Safety/risk assessment of electronic cigarettes

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E-cigarette facts

- ✓New in the market
- ✓Awareness and use growing exponentially
- ✓Used by millions, mostly of young age
- ✓Nicotine delivery, dealing with behavioral addiction
- ✓No tobacco, no combustion
- ✓Any regulation should be based on scientific evidence

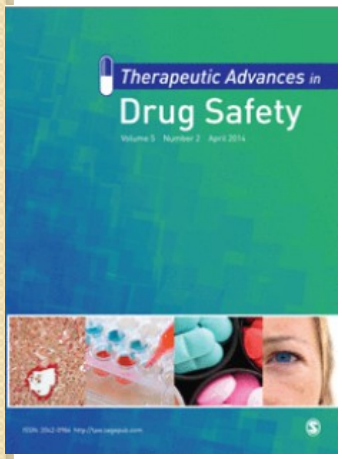
Why do e-cigarettes exist?

- NRTs < 6% success rate (Moore et al., BMJ 2009)
- Oral medications < 20% success rate (Rigotti et al., Circulation 2010)
- Smoking the most important controllable-reversible risk factor for disease
- Quit or die strategy (?)

Safety/risk assessment

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

Safety/risk assessment



Therapeutic Advances in Drug Safety *Review*

Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review

Konstantinos E. Farsalinos and Riccardo Polosa

Ther Adv Drug Saf
1–20
DOI: 10.1177/2042098614524430

Safety/risk assessment

- Compared to what?
  - Clean air?
  - Using nothing?

✓E-cigarettes should be marketed for smokers only

✓It is a **substitute** for smoking

✓Users would have been smokers if e-cigarettes did not exist

Safety/risk assessment

- Comparison with smoking
  - Comparison with other reduced-risk products
  - Take into consider the pleasure factor-acceptability by users

Safety/risk assessment

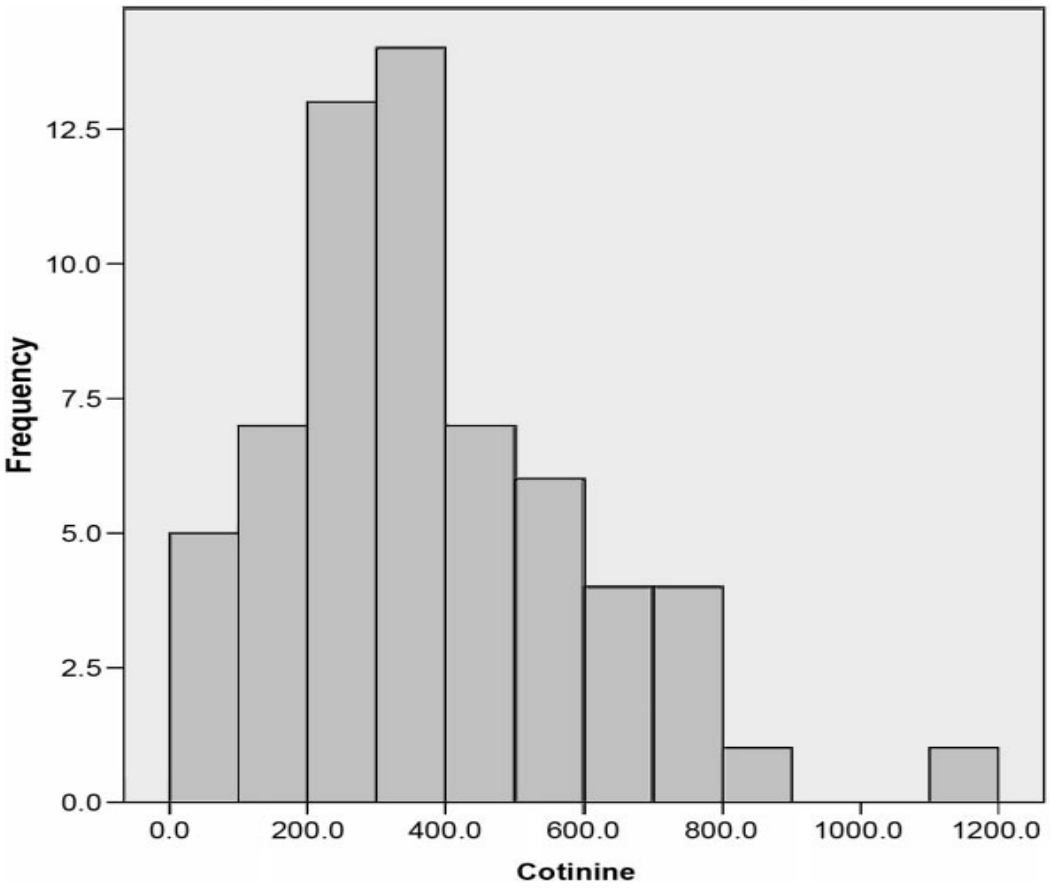
- Laboratory
  - **Chemical**
  - Toxicology
- Clinical
  - Pathophysiology (short-term)
  - Epidemiology (long-term)

Chemical studies

- Nicotine IS NOT the reason for smoking-related disease
- Officially IS NOT a carcinogen (IARC)
- DOES NOT cause lung disease
- Has minimal effect in CVD

- Even in e-cigarettes, it is NOT nicotine but other chemicals that may be problematic

Chemical studies

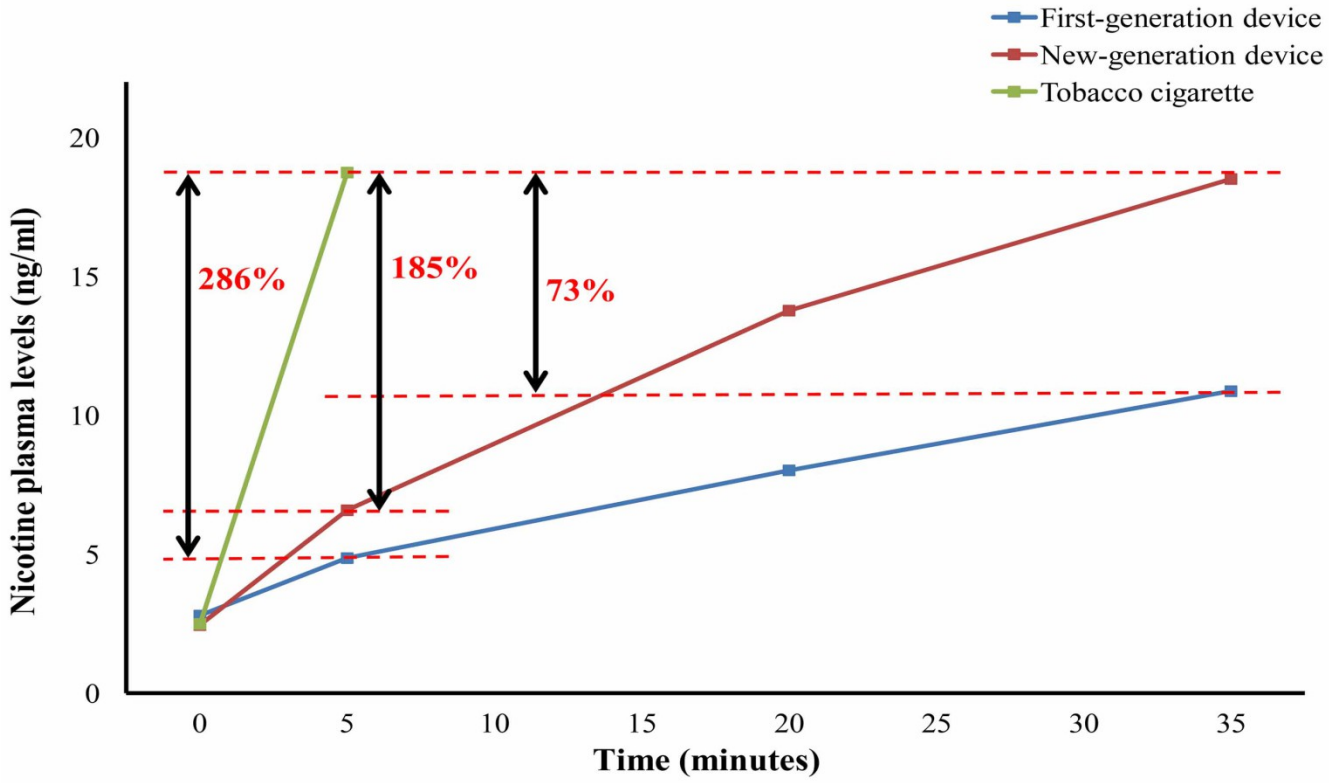


Daily nicotine intake from e-cigarettes similar or lower than smoking

Etter, *Addiction* 2014

Chemical studies

Nicotine IS NOT delivered at higher doses from e-cigarette compared to tobacco



Farsalinos et al., *Sci Rep* 2014

Chemical studies

Nitrosamines are major carcinogens in tobacco cigarettes

Table 3. Levels of nitrosamines found in electronic and tobacco cigarettes. Prepared based on information from Laugesen [2009], Cahn and Siegel [2011] and Kim and Shin [2013].

Product	Total nitrosamines levels (ng)	Daily exposure (ng)	Ratio[4]
Electronic cigarette (per ml)	13	52[1]	1
Nicotine gum (per piece)	2	48[2]	0.92
Winston (per cigarette)	3365	50 475[3]	971
Newport (per cigarette)	3885	50 775[3]	976
Marlboro (per cigarette)	6260	93 900[3]	1806
Camel (per cigarette)	5191	77 865[3]	1497

[1]Based on average daily use of 4ml liquid
[2]Based on maximum recommended consumption of 24 pieces per day
[3]Based on consumption of 15 cigarettes per day
[4] Difference (number-fold) between electronic cigarette and all other products in daily exposure to nitrosamines

Farsalinos & Polosa, *Ther Adv Drug Safety*

Chemical studies

OPEN ACCESS Freely available online

PLOS ONE

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].
Silicon	2.24		Upper respiratory irritation, coughing, shortness of breath, bronchitis [43,44].
Calcium	1.03		Nose/throat irritation, coughing/wheezing [45].
Iron	0.52	0.042 [40]	Respiratory irritation, fume metal fever, siderosis, fibrosis [46].
Aluminum	0.394	0.22 [40]	Impaired lung function, asthma, and pulmonary fibrosis [47].
Potassium	0.292	70 [40]	May originate from silicate beads along with sodium, 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].

Chemical studies

Table 1. Elemental Impurities for Drug Products

Element	Oral Daily Dose PDE[a] (µg/day)	Parenteral Daily Dose PDE (µg/day)	Inhalational Daily Dose PDE (µg/day)
Cadmium	25	2.5	1.5
Lead	5	5	5
Inorganic arsenic[b]	1.5	1.5	1.5
Inorganic mercury[b]	15	1.5	1.5
Iridium	100	10	1.5
Osmium	100	10	1.5
Palladium	100	10	1.5
Platinum	100	10	1.5
Rhodium	100	10	1.5
Ruthenium	100	10	1.5
Chromium	—[c]	—[c]	25
Molybdenum	100	10	10 (ERR 1-Oct-2012)
Nickel	500	50	1.5
Vanadium	100	10	30
Copper	1000	100	100 (ERR 1-Feb-2013)

[a] PDE = Permissible daily exposure based on a 50-kg person.
[b] See *Speciation* section.
[c] Not a safety concern.

US Pharmacopoeia, 2013

Chemical studies

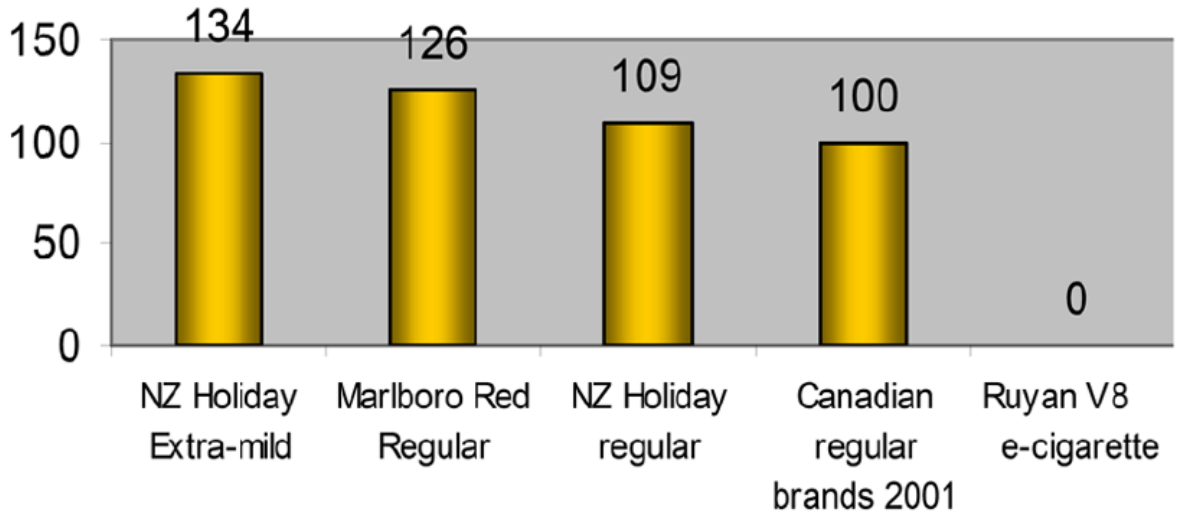


Figure 3. Toxic emissions score, adjusted for nicotine, for electronic cigarette and popular cigarette brands. (Reproduced with permission from Laugesen [2009]).

Farsalinos & Polosa, *Ther Adv Drug Safety*

Chemical studies

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

Toxic substances do exist, but levels far lower compared to tobacco cigarettes

Goniewicz et al, *Tob Control* 2013

Chemical studies

Passive vaping

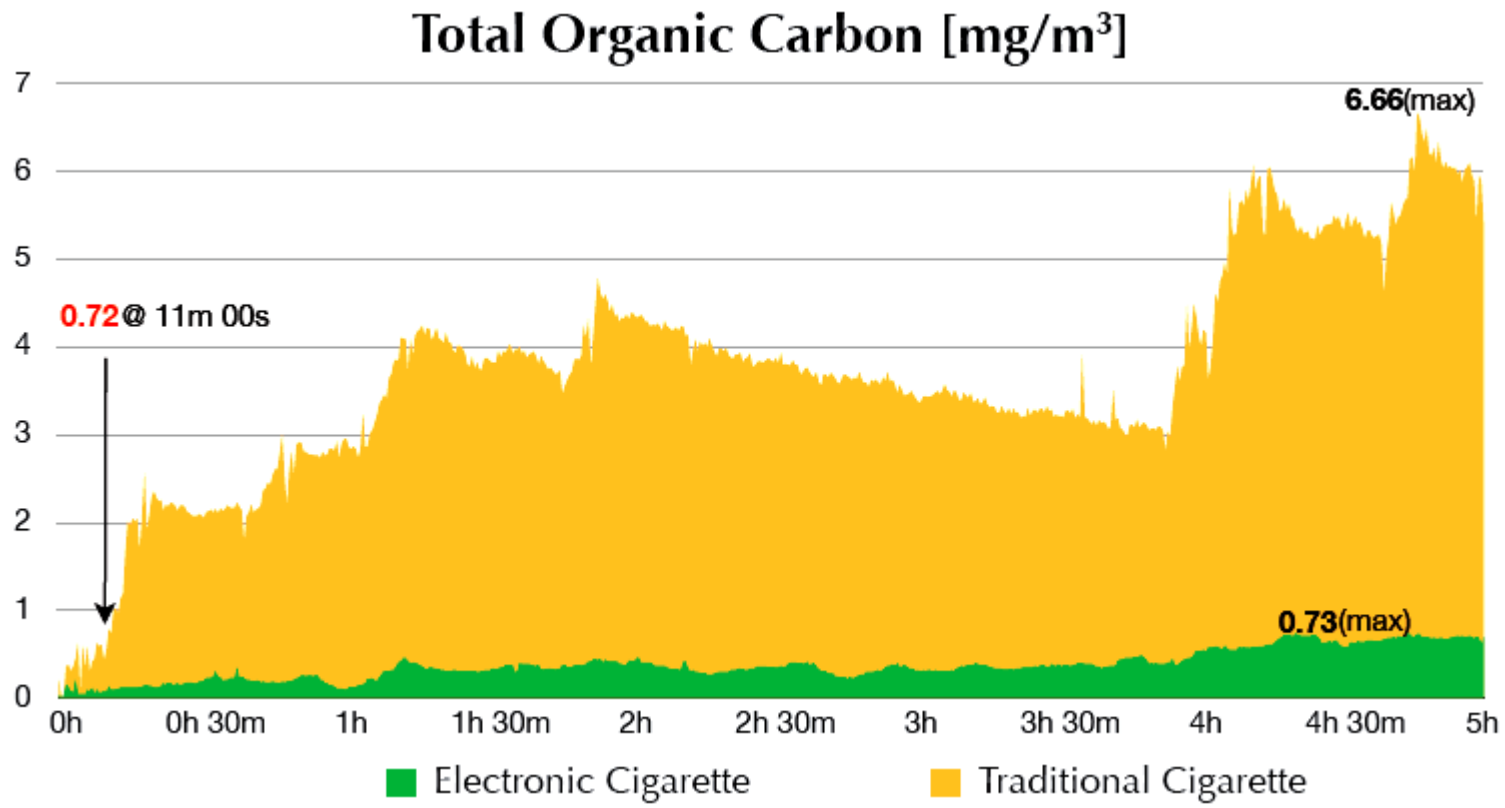
Table 4 Concentrations ($\mu g/m^3$) of selected compounds during the 8-m^3 emission test chamber measurement of e-cigarette A and conventional cigarette using Tenax TA and DNPH

			E-cigarette			Conventional cigarette
Compounds	CAS	Participant blank	Liquid 1	Liquid 2	Liquid 3	
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



Romagna, Farsalinos et al, *SRNT Europe* 2012

Chemical studies

- ✓In conclusion, chemical studies have found that exposure to toxic chemicals from ECs is by far lower compared with tobacco cigarettes.
- ✓Besides comparing the levels of specific chemicals released from tobacco and ECs, it should be taken into consideration that **the vast majority of the >4000 chemicals present in tobacco smoke are completely absent from ECs.**

Not enough done

Flavors ??

Aldehydes ?? Ingredients or contaminants ??

Temperature – wattage ??

Particle size and nicotine delivery

Farsalinos & Polosa, *Ther Adv Drug Safety*

Safety/risk assessment

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

Toxicological studies

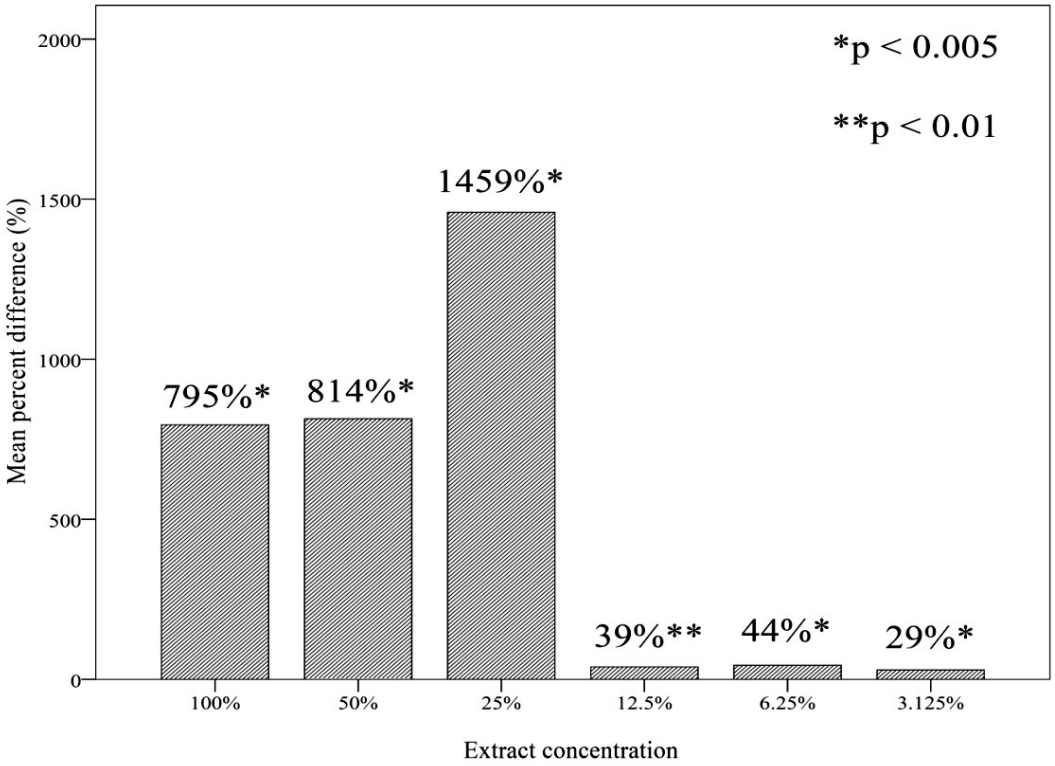
- Studies on cells and animals
- Provide more valuable information in terms of effects of use
- Methodological issues
  - Protocol design
  - Material handling in the lab
  - Dry puff phenomenon undetected

Toxicological studies

	Dilutions						
Extracts	**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

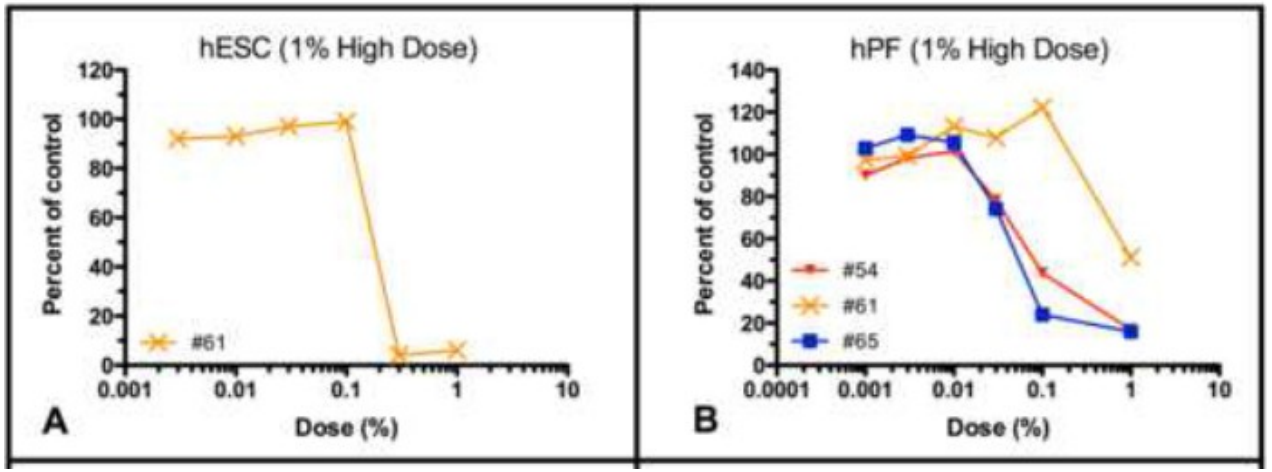
Toxicological studies

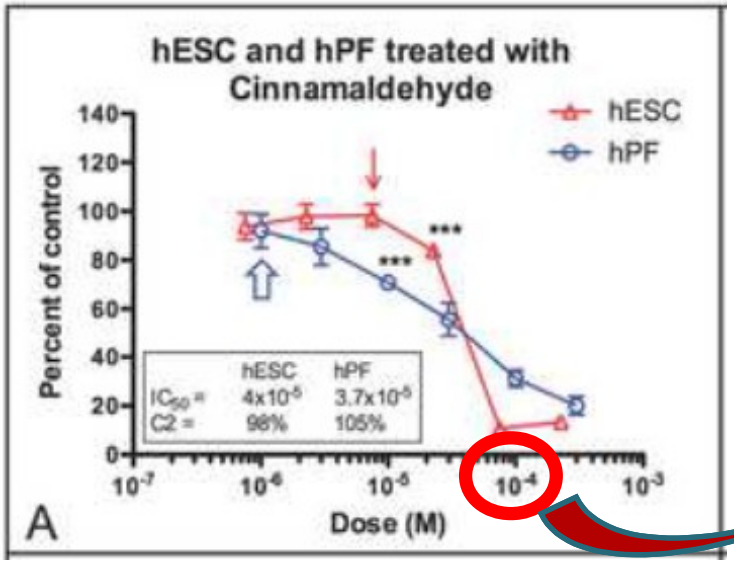


Relative difference in viability between cigarette smoke and worst-performing vapor extract

Romagna, Farsalinos et al, *Inhal Toxicol* 2013

Toxicological studies





Approved cinnamaldehyde dose up to 4 x 10^{-2} M (400 times higher) (EPA, 2000)

Cinnamon toxicity (?)

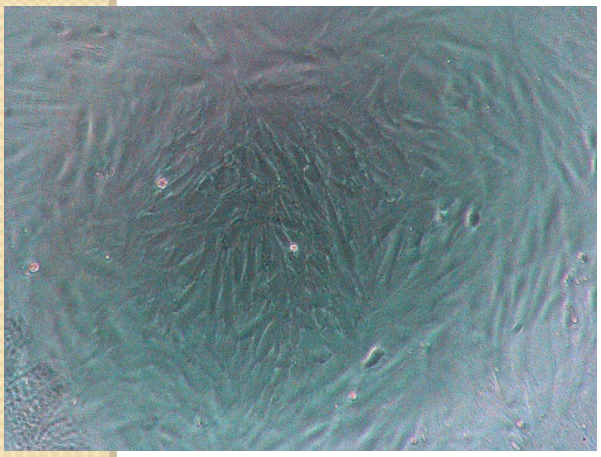
Behar et al, *Toxicol in Vitro* 2013

Toxicological studies

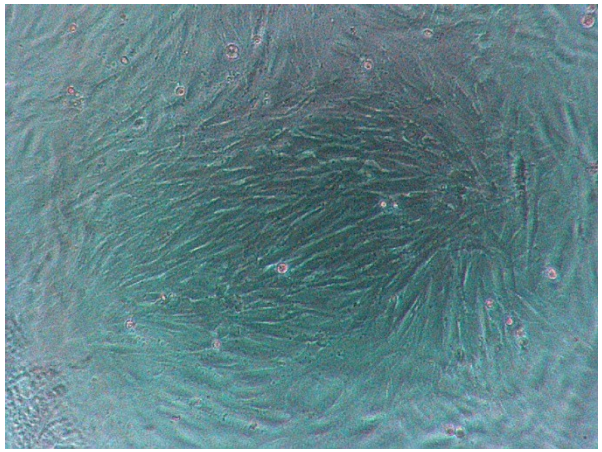
	Dilutions					
Samples-nicotine (mg/mL)	100% [a]	50% [b]	25% [c]	12.5% [d]	6.25% [e]	p *
Base-0	105.1 ± 1.2	103.5 ± 1.9	101.3 ± 4.2	100.7 ± 3.4	100.4 ± 2.3	0.251
Golden Margy-6	89.2 ± 0.2	93.0 ± 2.2	92.1 ± 1.3	95.3 ± 3.6	93.0 ± 6.3	0.361
RY69-6	98.9 ± 4.6	101.2 ± 5.4	96.0 ± 13.0	100.5 ± 2.7	100.2 ± 9.2	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

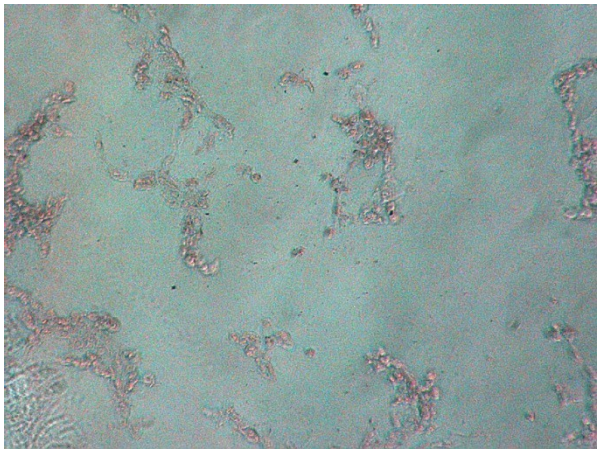
Toxicological studies



Untreated cells



E-cigarette vapor treated cells



Cigarette smoke treated cells

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

Toxicological studies

Are there really conflicting results ??

Farsalinos group
Experiments on vapor
Use of refill liquids
Using an e-cigarette device
Using ISO 10993-5 protocol
Tests on fibroblasts-heart cells

Talbot group
Experiments on liquids
Possible use of concentrated flavors
No use of an e-cigarette device
Using in-house methodology
Tests on nerve-stem cells-fibroblasts

Research should represent realistic use

Safety/risk assessment

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

Clinical studies

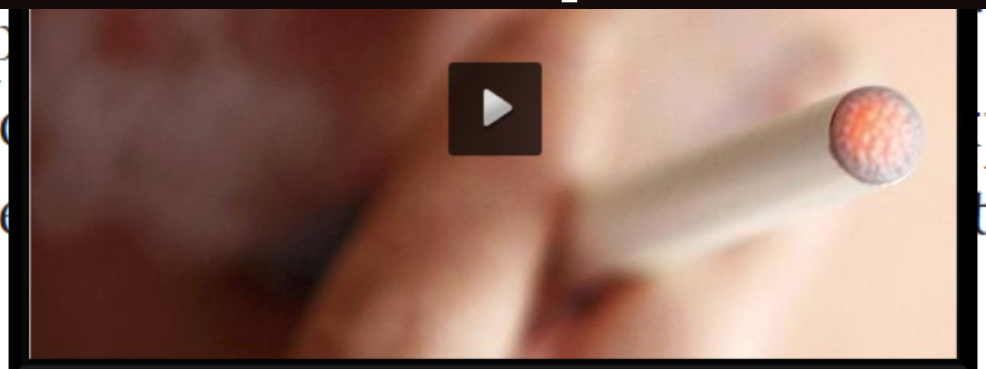
CHEST Postgraduate Education Corner

PULMONARY AND CRITICAL CARE PEARLS

An Unexpected Consequence of Electronic Cigarette Use

Secondary school chemistry

Glycerin is an ALCOHOL, not a lipid!!!



L c
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For this p her exog-
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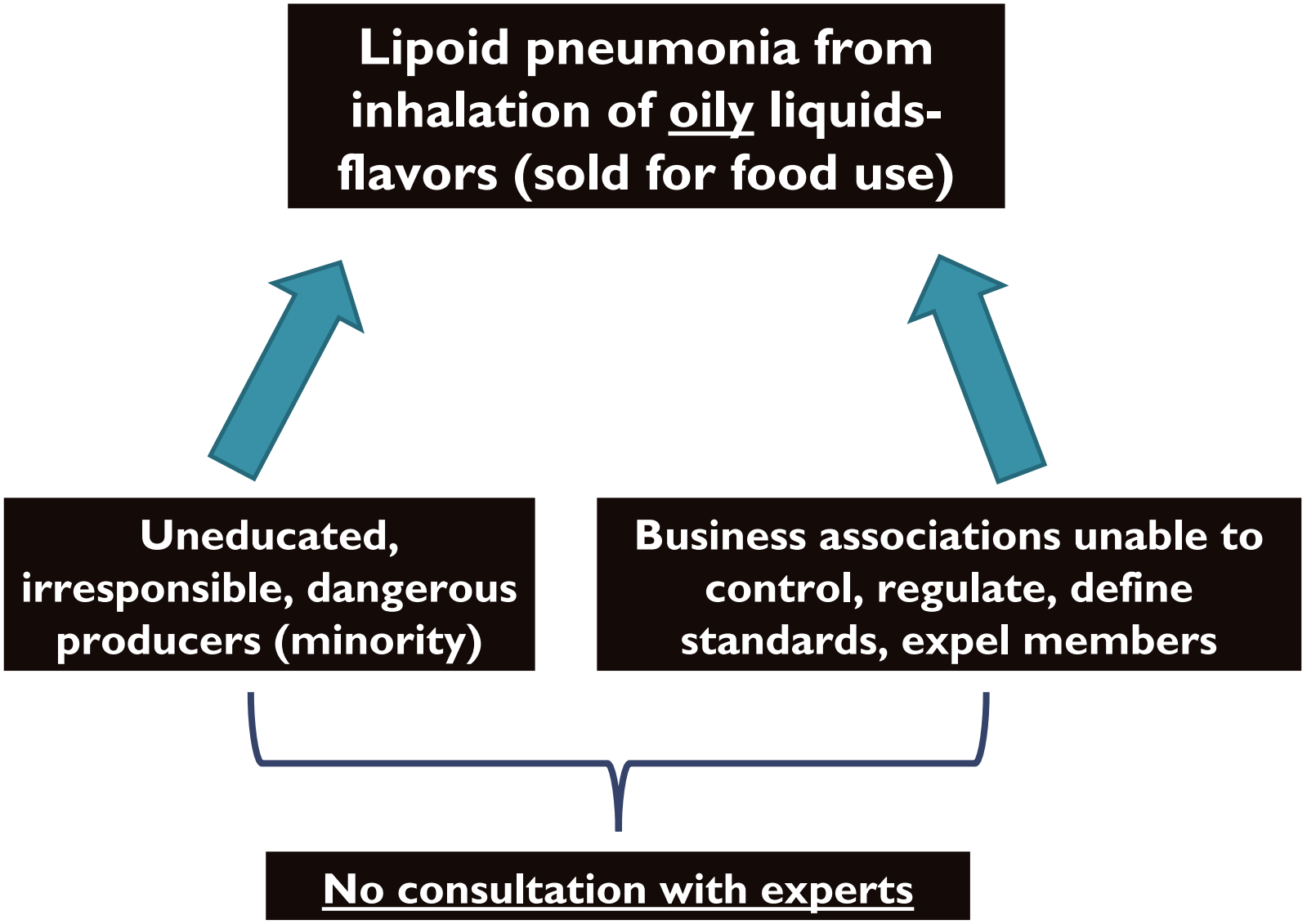
glycerin-base tine vapor.

Clinical studies



Clinical studies

- Surveys show that dedicated vapers have significant benefits
- Randomized trials show small smoking cessation potential
- Not easy to assess the variability of devices and batteries
- Long-term studies CANNOT be performed now
- Are long-term studies needed for medicines approval?
- Imagine any product that needs 15 year clinical studies before being marketed → IMPOSSIBLE to happen

Acute studies

- Lung function: one study showed mild restriction, another one showed no adverse effects (Vardavas et al., Chest 2012, Flouris et al., Inhal Toxicol 2013).

- Cardiovascular function: no adverse effects on heart function, no adverse effects on oxygen delivery to the heart, no adverse effects on arterial stiffness (Farsalinos et al., ESC 2012, ESC 2013, ESC 2014)

Worldwide survey

Int. J. Environ. Res. Public Health **2014**, *11*, 4356-4373; doi:10.3390/ijerph110404356

Article

Characteristics, Perceived Side Effects and Benefits of Electronic Cigarette Use: A Worldwide Survey of More than 19,000 Consumers

Konstantinos E. Farsalinos [1,*], Giorgio Romagna [2], Dimitris Tsiapras [1], Stamatis Kyrzopoulos [1] and Vassilis Voudris [1]

19441 dedicated vapers evaluated

Table 5. Changes in physiologic functions after electronic cigarette use initiation.

Changes	Total (n = 19,353)	Current smokers (n = 3682)	Former smokers (n = 15,671)	Statistic	*p* value
After initiating EC use, have you experienced any changes in:					
Physical status in general					
Worse	79 (0.4)	24 (0.7)	55 (0.4)		
No change	4769 (24.6)	1309 (35.6)	3460 (22.1)	$\chi^2 = 308.6$	<0.001
Better	14,409 (74.5)	2316 (62.9)	12,093 (77.2)		
Smell					
Worse	29 (0.1)	12 (0.3)	17 (0.1)		
No change	2538 (13.1)	894 (24.3)	1644 (10.5)	$\chi^2 = 518.4$	<0.001
Better	16,722 (86.4)	2743 (74.5)	13,979 (89.2)		
Taste					
Worse	62 (0.3)	26 (0.7)	36 (0.2)		
No change	3359 (17.4)	1051 (28.5)	2308 (14.7)	$\chi^2 = 431.6$	<0.001
Better	15,857 (81.9)	2572 (69.9)	13,285 (84.8)		
Breathing					
Worse	137 (0.7)	40 (1.1)	97 (0.6)		
No change	2497 (12.9)	784 (21.3)	1713 (10.9)	$\chi^2 = 304.0$	<0.001
Better	16,641 (86.0)	2824 (76.7)	13,817 (88.2)		
Appetite					
Worse	218 (1.1)	56 (1.5)	162 (1.0)		
No change	12,807 (66.2)	2564 (69.6)	10,243 (65.49)	$\chi^2 = 41.5$	<0.001
Better	6216 (32.1)	1022 (27.8)	5194 (33.1)		

Farsalinos et al, *Int J Environm Res Public Health* 2014

What is needed?

- Materials used in atomizers (wick, coil, plastics)
- Effects of high wattage
- New-generation devices-no tests
- Many vendors, many manufacturers, wrong criteria in production
- Vapers have not applied pressure for testing and research-wrong criteria in product selection

What is needed?

- No participation from the industry
- Lack of expertise
- No involvement of experts-none asks them, none pays them
- No consultation
- No testing, or wrong testing
- Big Tobacco is coming and will DOMINATE
- Regulators are forced to accept the Big Tobacco
- We need variability of products (competition) but also proof for benefit

Conclusions

- A public health revolution
- No doubt that they are less harmful by a big margin
- Need proof for benefit → more research
- Need to remove harmful ingredients when avoidable-liquid and vapor analyses
- Products need improvement
- Better nicotine delivery
- Inefficient products will disappear
- Companies will disappear when irresponsible and do not provide proof of analyses

Grazie tanto per la sua attenzione