

# SAFETY E-CIGS: CHEMICAL SAFETY

# LIQUID (“E-JUICE”) – VAPOUR

- liquid
  - propylene glycol/vegetable glycerine
  - (no) nicotine
  - aromas
- vapour (aerosol – liquid droplets)
  - no combustion of organic material:
    - no CO
    - no tar
    - small amounts of solid ultrafine particles (“particulate matter”)
    - trace amounts of toxicants & carcinogens

# SAFETY ECIGS

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

*Ther Adv Drug Saf*

1–20

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**Abstract:** Electronic cigarettes are a recent development in tobacco harm reduction. They are marketed as less harmful alternatives to smoking. Awareness and use of these devices has grown exponentially in recent years, with millions of people currently using them. This systematic review appraises existing laboratory and clinical research on the potential risks from electronic cigarette use, compared with the well-established devastating effects of smoking tobacco cigarettes. Currently available evidence indicates that electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes. Research will help make electronic cigarettes more effective as smoking substitutes and will better define and further reduce residual risks from use to as low as possible, by establishing appropriate quality control and standards.

# SAFETY ECIGS

**Table 1.** Types of studies performed to determine safety and to estimate risk from EC use.

Type of studies	Research subject	Advantages	Disadvantages
Chemical studies	Evaluate the chemical composition of liquids and/or aerosol. Examine environmental exposure (passive 'vaping').	Easier and faster to perform. Less expensive. Could realistically be implemented for regulatory purposes.	Usually targeted on specific chemicals. Unknown effects of flavorings when inhaled. No validated protocols for vapor production. Provide no objective evidence about the end results (effects) of use (besides by applying theoretical models).
Toxicological studies	Evaluate the effects on cell cultures or experimental animals.	Provide some information about the effects from use.	Difficult to interpret the results in terms of human <i>in vivo</i> effects. More expensive than chemical studies. Need to test aerosol and not liquid. Standards for exposure protocols have not been clearly defined.
Clinical studies	Studies on human <i>in vivo</i> effects.	Provide definite and objective evidence about the effects of use.	Difficult and expensive to perform. Long-term follow up is needed due to the expected lag from initiation of use to possible development of any clinically evident disease. For now, limited to acute effects from use.

# SAFETY ECIGS: chemical studies

- everything is chemical
- a majority of chemicals is carcinogenic/toxic, but only in very high doses
  - “the dose makes the poison”
- compared to...
  - smoke from tobacco cigarettes (relative safety)
  - medically approved NRT
  - certain established exposure/safety limits (absolute safety)
- vapour, not (only) liquid

# SAFETY ECIGS: chemical studies

Table 3

## Carcinogenicity in rodents of natural chemicals in roasted coffee<sup>a</sup>

Positive: $N = 21$	Acetaldehyde, benzaldehyde, benzene, benzofuran, benzo( <i>a</i> )pyrene, caffeic acid, catechol, 1,2,5,6-dibenzanthracene, ethanol, ethylbenzene, formaldehyde, furan, furfural, hydrogen peroxide, hydroquinone, isoprene, limonene, 4-methylcatechol, styrene, toluene, xylene
Not positive: $N = 8$	Acrolein, biphenyl, choline, eugenol, nicotinamide, nicotinic acid, phenol, piperidine
Uncertain	Caffeine
Yet to test	~ 1000 chemicals

<sup>a</sup>From the Carcinogenic Potency Database [1,3].

# SAFETY ECIGS: chemical studies

**Table 2.** Summary of chemical toxicity findings. (selection of studies)

Study	What was investigated?	What were the key findings?	
		Liquid	Vapor
Laugesen [2009]	Evaluation of 62 toxicants in the EC vapour from Ruyan 16 mg and mainstream tobacco smoke using a standard smoking machine protocol.	N/A	No acrolein, but small quantities of acetaldehyde and formaldehyde found. Traces of TSNAs (NNN, NNK, and NAT) detected. CO, metals, carcinogenic PAHs and phenols not found in EC vapour. Acetaldehyde and formaldehyde from tobacco smoke were 55 and 5 times higher, respectively.
Westenberger [2009]	Evaluation of toxicants in EC cartridges from two popular US brands.	TSNAs and certain tobacco specific impurities were detected in both products at very low levels. Diethylene glycol was identified in one cartridge.	N/A
Burstyn [2014]	Systematic review of 35 chemical toxicity studies/ technical reports of EC liquids/vapours.	No evidence of levels of contaminants that may be associated with risk to health. These include acrolein, formaldehyde, TSNAs, and metals. Concern about contamination of the liquid by a nontrivial quantity of ethylene glycol or diethylene glycol remains confined to a single sample of an early technology product and has not been replicated.	

Abbreviations. CO, carbon monoxide; EC, electronic cigarette; NAT, N-Nitrosoanatabine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-Nitrosornicotine; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; TSNAs, tobacco-specific nitrosamines; VOCs, volatile organic carbons.

Source: Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: A systematic review. *Ther Adv Drug Saf*, 2014, 5: 67–86.

# SAFETY ECIGS: chemical studies

**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 <sup>4</sup>
Electronic cigarette (per ml)	13	52 <sup>1</sup>	1
Nicotine gum (per piece)	2	48 <sup>2</sup>	0.92
Winston (per cigarette)	3365	50 475 <sup>3</sup>	971
Newport (per cigarette)	3885	50 775 <sup>3</sup>	976
Marlboro (per cigarette)	6260	93 900 <sup>3</sup>	1806
Camel (per cigarette)	5191	77 865 <sup>3</sup>	1497

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

Source: Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: A systematic review. *Ther Adv Drug Saf*, 2014, 5: 67–86.

# SAFETY ECIGS: chemical studies

Table 4 Comparison of toxins levels between conventional and electronic cigarettes

Toxic compound	Conventional cigarette ( $\mu\text{g}$ in mainstream smoke) <sup>35</sup>	Electronic cigarette ( $\mu\text{g}$ 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

NNK, N'-nitrosornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosornicotine.

Table 1 Selected toxic compounds identified in tobacco smoke <sup>20–23</sup>

Chemical compounds	Toxic effects
<b>Carbonyl compounds</b> Formaldehyde*, acetaldehyde*, acrolein*	Cytotoxic, carcinogenic, irritant, pulmonary emphysema, dermatitis
Volatile organic compounds (VOCs) Benzene*, toluene*, aniline	Carcinogenic, haematotoxic, neurotoxic, irritant
<b>Nitrosamines</b> N'-nitrosornicotine (NNN)*, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK)*, N'-nitrosoethylmethylamine	Carcinogenic
<b>Polycyclic aromatic compounds (PAHs)</b> Benzo(a)pyrene, benzo(a)anthracene, dibenzo(a)anthracene	Carcinogenic
Free radicals Methyl radical, hydroxyl radical, nitrogen monoxide	Carcinogenic, neurotoxic
Toxic gases <b>Carbon monoxide</b> hydrogen sulfide, ammonia, sulfur dioxide, hydrogen cyanide	Cardiovascular toxicants, carcinogenic, irritant
<b>Heavy metals</b> Cadmium (Cd)*, lead (Pb)*, mercury (Hg)*	Carcinogenic, nephrotoxic, neurotoxic, haematotoxic
Other toxicants Carbon disulfide	Neurotoxic

\*Indicates compounds analysed in this study.

Source: Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* doi:10.1136/tobaccocontrol-2012-050859

# SAFETY ECIGS: chemical studies

## Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks

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### Results

There was no evidence of potential for exposures of e-cigarette users to contaminants that are associated with risk to health at a level that would warrant attention if it were an involuntary workplace exposures. The vast majority of predicted exposures are < <1% of TLV. Predicted exposures to acrolein and formaldehyde are typically <5% TLV. Considering exposure to the aerosol as a mixture of contaminants did not indicate that exceeding half of TLV for mixtures was plausible. Only exposures to the declared major ingredients -- propylene glycol and glycerin -- warrant attention because of precautionary nature of TLVs for exposures to hydrocarbons with no established toxicity.

# SAFETY ECIGS: chemical studies

Table 1 Exposure predictions based on analysis of aerosols generated by smoking

Compound	N	Estimated concentration in personal breathing zone		Ratio of most stringent TLV (%)		Reference
		PPM	mg/m <sup>3</sup>	Calculated directly	Safety factor 10	
Acetaldehyde	1	0.005		0.02	0.2	[5]
	3	0.003		0.01	0.1	[4]
	12	0.001		0.004	0.04	[8]
	1	0.00004		0.0001	0.001	[3]
	1	0.0002		0.001	0.008	[3]
	150	0.001		0.004	0.04	[40,41]
Acetone	1	0.008		0.03	3	[38]
	1	0.002		0.0003	0.003	[38]
	150	0.0004		0.0001	0.001	[40,41]
Acrolein	12	0.001		1	13	[8]
	150	0.002		2	20	[40,41]
	1	0.006		6	60	[38]
Butanal	150	0.0002		0.001	0.01	[40,41]
Crotonaldehyde	150		0.0004	0.01	0.1	[40,41]
Formaldehyde	1	0.002		0.6	6	[5]
	3	0.008		3	30	[4]
	12	0.006		2	20	[8]
	1	<0.0003		<0.1	<1	[3]
	1	0.0003		0.1	1	[3]
	150	0.01		4	40	[40,41]
	1	0.009		3	30	[38]
Glyoxal	1		0.002	2	20	[38]
	150		0.006	6	60	[40,41]
	12		0.001	0.05	0.5	[8]
o-Methylbenzaldehyde						
p,m-Xylene	12		0.00003	0.001	0.01	[8]
Propanal	3	0.002		0.01	0.1	[4]
	150	0.0006		0.002	0.02	[40,41]
	1	0.005		0.02	0.2	[38]
Toluene	12	0.0001		0.003	0.03	[8]
Valeraldehyde	150		0.0001	0.0001	0.001	[40,41]

# average is presented when N > 1.

(a) acrolein: ~1% of TLV (average of 12 measurements) [40] and measurements at a mean of 2% of TLV (average of 150 measurements) [41] and

(b) formaldehyde: between 0 and 3% of TLV based on 18 tests (average of 12 measurements at 2% of TLV, the most reliable test) [40] and an average of 150 results at 4% of TLV [41].

Source: Peering through the mist: Systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks. *BMC Public Health*, 2014, 14-18.

# SAFETY ECIGS: chemical studies

Table 3 Exposure predictions based on analysis of aerosols generated by smoking machines: **Inorganic Compounds\***

Element quantified	Assumed compound containing the element for comparison with TLV	N**	Estimated concentration in personal breathing zone (mg/m <sup>3</sup> )	Ratio of most stringent TLV (%)		Reference
				Calculated directly	Safety factor 10	
Aluminum	Respirable Al metal & insoluble compounds	1	0.002	0.2	1.5	[26]
Barium	Ba & insoluble compounds	1	0.00005	0.01	0.1	[26]
Boron	Boron oxide	1	0.02	0.1	1.5	[26]
Cadmium	Respirable Cd & compounds	12	0.00002	1	10	[8]
Chromium	Insoluble Cr (IV) compounds	1	3E-05	0.3	3	[26]
Copper	Cu fume	1	0.0008	0.4	4.0	[26]
Iron	Soluble iron salts, as Fe	1	0.002	0.02	0.2	[26]
Lead	Inorganic compounds as Pb	12	7E-05	0.1	1	[26]
Magnesium	Inhalable magnesium oxide	12	0.000025	0.05	0.5	[8]
Manganese	Inhalable magnesium oxide	1	0.00026	0.003	0.03	[26]
Manganese	Inorganic compounds, as Mn	1	8E-06	0.04	0.4	[26]
Nickel	Inhalable soluble inorganic compounds, as Ni	1	2E-05	0.02	0.2	[26]
Nickel	Inorganic compounds, as Ni	12	0.00005	0.05	0.5	[8]
Potassium	KOH	1	0.001	0.1	1	[26]
Tin	Organic compounds, as Sn	1	0.0001	0.1	1	[26]
Zinc	Zinc chloride fume	1	0.0004	0.04	0.4	[26]
Zirconium	Zr and compounds	1	3E-05	0.001	0.01	[26]
Sulfur	SO <sub>2</sub>	1	0.002	0.3	3	[26]

# The actual molecular form in the aerosol unknown and so worst case assumption was made if it was physically possible (e.g. it is not possible for elemental lithium & sodium to be present in the aerosol); there is no evidence from the research that suggests the metals were in the particular highest risk form, and in most cases a general knowledge of chemistry strongly suggests that this is unlikely. Thus, the TLV ratios reported here probably do not represent the (much lower) levels that would result if we knew the molecular forms.

## average is presented when N > 1.

Source: Peering through the mist: Systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks. *BMC Public Health*, 2014, 14-18.

# SAFETY ECIGS: chemical studies

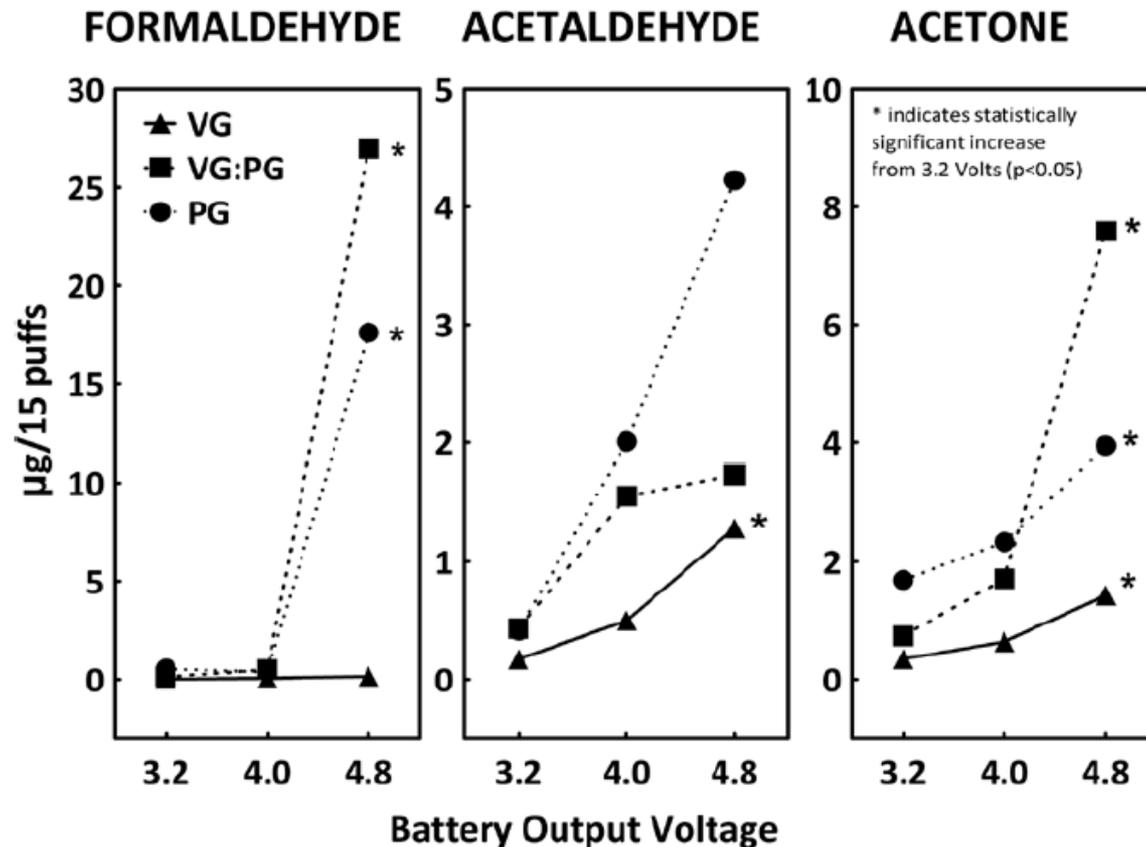
## Key conclusions:

- Even when compared to workplace standards for involuntary exposures, and using several conservative (erring on the side of caution) assumptions, the exposures from using e-cigarettes fall well below the threshold for concern for compounds with known toxicity. That is, even ignoring the benefits of e-cigarette use and the fact that the exposure is actively chosen, and even comparing to the levels that are considered unacceptable to people who are not benefiting from the exposure and do not want it, the exposures would not generate concern or call for remedial action.
- Expressed concerns about nicotine only apply to vapers who do not wish to consume it; a voluntary (indeed, intentional) exposure is very different from a contaminant.
- There is no serious concern about the contaminants such as volatile organic compounds (formaldehyde, acrolein, etc.) in the liquid or produced by heating. While these contaminants are present, they have been detected at problematic levels only in a few studies that apparently were based on unrealistic levels of heating.
- The frequently stated concern about contamination of the liquid by a nontrivial quantity of ethylene glycol or diethylene glycol remains based on a single sample of an early-technology product (and even this did not rise to the level of health concern) and has not been replicated.
- Tobacco-specific nitrosamines (TSNA) are present in trace quantities and pose no more (likely much less) threat to health than TSNA from modern smokeless tobacco products, which cause no measurable risk for cancer.
- Contamination by metals is shown to be at similarly trivial levels that pose no health risk, and the alarmist claims about such contamination are based on unrealistic assumptions about the molecular form of these elements.
- The existing literature tends to overestimate the exposures and exaggerate their implications. This is partially due to rhetoric, but also results from technical features. The most important is confusion of the concentration in aerosol, which on its own tells us little about risk to health, with the relevant and much smaller total exposure to compounds in the aerosol averaged across all air inhaled in the course of a day. There is also clear bias in previous reports in favor of isolated instances of highest level of chemical detected across multiple studies, such that average exposure that can be calculated are higher than true value because they are “missing” all true zeros.
- Routine monitoring of liquid chemistry is easier and cheaper than assessment of aerosols. Combined with an understanding of how the chemistry of the liquid affects the chemistry of the aerosol and insights into behavior of vapers, this can serve as a useful tool to ensure the safety of e-cigarettes.
- The only unintentional exposures (i.e., not the nicotine) that seem to rise to the level that they are worth further research are the carrier chemicals themselves, propylene glycol and glycerin. This exposure is not known to cause health problems, but the magnitude of the exposure is novel and thus is at the levels for concern based on the lack of reassuring data.



you only find what you are looking for

# SAFETY ECIGS: chemical studies



**Figure 1.** Effects of nicotine solvent and battery output voltage on levels of carbonyl compounds released from ECs (µg/15 puffs;  $N = 3$ ; puff duration 1.8 s, puff volume 70 ml, puff intervals 17 s).

Source: Carbonyl compounds in electronic cigarette vapors: Effects of nicotine solvent and battery output voltage. *Nicotine & Tobacco Research*, 2014, 16: 1319-1326.