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Research on safety of electronic cigarettes

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E-cigarette facts

- New in the market
- Developed due to inefficiency of currently approved methods for smoking cessation
- NRTs < 6% success rate (Moore et al., BMJ 2009)
- Oral medications < 20% success rate (Rigotti et al., Circulation 2010)
- Awareness and use growing exponentially
- Used by millions, mostly of young age (40 yo)
- Nicotine delivery, dealing with behavioral addiction
- No tobacco, no combustion
- Any regulation should be based on scientific evidence

Safety studies

- Laboratory
  - Chemical
  - Toxicology
- Clinical
  - Pathophysiology (short-term)
  - Epidemiology (long-term)

Safety studies

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Chemical studies

- Most commonly performed (mostly on liquids, fewer on vapor)
- More than 300 analyses in Greece for presence of TSNAs+PAH
- Provide indirect evidence on safety
- Findings depend on what you search for
- Flavorings used are GRAS for use in food
- We don't know implications when inhaled
- Example of diacetyl -> bronchiolitis obliterans

Chemical studies

Table 2: Maximum tobacco-specific nitrosamine levels[a] in various cigarettes and nicotine-delivery products (ng/g, except for nicotine gum and patch that are ng/patch or ng/gum piece)[6]

Product	*NNN*	*NNK*	*NAT*	*NAB*	*Total*
Nicorette gum (4 mg)[18]	2.00	ND	ND	ND	2.00
NicoDerm CQ patch (4 mg)[18]	ND	8.00	ND	ND	8.00
Electronic cigarettes[6]	**3.87**	**1.46**	**2.16**	**0.69**	**8.18**
Swedish snus[18]	980	180	790	60	2010
Winston (full)[18]	2200	580	560	25	3365
Newport (full)[18]	1100	830	1900	55	3885
Marlboro (ultra-light)[18]	2900	750	1100	58	4808
Camel (full)[18]	2500	900	1700	91	5191
Marlboro (full)[18]	2900	960	2300	100	6260
Skoal (long cut straight)[18]	4500	470	4100	220	9290

Cahn & Siegel, *J Public Health Policy 2011*

Chemical studies

Journal of Chromatography A

Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography–tandem mass spectrometry

Table 4
Analytical results of TSNAs in replacement liquids of E-cigarettes ($n = 105$).

Aanlyte	…al results (µg/L)
	…D
NNN	…34
NNK	…69
NAT	…2.52
NAB	…72
ΣTSNAs	… 18.23

The TSNAs were identified and quantified in 105 replacement liquid brands of 11 companies. The maximum concentrations of total TSNAs in replacement liquids of E-cigarettes were measured at 86.92 µg/L, which were 10 times more than those published by Ruyan E-cigarette Company. Manufacturers have claimed that

Farsalinos et al, *J Chromatogr A*, 2013

Kim & Shin, *J Chromatogr A 2013*

Chemical studies

Table 3 Levels of selected compounds in vapour generated from e–cigarettes (per 150 puffs)

Compound	BS	Levels in vapour from electronic cigarettes†												Reference
		Product code												
		EC01	EC02	EC03	EC04	EC05	EC06	EC07	EC08	EC09	EC10	EC11	EC12	Inhalator
Carbonyl compounds (μg)														
Formaldehyde	ND	44.2±4.1*	23.6±8.7*	30.2±2.3*	47.9±0.2*	56.1±1.4*	35.3±2.7*	19.0±2.7*	6.0±2.0	3.2±0.8	3.9±1.5	23.9±11.1	46.3±2.1*	2.0±1.1
Acetaldehyde	ND	4.6±0.2*	6.8±3.2	8.2±2.5*	11.5±2.0*	3.0±0.2*	13.6±2.1*	11.1±3.3*	8.8±1.6*	3.5±0.3*	2.0±0.1	3.7±1.5	12.0±2.4*	1.1±0.6
Acrolein	ND	41.9±3.4*	4.4±2.5	16.6±2.5*	30.1±6.4*	22.0±1.6*	2.1±0.4*	8.5±3.6	0.7±0.4	ND	2.7±1.6	1.1±0.6	7.4±3.2*	ND
o-methylbenzaldehyde	ND	1.9±0.5	4.4±1.2*	3.2±1.0*	4.9±1.2*	1.7±0.1*	7.1±0.4*	1.3±0.8	5.5±0.0*	6.0±0.7*	3.2±0.5*	5.1±0.1*	2.2±0.6*	0.7±0.4
Volatile Organic Compounds (VOCs) (μg)														
Toluene	ND	0.5±0.1*	ND	0.2±0.0*	0.6±0.1*	0.2±0.0*	ND	0.3±0.2	0.2±0.1	6.3±1.5*	0.2±0.1*	0.5±0.1*	0.5±0.0*	ND
p,m-xylene	0.1	0.1±0.0*	ND	0.1±0.0*	0.2±0.1*	0.1±0.0	ND	0.1±0.1	0.1±0.0	0.1±0.0*	0.1±0.0*	0.1±0.1*	0.1±0.0	ND
Tobacco-Specific Nitrosamines (TSNAs) (ng)														
NNN	ND	ND	2.7±2.2	0.8±0.8	ND	ND	0.9±0.4	4.3±2.4	1.9±0.3*	1.2±0.6	2.0±1.1	3.2±0.6*	1.3±0.1	ND
NNK	ND	2.0±2.0	3.6±1.8	3.5±1.8	ND	ND	1.1±1.1	21.1±6.3*	4.6±0.4*	28.3±13.2	2.1±2.1	13.0±1.4*	ND	ND
Metals (μg)														
Cd	0.02	0.17±0.08	0.15±0.03*	0.15±0.05	0.02±0.01	0.04±0.01	0.22±0.16	0.02±0.01	0.08±0.03	0.01±0.01	0.17±0.10	0.03±0.03	ND	0.03±0.01
Ni	0.17	0.28±0.22	0.29±0.08	0.21±0.03	0.17±0.07	0.14±0.06	0.11±0.06	0.23±0.09	0.26±0.10	0.19±0.09	0.12±0.04	0.11±0.08	0.11±0.05	0.19±0.04
Pb	0.02	0.06±0.01	0.06±0.03	0.07±0.01	0.03±0.01	0.05±0.01	0.03±0.01	0.04±0.01	0.57±0.28	0.09±0.04	0.06±0.02	0.04±0.03	0.03±0.03	0.04±0.01

Goniewicz et al, *Tob Control 2013*

Chemical studies

Huge variety of devices, with different battery, liquid capacity and resistance. HOWEVER, all were handled in the same way (2-seconds puff every 10 seconds)

<u>Unrealistic conditions</u>

Goniewicz et al, *Tob Control 2013*

Chemical studies

Despite that

Table 4 Comparison of toxins levels between conventional and electronic cigarettes

Toxic compound	Conventional cigarette (µg in mainstream smoke) [35]	Electronic cigarette (µg per 15 puffs)	Average ratio (conventional vs electronic cigarette)
Formaldehyde	1.6–52	0.20–5.61	9
Acetaldehyde	52–140	0.11–1.36	450
Acrolein	2.4–62	0.07–4.19	15
Toluene	8.3–70	0.02–0.63	120
NNN	0.005–0.19	0.00008–0.00043	380
NNK	0.012–0.11	0.00011–0.00283	40

Goniewicz et al, *Tob Control 2013*

Chemical studies

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Metal and Silicate Particles Including Nanoparticles Are Present in Electronic Cigarette Cartomizer Fluid and Aerosol

Monique Williams[1], Amanda Villarreal[1], Krassimir Bozhilov[2], Sabrina Lin[1], Prue Talbot[1]*

Table 1. Elemental abundance in EC aerosol and cigarettes and associated health effects.

Element	Aerosol µg/10 puffs	Smoke µg/cig (~10 puffs)	Health Effects
Sodium	4.18	1.3 [40]	Inhalation may cause lung irritation, shortness of breath, bronchitis [41].
Boron	3.83		Inhalation exposure: acute respiratory and ocular irritation [42].
			calcium, and magnesium.
Sulfur	0.221		Nose/throat/lung irritation, coughing, shortness of breath, and bronchitis [48].
Copper	0.203	0.19 [40]	Respiratory irritation, coughing, sneezing, thoracic pain, runny nose and vineyard sprayer's lung [49].
Magnesium	0.066	0.070 [40]	Metal fume fever, respiratory irritation, tightness in chest, difficulty breathing [50].
Zinc	0.058	0.12–1.21 [40] 11.9 [51]	Metal fume fever, impaired pulmonary function, chest pain, coughing, dyspnea, shortness of breath [52].
Tin	0.037		Inorganic tin: pneumoconiosis (stannosis) and inflammation [53].
Lead	0.017	0.017–0.98 [40] 0.072 [54] 0.14 [51]	Can damage nervous system and kidneys [55]. Is a CA, RT, and RDT [56].

We need more studies on e-cigarette materials

Williams et al, *PLoS One 2013*

Chemical studies

Passive vaping

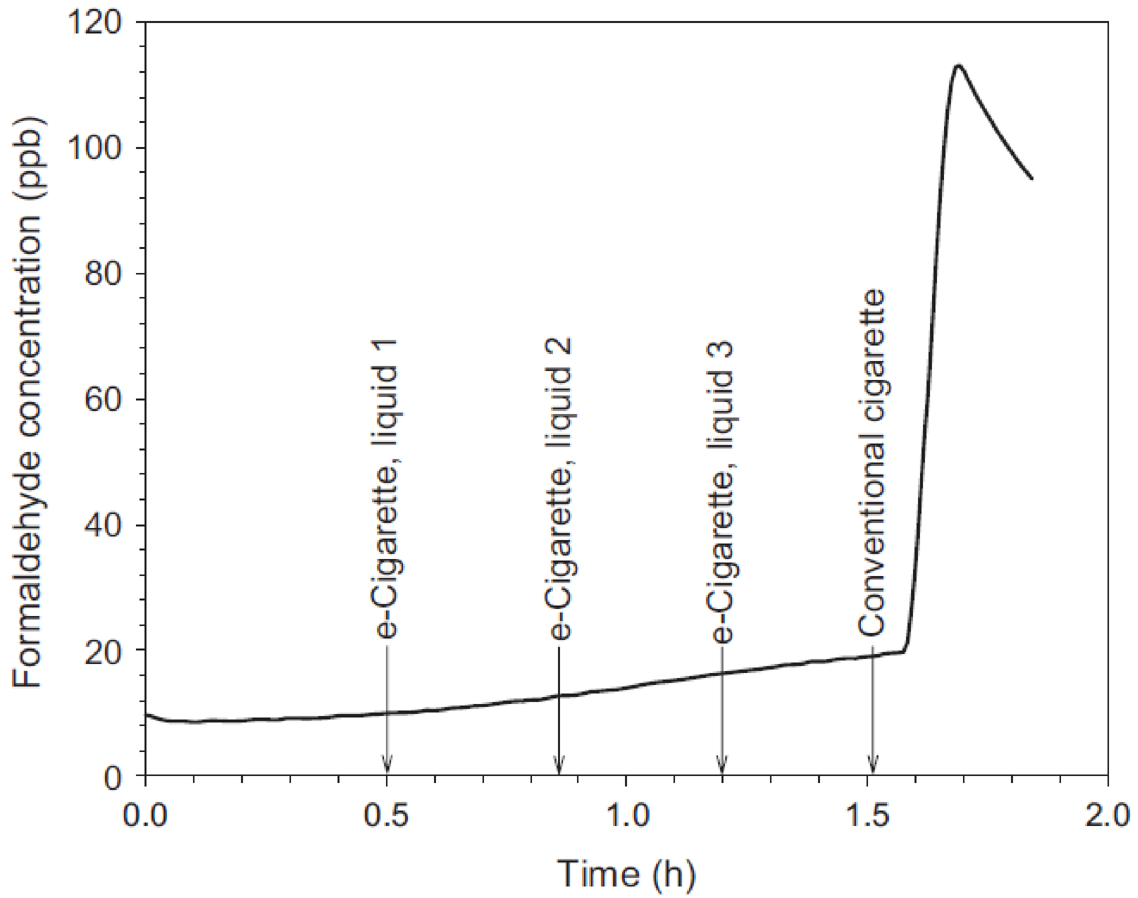
Table 4 Concentrations ($\mu g/m^3$) of selected compounds during the 8-m^3 emission test chamber measurement of e-cigarette A and conventional cigarette using Tenax TA and DNPH

Compounds	CAS	Participant blank	E-cigarette Liquid 1	E-cigarette Liquid 2	E-cigarette Liquid 3	Conventional cigarette
1,2-Propanediol	57-55-6	<1	<1	<1	<1	112
1-Hydroxy-2-propanone	116-09-6	<1	<1	<1	<1	62
2,3-Butanedione	431-03-8	<1	<1	<1	<1	21
2,5-Dimethylfuran	625-86-5	<1	<1	<1	<1	5
2-Butanone (MEK)	78-93-3	<1	2	2	2	19
2-Furaldehyde	98-01-1	<1	<1	<1	<1	21
2-Methylfurane	534-22-5	<1	<1	<1	<1	19
3-Ethenyl-pyridine[a]	1121-55-7	<1	<1	<1	<1	24
Acetic acid	64-19-7	<1	11	13	14	68
Acetone	67-64-1	<1	17	18	25	64
Benzene	71-43-2	<1	<1	<1	<1	22
Isoprene	78-79-5	8	6	7	10	135
Limonene	5989-27-5	<1	<1	<1	<1	21
m,p-Xylene	1330-20-7	<1	<1	<1	<1	18
Phenol	108-95-2	<1	<1	<1	<1	15
Pyrrole	109-97-7	<1	<1	<1	<1	61
Toluene	108-88-3	<1	<1	<1	<1	44
Formaldehyde[b]	50-00-0	<1	8	11	16	86
Acetaldehyde[b]	75-07-0	<1	2	2	3	119
Propanal[b]	123-38-6	<0.2	<0.2	<0.2	<0.2	12

Schripp et al, *Indoor Air 2013*

Chemical studies

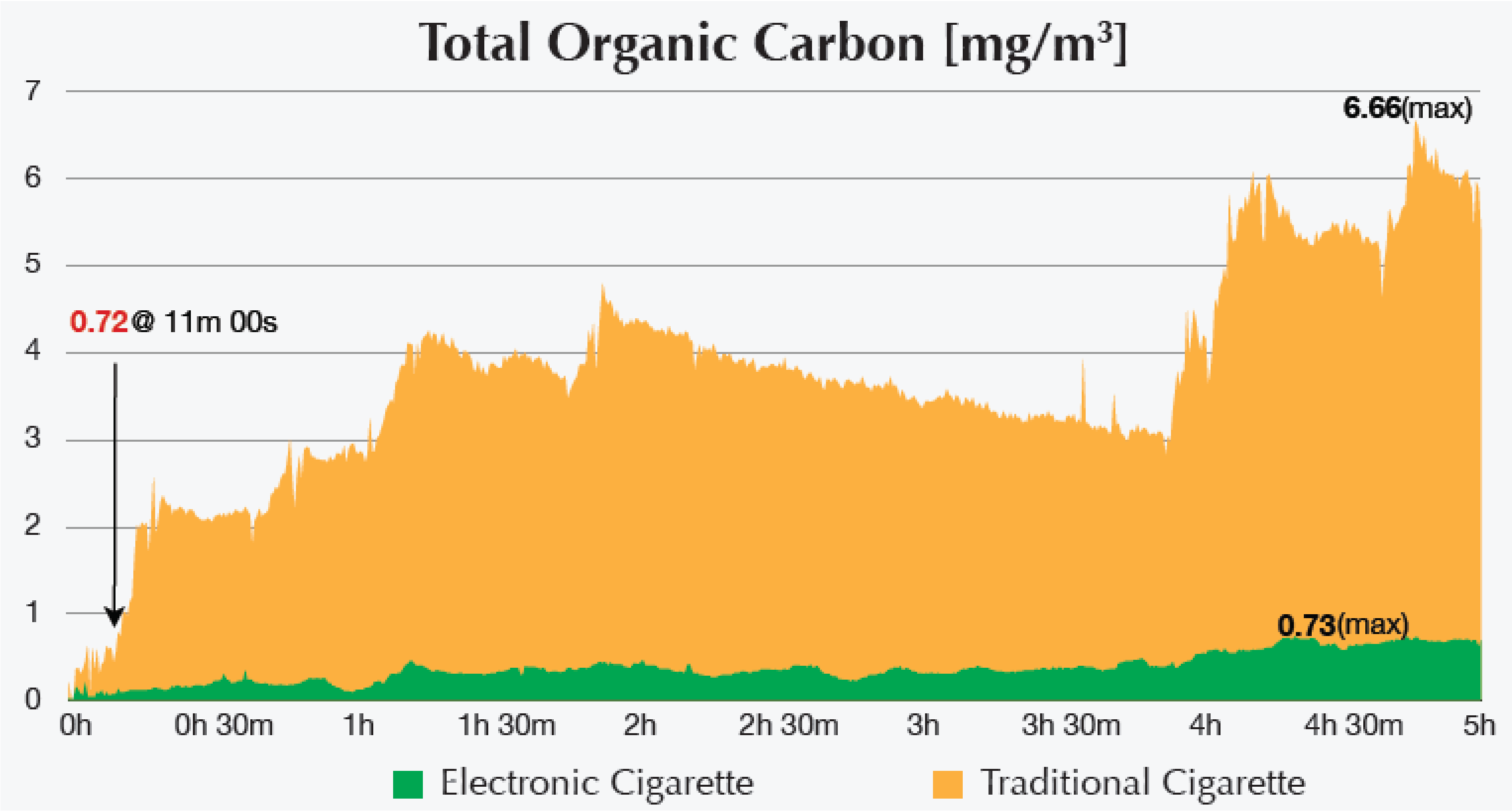
Passive vaping



Schripp et al, *Indoor Air 2013*

Chemical studies

Passive vaping



Romagna, Farsalinos et al, *SRNT Europe 2012*

Chemical studies

Passive vaping

Parameter	Measured Levels Mean Concentration [µg/m³] Traditional Cigarette	Electronic Cigarette
TOC*	6660	730
Nicotine	34	0
Acrolein	20	0
Toluene	1.7	0
Xylene	0.2	0
PAHs	9.4	0

*peak concentration

Romagna, Farsalinos et al, *SRNT Europe 2012*

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Toxicology studies

Table 1 Supplement: NOAELs, and IC_{50}s for E-juice Products in the Screen

Inv. No	E Juice	Company	Nicotine (mg /ml)	hESC IC_{50}	hESC NOAEL	mNSC IC_{50}	mNSC NOAEL	hPF IC_{50}	hPF NOAEL
32	Propylene Glycol	FS-USA[1]		>1	0.3	>1	0.3	>1	>1
33	Vegetable Glycerin	FS-USA		>1	>1	>1	>1	>1	>1
18	Bubblegum	FS-USA	24mg	>1	0.3	>1	0.3	>1	>1
30	Butterscotch	FS-USA	0mg	>1	0.3	>1	0.1	>1	0.001
29	Butterscotch	FS-USA	6mg	>1	0.1	>1	0.1	>1	>1
26	Caramel	FS-USA	0mg	>1	0.3	>1	0.1	>1	>1
27	Caramel	FS-USA	6mg	>1	0.3	>1	0.3	>1	0.1
28	Caramel	FS-USA	6mg	>1	0.3	>1	0.3	>1	0.3
40	Caramel	Global Smoke	18mg	0.75	0.1	>1	0.3	0.41	0.01
19	Butterfing	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	>1
23	Menthol A	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.45	0.3
7	Wisconsir	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	>1
1	Domestic	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	>1
13	JC Origina	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	>1
12	French Va	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.97	0.3
25	Vanilla Ta	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.19	0.03
17	Tennesse	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	0.3
5	Tennesse	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	0.03
2	Island	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	>1
24	Pure Nico	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.35	0.001
6	Valencia	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	0.03
14	Mint Choc	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	0.1
4	Swiss Dar	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.30	0.1
21	Caramel	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.22	0.01
11	Espresso	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	>1	0.3
3	Mercado	Red Oak	18mg	0.08	0.01	0.09	0.03	0.82	0.3
15	Simply Strawberry	Johnson Creek	18mg	0.06	0.01	0.43	0.3	>1	0.1
8	Arctic Menthol	Johnson Creek	18mg	0.05	0.01	0.19	0.1	>1	0.3
20	Butterscotch	FS-USA	0mg	0.06	0.03	0.22	0.03	0.26	0.03
16	Summer Peach	Johnson Creek	18mg	0.04	0.01	0.45	0.1	>1	0.3
9	Black Cherry	Johnson Creek	18mg	0.05	0.01	0.16	0.1	>1	0.3
34	JC Original	Johnson Creek	11mg	0.04	0.01	0.46	0.1	>1	>1
10	Chocolate Truffle	Johnson Creek	18mg	0.03	0.01	0.26	0.03	>1	>1
31	Tennessee cured	Johnson Creek	11mg	0.03	0.01	0.30	0.1	>1	0.001
22	Cinnamon Ceylon	FS-USA	0mg	0.01	0.01	0.04	0.01	0.07	0.03
41	Butterscotch[2]	Freedom Smoke FlavourArt	0mg	-		0.58	0.3	0.26	0.03

Main problem

Test on LIQUID, not on VAPOR

Bahl et al, *Reprod Toxicol 2012*

Toxicology studies

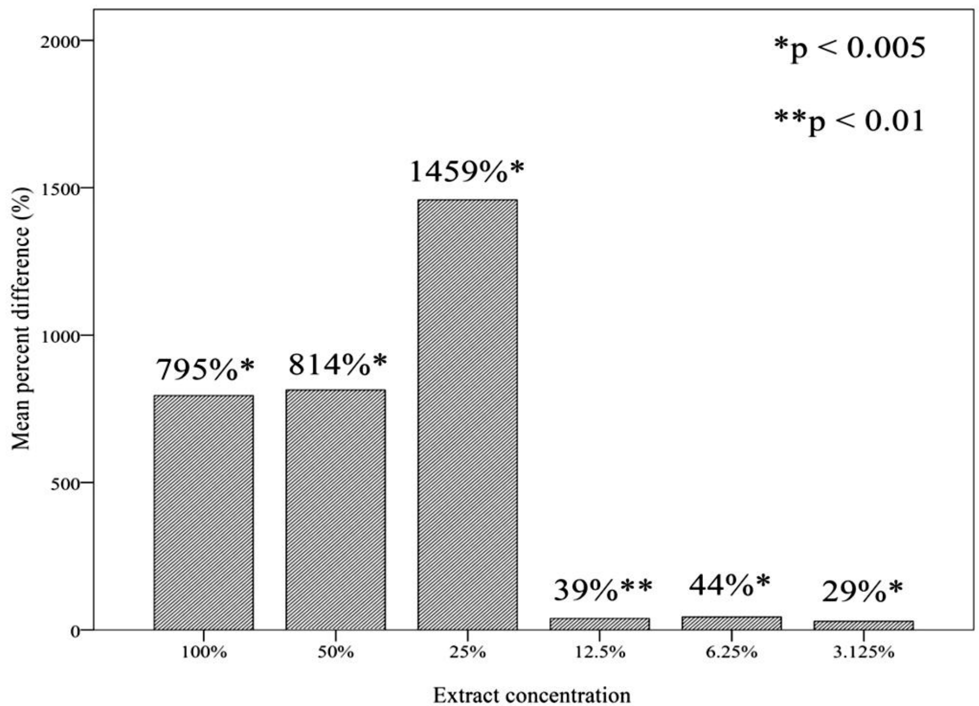
Tests on vapor

Extracts	Dilutions 100%[a]	50%[b]	25%[c]	12.5%[d]	6.25%[e]	3.125%[f]	P*
Tuscan[1]	94.5 ± 2.8	99.8 ± 5.7	104 ± 1.5	101.4 ± 4.1	100.7 ± 5.9	98.6 ± 3.8	0.216
Black fire[1]	96.3 ± 9.9	93.4 ± 2.5	94.4 ± 1.6	104.6 ± 2.9	95.3 ± 4.3	97 ± 3.2	0.159
Ozone[1]	90.7 ± 9.9	95.9 ± 9.1	96.2 ± 4.3	94.9 ± 6	96.7 ± 5.1	97 ± 4.9	0.879
Reggae night[1]	81.3 ± 5.1	90.3 ± 3.7	89.5 ± 4.2	89.7 ± 3.4	90.2 ± 5.7	91.6 ± 4.2	0.132
Vanilla	100 ± 2.4	98.5 ± 3.5	100.3 ± 2.0	100.1 ± 0.8	104.1 ± 3.1	98.3 ± 3.3	0.183
7foglie[1]	81.4 ± 2.9	87.5 ± 1.5	89.4 ± 4.0	87.1 ± 8.3	89.6 ± 12.1	93.2 ± 10.7	0.587
Max blend[1]	96.2 ± 6.0	97 ± 6.9	102.1 ± 7.4	111.8 ± 4.5	114.3 ± 1.7	115.5 ± 5.3	0.003
Virginia[1]	78.4 ± 14.4	86.1 ± 13.5	91.3 ± 15.6	96.4 ± 16.2	106.3 ± 9.7	104.4 ± 10.7	0.478
Perique black[1]	79.3 ± 1.5	89.8 ± 2.4	94.7 ± 1.2	95.3 ± 5.2	95.1 ± 2.4	93.9 ± 3.4	< 0.001
Layton blend[1]	101.1 ± 1.0	103.7 ± 0.8	102.7 ± 2.8	100.6 ± 2.1	103.4 ± 5.5	97.9 ± 4.2	0.295
Hypnotic[1]	93.8 ± 10.8	95.2 ± 14.0	106.2 ± 6.5	97.4 ± 5.1	100.6 ± 7.4	98.5 ± 3.9	0.579
Hazelnut	88.7 ± 1.4	90.1 ± 5.6	93.5 ± 6.7	91.5 ± 1.5	115.3 ± 8.0	117.8 ± 13.4	0.001
Shade[1]	83.6 ± 5.1	92.5 ± 3.9	94.6 ± 5.0	97.8 ± 5.9	101.5 ± 2.5	101.9 ± 1. 3	0.002
RY4[1]	88.4 ± 8.1	96.1 ± 3.7	98.7 ± 6.4	95.8 ± 7.4	98.9 ± 6.3	98.9 ± 5.9	0.378
Strawberry	85.8 ± 2.8	95.4 ± 2.3	97.5 ± 1.5	104.0 ± 6.2	99.6 ± 1.4	107.5 ± 1.2	< 0.001
Managua	79.1 ± 2.4	79.9 ± 3.3	79.1 ± 3.1	85.8 ± 2.0	86.4 ± 1.7	88.5 ± 3.5	0.002
Burley	102.2 ± 3.4	95.8 ± 2.9	97.6 ± 1.3	97.3 ± 3.4	106.2 ± 8.3	100.5 ± 6.2	0.171
Apple	95.2 ± 1.2	87.4 ± 2.7	100.8 ± 8.2	95.6 ± 3.9	101.8 ± 3.1	106.6 ± 15.6	0.106
Licorice	95.4 ± 3.9	93.9 ± 2.8	96.5 ± 2.6	98.5 ± 4.4	98.9 ± 2.0	99.6 ± 2.5	0.252
Chocolate	87.6 ± 2.2	89.6 ± 0.6	93.2 ± 1.3	93.4 ± 1.5	93.7 ± 1.9	98.9 ± 1.2	< 0.001
Coffee	51.0 ± 2.6	85.9 ± 11.8	92.0 ± 8.9	101.5 ± 3.1	112.2 ± 3.6	114.5 ± 1.1	<0.001
CS	**5.7 ± 0.7**	**9.4 ± 5.3**	**5.9 ± 0.9**	**72.8 ± 9.7**	**77.8 ± 1.8**	**89.1 ± 3.5**	**< 0.001**

Romagna, Farsalinos et al, *Inhal Toxicol 2013*

Toxicology studies

Tests on vapor



Relative difference in viability between cigarette smoke and worst-performing vapor extract

Romagna, Farsalinos et al, *Inhal Toxicol 2013*

Toxicology studies

Tests on vapor
Myocardial cells

Farsalinos et al, *Int J Environm Res Public Health 2013*

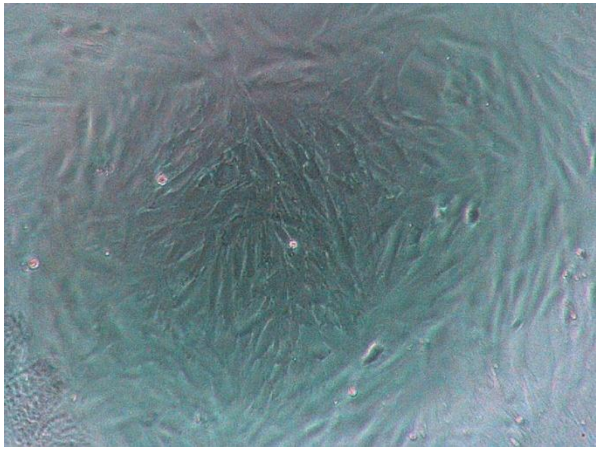
Table 2. Myocardial cell viability in cigarette smoke extract and in electronic cigarette vapour extracts produced at 3.7 volts.

	Dilutions					
Samples-nicotine (mg/mL)	100% [a]	50% [b]	25% [c]	12.5% [d]	6.25% [e]	*p* *
Base-0	105.1 ± 1.2	103.5 ± 1.9	101.3 ± 4.2	100.7 ± 3.4	100.4 ± 2.3	0.251
Golden Margy-6	89.2 ± 0.2	93.0 ± 2.2	92.1 ± 1.3	95.3 ± 3.6	93.0 ± 6.3	0.361
RY69-6	98.9 ± 4.6	101.2 ± 5.4	96.0 ± 13.0	100.5 ± 2.7	100.2 ± 9.2	0.932
City-6	93.6 ± 2.5	89.4 ± 4.2	94.6 ± 2.3	93.3 ± 2.3	93.8 ± 2.8	0.282
Cinnamon Cookies-6	64.8 ± 2.5	100.8 ± 2.0	97.2 ± 2.9	99.3 ± 1.7	99.2 ± 3.8	<0.001
Golden Virginia-8	86.6 ± 1.8	89.1 ± 1.0	94.2 ± 3.0	95.5 ± 0.7	97.1 ± 1.4	<0.001
RY4-9	73.8 ± 3.7	106.6 ± 1.1	104.4 ± 1.9	103.6 ± 4.0	100.7 ± 0.8	<0.001
MaxBlend-9	104.4 ± 1.6	102.4 ± 2.0	102.4 ± 2.8	101.2 ± 7.6	102.7 ± 2.0	0.901
Americano-9	85.0 ± 2.0	98.3 ± 1.7	90.9 ± 4.4	94.7 ± 3.5	94.1 ± 5.9	0.017
American Tobacco-11	109.0 ± 1.6	106.8 ± 0.5	104.9 ± 1.0	101.3 ± 3.1	103.6 ± 2.5	0.007
Tribeca-12	110.8 ± 2.8	103.9 ± 5.5	106.6 ± 7.9	102.4 ± 5.1	101.7 ± 3.0	0.268
Green apple-12	106.6 ± 2.0	106.8 ± 2.0	105.2 ± 3.3	103.6 ± 4.5	99.2 ± 2.5	0.060
El Toro Cigarrillos-12(1) [f]	39.1 ± 1.2	52.5 ± 1.8	81.0 ± 2.0	92.6 ± 0.4	99.2 ± 1.0	<0.001
El Toro Cigarrillos-12(2) [f]	22.3 ± 4.0	66.9 ± 6.2	104.1 ± 5.8	109.9 ± 6.0	112.0 ± 8.8	<0.001
Silverberry-12	108.2 ± 8.5	107.2 ± 2.7	106.0 ± 1.7	103.2 ± 0.7	100.3 ± 2.0	0.200
Virginia-18	82.1 ± 0.8	95.8 ± 8.6	95.1 ± 3.0	90.6 ± 7.0	93.3 ± 8.5	0.136
Classic-18	95.0 ± 5.1	104.0 ± 9.1	101.1 ± 12.9	107.3 ± 8.3	89.7 ± 6.4	0.176
Tobacco echo-18	96.1 ± 5.0	96.4 ± 7.7	101.7 ± 3.1	102.7 ± 4.7	96.3 ± 7.3	0.479
Bebeka-18	75.7 ± 8.6	87.5 ± 2.2	90.8 ± 1.6	95.9 ± 1.9	99.0 ± 2.3	<0.001
El Toro Guevara-18 [f]	84.5 ± 3.0	91.0 ± 3.5	94.6 ± 1.3	98.8 ± 2.0	102.5 ± 1.7	<0.001
El Toro Puros-24 [f]	2.2 ± 0.6	7.4 ± 3.9	84.5 ± 6.5	115.3 ± 11.7	111.9 ± 7.4	<0.001
CS [g]	3.9 ± 0.2	5.2 ± 0.8	3.1 ± 0.2	38.2 ± 0.6	76.9 ± 2.0	<0.001

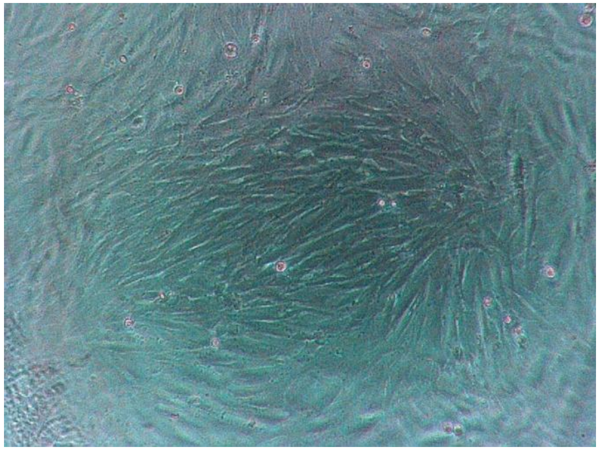
Farsalinos et al, *Int J Environm Res Public Health 2013*

Toxicology studies

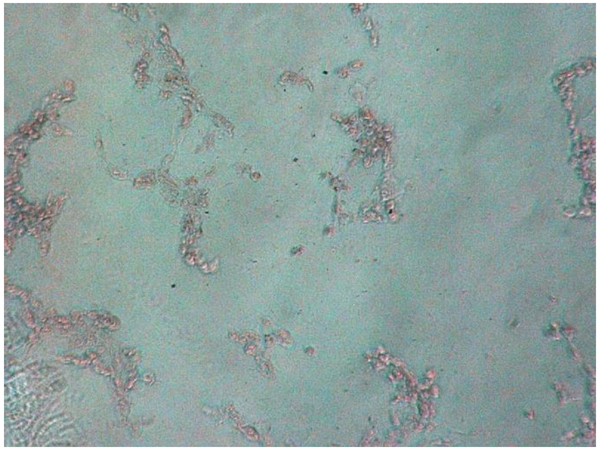
Tests on vapor
Myocardial cells



Untreated cells



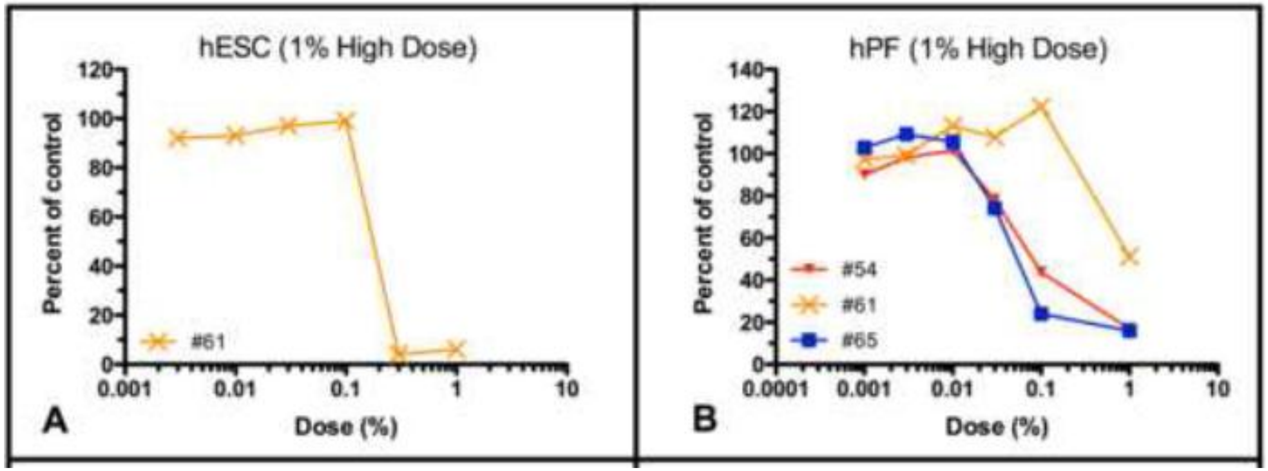
E-cigarette vapor treated cells



Cigarette smoke treated cells

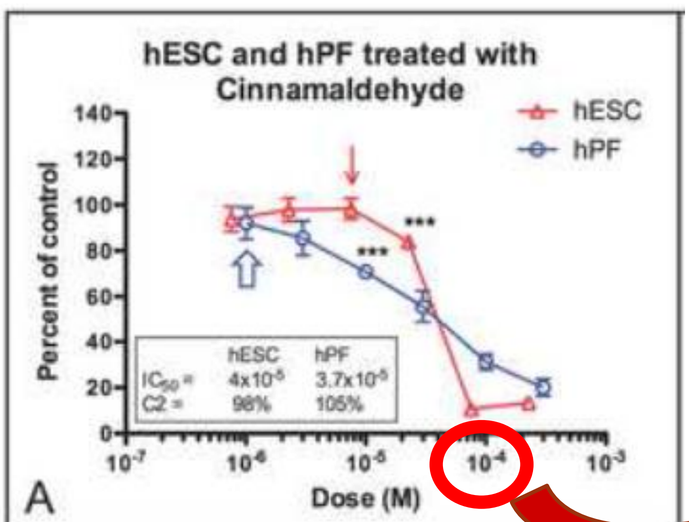
Farsalinos et al, *Int J Environm Res Public Health 2013*

Toxicology studies



Cinnamon toxicity (?)

Tests on liquid
Irrelevant to e-cig



Approved
cinnamaldehyde dose
up to 4 x 10^{-2} M
(EPA, 2000)

Behar et al, *Toxicol in Vitro 2013*

Safety studies

- Laboratory
  - Chemical
  - Toxicology
- Clinical
  - Pathophysiology (short-term)
  - Epidemiology (long-term)

Safety studies

- Laboratory
  - Chemical
  - Toxicology
- Clinical
  - **Pathophysiology (short-term)**
  - **Epidemiology (long-term)**

Clinical studies

- Few studies performed on safety
- Long-term studies cannot be performed
- May get valuable information from studies on pathophysiology of smoking-related disease, immediate effects of use, short-term follow-up and surveys

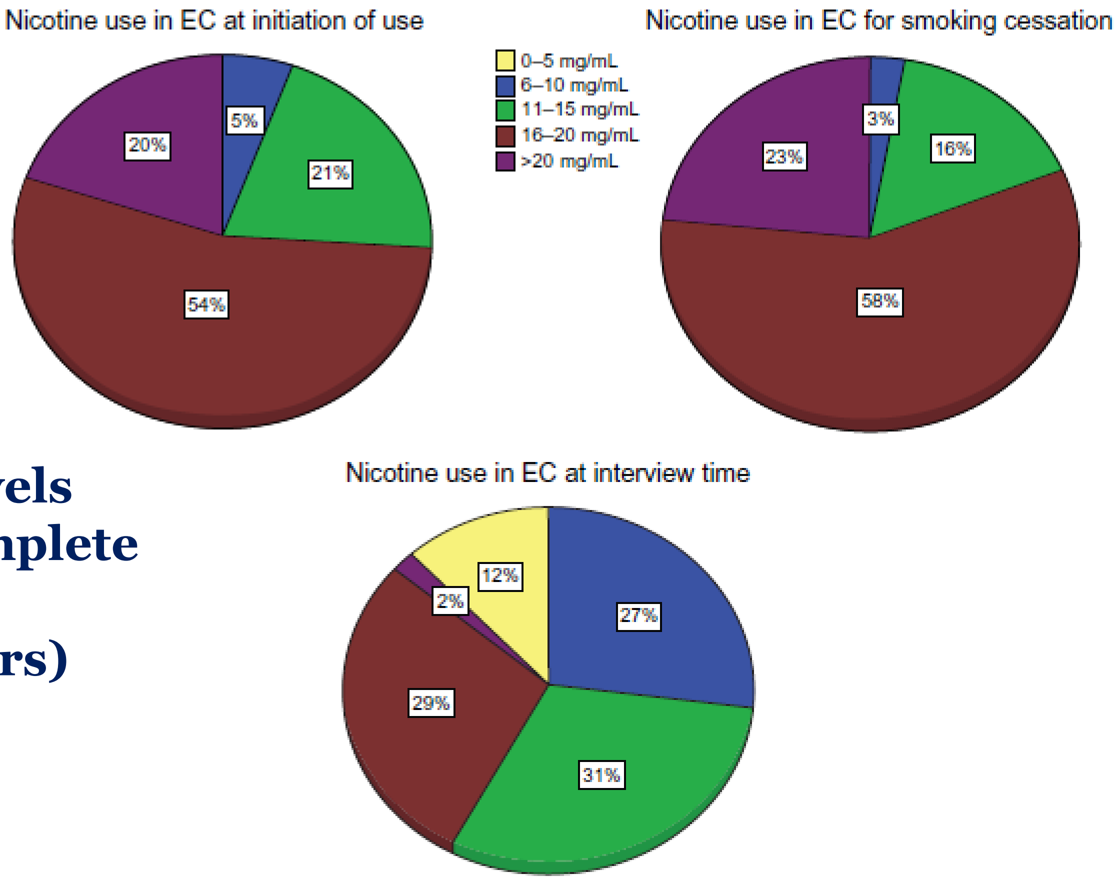
Clinical studies

Nicotine levels in e-cigarette unlikely to cause overdose

- Experienced e-cigarette users
- 5 minutes-13 puffs
- Liquid consumption: 0.052 ± 0.13ml
- Nicotine consumption: ≈ **1mg** from 18mg/ml nicotine-containing liquid
- Levels of nicotine absorption lower than smoking (Dawkins et al, 2013)

Farsalinos et al, *Subst Abuse 2013*

Clinical studies



High nicotine levels important in complete substitution of smoking (111 users)

Farsalinos et al, *Subst Abuse 2013*

Clinical studies

Effects on lung function

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*

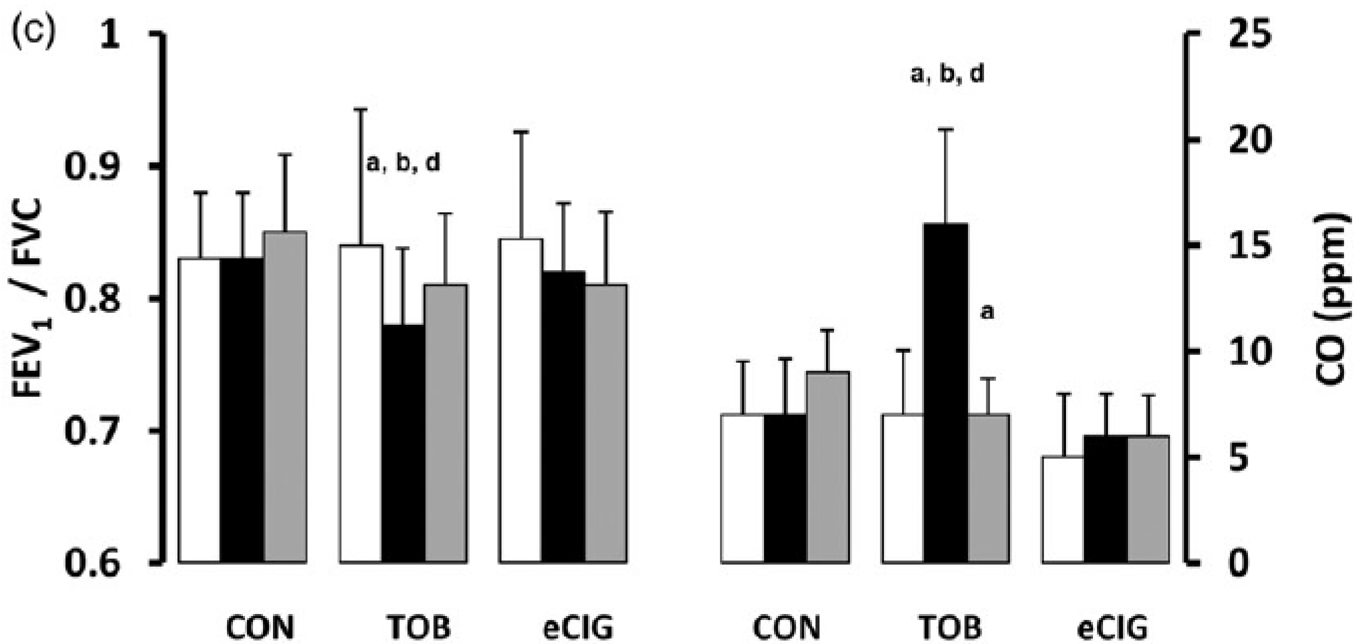
Variable	R^2	β	95% CI	*P* Value[a]
FENO, ppb	0.950	−2.194	−4.038 to −0.350	.021[b]
IOS Z5Hz, kPa/(L/s)	0.991	0.040	0.015 to 0.065	.003[b]
IOS R5Hz, kPa/(L/s)	0.991	0.040	0.015 to 0.065	.003[b]
IOS R10Hz, kPa/(L/s)	0.990	0.034	0.009 to 0.058	.008[b]
IOS R20Hz, kPa/(L/s)	0.981	0.043	0.012 to 0.074	.007[b]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

- No mention on changes in FEV1/FVC
- Could be due to short-term mechanical irritation and not damage
- Data from surveys report temporary cough as initial symptom
- No comparison with regular cigarettes

Vardavas et al, *Chest 2012*

Clinical studies

Effects on lung function



Flouris et al, *Inhal Toxicol 2013*

Clinical studies

Effects on cardiac function

	Smokers (n=20)	ECIG users (n=22)	P-value
Age (years)	36 ± 5	36 ± 5	0.971
Body-mass index (kg/m^2)	25.3 ± 2.5	26.5 ± 2.4	0.129
Body-surface area (m^2)	2.02 ± 0.22	2.09 ± 0.15	0.292
Systolic BP (mmHg)	125 ± 10	127 ± 9	0.479
Diastolic BP (mmHg)	76 ± 6	77 ± 7	0.913
Heart rate (per minute)	67 ± 8	67 ± 9	0.915
LVEDV (ml)	115 ± 23	120 ± 22	0.459
LVESV (ml)	45 ± 8	47 ± 10	0.492
SV (ml)	70 ± 17	73 ± 14	0.497
Ejection fraction (%)	60 ± 4	61 ± 4	0.578
LAd	35 ± 4	34 ± 4	0.688
LAVi (ml/m^2)	22 ± 5	20 ± 5	0.122
LVMi (g/m^2)	63 ± 10	68 ± 13	0.154

Farsalinos et al, *ESC 2012-Munich*

Clinical studies

Effects on cardiac function

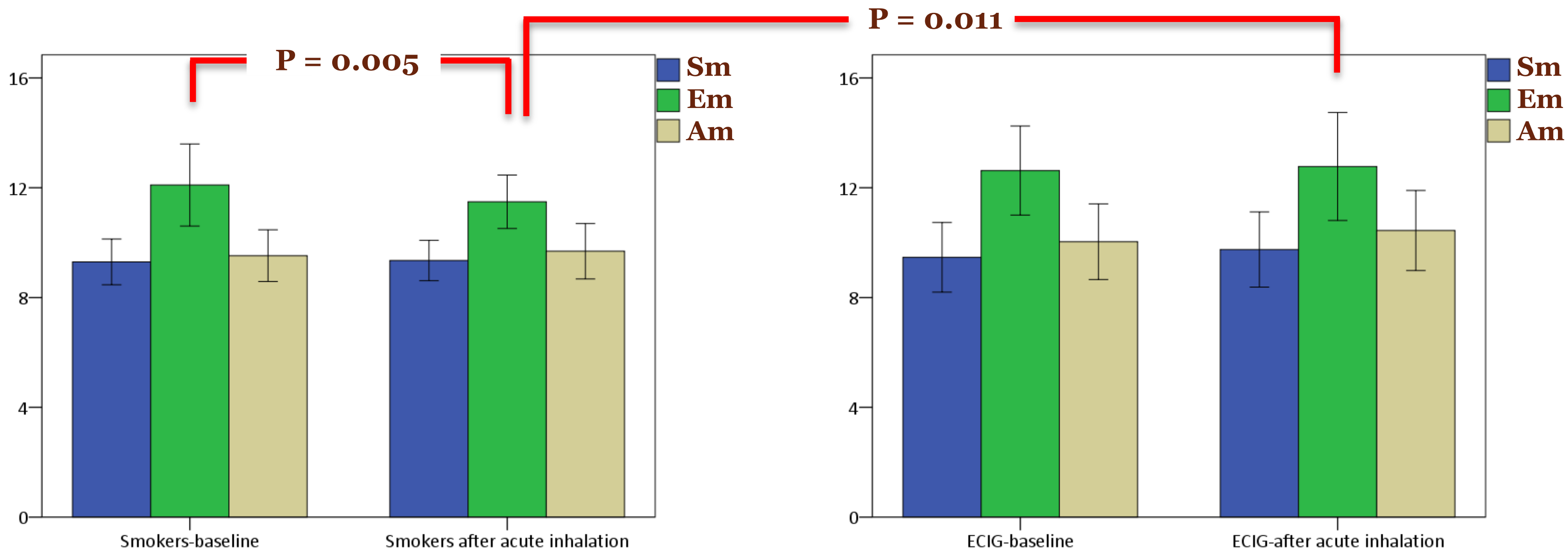
Hemodynamic changes
Post-use

	Smokers (n=20)	ECIG users (n=22)	P-value (smokers intra-group)	P-value (ECIG users intra-group)	P-value (inter-group after inhalation)
SBP (mmHg)	135 ± 7	128 ± 10	< 0.001	0.433	0.028
DBP (mmHg)	80 ± 7	81 ± 6	< 0.001	0.001	0.57
HR bpm	74 ± 8	68 ± 10	< 0.001	0.245	0.055
Ejection fraction (%)	60 ± 4	62 ± 4	0.317	0.224	0.571

Farsalinos et al, *ESC 2012-Munich*

Clinical studies

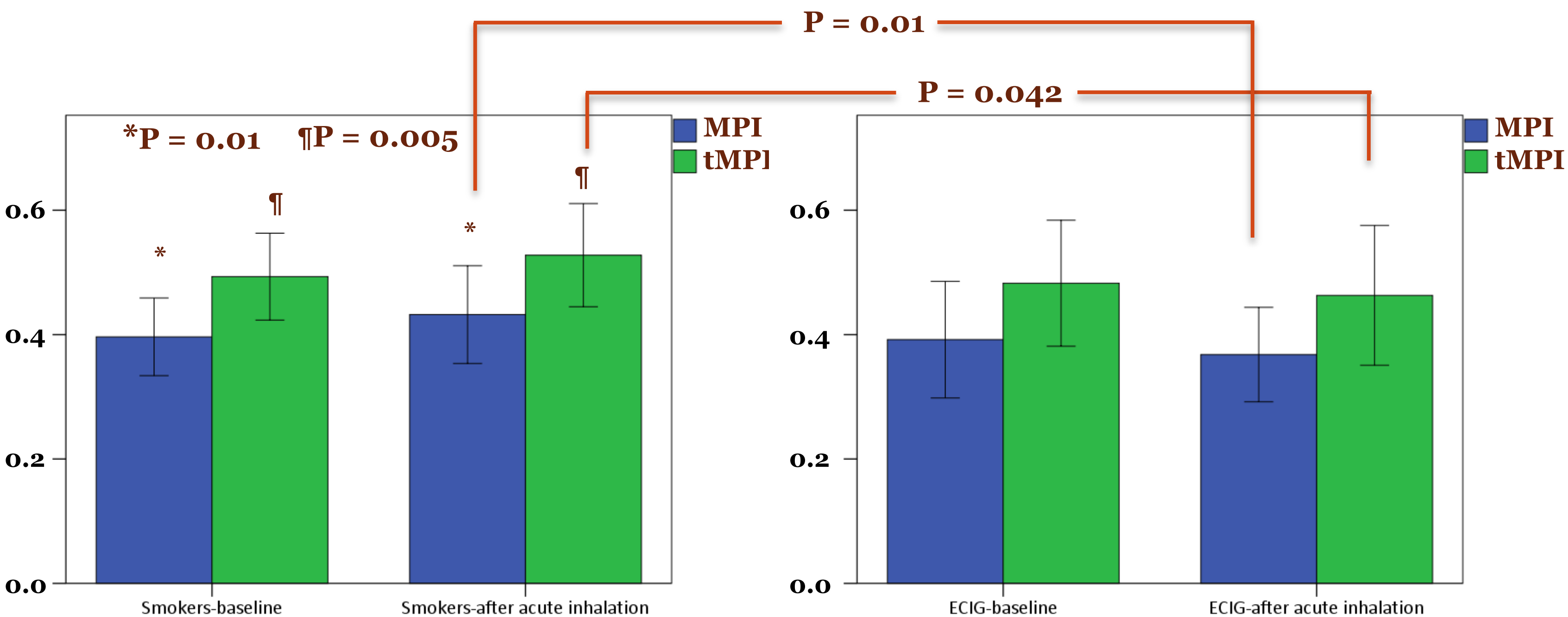
Effects on cardiac function



Farsalinos et al, *ESC 2012-Munich*

Clinical studies

Effects on cardiac function

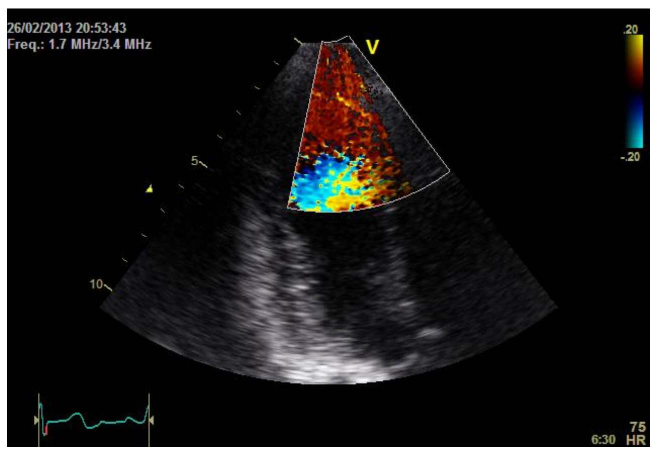


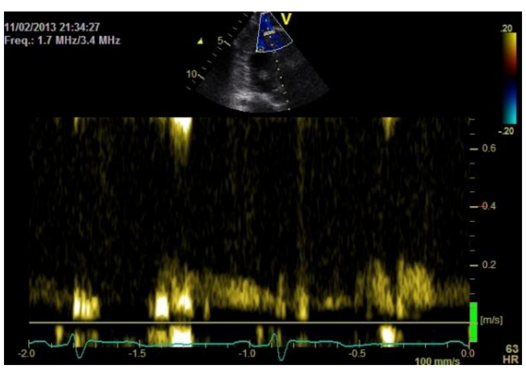
Farsalinos et al, *ESC 2012-Munich*

Clinical studies

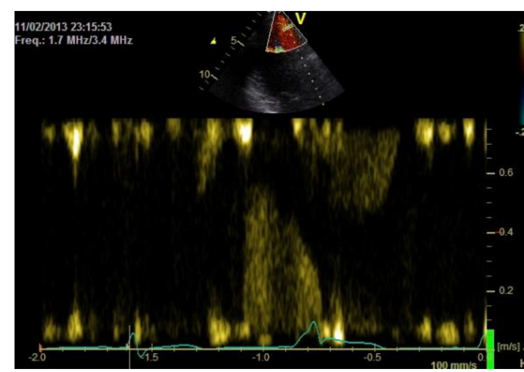
CFVR = velocity$_{\text{post-adenosine}}$ / velocity$_{\text{baseline}}$

CVRI = (MAP / velocity)$_{\text{post-adenosine}}$ / (MAP / velocity)$_{\text{baseline}}$





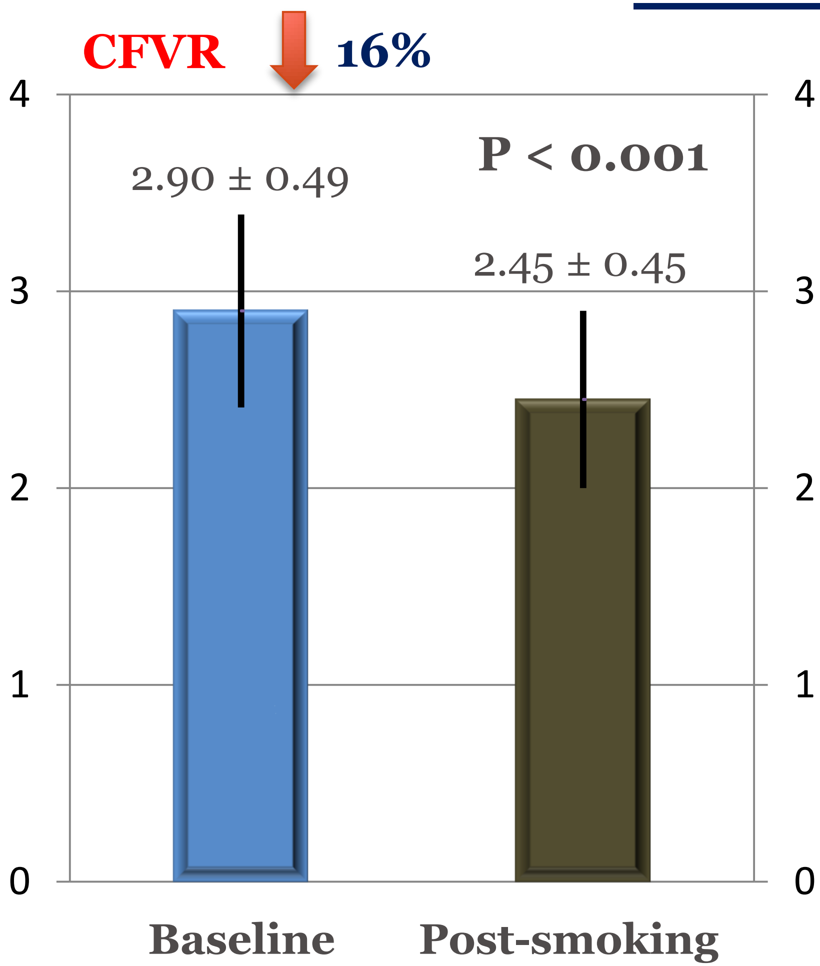
60 participants

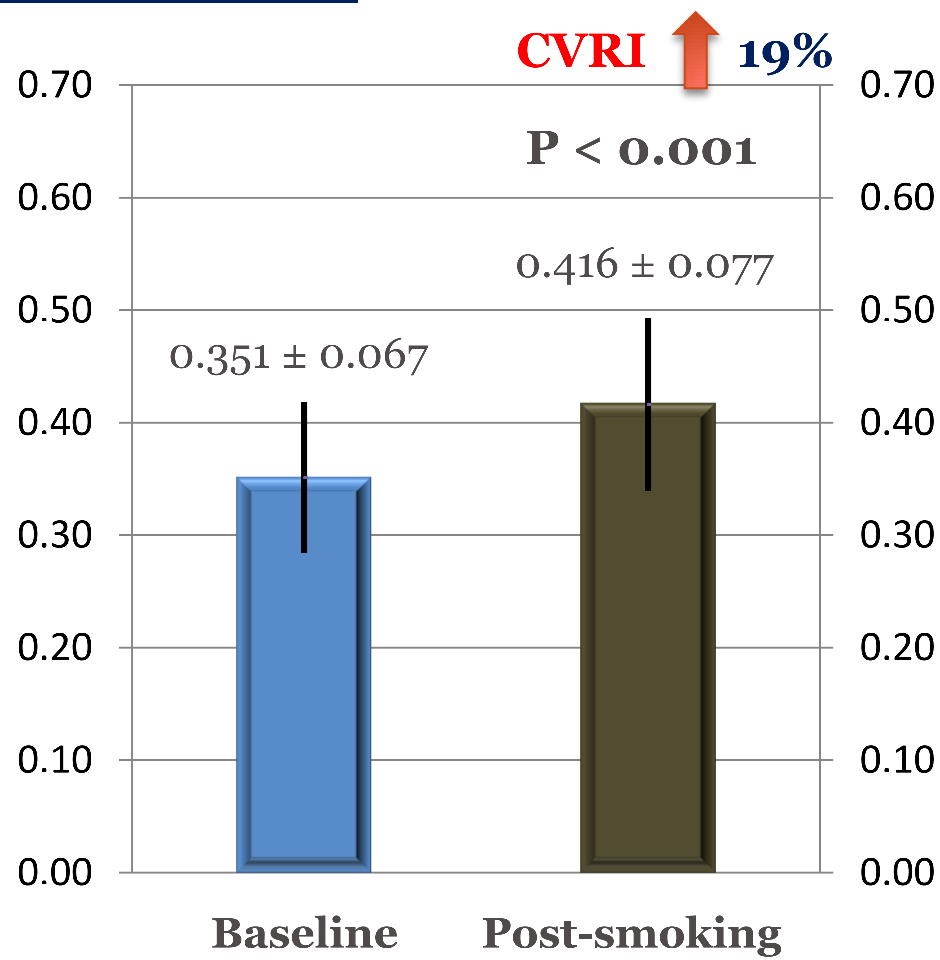


Farsalinos et al, *ESC 2013-Amsterdam*

Clinical studies

Smokers / cigarette

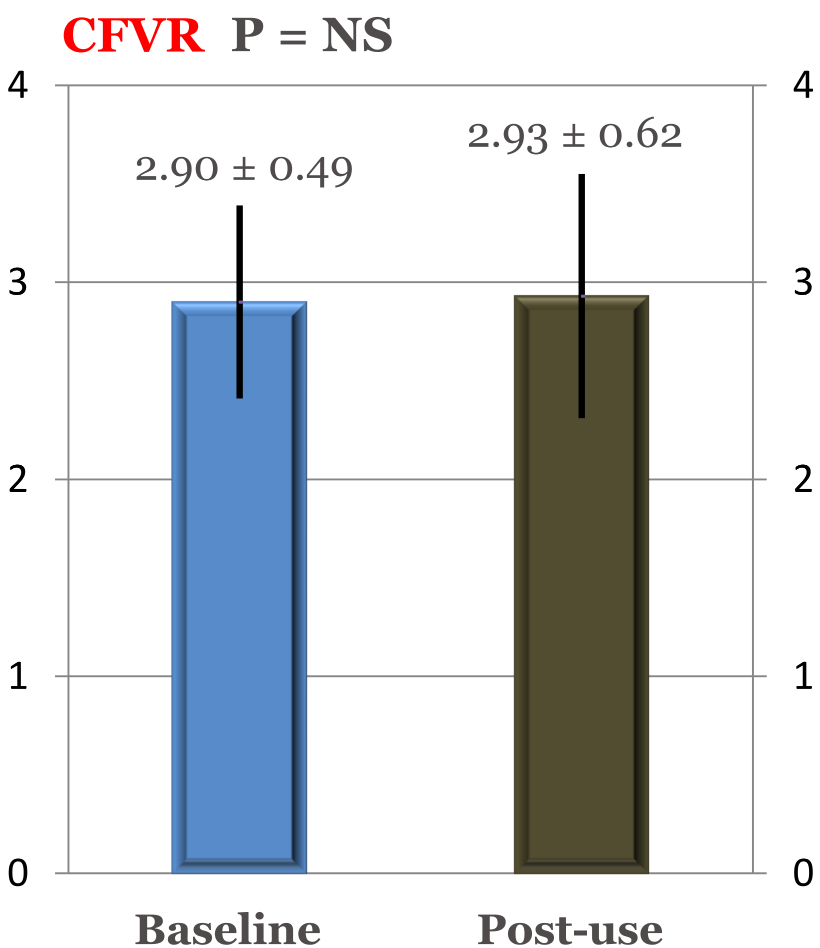


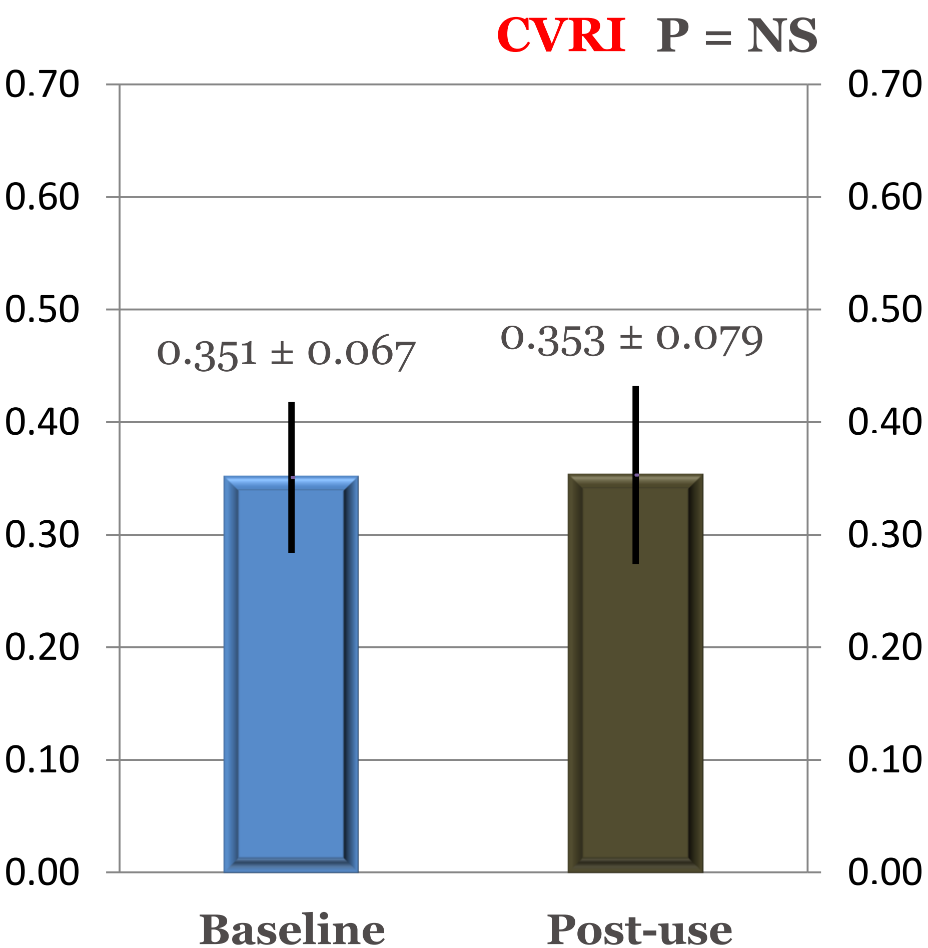


Farsalinos et al, *ESC 2013-Amsterdam*

Clinical studies

Smokers / e-cigarette

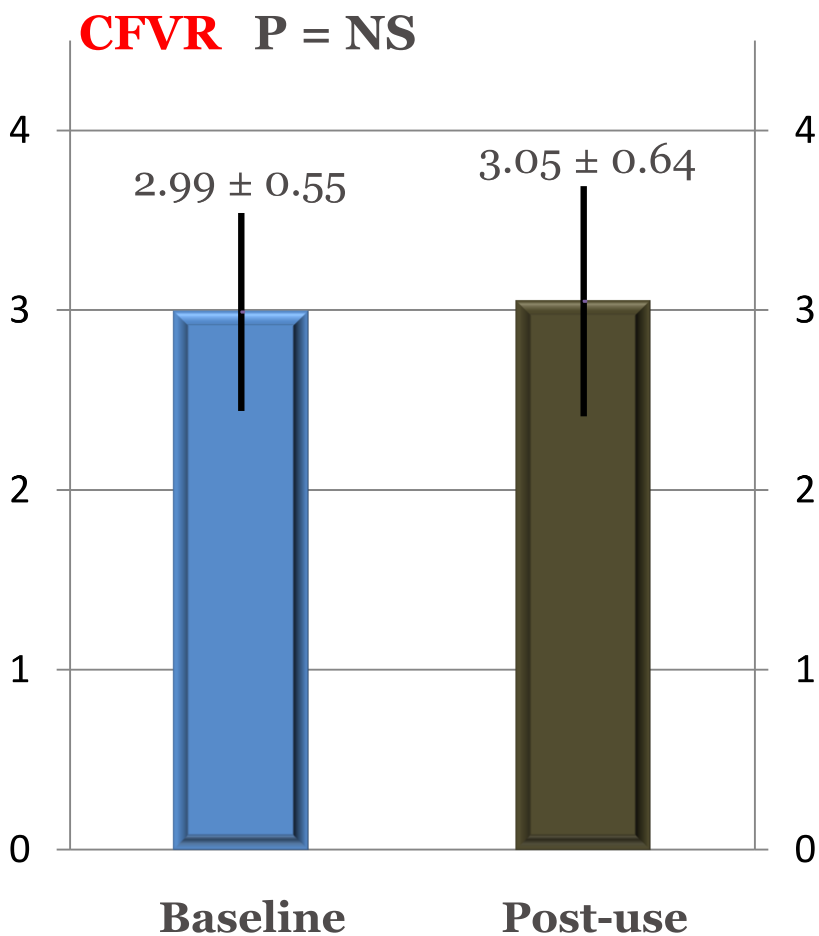


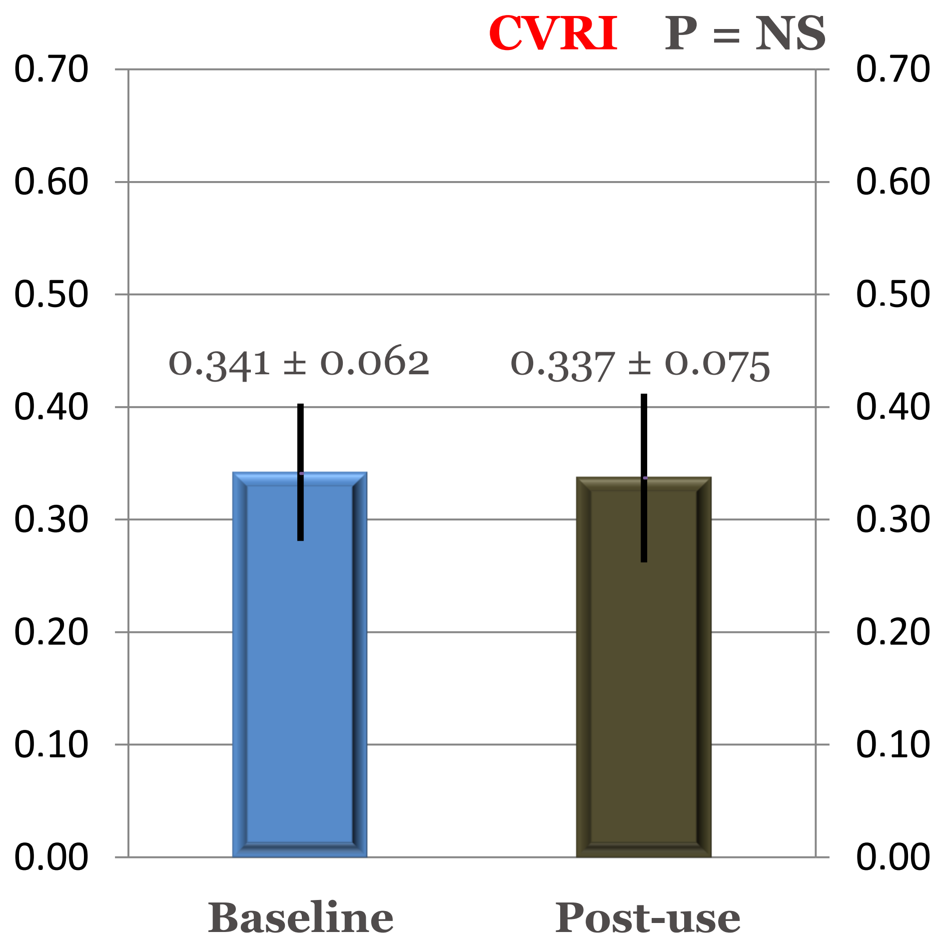


Farsalinos et al, *ESC 2013-Amsterdam*

Clinical studies

E-cigarette users

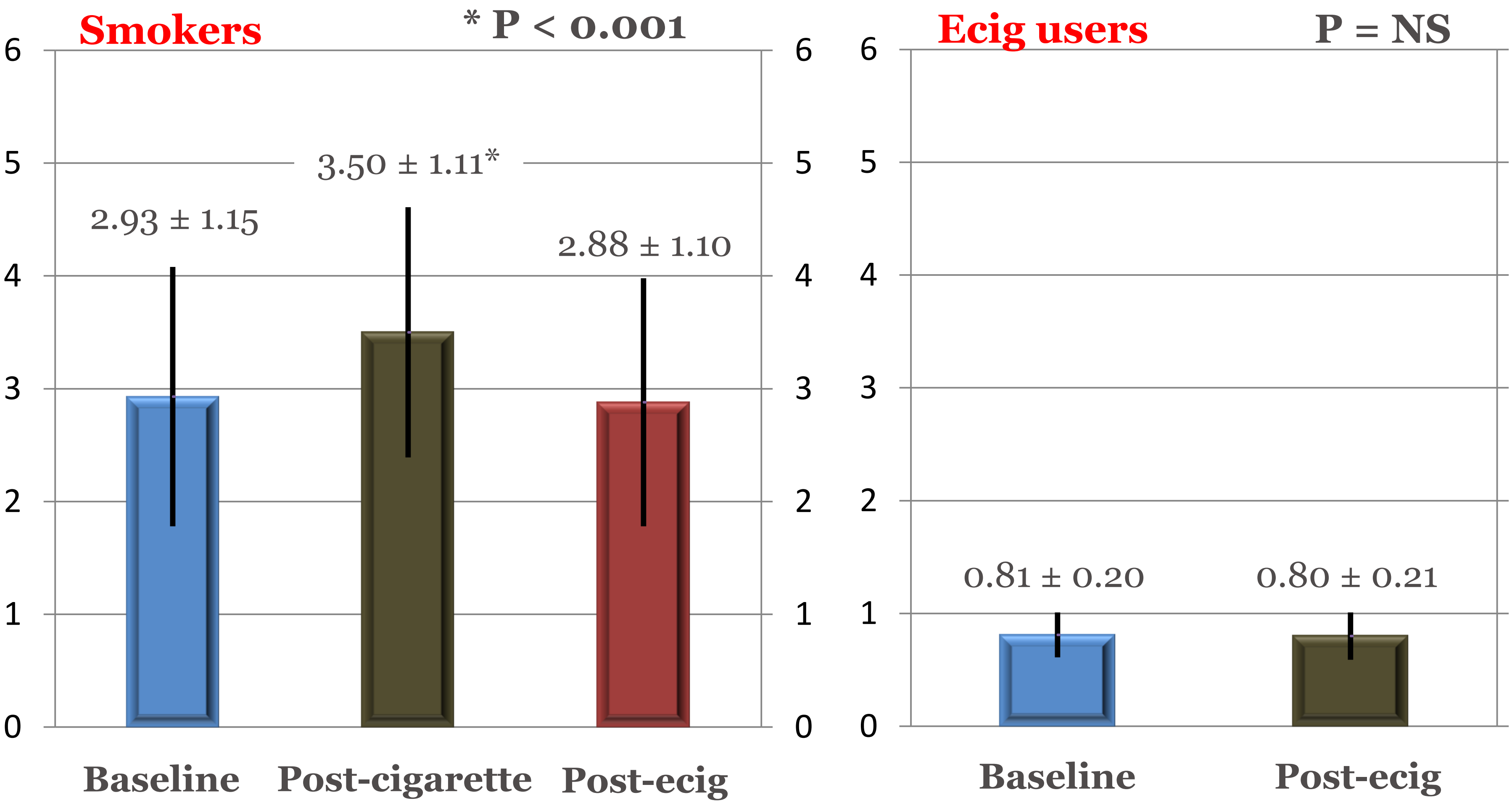




Farsalinos et al, *ESC 2013-Amsterdam*

Clinical studies

Carboxyhemoglobin



Farsalinos et al, *ESC 2013-Amsterdam*

Clinical studies

More to come…

- Effect on aortic elasticity (EUROECHO 2013)
- Effect on pulsed-wave velocity (measure of arterial stiffness)
- Always comparison with tobacco cigarettes

Clinical studies

What we need to know

- Long-term safety cannot be assessed unless 10-15 years have passed, because:
    - Smoking causes disease after many years of use
    - Current e-cigarette users are of young age (disease incidence is very low in this population)
    - E-cigarette is a new product

Clinical studies

What we need to know

- Lung function:
  - Need to compare with tobacco cigarettes
  - Acute lung dysfunction may be caused by pure mechanical irritation, which does not predict harm (e.g. cold weather)
  - Surveys have shown some irritation which is temporary, with subsequent beneficial effects (subjectively perceived)

- Cardiac function:
  - Variety of mechanisms by which smoking causes disease
  - Some of smoking adverse effects take long time to reverse (e.g. inflammatory markers)

Conclusions

- Although there are several chemical studies, few are performed on vapor
- Need for more toxicology studies
- Need for studies on atomiser materials
- Protocol and device handling are the most crucial factors in getting results applicable to real use
- Clinical studies are scarce; some already scheduled, need more
- Long-term studies impossible right now

Based on currently available data, it is reasonable to expect a significant benefit for the health of smokers who switch from tobacco to e-cigarette use, even in long-term users.

Conclusions

Research will help us define the best possible materials in e-liquids and devices, which should be done <u>without</u> killing variability and innovation


THANK YOU!