THE E-CIGARETTE SUMMIT
Science, Regulation & Public Health
The Royal Society ▪ London ▪ November 17th 2017

Cardiovascular effects of nicotine vs. cigarette smoke

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National School of Public Health, Athens-Greece

1st (and last) slide

- Please look at last year's presentation by Prof. Neil Benowitz

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

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Emerging harm reduction (?) choices
Tobacco heated products

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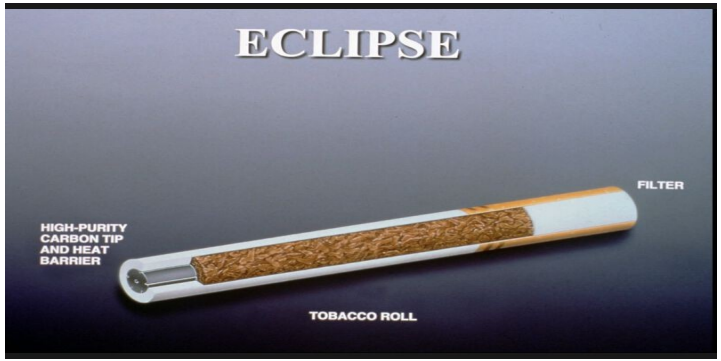
Tobacco heated products
An old story

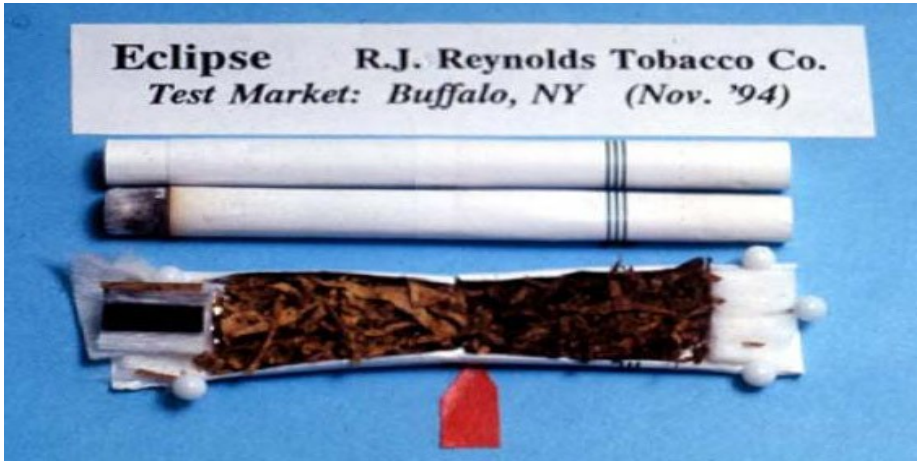
1998, RJ Reynolds launched Premier

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Tobacco heated products
An old story

- Premier replaced by Eclipse





Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Tobacco heated products

New developments

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Tobacco heated products

New developments

- Tobacco companies: JTI, PMI, BAT
- Two of them (PMI-IQOS, BAT-Glo) are heating tobacco through a resistance (maximum 350^{o}C and 240^{o}C respectively)
- PMI: heats tobacco by penetrating the stick with a metal blade (heat source)
- BAT: heats the tobacco through resistors (heat source) surrounding the tobacco stick
- JTI product (Ploom TECH) is an e-cigarette with a tobacco cartridge at the mouth piece (indirect heating of tobacco by the aerosol passing through the cartridge)

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Tobacco heated products marketing

- PMI launched product in Japan in late 2014
  - Market share > 14% in Japan
  - Available in about 30 countries
- JTI launched product in March 2016
  - Also available in Switzerland
- BAT launched product in late 2016
  - Market share 1.8% in Japan
  - Now in Canada, S. Korea, Switzerland, Russia

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

A lot of research

Almost all by the manufacturers

- Chemistry
- Toxicology
- Clinical

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Chemistry

Table 8
3R4F reference cigarette mainstream smoke yields and THP1.0 emission yields for the nine TobReg priority constituents, presented on per-consumable and per-puff bases, with calculated reductions per puff.

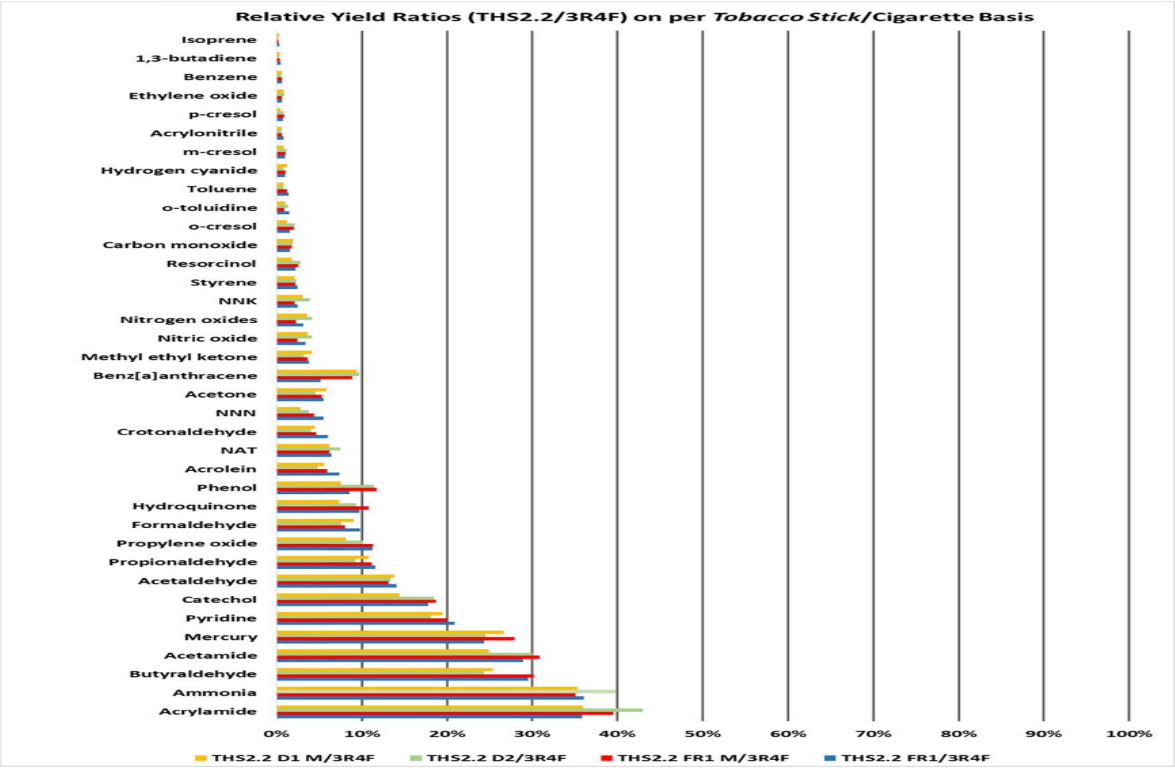
Parameter	Unit	3R4F		THP1.0(T)			THP1.0 (M)		
		Mean per consumable	Mean per puff[a]	Mean per consumable	Mean per puff[a]	%Red[n] per puff	Mean per consumable	Mean per puff[a]	%Red[n] per puff
1,3-Butadiene	µg	108	11.1	BDL (0.029)	0.002	>99.9	BDL (0.029)	0.002	>99.9
Acetaldehyde	µg	2200	208	111	13.9	93.3	115	14.4	93.1
Acrolein	µg	157	14.9	2.22	0.278	98.1	2.50	0.313	97.9
Benzene	µg	78.6	8.08	NQ (0.056)	0.005	99.9	NQ (0.056)	0.005	99.9
Benzo[*a*]pyrene	ng	12.9	1.26	NQ (0.354)	0.037	97.1	0.356	0.045	96.5
CO	mg	32.0	2.99	NQ (0.223)	0.010	99.7	NQ (0.223)	0.015	99.5
Formaldehyde	µg	54.10	5.11	3.29	0.411	92.0	3.51	0.439	91.4
NNK	ng	281	26.6	6.61	0.826	96.9	5.32	0.665	97.5
NNN	ng	263	24.8	24.7	3.09	87.6	19.1	2.39	90.4
					Average	96.1		**Average**	96.2

Glo
average > 95% reduction in toxic emissions

Forster et al., Regul Toxicol Pharmacol 2017

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Chemistry



IQOS
average 90% reduction in toxic emissions

Schaller et al., Regulatory Toxicol Pharmacol 2016 (PMI - IQOS)

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Chemistry

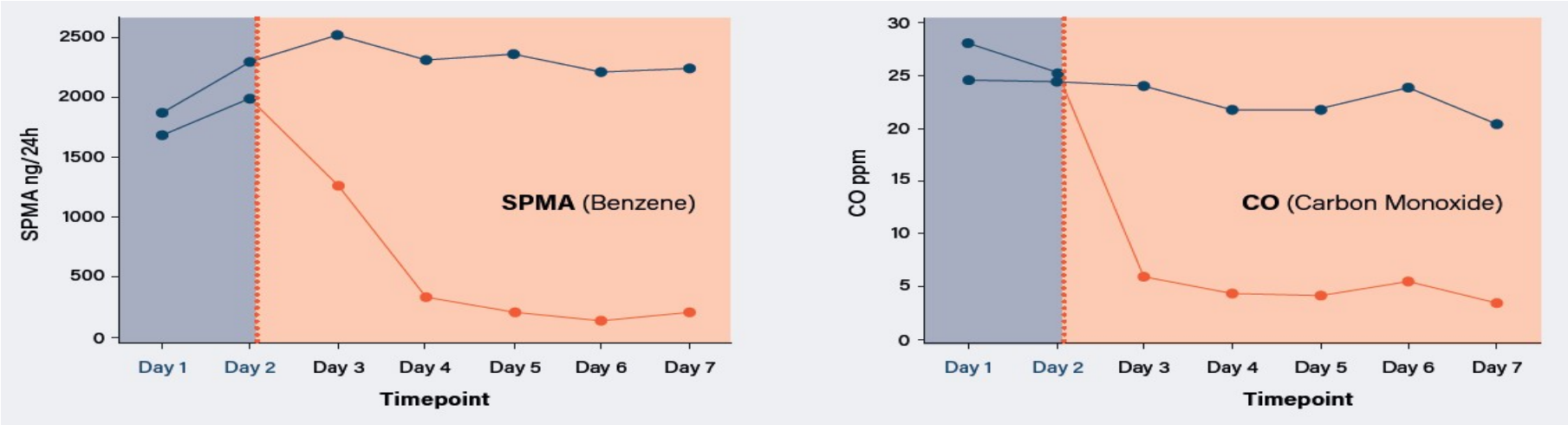
	Analytes	units (/cig or capsule)	3R4F(A)	NTV(B)	B/A ratio
	TPM	mg	42.5	86.4	2.03
	Puff count	puffs	10.6	60.0	5.66
	Water	mg	15.5	15.1	0.974
	Nicotine	mg	1.92	1.15	0.600
Hoffmann analyte	Carbon monoxide	mg	30.7	ND(<0.26)	<0.0085
	NNN	ng	249	ND(<6.0)	<0.024
	NAT		250	ND(<12.0)	<0.0480
	NAB		25.6	NQ(<8.5)	<0.33
	NNK		223	ND(<7.1)	<0.032
	Formaldehyde	µg	108	ND(<0.6)	<0.006
	Acetaldehyde		1757	ND(<2.7)	<0.0015
	Acetone		602	ND(<1.9)	<0.0032
	Acrolein		177	ND(<0.4)	<0.002
	Propionaldehyde		131	ND(<0.6)	<0.005
	Crotonaldehyde		56.1	ND(<1.3)	<0.023
	Methyl Ethyl Ketone		150	NQ(<2.7)	<0.018
	n-Butyraldehyde		83.7	ND(<0.6)	<0.007
	1,3-Butadiene	µg	99.4	ND(<22.2)	<0.223
	Isoprene		912	ND(<95.7)	<0.105
	Acrylonitrile		30.2	ND(<3.4)	<0.11
	Benzene		105	ND(<6.1)	<0.058
	Toluene		200	ND(<6.0)	<0.030
	Hydrogen Cyanide	µg	476	ND(<0.7)	<0.001
	Benzo[a]pyrene	ng	18.7	ND(<0.2)	<0.01
	Hydroquinone	µg	84.6	ND(<0.82)	<0.010
	Resorcinol		2.04	ND(<0.2095)	<0.103
	Catechol		89.0	ND(<1.7125)	<0.0192
	Phenol		12.6	ND(<0.76)	<0.060
	m-Cresol		8.36	ND(<0.7025)	<0.0840
	p-Cresol		2.95	ND(<0.3675)	<0.125
	o-Cresol		3.45	ND(<0.545)	<0.158
	Ammonia	µg	31.8	8.22	0.258
	Nitric Oxide	µg	520	ND(<0.65)	<0.0013
	Total Oxides of Nitrogen		561	ND(<1.10)	<0.00196
	Pyridine	µg	41.0	ND(<1.46)	<0.0356
	Quinoline		0.494	ND(<0.27)	<0.55
	Styrene		27.1	ND(<0.76)	<0.028
	1-Aminonaphthalene	ng	22.2	ND(<1.13)	<0.0509
	2-Aminonaphthalene		14.5	ND(<1.17)	<0.0807
	3-Aminobiphenyl		5.18	ND(<0.41)	<0.079
	4-Aminobiphenyl		3.51	ND(<0.35)	<0.10
	Mercury	ng	5.63	ND(<1.93)	<0.343
	Lead		31.6	ND(<6.48)	<0.205
	Cadmium		113	ND(<7.17)	<0.0635
	Chromium		NQ	ND(<3.40)	-
	Nickel		ND	ND(<7.04)	-
	Beryllium		ND	ND(<3.81)	-
	Cobalt		NQ	ND(<1.15)	-
	Selenium		ND	ND(<9.10)	-
	Arsenic		8.62	ND(<3.78)	<0.439

Ploom-Tech
average > 95% reduction in toxic emissions

JTI poster, Global Forum on Nicotine 2017 (Ploom TECH)

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Clinical studies



Clinical confinement for 5 days
Comparison between continuous smoking and switch to THP product

BAT, poster presentation at Global Forum on Nicotine 2017 (Glo)

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Clinical studies

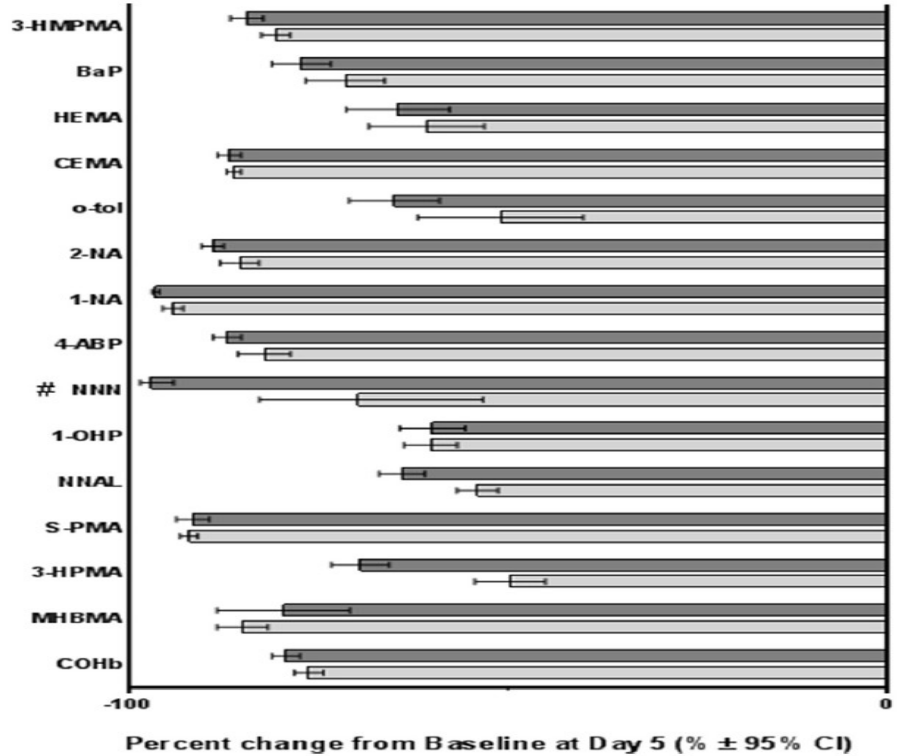
Table 4
Biomarkers of exposure, ratios of THS relative to CC.

Biomarkers	Ratio[a] % and CI THS (N = 81)/CC (N = 41)
NEQ (mg/g creat)	104.9 (92.0; 119.6)
Nicotine[b,c] (ng/mL)	112.9(91.3; 139.5)
Cotinine[b,c](ng/mL)	111.0 (90.8; 135.7)
Total NNAL (pg/mg creat)	43.5 (39.3; 48.2)
Total NNN (pg/mg creat)	24.1 (17.7; 32.8)
COHb[c] (%)	23.5 (22.0; 25.0)
MHBMA (pg/mg creat)	8.4 (6.8; 10.2)
3-HPMA (ng/mg creat)	41.6 (37.7; 46.0)
S-PMA (pg/mg creat)	6.0 (5.2; 6.9)
Total 1-OHP (pg/mg creat)	44.3 (39.8; 49.4)
4-ABP (pg/mg creat)	14.9 (12.8; 17.4)
1-NA (pg/mg creat)	3.7 (3.1; 4.5)
2-NA (pg/mg creat)	11.5 (10.0; 13.3)
o-tol (pg/mg creat)	41.7 (36.0; 48.3)
CEMA (ng/mg creat)	13.2 (11.5; 15.0)
HEMA (pg/mg creat)	32.0 (27.1; 37.8)
3- HMPMA (ng/mg creat)	22.5 (20.1; 25.3)
Total 3-OH-B[a]P (fg/mg creat)	27.5 (23.2; 32.6)

Clinical confinement study
Comparison between continuous smoking, smoking cessation and switch to THP product

Haziza et al., Regulatory Toxicol Pharmacol 2016 (PMI – IQOS)

Clinical studies



SA = smoking abstinence
THS = THP

Haziza et al., Regulatory Toxicol Pharmacol 2016 (PMI - IQOS)

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Research replication

- Although science should not be discarded, a critical and very cautious approach is need due to the source of the information (manufacturers, tobacco industry)

- It is of outmost importance to replicate the studies, carefully reviewing the methodology, testing several puffing regimes, checking the accuracy of the reported values

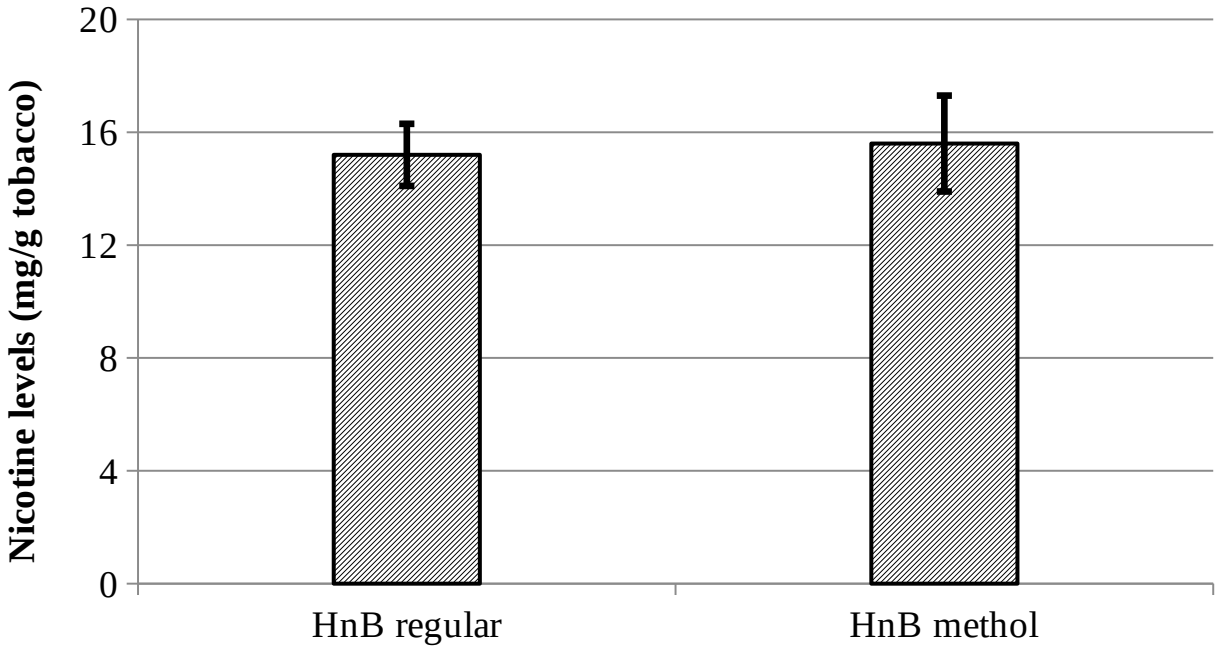
Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Independent studies

- Mainly 3 independent studies have attempted to replicate manufacturer publications for 1 HnB product (IQOS)

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Independent studies

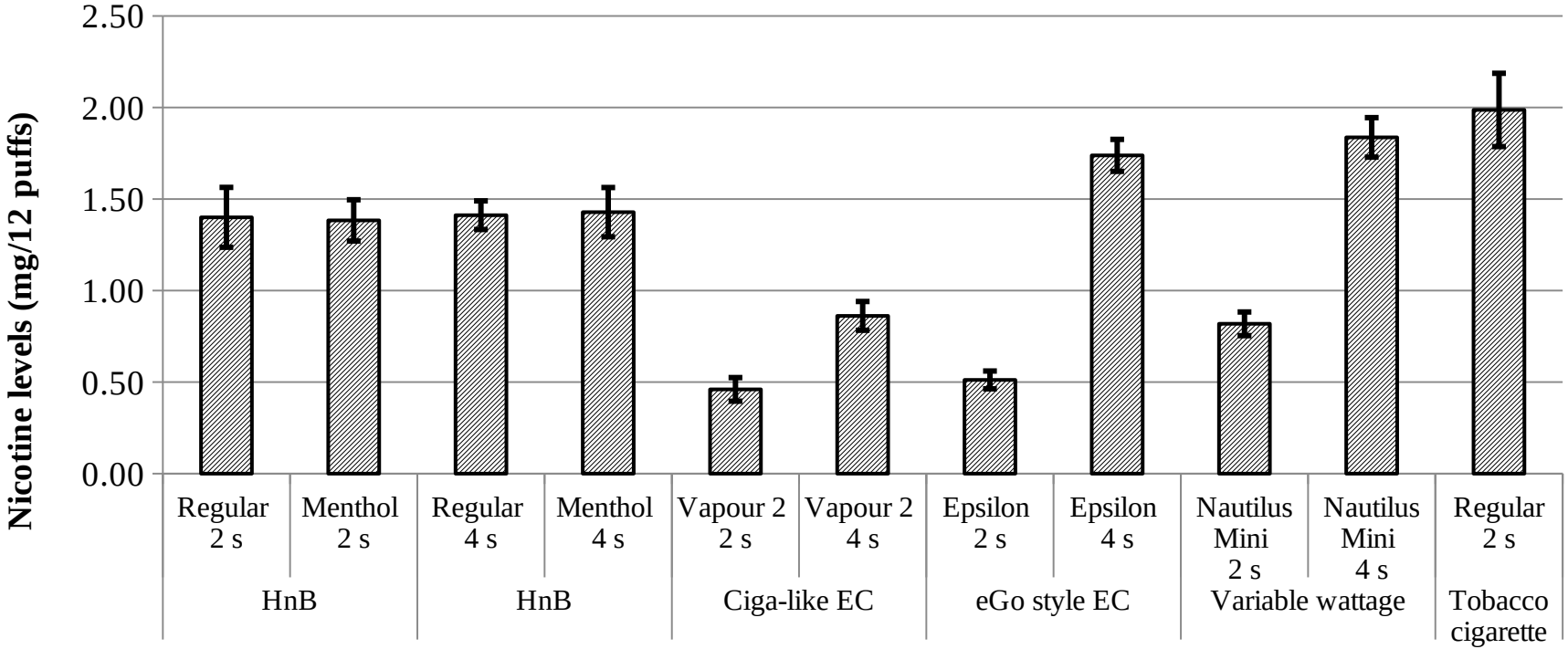


Nicotine concentration (mg/g) in unused tobacco sticks of IQOS appear to be similar to tobacco cigarettes

Farsalinos et al. Nicotine Tob Res 2017

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

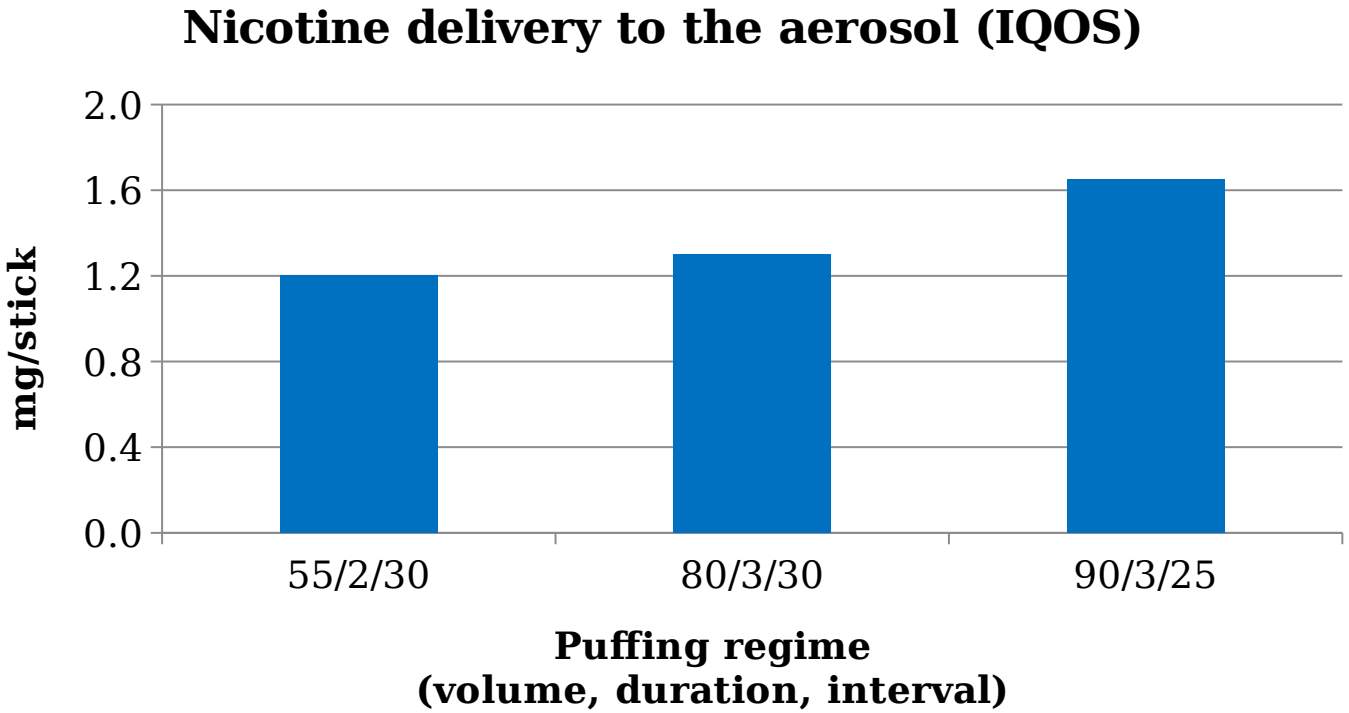
Independent studies



Lower nicotine levels (-30%) to the aerosol compared to tobacco cigarette smoke

Farsalinos et al. Nicotine Tob Res 2017

Independent studies



Farsalinos, Leischow et al. (under preparation for submission)

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Independent studies

Table. Concentrations of 8 Volatile Organic Compounds, 16 Polycyclic Aromatic Hydrocarbons, 3 Inorganic Compounds, and Nicotine in Mainstream Aerosol and Temperature of the HNB IQOS Cigarette and Conventional Cigarettes

Analyzed Compound	HNB Cigarette		Conventional Cigarette		Proportion of the Chemical in HNB and Conventional Cigarettes, %
	Amount, Mean (SD)	No. of Replications for Each Assay	Amount, Mean (SD)	No. of Replications for Each Assay	
Volatile organic compounds, µg per cigarette[a]					
Acetaldehyde	133 (35)	5	610[b]	1	22
Acetone	12.0 (12.9)	5	95.5 (13.5)	2	13
Acroleine	0.9 (0.6)	2	1.1	1	82
Benzaldehyde	1.2 (1.4)	5	2.4 (2.6)	2	50
Crotonaldehyde	0.7 (0.9)	5	17.4	1	4
Formaldehyde	3.2 (2.7)	5	4.3 (0.4)	2	74
Isovaleraldehyde	3.5 (3.1)	5	8.5 (10.8)	2	41
Propionaldehyde	7.8 (4.3)	5	29.6 (36.6)	2	26

Auer et al. JAMA Int Med 2017

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

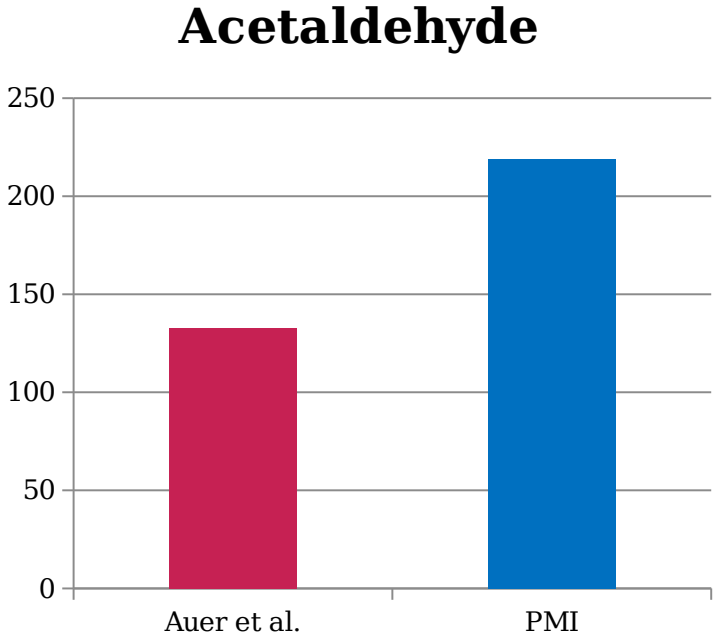
Independent studies

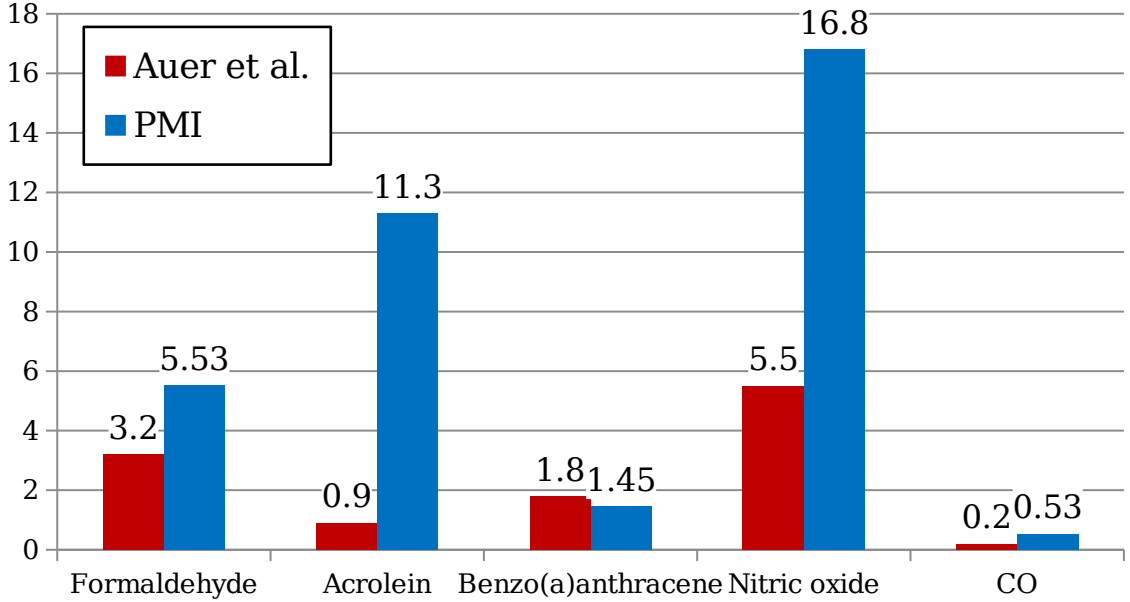
Polycyclic aromatic hydrocarbons, ng per cigarette[c]					
Naphthalene	1.6 (0.5)	4	1105 (269)	7	0.1
Acenaphthylene	1.9 (0.6)	4	235 (39)	7	0.8
Acenaphthene	145 (54)	4	49 (9)	7	295
Fluorene	1.5 (0.6)	4	371 (56)	7	0.4
Anthracene	0.3 (0.1)	4	130 (18)	7	0.2
Phenanthrene	2.0 (0.2)	4	292 (44)	7	0.7
Fluoranthene	7.3 (1.1)	4	123 (18)	7	6
Pyrene	6.4 (1.1)	4	89 (15)	7	7
Benz[a]anthracene	1.8 (0.4)	4	33 (4.2)	7	6
Chrysene	1.5 (0.3)	4	48 (6.2)	7	3
Benzo[b]fluoranthene	0.5 (0.2)	4	24 (2.9)	7	2
Benzo[k]fluoranthene	0.4 (0.2)	4	4.3 (2.8)	7	9
Benzo[a]pyrene	0.8 (0.1)	4	20 (2.9)	7	4
Indeno[1,2,3-cd]pyrene	ND	4	NA	NA	NA
Benzo[ghi]perylene	ND	4	NA	NA	NA
Dibenzo[a,h]anthracene	ND	4	NA	NA	NA
Inorganics, ppm in the mainstream smoke[d]					
Carbon dioxide	3957 (533)	5	>8000	3	NA
Carbon monoxide	328 (76)	5	>2000	3	NA
Nitric oxide	5.5 (1.5)	5	89.4 (71.6)	3	6
Other measures					
Nicotine, µg per cigarette[a]	301 (213)	4	361	1	84
Temperature, °C	330 (10)	2	684 (197)	1	NA
Puff total count	12.6 (2.4)	32	13.3 (3.1)	6	NA

Auer et al. JAMA Int Med 2017

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Independent studies





Auer et al. JAMA Int Med 2017

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Independent studies

	IQOS		Tobacco cigarette		% difference
Polycyclic aromatic hydrocarbons, ng per cigarette[c]					
Naphthalene	1.6 (0.5)	4	1105 (269)	7	0.1
Acenaphthylene	1.9 (0.6)	4	235 (39)	7	0.8
Acenaphthene	145 (54)	4	49 (9)	7	295

- PMI responded that this is not a listed HPHC, but this is not good enough justification
- Anything potentially toxic should be tested, irrespective of being listed in HPHC lists
- Limited data on toxicity of acenaphthene, but it is a PAH produced during high temperature carbonization – more studies are needed to verify the levels, source and reasons it is formed
- Aldehyde levels were low in IQOS but were unusually low in tobacco cigarettes

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Independent studies

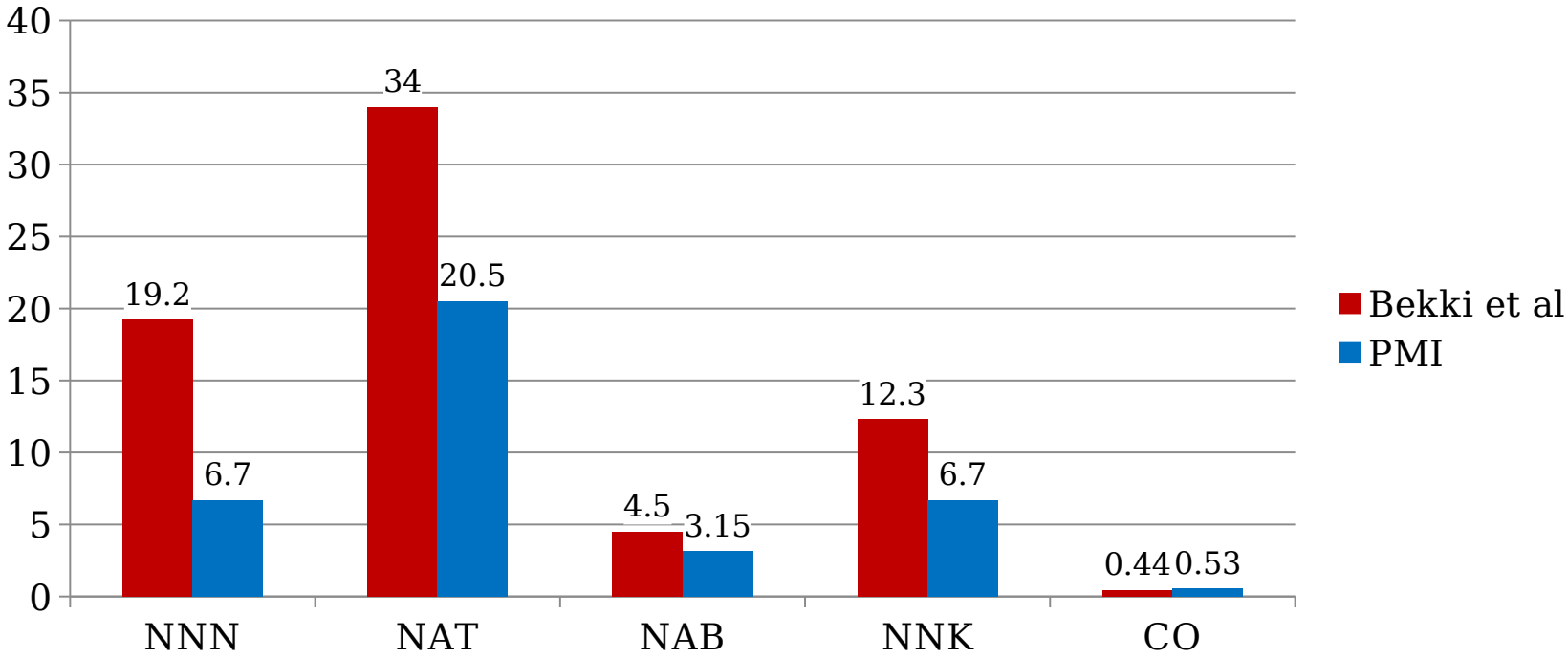
Table 2. Concentrations of tar, nicotine, CO and TSNAs in mainstream cigarette smoke and transfer rates of each component in iQOS (regular and menthol) and conventional combustion cigarettes (3R4F and 1R5F)

Element	Mainstream cigarette smoke				Transfer rate (%)			
	iQOS regular	iQOS menthol	3R4F	1R5F	iQOS regular	iQOS menthol	3R4F	1R5F
TPM (mg/cig)	44.0 ± 11.4	49.9 ± 8.6	36.9 ± 1.9	28.9 ± 2.3	–	–	–	–
Water (mg/cig)	33.1 ± 10.2	35.3 ± 8.3	10.1 ± 0.9	8.8 ± 1.1	–	–	–	–
Tar (mg/cig)	9.8 ± 3.0	13.4 ± 2.2	25.2 ± 1.5	19.2 ± 1.3	–	–	–	–
Nicotine (mg/cig)	1.1 ± 0.1	1.2 ± 0.1	1.7 ± 0.1	1.0 ± 0.1	23.4	23.5	11.3	11.5
CO (mg/cig)	0.44 ± 0.04	0.43 ± 0.04	33.0 ± 1.8	29.7 ± 1.7	–	–	–	–
TSNAs (ng/cig)								
NNN	19.2 ± 2.1	24.9 ± 3.5	311.1 ± 24.3	240.7 ± 6.6	20.3	24.7	16.4	14.2
NAT	34.0 ± 3.1	37.2 ± 3.9	246.4 ± 16.9	183.1 ± 6.0	34.1	39.4	18.3	20.1
NAB	4.5 ± 0.5	5.5 ± 0.6	30.4 ± 2.0	26.2 ± 0.5	80.3	211.5	46.8	57.0
NNK	12.3 ± 1.5	13.8 ± 2.6	250.4 ± 13.7	107.0 ± 5.0	24.1	23.7	47.1	26.0
Total of TSNA	70.0 ± 7.2	81.4 ± 10.4	838.2 ± 53.7	557.1 ± 15.7	27.9	31.4	21.9	18.2

Bekki et al. J UOEH 2017

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

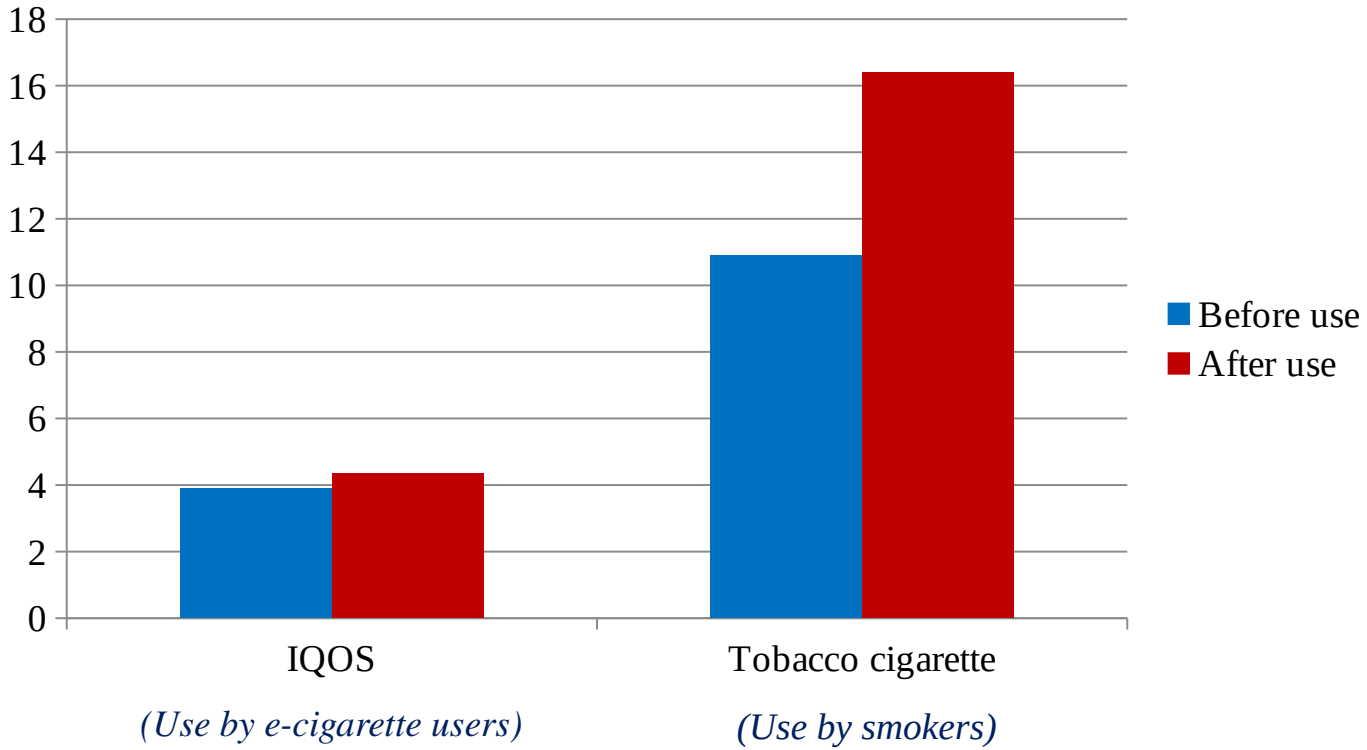
Independent studies



Bekki et al. J UOEH 2017

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

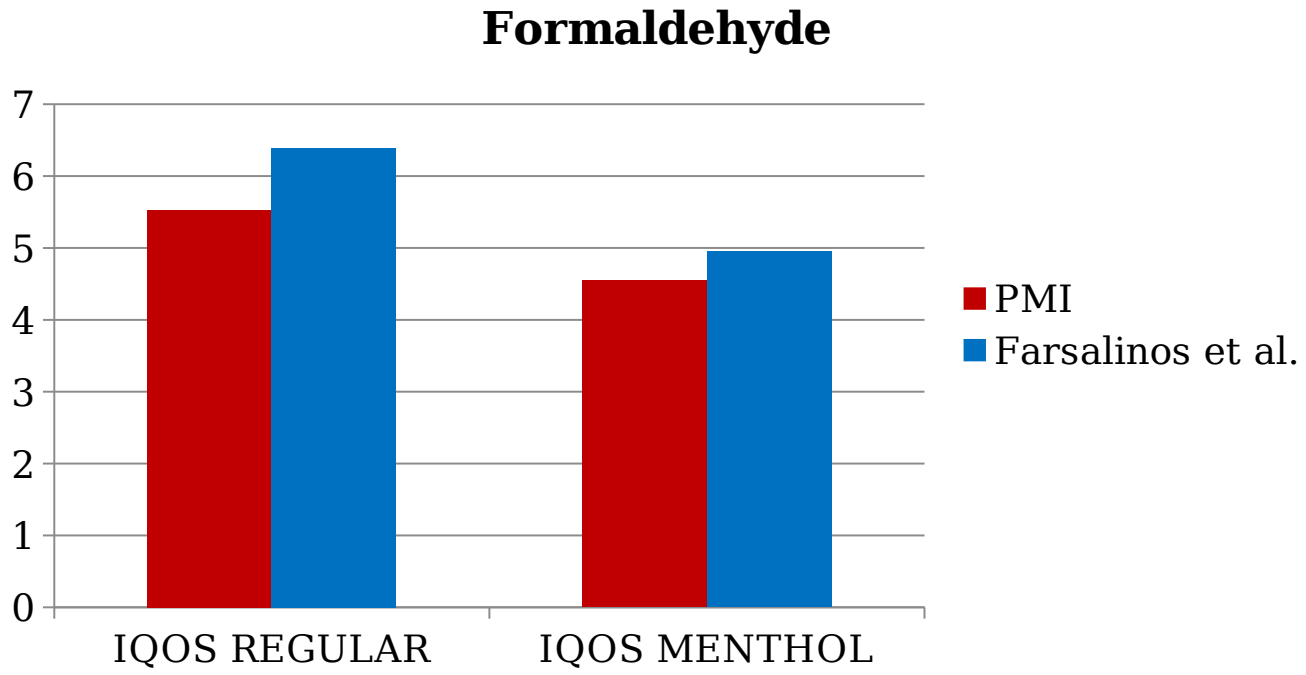
Exhaled carbon monoxide



Farsalinos et al. (unpublished data)

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Aldehydes in THP



Farsalinos, Leischow et al. under preparation for submission

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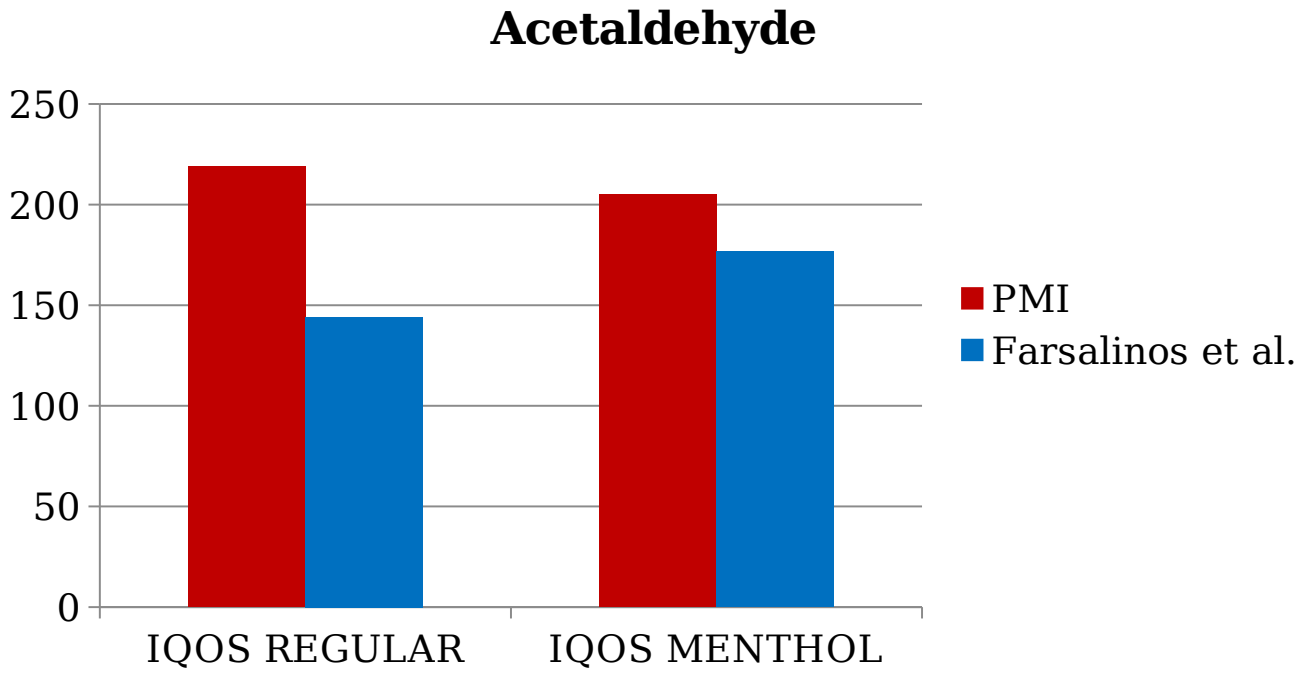
Aldehydes in THP



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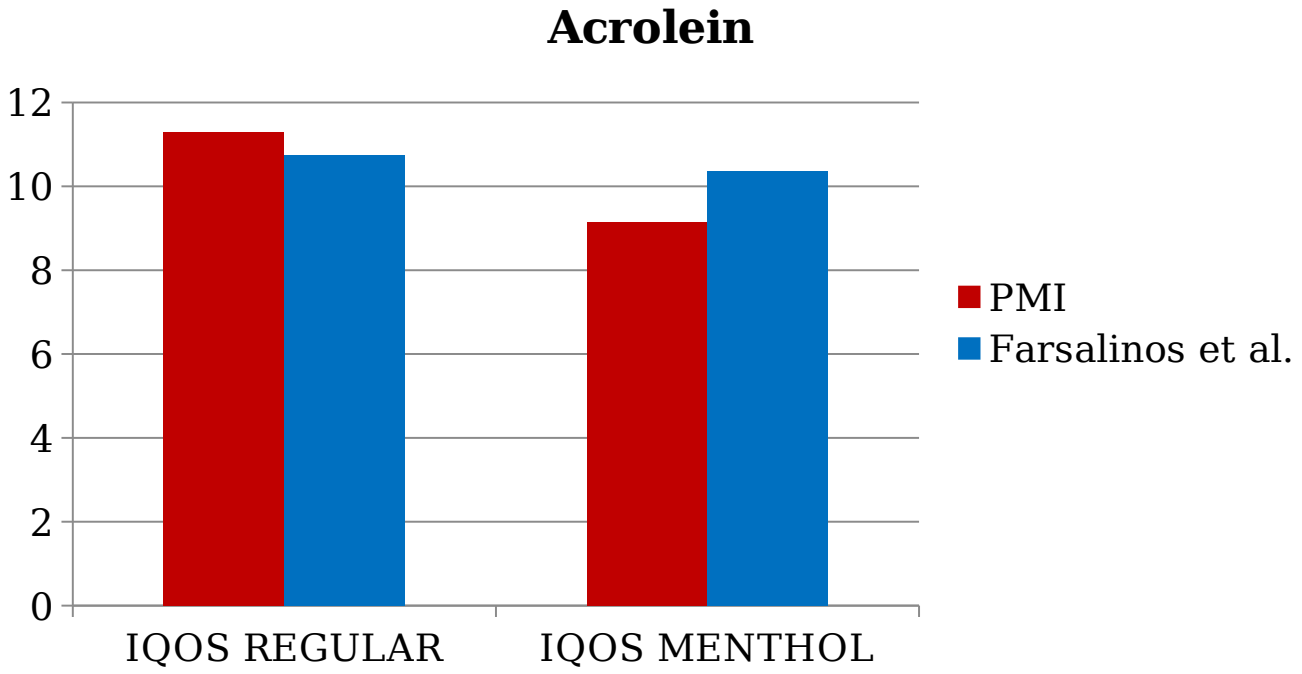

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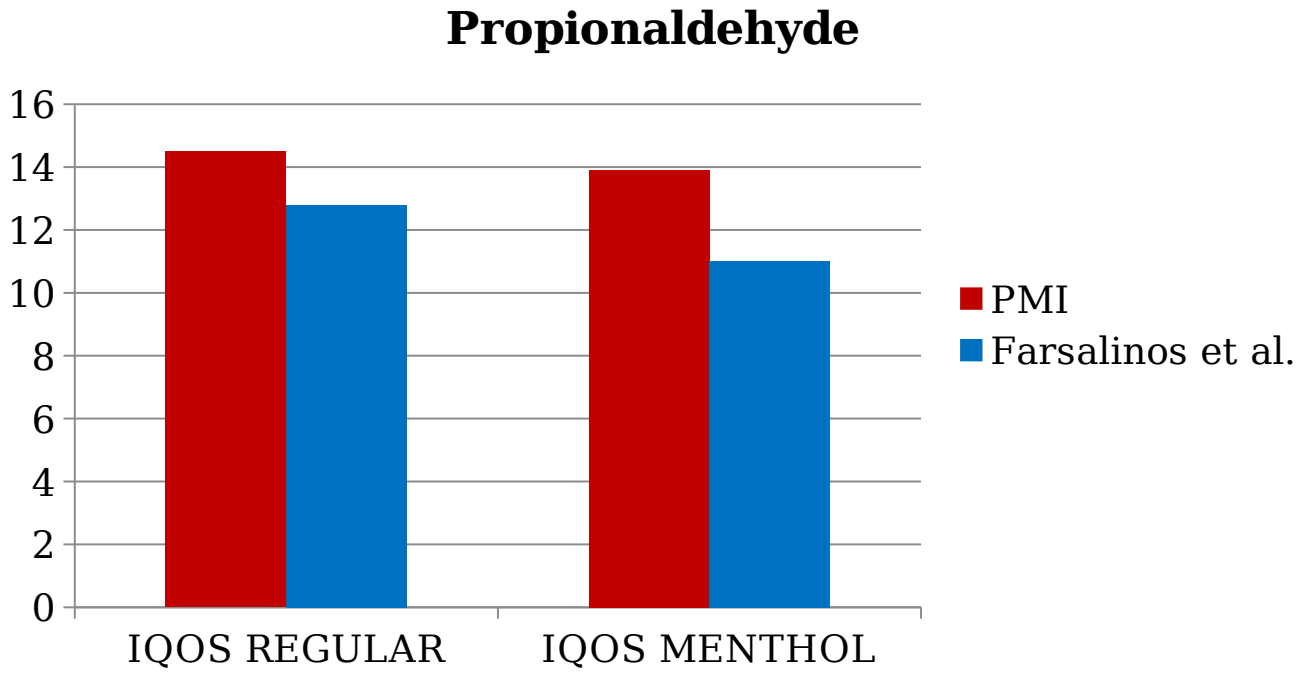
Aldehydes in THP



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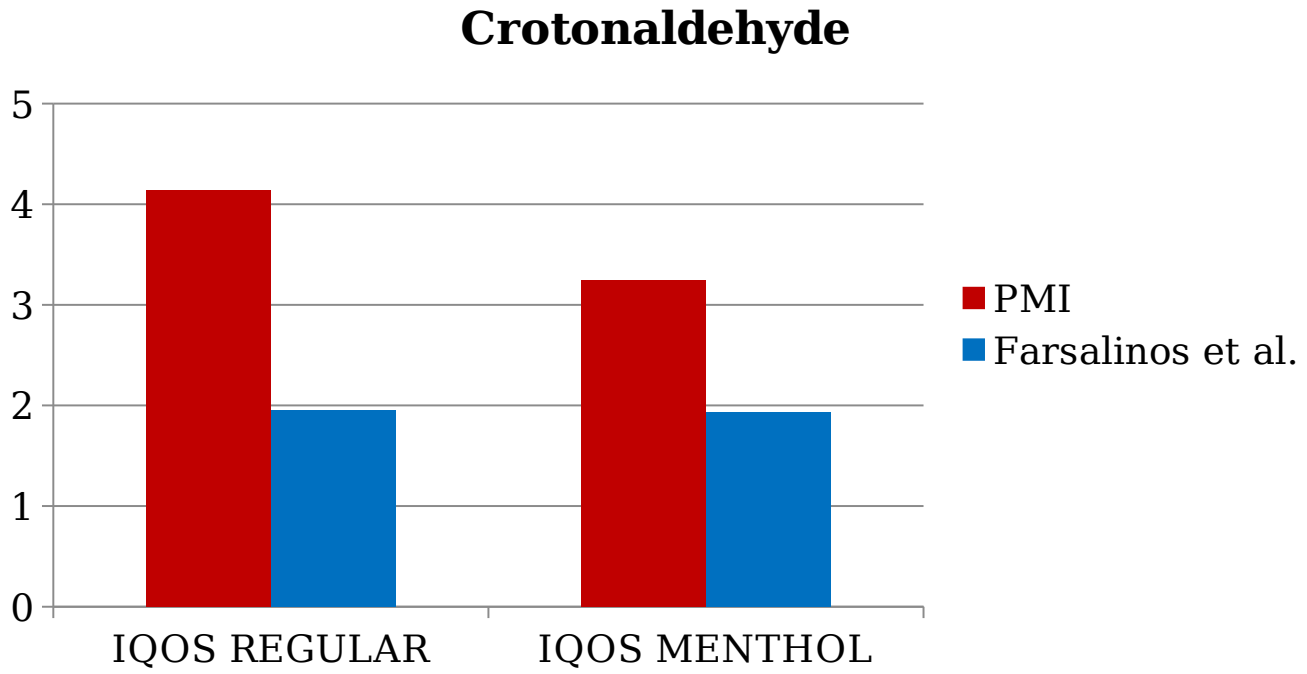
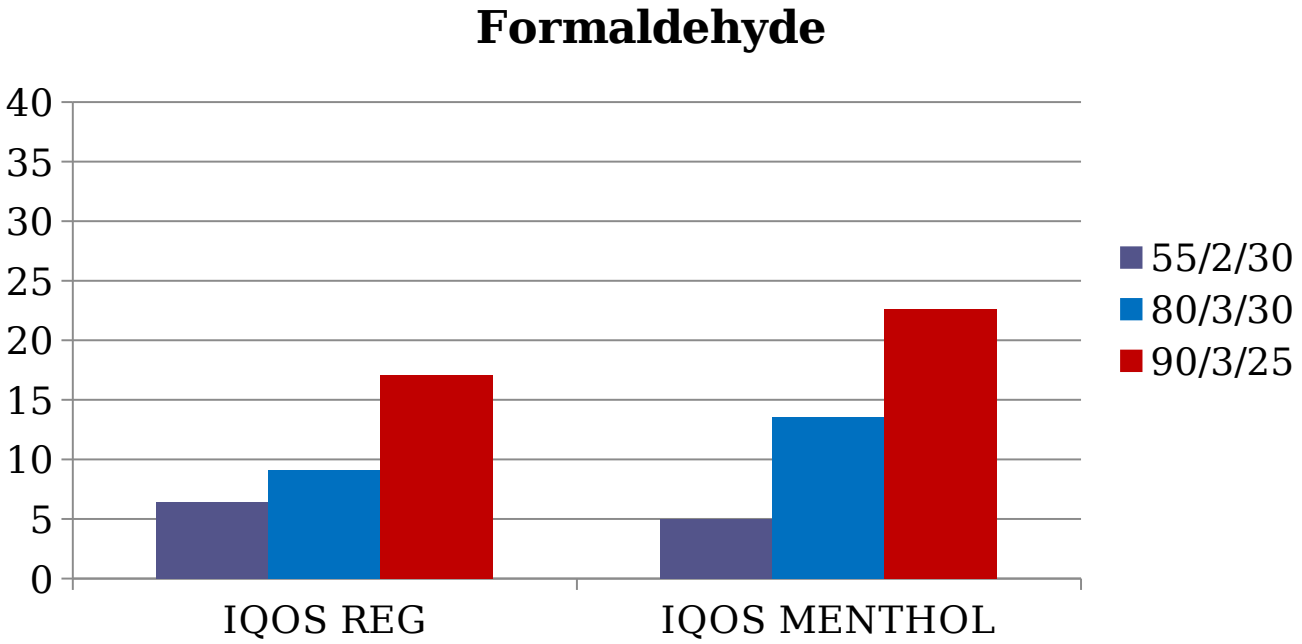
Aldehydes in THP



Farsalinos, Leischow et al. under preparation for submission

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Aldehydes in THP
different puffing regimes



Farsalinos, Leischow et al. under preparation for submission

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

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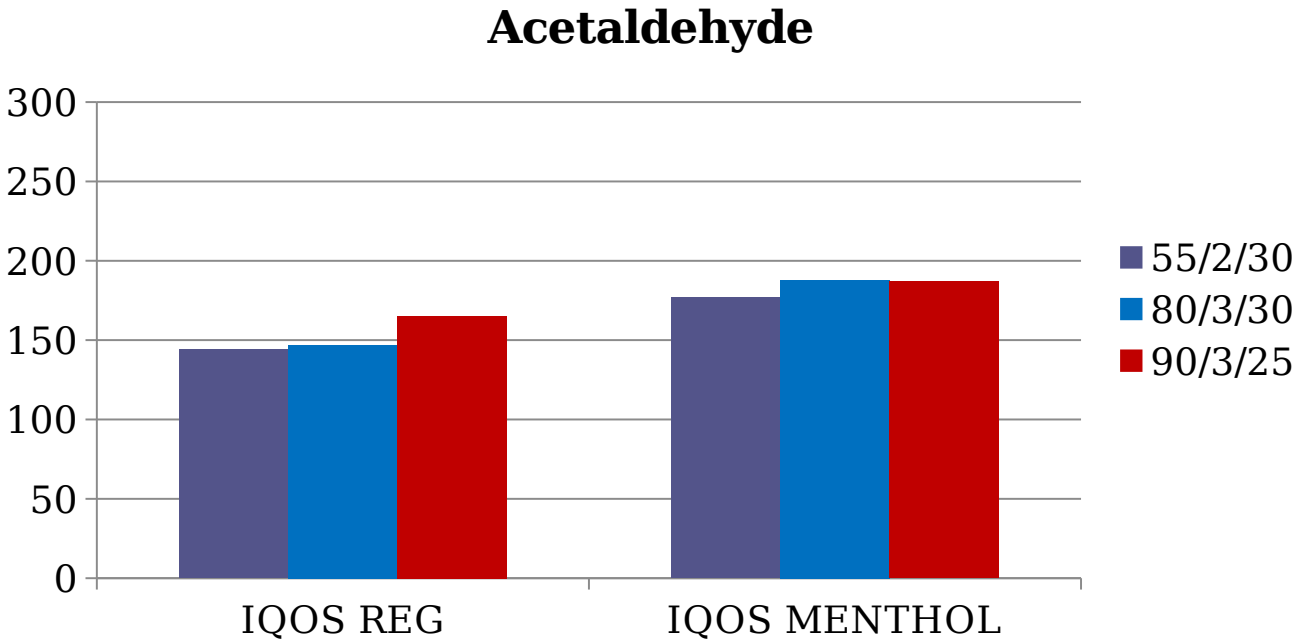

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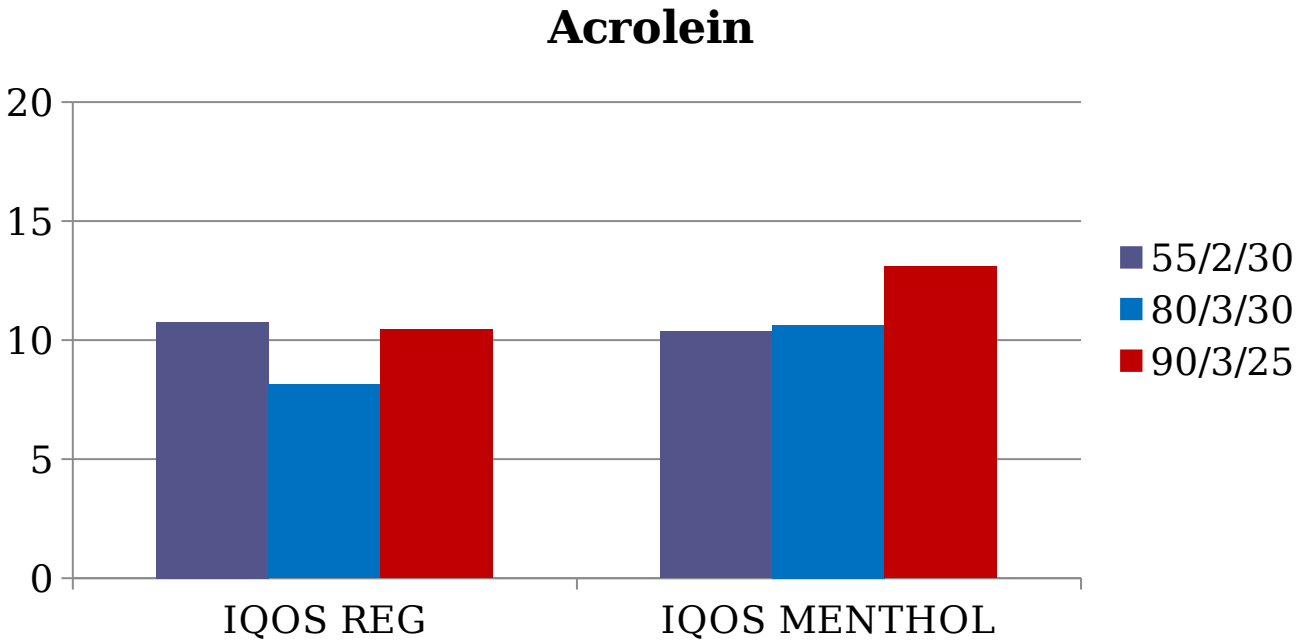

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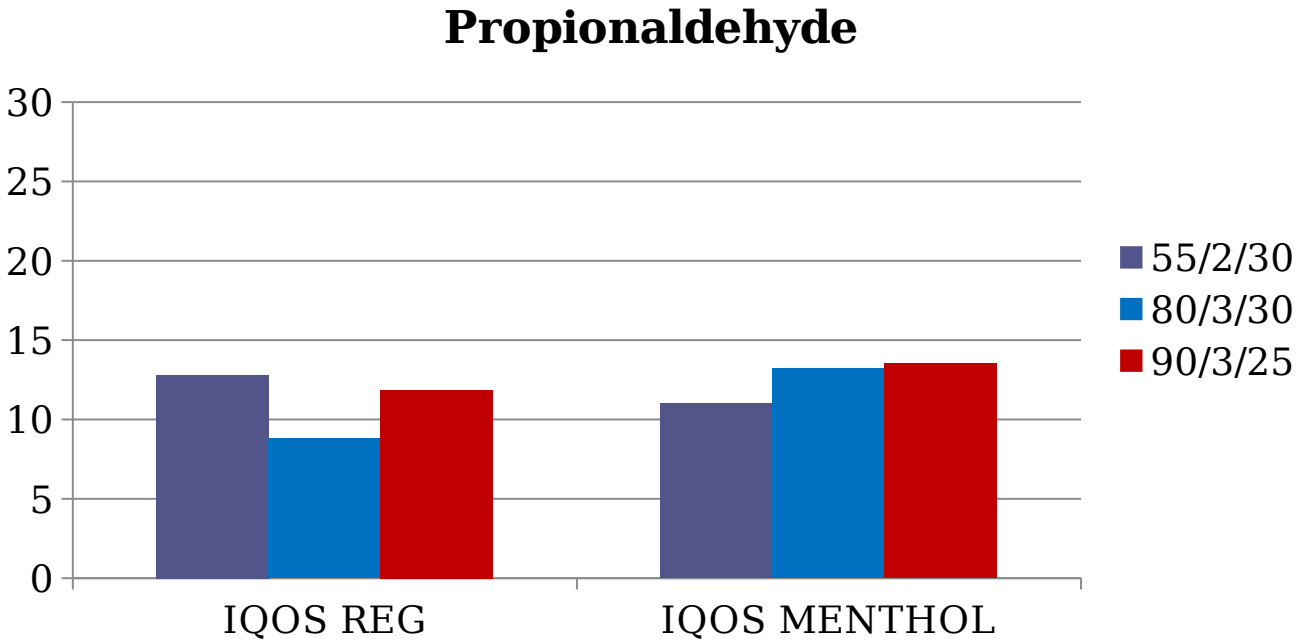

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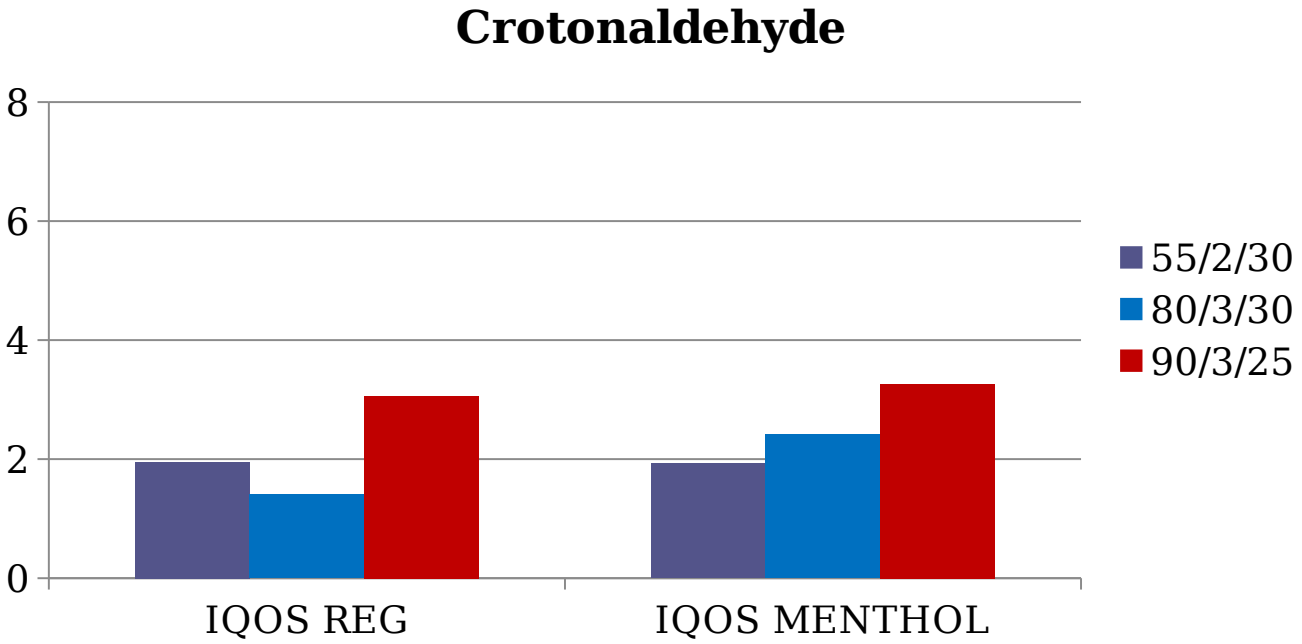

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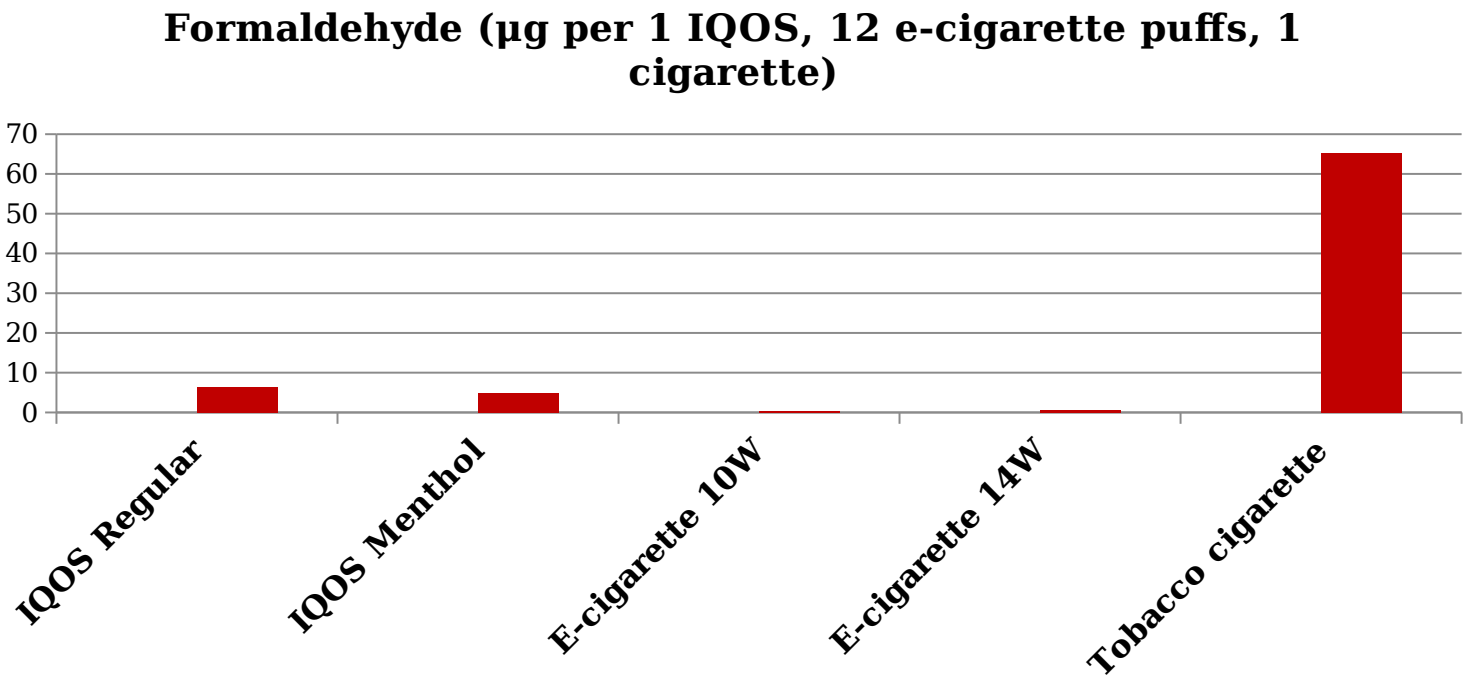
Aldehydes in THP

Comparing IQOS, tobacco cigarette and e-cigarette



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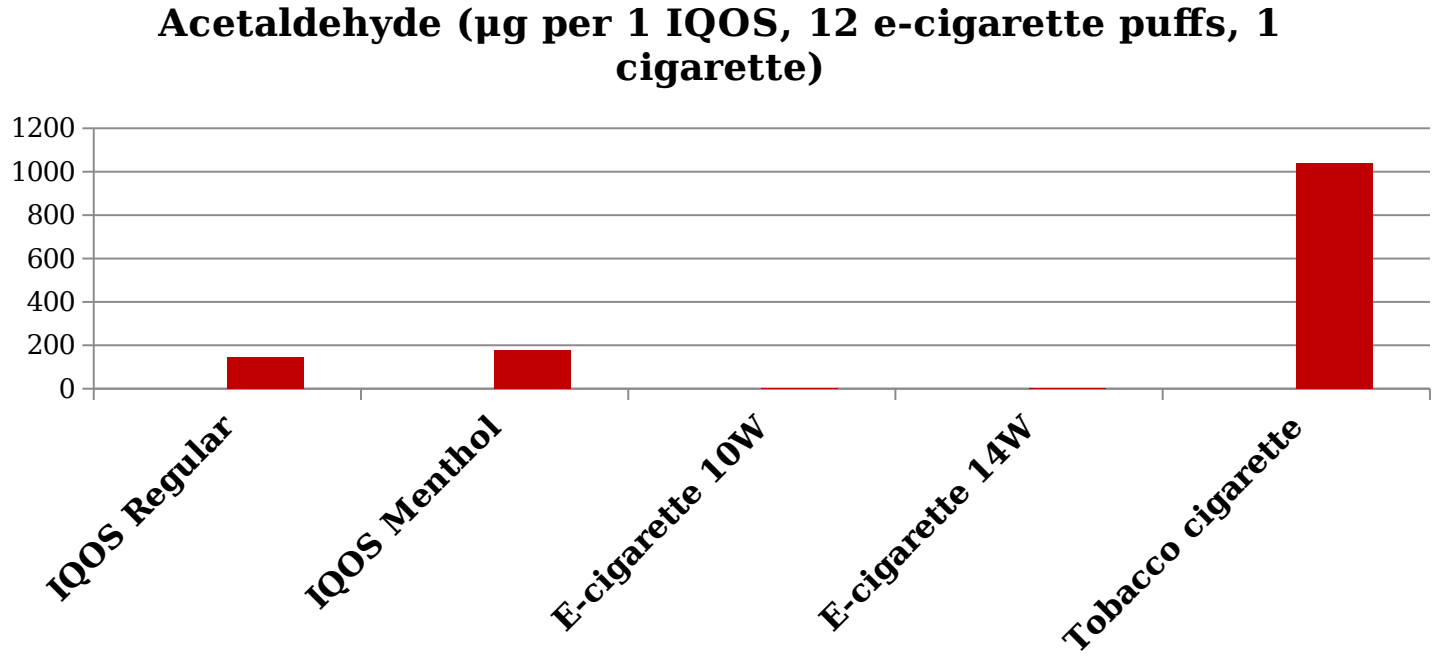

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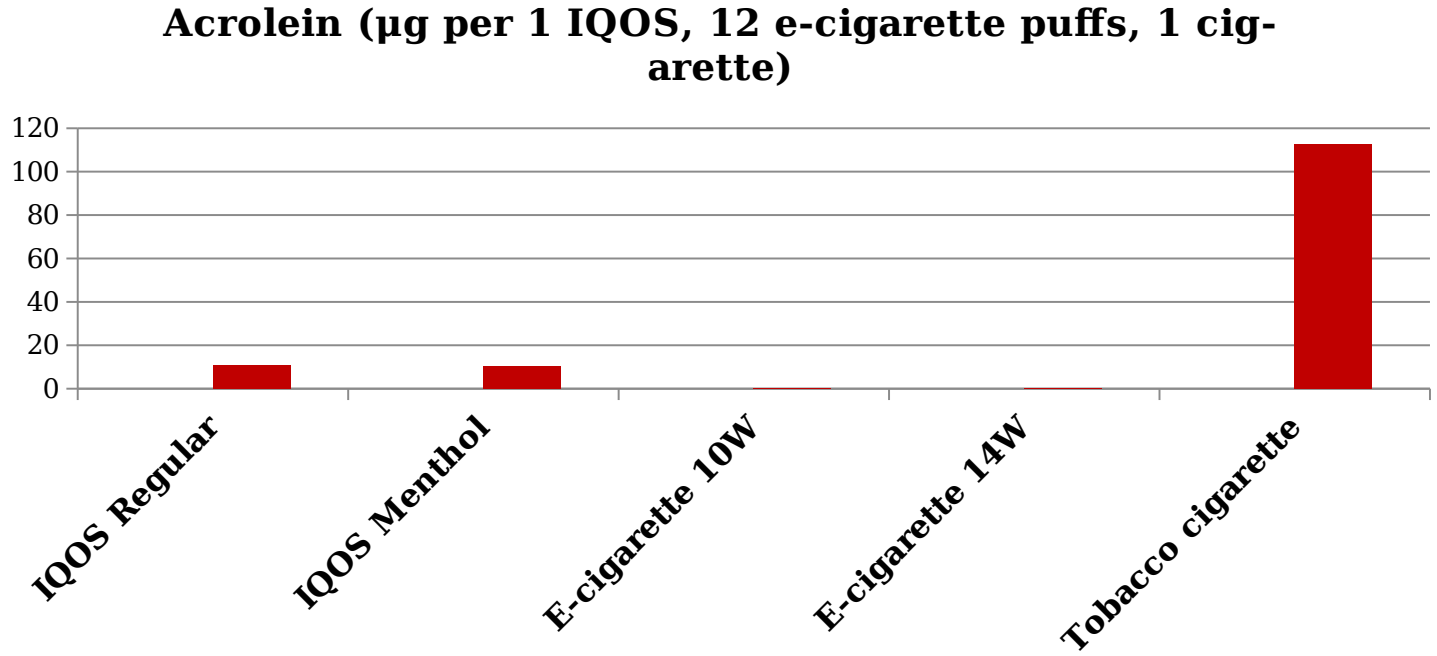

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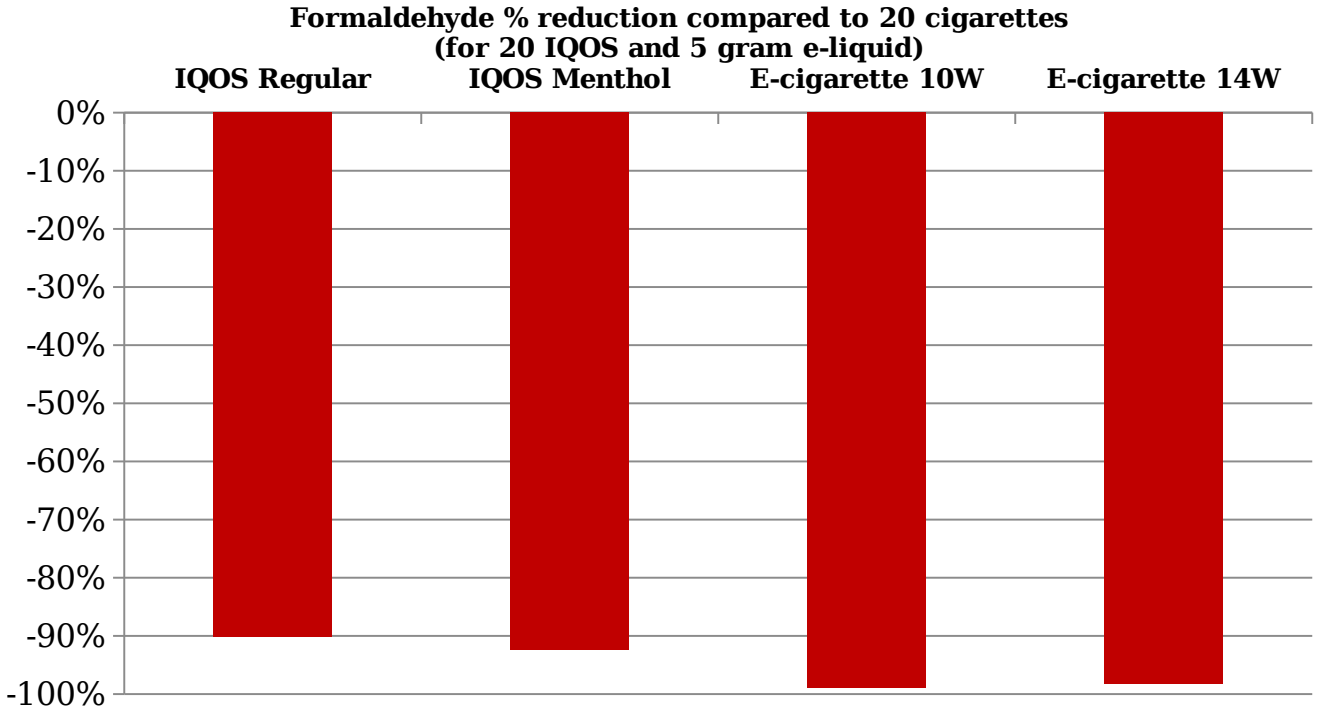
Aldehydes in THP

difference from tobacco cigarettes



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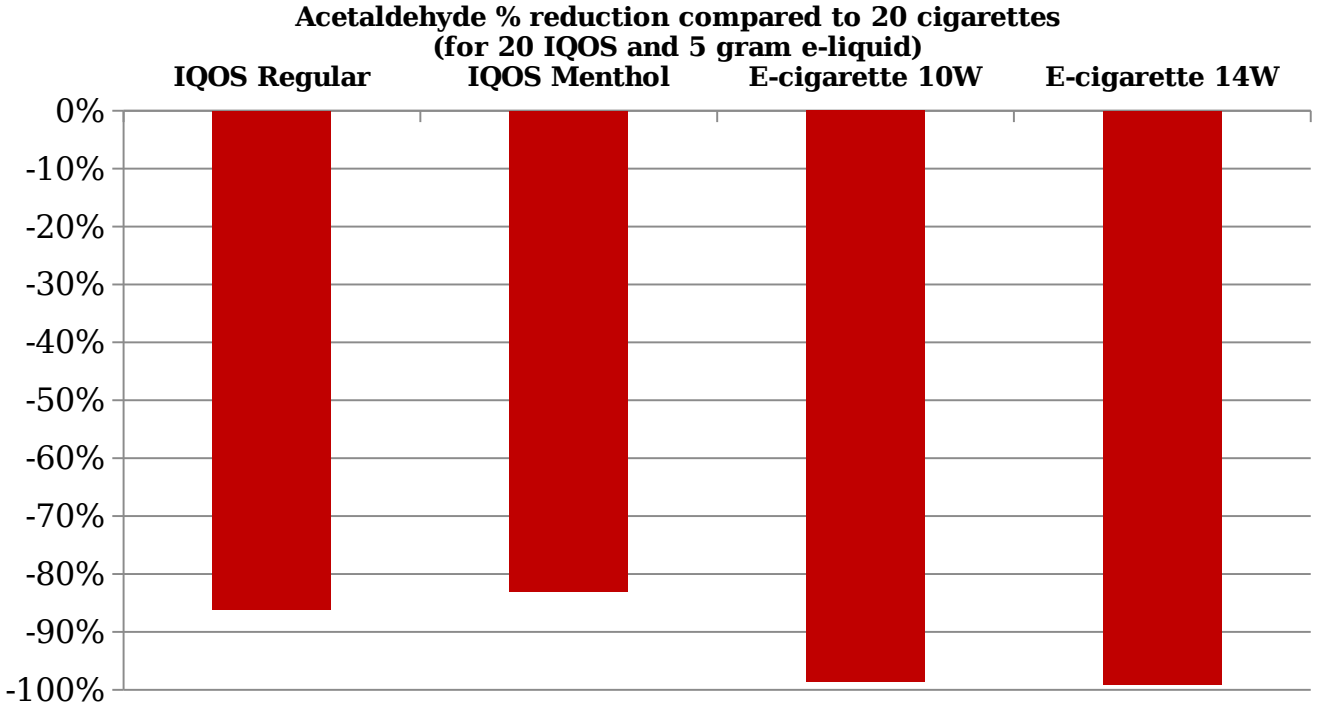

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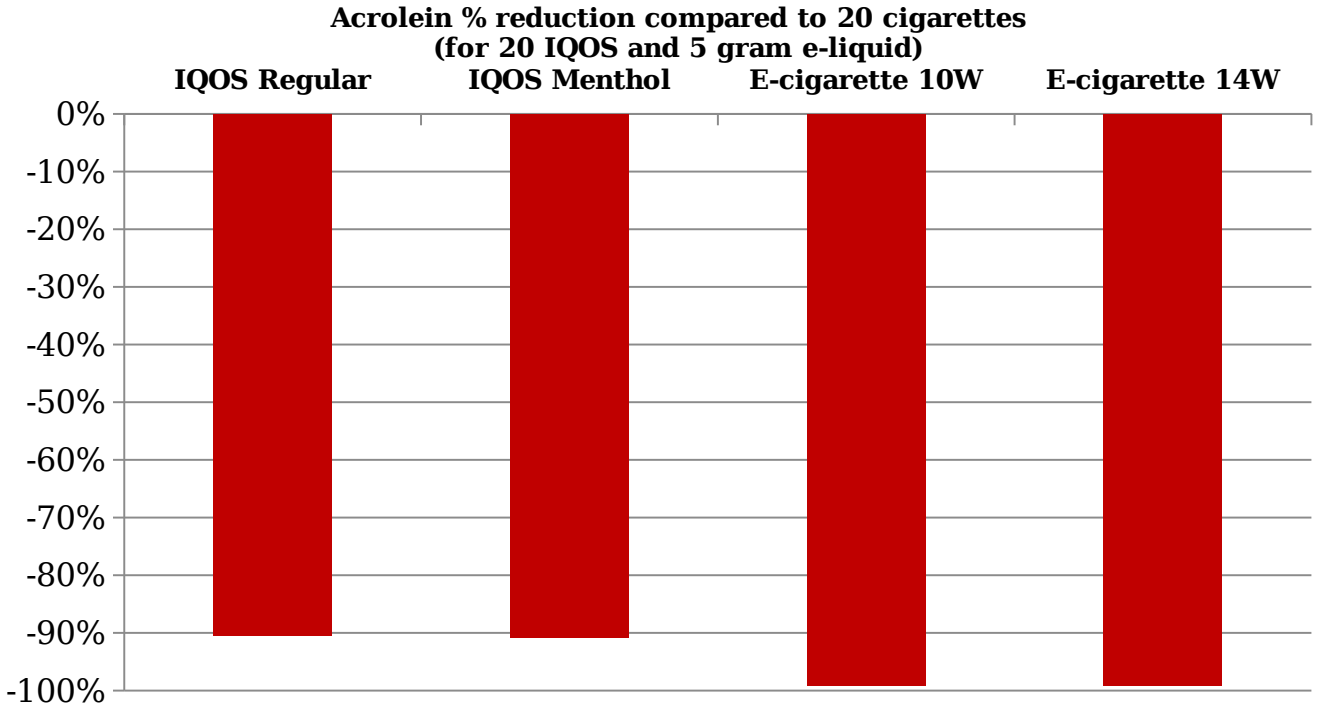

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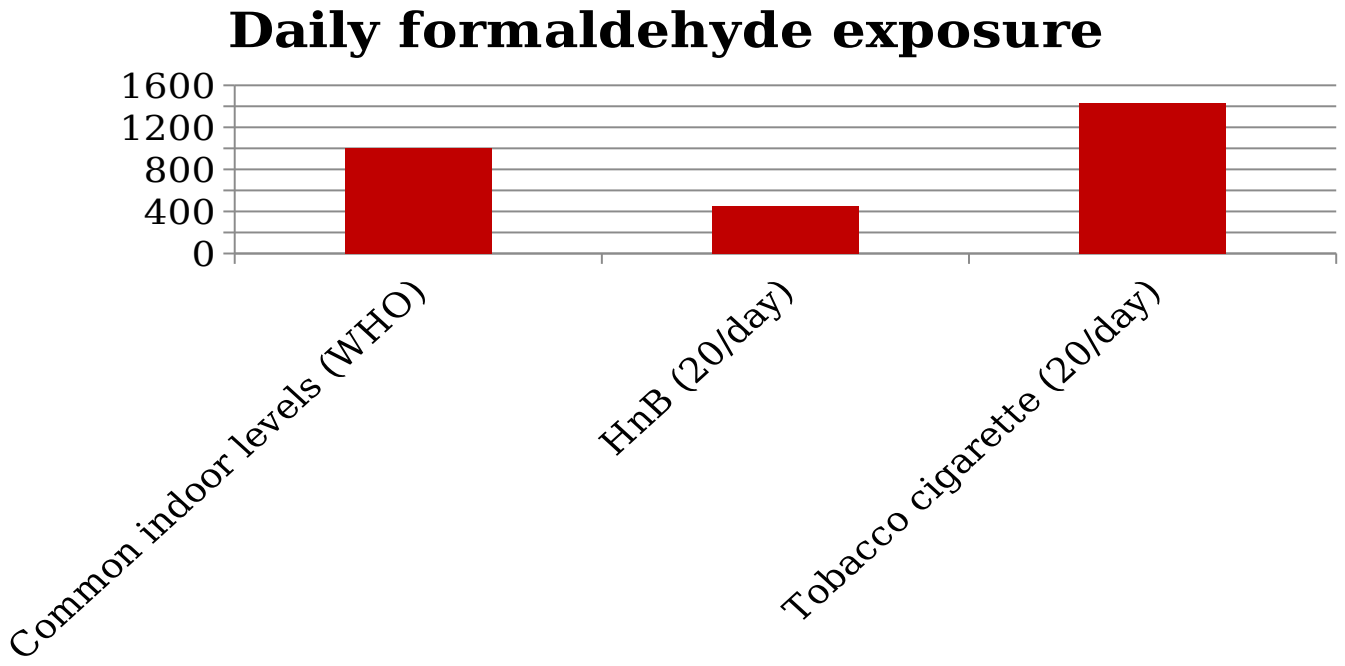
Aldehydes in the environment



20m³ ventilation volume/day

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

THPs and heart disease risk?

University of California San Francisco

Inhalation of Heat-Not-Burn Tobacco Aerosol Impairs Vascular Endothelial Function

Pooneh Nabavizadeh MD[1], Jiangtao Liu MD[1], Sharina Ibrahim BSc[2], Ronak Derakhshandeh MS[1], Matthew L. Springer PhD[1,2,3]

Cardiovascular Research Institute[1], Division of Cardiology[2], and Center for Tobacco Control Research and Education[3]
University of California, San Francisco, San Francisco, California

American Heart Association. life is why

SCIENTIFIC SESSIONS 2017

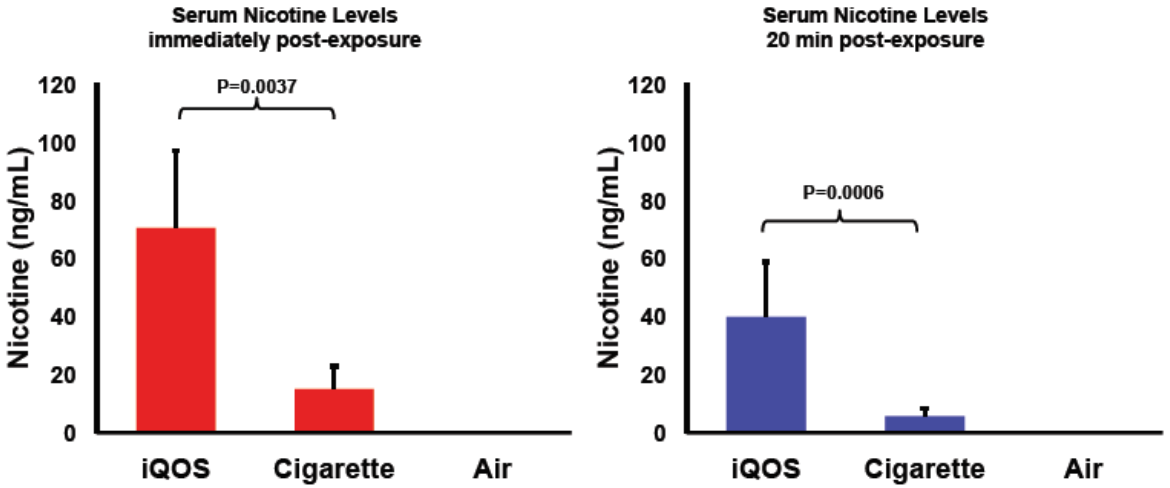
Heat-not-burn tobacco products may be 'not so hot' at protecting blood vessel function

- Exposed rats (n=8/group) via nose cone to 15 seconds of iQOS aerosol, Marlboro cigarette mainstream smoke, or air 10 times over 5 min
- FMD was quantitated pre- and post-exposure by measuring femoral artery diameter with micro-ultrasound before and after 5 min of transient surgically induced ischemia
- **Results: Acute exposure to iQOS aerosol can substantially impair endothelial function in rats comparably to cigarette smoke**

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

THPs and heart disease risk?

4.5-fold higher levels



3 studies (2 independent) showed IQOS delivers *30% lower* nicotine levels to the aerosol than tobacco cigarettes

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

FMD and acute nicotine intake

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PII S0735-1097(01)01732-6

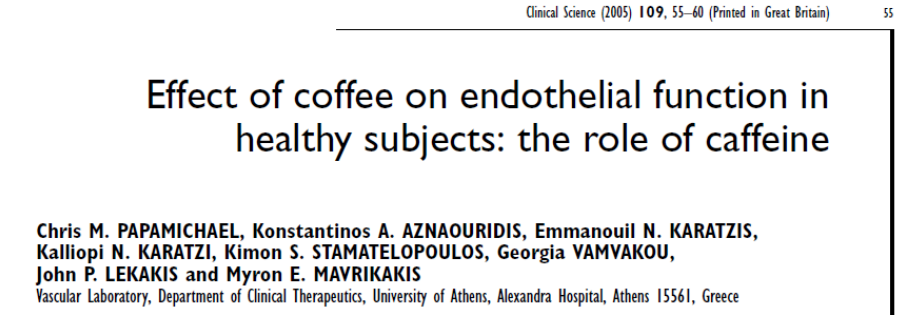
Endothelial Function

Contribution of Nicotine to Acute Endothelial Dysfunction in Long-Term Smokers

Thomas Neunteufl, MD,* Sandra Heher, MD,* Karam Kostner, MD,* Goran Mitulovic, PHD,† Stephan Lehr,‡ Gholamali Khoschsorur, PHD,§ Rainer W. Schmid, PHD,† Gerald Maurer, MD, FACC,* Thomas Stefenelli, MD, FACC*

Vienna and Graz, Austria

… nicotine *(NRT)* alone causes acute endothelial dysfunction, although to a lesser extent than smoking a cigarette of the same nicotine yield.



Clinical Science (2005) **109**, 55–60 (Printed in Great Britain) 55

Effect of coffee on endothelial function in healthy subjects: the role of caffeine

Chris M. PAPAMICHAEL, Konstantinos A. AZNAOURIDIS, Emmanouil N. KARATZIS, Kalliopi N. KARATZI, Kimon S. STAMATELOPOULOS, Georgia VAMVAKOU, John P. LEKAKIS and Myron E. MAVRIKAKIS

Vascular Laboratory, Department of Clinical Therapeutics, University of Athens, Alexandra Hospital, Athens 15561, Greece

… coffee exerts an acute unfavourable effect on the endothelial function in healthy adults... This effect might be attributed to caffeine, given that decaffeinated coffee was not associated with any change in the endothelial performance.

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Conclusions (1)

- HnB products are not absolutely safe
  - The presence of tobacco and the temperatures of heating (at least for 2 of them) result in the unavoidable emission of some potentially toxic compounds
- Manufacturers report exposure reductions from 85% to 99% (the latter for JTI product)
- Almost all scientific data is coming from the manufacturers
  - This is currently the biggest problem, related to the justified mistrust for the industry
- Currently available evidence suggest substantial reduction in toxins and reduction in biomarkers of exposure – but more evidence is needed, especially from independent sources

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301

Conclusions (2)

- Other factors besides the safety/risk profile should be considered in assessing the public health effects of these products.
  - $Public\ health\ impact_{THP} = (hazard_{SM\text{-}THP}\ x\ smoking\ cessation) - (hazard_{THP}\ x\ use\ among\ non\text{-}smokers) - (hazard_{SM}\ x\ smoking\ initiation)$

- Other key issues:
  - Do they lead to sustained smoking cessation?
  - Are they promoted and used by never-smokers?
  - Is there a “gateway to smoking” effect?

- Eventually, it depends on whether tobacco harm reduction is considered an acceptable and viable additional tool to combat the smoking epidemic

Conclusions (3)

- Current evidence (verified in a small part by independent studies) support that THPs can be considered harm reduction products
- There is a risk-continuum among harm reduction products, with e-cigarettes (new-generation) emitting lower levels of toxins compared to THPs
  - The absolute difference in toxic emissions from tobacco cigarettes is much higher than the absolute difference between harm reduction products – smokers should make informed decisions
- THPs could be a viable option for smokers unable to quit by themselves or with medications or with e-cigarettes or with snus (where available)

Source: https://www.industrydocuments.ucsf.edu/docs/xxbx0301