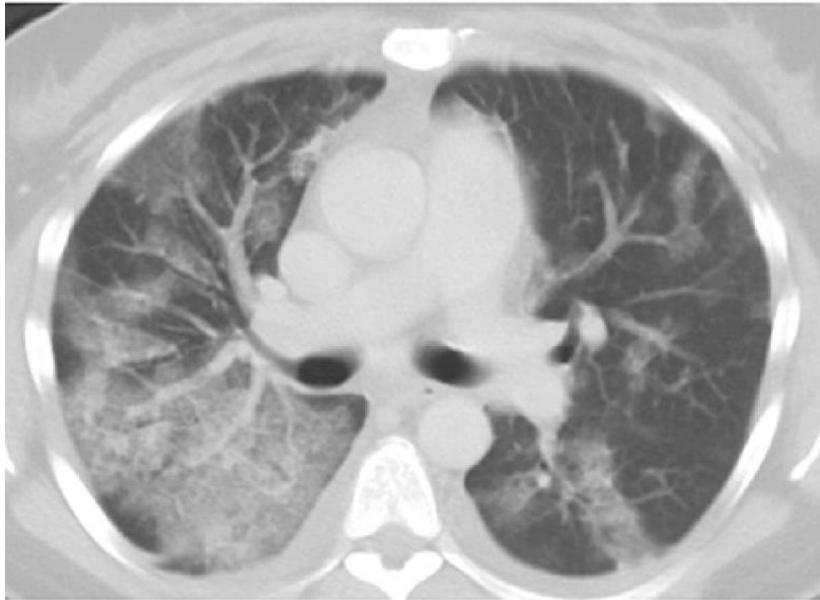


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# Lipoid pneumonia due to e-cigarette use

- F/42
- 7-month history of dyspnea, productive cough, fever
- Multiple times in the ED with similar complaints and had received several courses of antibiotics
- No evidence of infection



# EVALI – outbreak identification

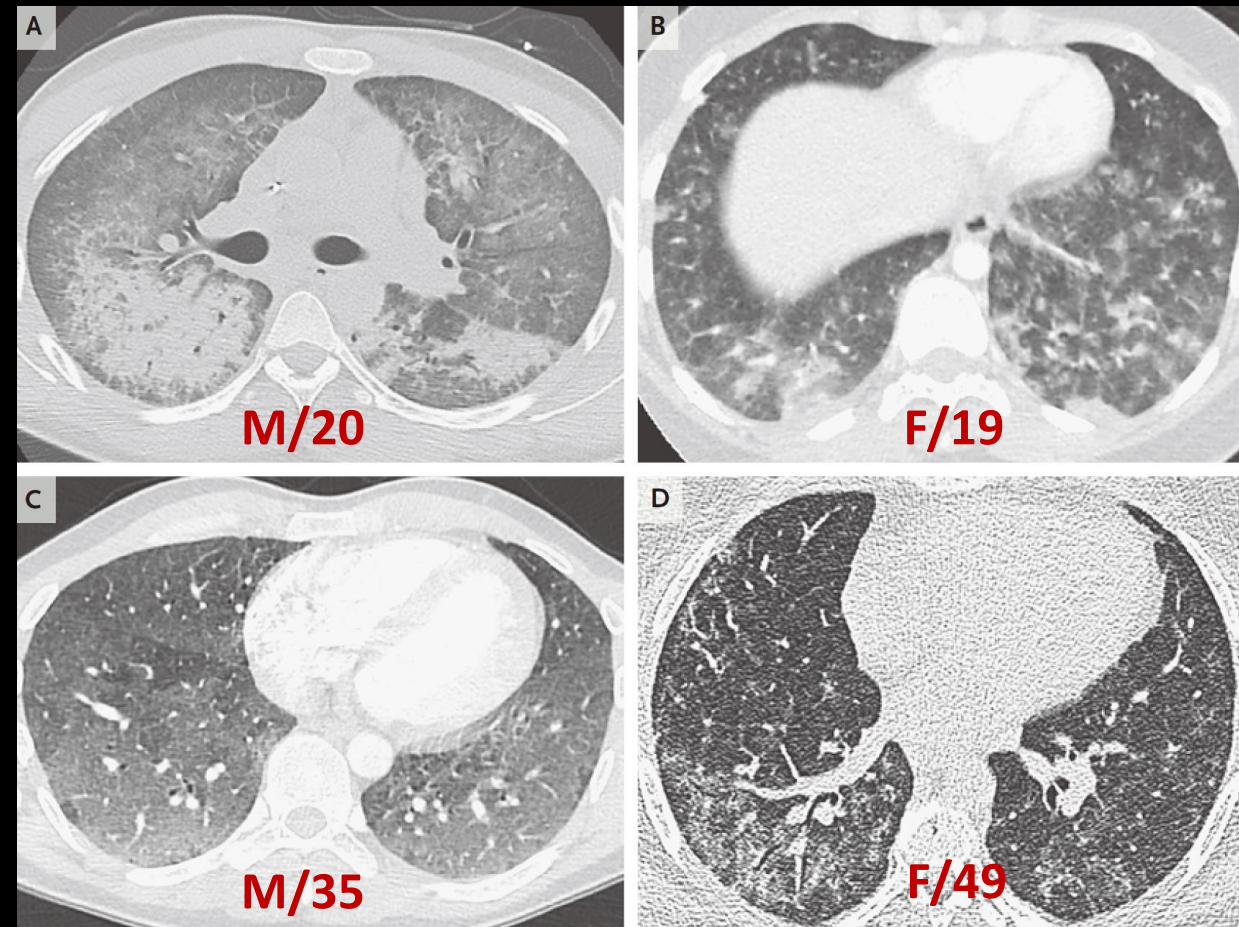
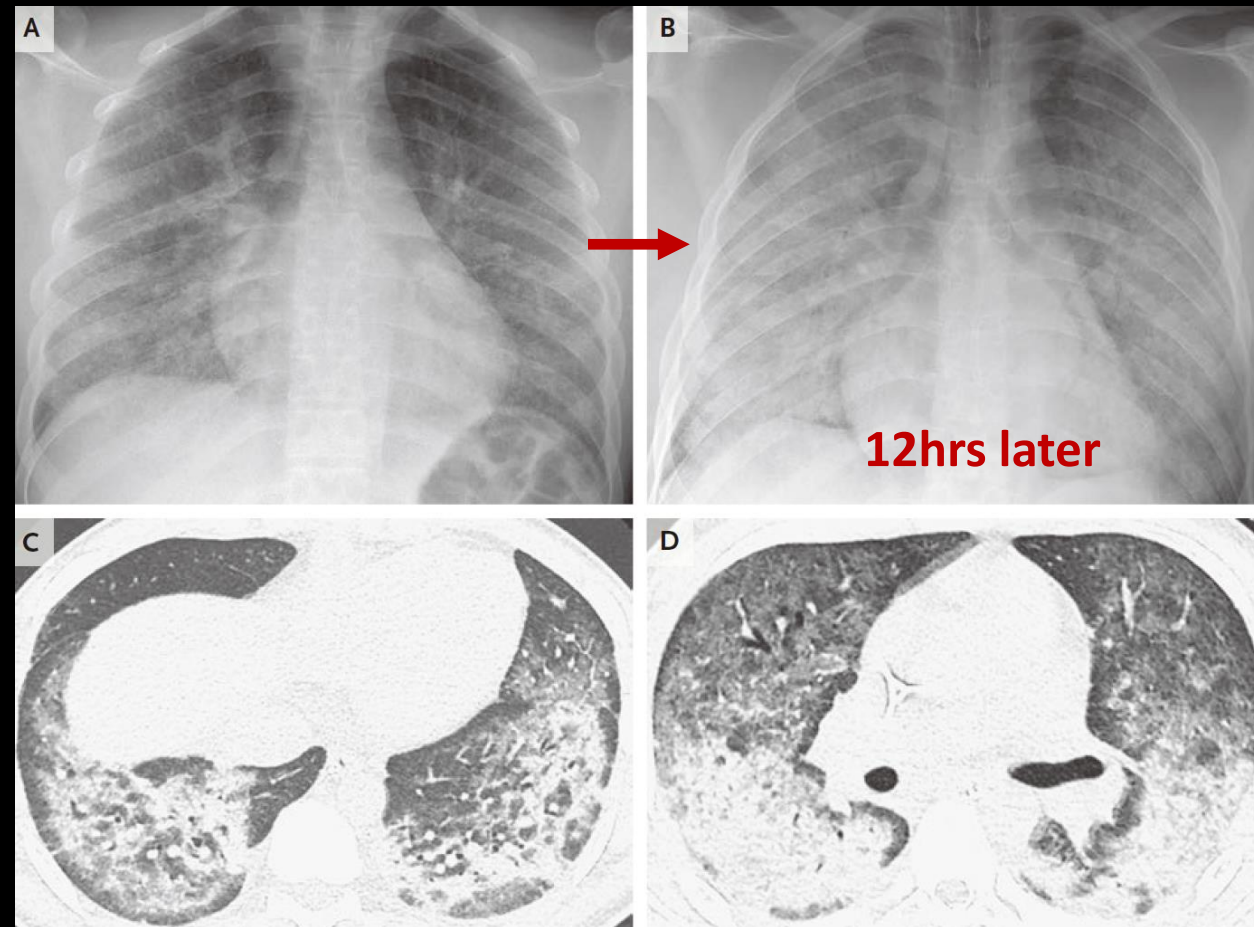
Date	Event
<b>July 10, 2019</b>	Children’s Hospital of Wisconsin: 5 previously healthy adolescents - Progressive dyspnea, fatigue, hypoxemia - Chest CT: GGO, predominantly in BLL - No infectious, rheumatologic, oncologic causes - History of e-cigarette use (+)
<b>July 25, 2019</b>	WDHS issued an alert to clinicians. A physician in Illinois contacted WDHS for a patient with similar manifestation.
<b>July 31, 2019</b>	WDHS notified IDPH.
<b>Aug 1, 2019</b>	WDHS–IDPH public health investigation was initiated.
<b>Aug 20, 2019</b>	CDC epidemiologic assistance field team (Epi-Aid) was deployed.

Wisconsin Department of Health Services (WDHS)  
Illinois Department of Public Health (IDPH)

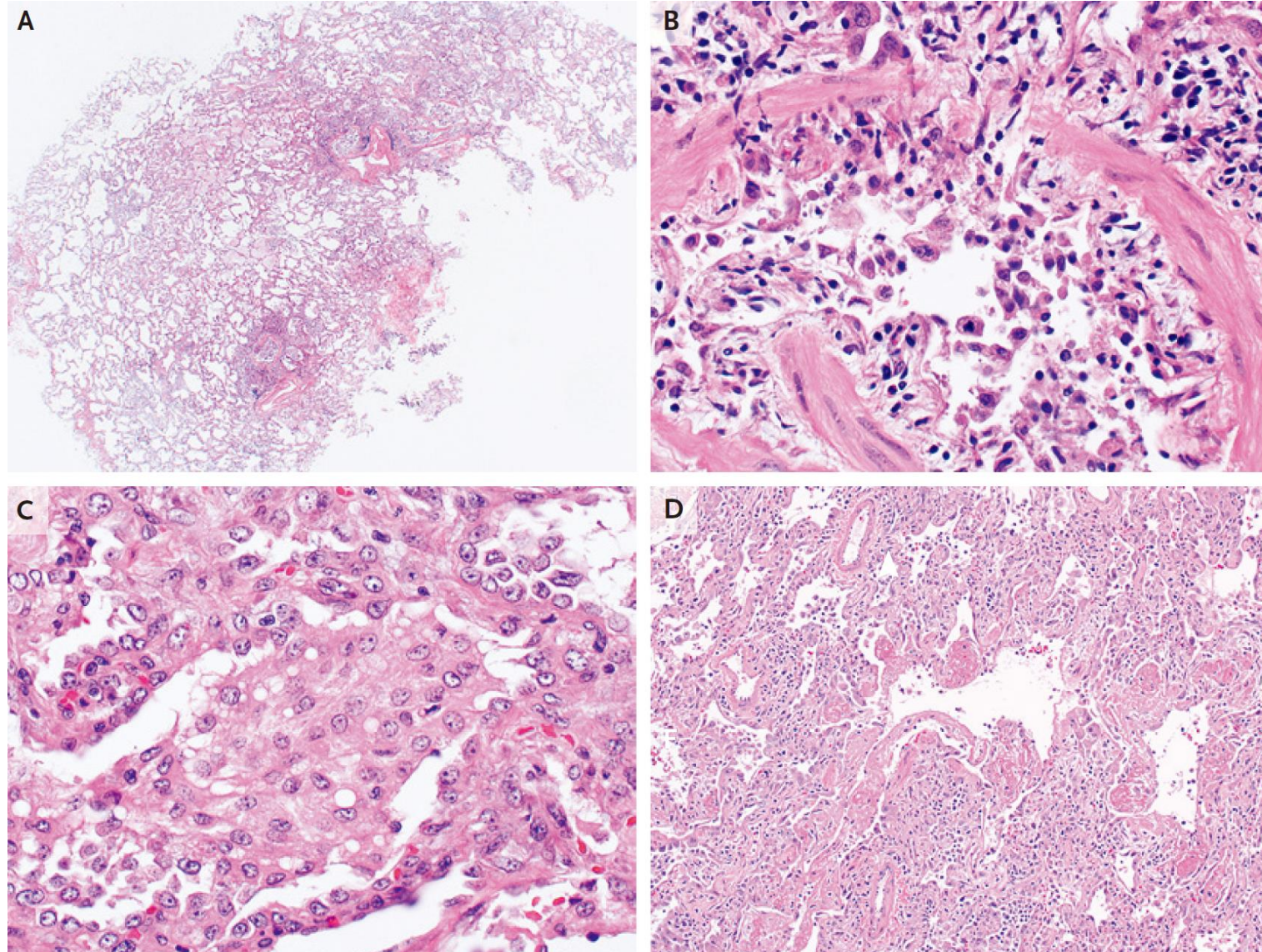
# EVALI – case definition

Confirmed case	Probable case
Use of an e-cigarette (vaping) or dabbing in <b>90 days</b> before symptom onset	
<b>Pulmonary infiltrate</b> on chest X-ray or CT	
<b>Absence of pulmonary infection</b> by minimum criteria (respiratory viral panel and influenza PCR or rapid test negative) All other clinically indicated testing must be negative, if done (e.g., urine antigen testing for <i>S. pneumoniae</i> and legionella, sputum culture, BAL culture, blood culture, and presence of HIV-related opportunistic respiratory infections)	<b>Infection identified</b> by culture or PCR, but the caring team believes that this is not the sole cause of the underlying respiratory disease process <b>or</b> the minimum criteria not met ( <b>testing not performed</b> ) and the caring team believes that this is not the sole cause of the underlying respiratory disease process
<b>No evidence</b> in medical record of <b>alternative plausible diagnoses</b>	

# EVALI – radiographic findings

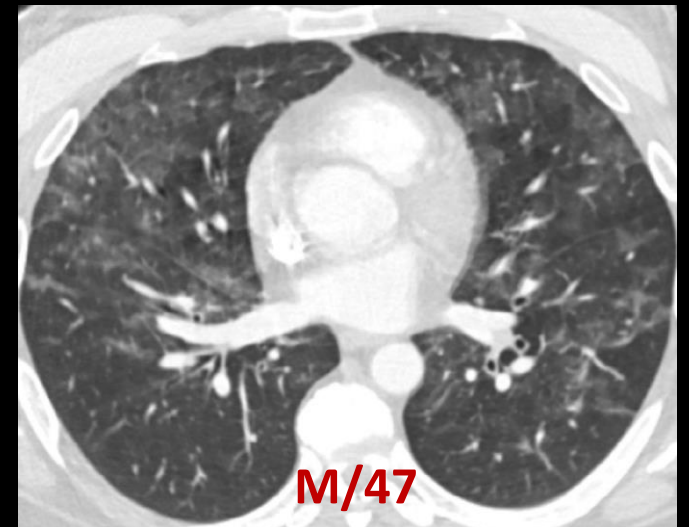
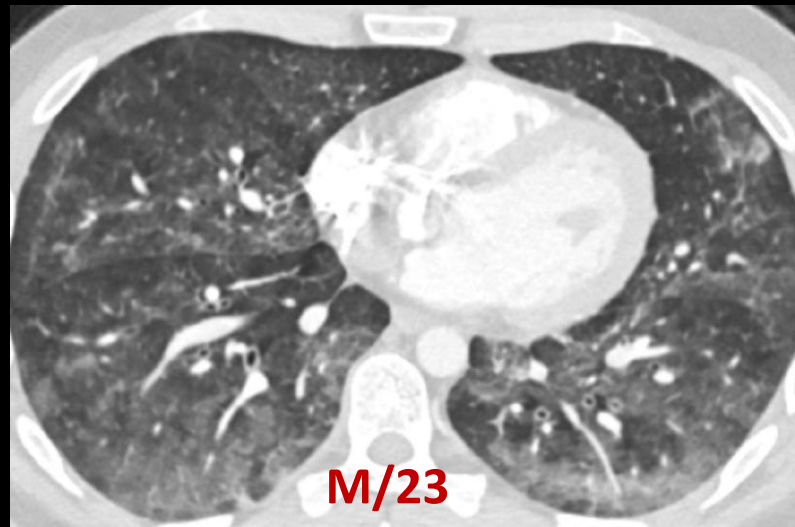
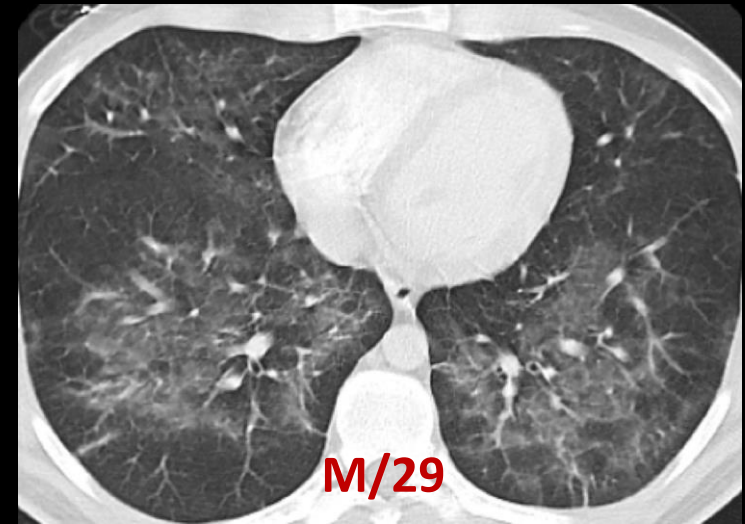
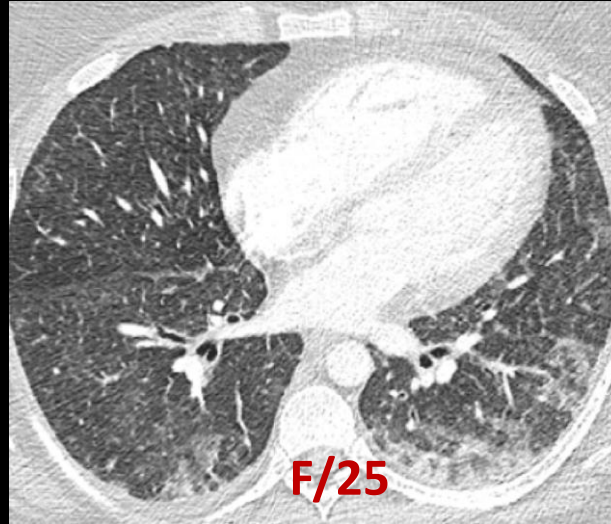


# EVALI – pathologic findings



# Pulmonary Lipid-Laden Macrophages and Vaping

- 6 cases of EVALI



# Pulmonary lipid-laden macrophages and vaping

- Elevated levels of lipid laden macrophages on BAL assessment

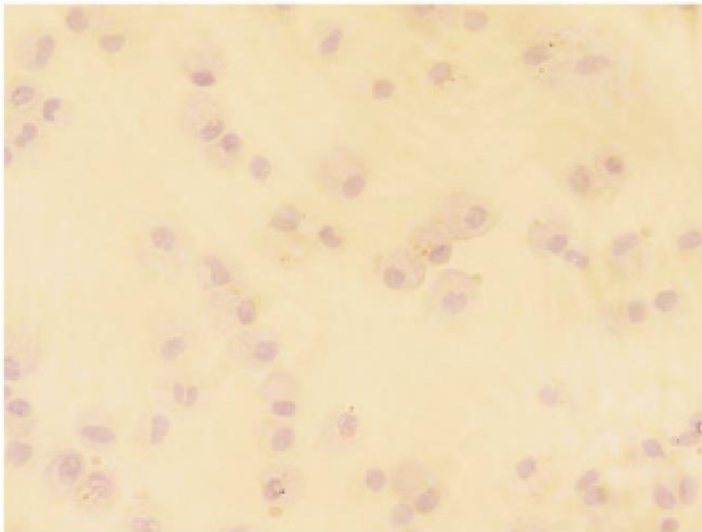
Bronchoalveolar lavage	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Lipid-laden macrophages (%)	>50	Approx. 50	30	25	>75	Approx. 60
Differential count (%)						
Macrophages	32	79	71	61	43	46
Bronchial lining cells	12	2	7	1	5	0
Lymphocytes	5	0	3	9	14	25
Neutrophils	49	18	19	26	38	27
Eosinophils	12	1	0	3	0	2

# Pulmonary lipid-laden macrophages

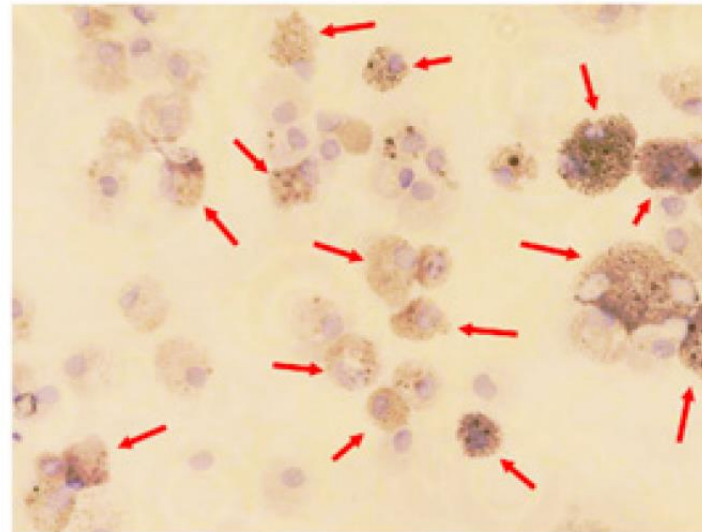
## – not unique for EVALI

- LLM typically results from impaired pulmonary surfactant recycling and/or uptake of exogenous lipids and is indicative of impaired innate defense
- Research bronchoscopy on healthy nonsmokers, smokers, and vapers

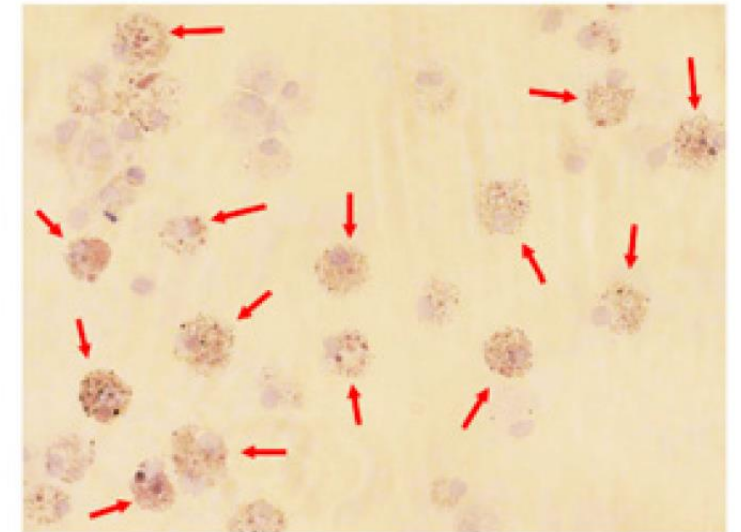
Nonsmoker



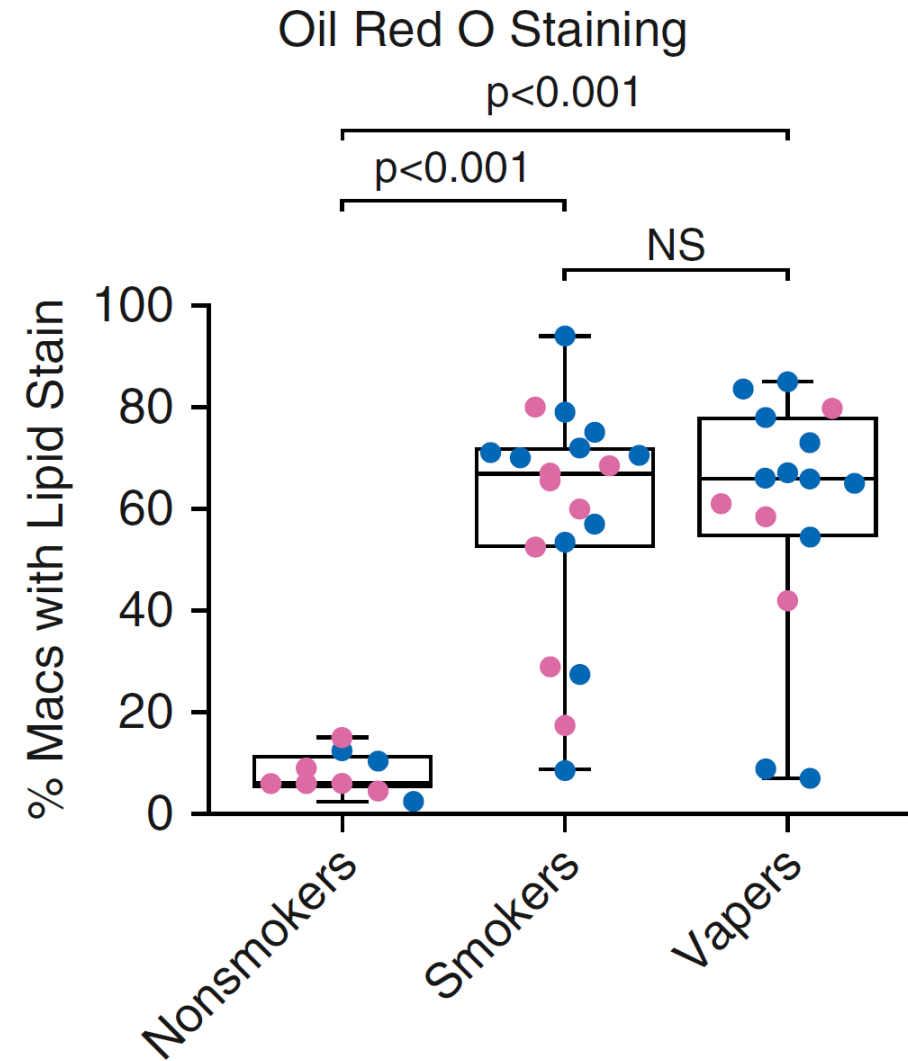
Smoker



Vaper



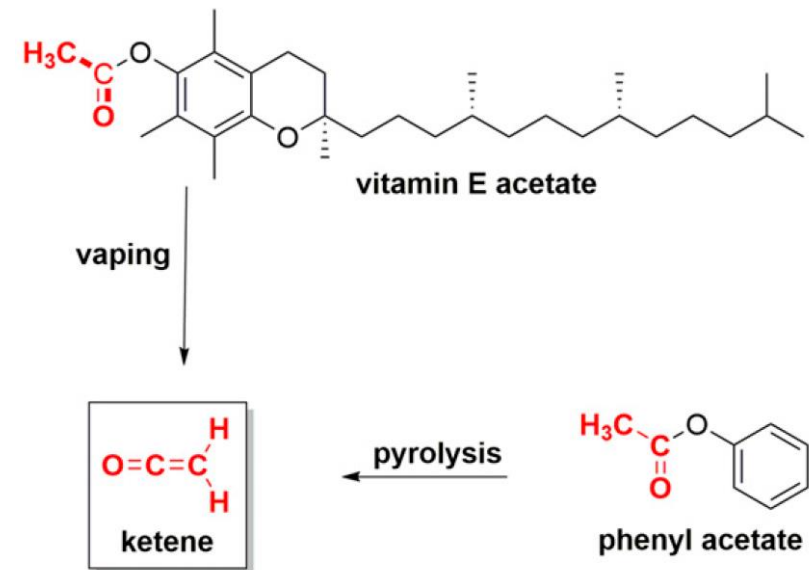
# Pulmonary lipid-laden macrophages – not unique for EVALI



# EVALI – vitamin E acetate in BAL fluid

- BAL fluid from 51 EVALI and 99 healthy participants
- Impair the ability of surfactant and form a toxic compound, ketene

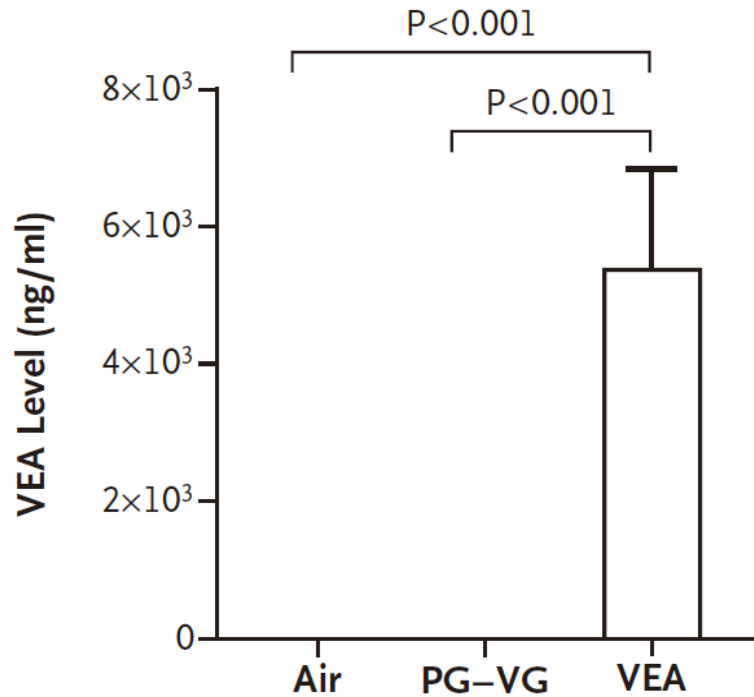
Toxicants	EVALI	Healthy participants
Vitamin E acetate	48/51 (94)	0/99
Medium-chain triglyceride oil	0/49	0/63
Plant oil	0/49	0/62
Coconut oil	1/48 (2)	0/63
Squalane	0/38	0/98
Limonene	1/39 (3)	0/97
Petroleum distillates	0/12	0/98



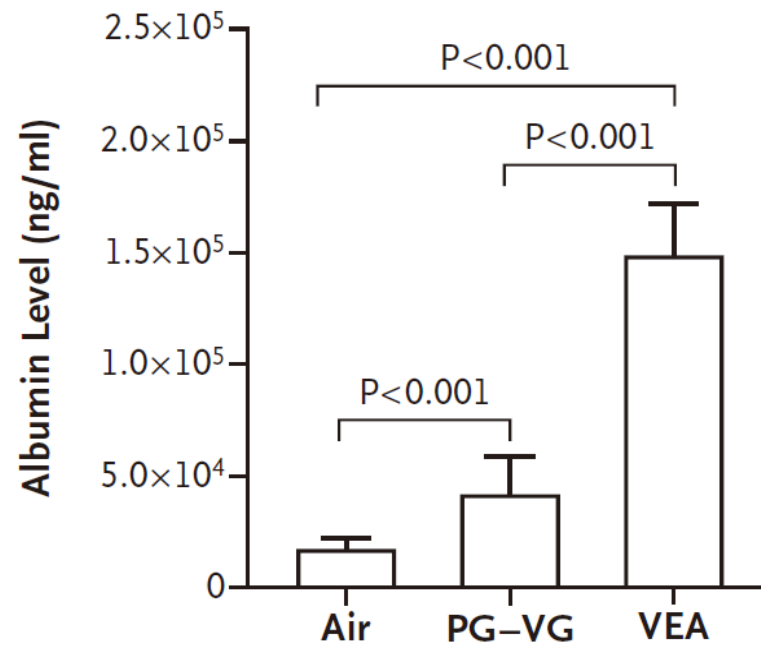
# An animal model of inhaled vitamin E acetate

- Exposure 10 mice to aerosols generated from vitamin E acetate, 10 mice to PG and VG, and 10 mice to air

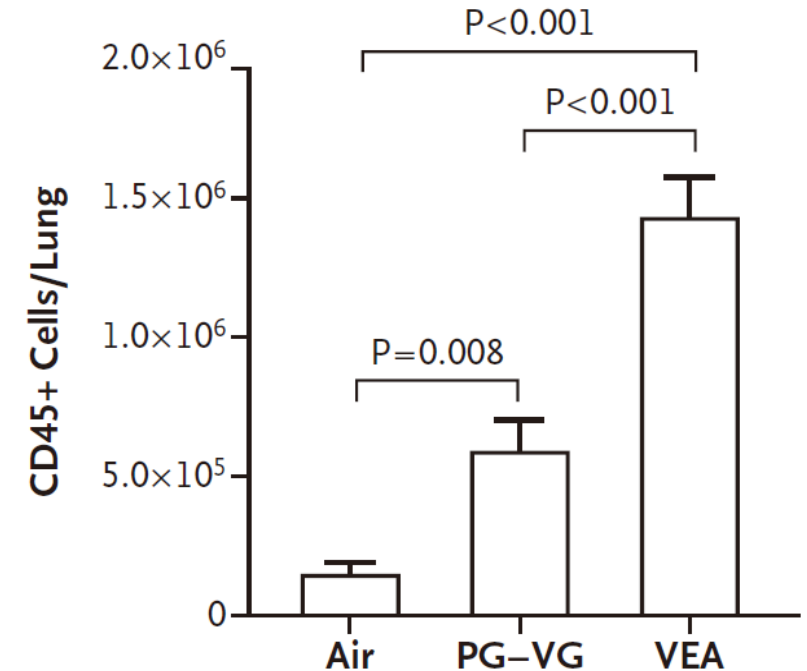
**A** VEA Levels in BAL Fluid



**B** Albumin Levels in BAL Fluid



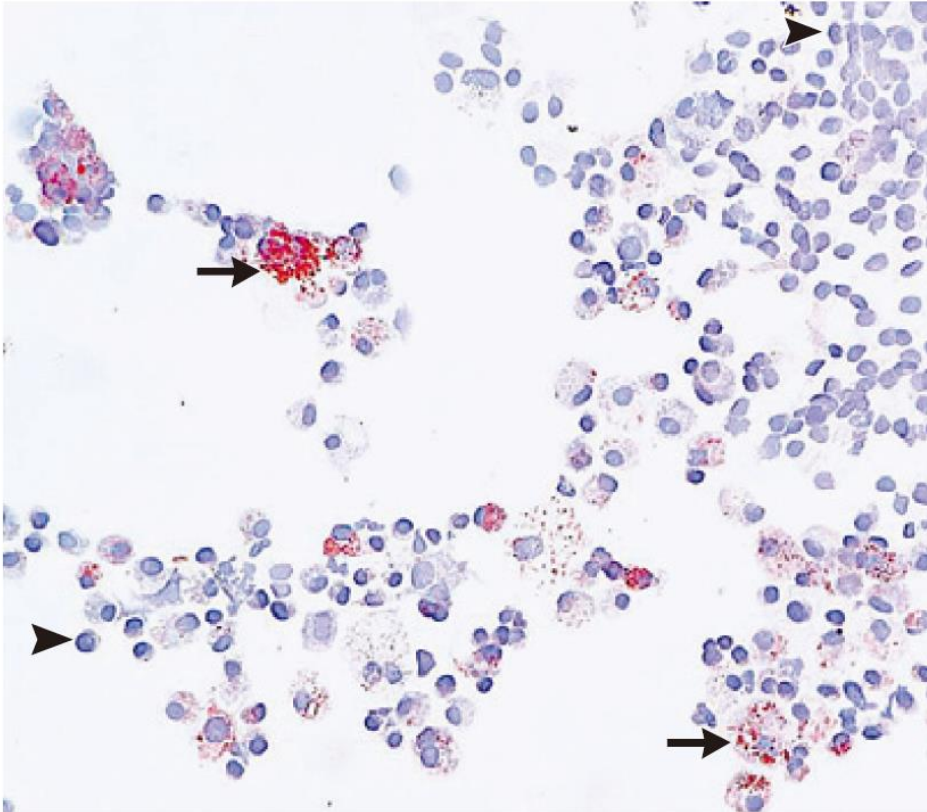
**C** CD45+ Cell Counts in Lung



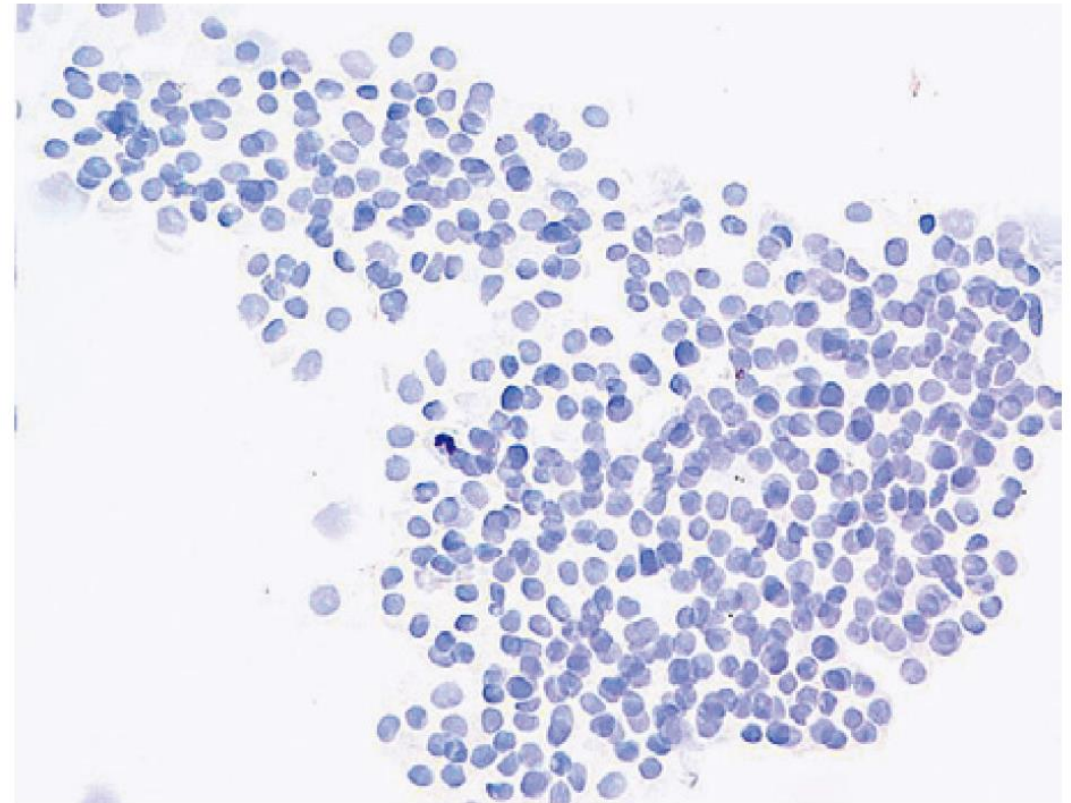
# An animal model of inhaled vitamin E acetate

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D Cells in BAL Fluid from Mouse Exposed to VEA



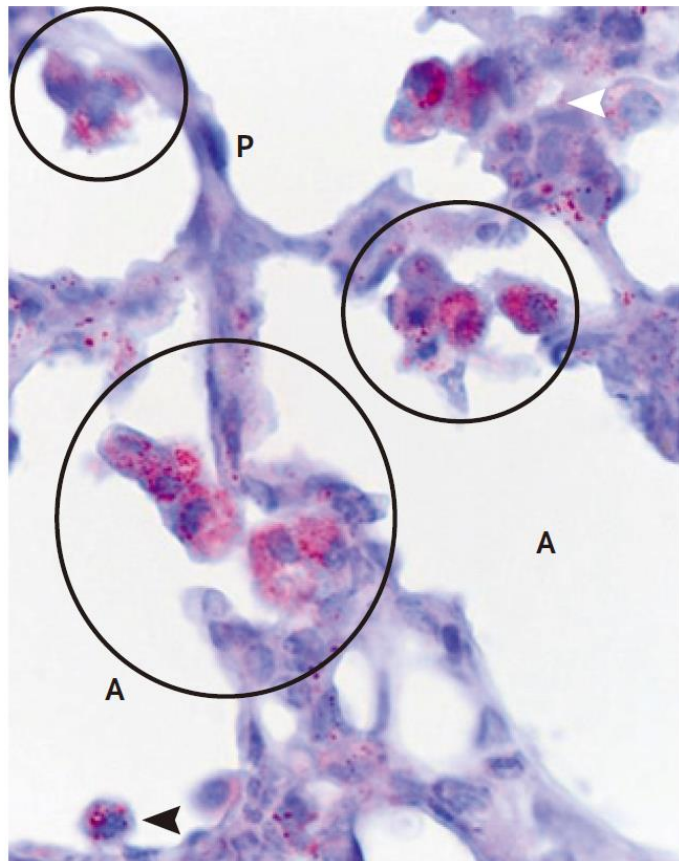
E Cells in BAL Fluid from Mouse Exposed to PG-VG



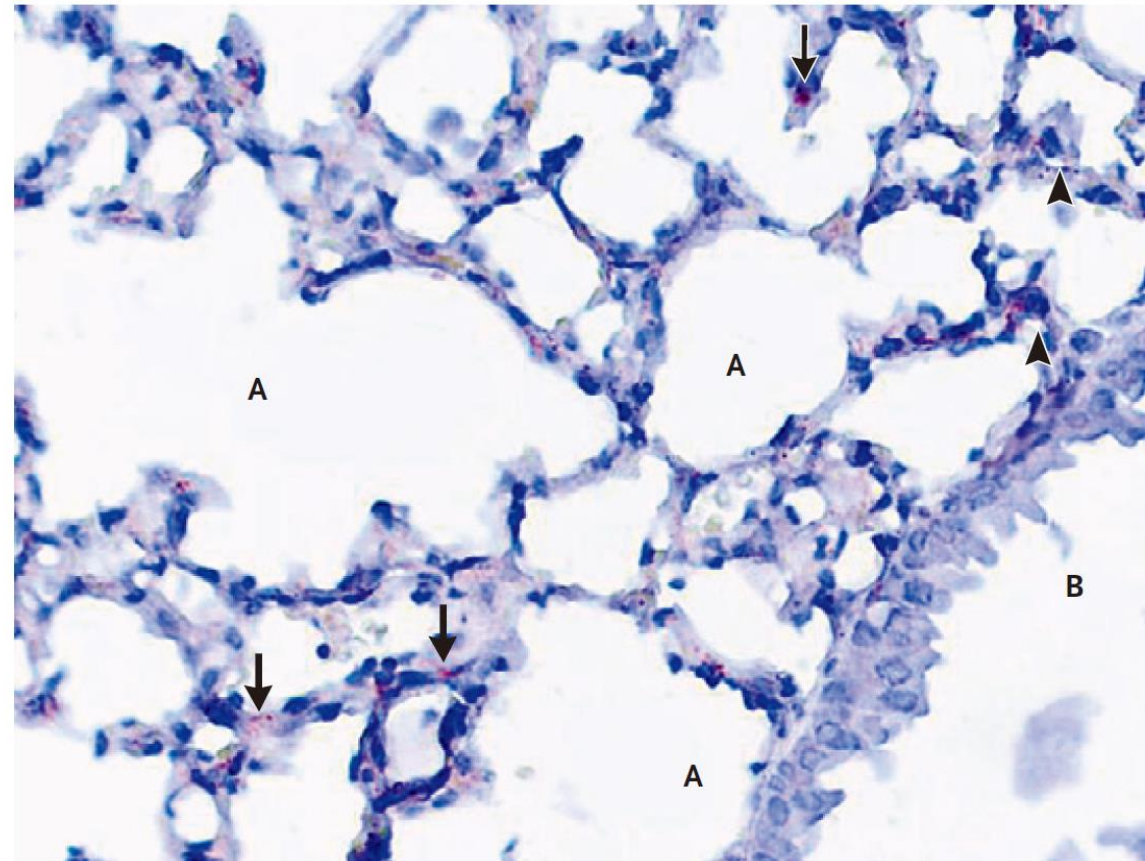
# An animal model of inhaled vitamin E acetate

- Exposure 10 mice to aerosols generated from vitamin E acetate, 10 mice to PG and VG, and 10 mice to air

F Lung Section from Mouse Exposed to VEA



G Lung Section from Mouse Exposed to PG-VG



# Hospitalizations and Deaths Associated with EVALI

- Reported cases of EVALI to CDC

Variable	Patients with Fatal Cases (n=60)	Patients with Nonfatal Cases (n=2558)
Presented initially in an outpatient setting	25/54 (46)	479/2320 (21)
Respiratory symptoms	55/56 (98)	1707/1779 (96)
Gastrointestinal symptoms	26/49 (53)	1343/1681 (80)
Admitted to an ICU	52/57 (91)	638/1504 (42)
Received ventilatory support with CPAP or BiPAP	32/56 (57)	179/1068 (17)
Underwent endotracheal intubation	47/58 (81)	131/755 (17)
Received antibiotics	57/57 (100)	1154/1183 (98)
Received glucocorticoids	45/58 (78)	1252/1419 (88)

# Contents

- E-cigarettes (electronic cigarettes) vs. heated tobacco products
- Device
  - Battery: inhalation injury
  - Atomizer: silica and metal
  - E-liquid: VG, PG, flavoring components
- Spirometry
- Host defense
- E-cigarette, or vaping, product use-associated lung injury (EVALI)
- **Challenges in e-cigarette study**

# Challenges in the study of e-cigarettes

- **Rapid** introduction of new devices (Heat-Not-Burn/IQOS) and rapid evolution of existing e-cigarette technology
- **Minimal information** from vendors about e-liquid content
- **Lack of a standard** “e-cigarette liquid/device” and standardization for e-cigarette aerosol generation and exposure
- **Variability** in operating parameters for devices (power, ambient conditions)
- **Dual use** of combustible cigarettes with other tobacco products including e-cigarettes, hookah, and marijuana
- **Different devices across different countries and regulatory domains**—for example, Juul contains 59 mg/mL nicotine in the US and 18 mg/mL in the UK
- **Ethical considerations** make study of addictive and potentially harmful liquids/devices in never-smokers challenging
- **Outcomes related to chronic toxicity** (for example, COPD) take many years to develop, so the true effects may not be known for decades

# Summary

- E-cigarettes (electronic cigarettes) vs. heated tobacco products
- Device
  - Battery: inhalation injury
  - Atomizer: silica and metal
  - E-liquid: VG, PG, flavoring components
- Spirometry (short-term effects): mixed results, but prominent effects on patients with pre-existing airway disease
- May impair host defense
- E-cigarette, or vaping, product use-associated lung injury (EVALI)
- Challenges in e-cigarette study

A large number '5' is formed by several cigarette butts and scattered ash on a white background. The number is composed of five main parts: a top horizontal bar, a left vertical stem, a bottom curve, a right vertical stem, and a top-right curve. Each part is made of a cigarette butt with a yellow filter and a brown ash tip. The ash is scattered around the butts, creating a textured effect.

**Thank you**