

Is electronic cigarette a serious matter ?



At first glance, the electronic cigarette, which was patented in 2003 by Hon Lik, a chinese chemist, seemed to me a mere gadget, allowing smokers to defy smoking bans with impunity. Because they are not blowing smoke, but little clouds of condensed water vapor only, as one can see getting out of the mouth of passers-by on a cold winter morning. As I am convinced that nicotine is not able to induce dependence, thus that I thought that e-cig would not be profitable to its makers, I thought that the craze for it would be passing. I thought that it would end quickly in the store of transient passions such as eucalyptus cigarettes, yo-yo or hula-hoop.

It did not happen. Provocative smokers, who did not want quitting at all, get caught up in the game and use electronic cigarettes to smoking less, even to stop. The market expands almost exponentially (Figure 1) [1]. It is difficult to evaluate it in France, where around 500.000 regular users (vapers) are “vaping” already [2]. For sure, e-cig is no longer a mere gadget. In 2013, it justifies a real scientific approach.

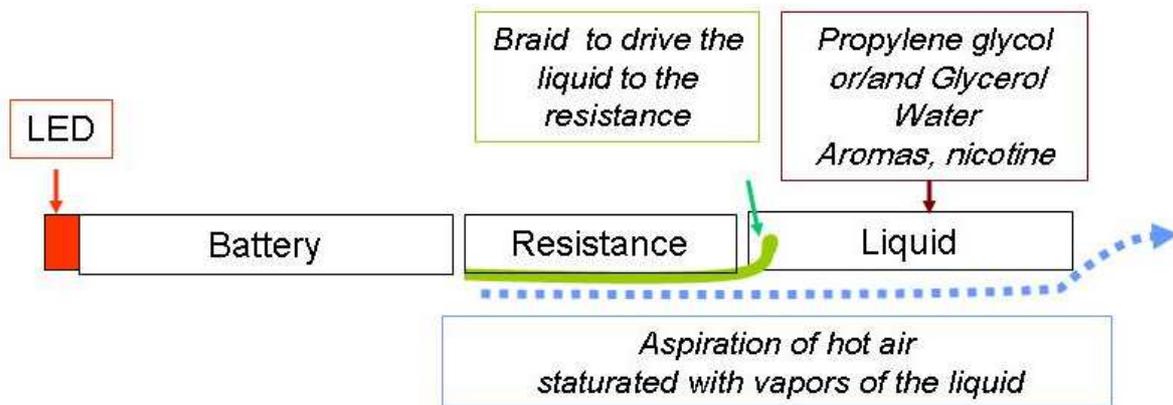
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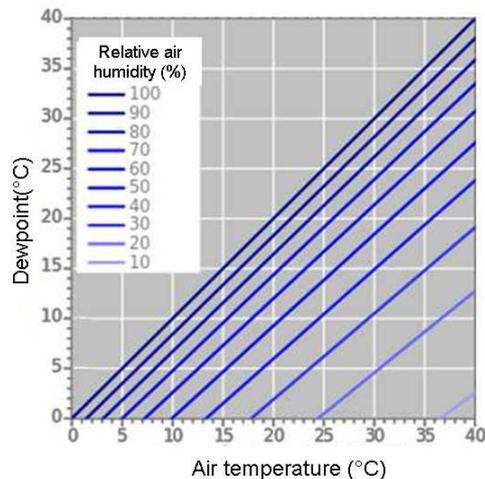
1.- How does an electronic cigarette work?

Propylene glycol, and to a lesser degree glycerol, are extremely hydrophilic. They are the basis of a liquid to be vaporized, which contains some water, various aromas and most often various amounts of nicotine. However some liquids do not contain nicotine. A battery powers a resistance, which heats the inspired air. Vapors of the liquid saturates it, either while it passes through a soaked flock, or directly from the surface of the resistance, to which a braid brings about the liquid by capillarity from a tank. An *atomiser* is a resistance with incorporated braid. A *cartomiser* groups an atomiser and a tank.

As soon as the power is on, sometimes automatically as a vaper begins to aspire, the resistance heats, while sometimes a red LED lightens at the end of the e-cig, mimicking burning. Nowadays, this LED is lacking, or is blue, or on the lateral side, to prevent mistaking for a real tobacco cigarette, hence to avoid potential source of conflicts.(Figure 2)



Heated around 60°C, the aspired air vaporizes the propylene glycol and/or the glycerol. It saturates with water vapor and others components of the liquid. It completes its saturation in the humid atmosphere of the lungs. The expired air encounters the ambient air, which is usually colder, at a lower maximal water vapor saturation level. Thus, the excess of water vapor condensates, forming a visible little cloud of steam, mimicking a puff of smoke. It disperses quickly, if the ambient air is not saturated. This cloud is all the more important that the outer temperature is lower. At each degree of air humidity and temperature corresponds a critical point at which condensation occurs (Figure 3)



Thus, at 25°C, if the air is 100% saturated, steam will appear at this 25°C. If the air is saturated at 40% only, it will appear at and below 10°C. Above 37°C in a dry air, no condensation will occur. Thus, no mirage of smoke from an electronic cigarette while crossing the Sahara at noon under a burning sun.

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2.- A great variety of models

The device, sometimes fitted out with a cigarette-holder, may be mistaken for a tobacco cigarette. But it may appear in the most varied forms. It may look like a cigar, or a pipe, or an automatic narghile to vape in society.

Throwaway e-cigarettes may be used many times, until exhaustion of the liquid and of the battery (about 400 puffs, i.e. about a pack of cigarettes, for about 10€

Rechargeable cigarettes are economically cheaper. The tank may be refilled, the flock re-soaked, the battery recharged. One can choose his own kind of liquid. An intermediate model consists of a pre-filled capsule to be screwed to the rechargeable battery, thus avoiding handling.

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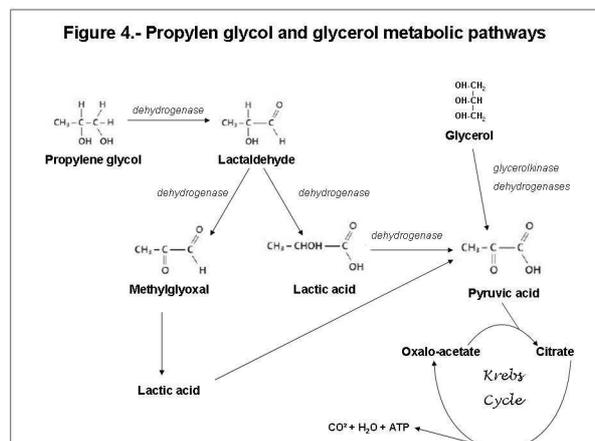
3.- The liquids

3-1. Main components

3.11. Propylene glycol (PG) or propane 1-2 diol (HO-CH-CHOH-CH₃) [3].

Chemiosynthetic, it has no natural source. Two stereoisomers exist, but the racemic is generally used. It is a colorless liquid, almost odorless, with a light sugary taste. It is viscous, and very hydrophilic. It is slightly flammable. At 99°C, a spark may explode a mixture of its vapor with air. At room temperature, it is not much volatile, but vaporizes quickly between 60 to 100°C. It boils at 188°C. Its oxidation gives irritant substances, propionaldehyde, acetic, lactic and pyruvic acids.

- Metabolism



The kidneys eliminate PG, either unchanged, or conjugated. The liver oxidizes it to lactaldehyde by alcoholdehydrogenase, then by successive dehydrations to lactic acid and pyruvic acid, which enters the Krebs cycle. Its half-life is about 2 hours in the blood, 4 hours for the whole body (figure 4).

Industrial PG production is very large, of the order of 600,000 tons a year. The main part is used to manufacture plastics, paints, antifreeze and de-icing, mainly for aircrafts at airports. For cosmetics, it is also largely used because of it is viscous, a moisturizer and a good solvent. It is an essential pharmaceutical excipient for syrups, ointments, nasal and ocular solutions.. An amazing application is the production of artificial smoke in theatrical performances or movies.

It is an authorized food additive (E1520), at a dose of 1g/kg of food. It is kosher and halal. Humectant, it prevents dehydration of sliced breads and pastries. Emulsifier, binder and thickener, it is used for sauces, creams, desserts. It is a solvent for dyes and aromas [4]. The FDA authorizes its food use since 1981 as an anti-drying agent , antioxidant, booster of pasta, emulsifier, solvent, stabilizer ant thickener. It limited to 2% its concentration in the majority of products, 2.5% in dairy, frozen products, and 5% in alcoholic beverages [5]. PG maintains an adequate level of humidity in tobacco and cigarettes. In contrast, it keeps a very low air humidity for conservation of dry food.

PG aerosol has potent antimicrobial and antiviral properties (Figure 5 and 6)

Figure 5
Inoculation of Mice with Pneumococcus Type I Exposed to Propylene Glycol Vapor
 (from Robertson et al. [6])

	Material introduced into chamber	Air samples		N° of pneumococcus colonies		Mice inoculated with 1 cc of fluid from bead tower
		Time taken	Method of culture	On plate	In fluid from bead tower	
Test chamber	Propylene glycol vapour. 1/3,000,000 followed by pneumococcus spray	Immediately after bacterial spray	Plate	0	0	10 mice. All remained well
		10 mn later	Bead tower			
		30 mn later	Plate	0		
Control chamber	Pneumococcus spray	Immediately after bacterial spray	Plate	1128	1 cc=228 Total=5700*	10 mice. All died from pneumococcus infection in 24 to 34 hrs
		10 mn later	Bead tower			
		30 mn later	Plate	484		

* The 2 liter air sample was drawn through 25cc of 50 per cent broth-water mixture

The vapor state is the most effective condition for air disinfection, as PG penetrates germs carried by droplets of Pflüge [6]. Paradoxically, germs in pure PG retain their vitality and virulence. The effect increases with temperature, which rises the vapor pressure of PG. It is

more important if the size of the aerosol particles is lower [7]. An antifungal action has also been demonstrated [8].

Figure 6. Bactericidal effect of propylene glycol (from Putt et al. 1943 [7])

Relationship between Numbers of Bacteria Suspended in Air and the Effectiveness of Different Glycol Concentrations Employing Staphylococcus albus as the Test Microorganisms
(Total number of droplets of culture inoculum kept constant. Temperature 27–30°C. Relative humidity about 50 per cent)

Amount of propylene glycol introduced: mg. glycol per liter of air	Calculated glycol concentration in chamber air	No. of bacteria on "immediate" control plate	Per cent reduction in No. of bacteria in glycol chamber* relative to control		
			Immediately (15 sec. after bacterial spray)	5 min. later	15 min. later
0.66	Greater than saturation	4,000–13,000	per cent 99.3	per cent 100	per cent 100
0.4–0.45	Saturation (about) 1:2,500,000	500–6,000	96.7	99.8	100
0.32	Slightly below saturation 1:3,000,000	400–1,400	83.6	99.8	99.6
		6,000	84.4	85	100
0.25–0.27	Unsaturated	73–199	72.7	99.0	97.8
		450–1,300	11.6	36.2	85.7
0.16	1:6,000,000	36–122	0	0	0

* The percentages are based on comparison with the numbers of bacteria in samples taken simultaneously from control chambers; *i.e.*, Per cent reduction =
(No. of bacteria from control chamber – No. of bacteria from glycol chamber) ÷ No. of bacteria from control chamber.

In wartime, to sterilize the air with vapors or aerosols of propylene glycol was one of the objectives for inexpensive protection against epidemics in barracks. However, it has fallen into disuse, mainly because it was difficult to get sufficient air concentrations of PG in open premises. The advent of antibiotics, driven by industrial interests, has also hindered the development of this application. However, it is still officially confirmed. PG is used for disinfection of surfaces, and in combination with ethanol to disinfect hands. Interestingly, electronic cigarettes lead directly concentrated propylene glycol vapor in the respiratory tree. This could therefore create a renewed interest in this application to fight against pathogenic microorganisms, and justify clinical studies on this subject.

It is often cited that aerosols of propylene glycol have been or are used against asthma. I could not find confirmation of it either in the literature or among the patented medicines. Only an old article from the Mayo Clinic advocates its use in aerosol to fluidify mucus during acute broncho-pulmonary episodes. The articles by Robertson, 20 years before, were not mentioned, so that an anti-microbial effect was probably not looked for. This was presented as a routine practice, suggesting it had been widely used. I could not find any article about adverse effects. [9]

- Toxicity

Semantic confusion with ethylene glycol, also used as antifreeze, wrongly attributed to PG a renal toxicity, with formation of stones. PG itself is completely innocent on this point. However, various potentially toxic impurities were found in some samples available in the market for industrial uses. It is therefore necessary to use food PG, pure guaranteed.

In animal studies, except irritant effects on ocular or nasal mucosa, likely related to its drying power, PG showed no acute or chronic toxicity, no skin sensitization. The NOAEL (no observed adverse effect level) is of the order of 2g/kg (rat and dog). At higher dose, minor erythrocyte anomalies are observed only. It is neither mutagenic, nor carcinogenic or teratogenic. No significant alterations were found in monkeys and rats exposed between 12 and 18 months at very high air vapor concentrations of propylene glycol [10].

In man, tolerance is considerable. Poisoning by massive doses induces sedation only, possibly a regressive coma, sometimes after an epileptic fit. These events are linked to hyperosmolarity, lactic acidosis and hypoglycemia. They occur especially during intravenous infusions, for PG is often used as a solvent for various drugs. So a 70 year old woman received in 24 hours a dose of 479 g. She developed a severe lactic acidosis, which disappeared after stopping the infusion [11]. In patients with severe burns, absorption of PG from skin topics may be considerable (10.5 g/l of blood in a baby) [12]. At 1.5 g/kg orally in the treatment of glaucoma, a feeling of giddiness was observed only [13]. WHO considers as allowable a daily intake of 25 mg/kg , a large safety margin. Absorption from various sources was estimated in USA at 34 mg/kg per day in 2004, before the appearing of electronic cigarettes[14]. No toxicity, no detrimental effect on development or reproduction have been found. [15].

It is difficult to estimate the average absorption of PG by a vaper. A 10 ml refill bottle of a liquid containing 91.5% of propylene glycol would last three to five days, or about 25 mg/kg a day for a standard adult of 73 kg if absorption is complete. I found no studies on the absorbed proportion of inhaled PG vapor. Presumably a vaper disposes of PG in his exhaled air, otherwise it would be difficult to understand how the pseudo-smoke is formed. However, paradoxically, one study did not find any PG in the ambient air of a closed room after a vaping session [16]. Acute exposures (inhalation, artificial fog) have given rise to respiratory and eye irritation only. These are obviously due to mere dryness of mucous membranes, because PG has not been shown to be allergenic. PG is well tolerated as an excipient in some eye drops and nasal solutions.

3.1.2 - Glycerol. HOH2C–CHOH–CH2OH

It is a colorless sweet tasting liquid, more viscous than propylene glycol. It is also very hydrophilic. It is obtained from hydrolysis of animal as well as plant fats. In this case, it can be classified as halal under the name of vegetable glycerin. It is often used in electronic cigarettes, either alone or mixed with from 50 to 80% PG. It is sometimes also found in tobacco cigarettes to keep adequate moisture. It produces more vapor than PG, but the tingling sensation of contraction of the throat that is sought in tobacco smoke (throat hit) would be lower. Perception of aromas would be mitigated. Another disadvantage is that it tends to clog the braid of atomizers.

- Metabolism

Glycerol is phosphorylated to triphosphoglyceraldehyde, then to pyruvic acid which enters the Krebs cycle. It does not produce lactic acid directly.

- Toxicity

Directive 67/548/EEC regards it as non-hazardous. It has no toxicity, except its decomposition to acrolein at boiling point (290°C). Acrolein is extremely irritating, as one can realize if one allows fat to decompose in an overheated pan. It is present in tobacco smoke. However the temperature reached in the electronic cigarette is usually 60 to 70°C only, but it may reach 100 to 150°C. At this temperature, small amounts of acrolein can be produced, but the cough it provokes at very low concentration may protect against poisoning.

3.1.3 – Nicotine

Most electronic cigarettes not only produce a pseudo-smoke, but provide nicotine. The amount varies widely depending on the e-liquid. Most brands usually offer several concentrations from zero to 24mg per ml in cartridges or liquids for refilling. However, analyses of these liquids show considerable differences between announced nicotine concentration and assay results. However, some European brands already would control more precisely the nicotine content of their e-liquids. Similarly, by comparing concentrations between new and used cartridges, the percentage vaporized after 300 puffs varies greatly, from 21 to 81%, depending on the brand [17]. Such variations may perhaps explain the conflicting results of measured nicotine absorption levels, when a study found that it is zero for cigarettes with high nicotine levels [18], while the same author finds the contrary two years later, but in a study where the vapers used different hardware with more powerful batteries [19].

3.2 – Other components

The list of other components can not be exhaustive. Free rein was given to the imagination of manufacturers, and also of vapers engaged in artisanal compositions. By a research on commercial sites, I could have a partial idea of the commercial liquid composition, although many sites do not give information about it.

3.2.1 – Ethanol

It is used as a solvent of aromas and fluidifies e-liquids, often in a 4.5% concentration. It would also promote the feeling of "*hit*." This alcohol can be mere ethanol, but also vodka, rum, whiskey (scotch, irish, bourbon). This is useful to know for abstinent alcoholics, because non-alcoholic e-liquids exist, that are also halal.

3.2.2 – Organic acids

Many e-liquid contain 0.9% lactic acid. In aqueous solution, this would correspond to pH = 3.72, but it did not make sense in a PG solution. Anyway, this gives the steam a high acidity, probably partly responsible for the *hit*. Malic acid, which is stronger, and even citric acid may be found. Citric acid aerosol is used to test drugs against cough. Smokers say the feeling it brings about is pretty similar to the satisfaction of smoking tobacco. Such an aerosol has been proposed to help quitting [20].

3.2.3 – Aromas

An exploration of sites dedicated to electronic cigarette allows to draw up a list of flavored e-liquid or of aromas proposed for sale for home-made preparation. The list is impressive, certainly not exhaustive. I can unintentionally provide advertising for some brand names. All the food aromas are apparently used. Many sites propose compositions of aromas, sometimes coming from suppliers of perfumers. In addition, many vapers use their own preparations, from plants and possibly from synthetic products. The variety of aromatic chemical compounds of plants is huge. Tobacco holds the record with more than 2,200 volatile compounds. Obviously, the search for a perfect tobacco aroma is a challenge.

Figure 7. Aromas on sale on websites			
"Tobacco" aromas	"Fruit" aromas	Cooking aromas	Miscellaneous
Captain Black Cold	Apricot	Anise	Almonds
Desert Ship	Pineapple	Cinnamon	Bailey's whisky cream
Flue-Cured Tobacco	Banana	Chocolate	Butter of cacahuettes
Fortune Strike	Blackcurrant	Catalan cream	Bier
Gold & Silver	Cherry	Coffee	Red Bukk
Hillington	Citrus	Crème brûlée	Burbon
Parmal	Lime	Crepe	Cacahuettes
Peter	Strawberry	Eucalyptus	Capuccino
TAB blended	Fruit	Jasmin	Chewin-gum
Blond tobacco	Red fruits	Honey	Coca-cola
Brown tobacco	Kaki	Mint	Free Cuba
Cigar tobacco	Kiwi	Icy mint	Marshmallow
Deluxe tobacco	Lytchees	Spearmint	Hazelnut
French pipe tobacco	Tangerine	Gingerbread	Cashew nut
American blend tobacco	Mango	Pimant Jalapeno	Pecan nut
Turkish tobacco	Melon	Pepper	Mate
Virginia tobacco	Blackberry	Black pepper	Nougat
	Blueberry	Apple in the oven	Licorice
	Coconut	Tatin pie	Rum
	Orange	Rose	Fir tree
	Grapefruit	Tiramitsu	Peach schnapps
	Watermelon	Vanilla	Maple sirup
	Peach	Vanillin	Green tea
	Pear	Violette	Vodka
	Appel		Whisky
	Prune		Vitamin A
	Grape		

A food aroma is desired for its olfactory or gustatory effect, but it is usually ingested. Its safety is admitted by this route. After ingestion, some undergo the action of digestive enzymes. To reach the general circulation, an aroma must be absorbed through the intestinal mucosa, then possibly be modified by the liver, which can eliminate it. We have no data on the possible toxic effects of some of these products when inhaled. By this route, they enter the peripheral blood directly. We do not know what would happen after several daily use for

months, even years. However, olfactory sensors usually need only very small concentrations to detect aromas. Now the safety margin of food aromas seems relatively wide. However, the actually absorbed doses by inhalation might be much more important than by oral route. This could be the case of licorice, which should be watched for its role in arterial blood pressure increase, or by diacetylene, the butter aroma authorized by ingestion, but responsible by inhalation of very severe bronchiolitis obliterans in industrial environment. It could also be a factor in the development of diseases like Alzheimer. Moreover, internet advertising for aromas often mention "without diacetylene, paraben or ambrox (synthetic scent of ambergris, close to some tobacco aromas) ". Vaping experimenters desperate look for pepper aromas they hope able to generate good *hit*. We can hope that they will not try pure capsaicin !

3.2.4 – Water

Most e-liquids contain a small quantity of water, until 5%, to fluidify the liquid, solubilize certain aromas and begin to saturate the vapor.

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4 – The thermal effect

The aspired vapor reaches the mouth at around 50°C. A little investigation on a forum taught me that out of 88 responders, 53 found it tepid, 21 hot and two very hot. But whereas 9 inhaled it directly as narghile smokers do, 68 had kept their smoker's habit to keep a puff in the mouth for a while, and then inhaling a mixture of it with outside air, which cools it [21].

This detail is important because the French Nobel laureate André Lwoff, who showed that a temperature rise inhibits the multiplication of viruses, led the Pasteur Institute to patent a device that sends moist air at 43°C into the nostrils (Rhinotherm®) [22]. It was a commercial flop, perhaps because it weighed 3.5 kg and cost around € 350. But it was very effective to abort seasonal colds and treat persistent allergic rhinitis by a single 30 minutes inhalation, sometimes repeated two to four hours later (Figure 8).

Figure 8 . Effect of treatment by hyperthermia on infectious coryza and persistent allergic rhinitis (from Yerushami A, Lwoff A.[22]).

Table I
Hyperthermia treatment of patients suffering from infectious coryza

		After 1 day		After 1 week	
		+	0	+	0
Group 1	Treated	23	17 (74)	6 (26)	16 (70)
	Placebo	18	4 (22)	14 (78)	4 (22)
Group 2	Treated	23	18 (78)	5 (22)	18 (78)
	Placebo	2	0	2	0
Group 3	Treated	48	34 (70)	14 (30)	34 (70)
	Placebo	37	8 (22)	29 (78)	8 (22)
TOTAL	Treated	94	69 (73)	25 (27)	68 (72)
	Placebo	57	12 (18)	45 (82)	12 (18)

+: healed; 0: no improvement. *In brackets, the percentage*

Table II
Hyperthermia treatment of patients suffering from persistent allergic rhinitis

		After 1 day			After 1 week			After 1 month	
		+	?	0	+	?	0	+	0
Treated	141	111 (79)	13 (9)	17 (12)	98 (70)	2 (1)	41 (29)	91 (65)	50 (35)
Placebo	71	42 (59)	9 (13)	20 (28)	22 (31)	2 (3)	47 (65)	11 (15,5)	60 (84,5)

+: Clinically healed ? : Dubious result 0: no improvement *In brackets, the percentage*

As cold viruses take advantage of the low temperature of the nasal mucosa (31-36°C), vapor of electronic cigarette should be inhaled through the nostrils to take profit of it, with obvious precautions to avoid burns. The combination of heat rise and vapor of propylene glycol could create an antiviral synergy that would justify clinical studies.

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5 - The matériel

5.1 - Atomisers

It is the heating resistance of e-cigs. It is a pretty fragile part, that has sometimes to be replaced. According to type, it varies from 1.5 to 6 Ohms. For a given battery voltage, atomizers LR (low resistance) produce more heat. The liquid evaporates faster, generates more dense vapors. But then batteries run down faster and have a short expectancy of life. Handymen manipulate atomizers and batteries for a more intense heating.

5.2 – Liquid storage

The liquid may be contained in a flock or in a tank, with a risk of leaks. A cartomizer combines tank with atomizer. Some vapers put one or two drops of liquid on the resistance (*dry vaping*). This would promote a stronger *hit*. It is important that a vaper keeps his e-cig in a horizontal position, and more inclined slightly forward. Indeed, gravity is important to drive the e-liquid to the atomizer. If it heats without enough power, not only it badly vaporizes, but the liquid may be overheated and the plastic parts of the body of the e-cig may burn, emitting ineffective, unpleasant or even toxic vapors.

5.3 – Batteries

Primary batteries are used for disposable cigarettes only. Otherwise, rechargeable batteries are the rule. Their voltage extends from 3.0 to 4.8 volts, with a possibility of varying it between these limits. Capacity ranges from 650 to 1000 mAh. They can be equipped with complex functions, circuit breakers, on-off button, detector of aspiration to connect battery, power LED etc.. They can be recharged by a charger that plugs into the mains, or on a computer through a USB port, allowing to vape during recharging. A tinked electronic cigarette exploded to the face of a Florida vaper in February 2012. It was attributed to the explosion of the battery, but perhaps could be linked to leakage of liquid as well, because PG vapors mixed with air may produce an explosive gas. Other explosions during recharging with less serious effects are occasionally reported. The risk of explosion of lithium-ion batteries is well known. It has recently grounded an entire fleet of Boeing 787. For electrical safety (CE), devices that work with the most often used lithium-ion rechargeable batteries (unstable technology), sound or visual indication that the battery is discharged is required. This role can be played by the LED. Vapers are looking for thrills. Thus one of them, wishing "to vape on 6 volts", used two batteries of 3.7 V connected in series. First, it gives 7.4 V, so that such an arrangement may create an imbalance leading to explosion. Happily, it happened in a rucksack. I would not leave an e-cig in the glove box of a car in direct sunlight.

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6.6 - Controverses

1 – Toxicity

The rapid development of electronic cigarettes has quickly attracted hostile reactions, especially regarding their toxicity. In a press release dated May 30, 2011, AFSSAPS recommended not to use electronic cigarettes, because of the toxicity of nicotine, "classified as very dangerous by the WHO" and of the risk of dependence in non-smokers! Introducing the new concept of "Products containing nicotine (NCP)", the proposal for a Directive to the European Parliament and the European Council of 19/12/2012 on tobacco products goes in the same direction: "The NCP having a nicotine level greater than 2 mg or a nicotine concentration higher than 4 mg/ml, or whose use for the intended purposes results in an average maximum plasma concentration greater than 4 ng/ml, may not be placed on the market unless they were authorized as medicinal products on the basis of their quality, their safety and efficacy, and if their benefits outweigh the potential risks. NCPs with nicotine levels below these thresholds may be sold as a consumer product, providing that is affixed an appropriate health warning. The nicotine thresholds referred to in this proposal have been decided in relation to the nicotine content of smoking cessation medications (nicotine replacement therapy) ... "[23]. Such a proposal could be adopted one of these days. Europe persists also to ban the snus. It deliberately fight anything that might reduce the risk that threatens smokers, that a group of experts as clear-sighted as Clive Bates, former director of the British anti-smoking organization ASH [24], described as "criminal" [25]. This attitude is clearly dictated by the industry lobbies. Health warning criteria, that the pharmaceutical industry alone can overstep, would reserve indeed a quasi-monopoly on the nicotine market on the basis of nicotine toxicity, when selling tobacco remains free! Limiting at 4 ng/ml the plasma concentration of nicotine reached after vaping, while a smoker can obtain 25 ng/ml from his cigarettes, 9 ng/ml from a single 2 mg gum and 25 ng/ml from a patch, is the demonstration of it.

Doses of propylene glycol and glycerol possibly absorbed by a vaper showed no toxicity. The amount of toxic or carcinogenic compounds in the vapor, such as carbonyl, volatile organic compounds, heavy metals and nitrosamines was found from 9 to 450 times lower than in the cigarette smoke and often comparable to traces found in nicotine inhalers, regarded as reference products [26]. Whatever the arguments of his opponents, "*the die is cast*": electronic cigarettes do not present real dangers. They are infinitely safer than tobacco cigarettes and, on this level, could be a beneficial alternative to public health.

6.2 – Dépendence

Nicotine is supposed allowing to smoke less or to quit completely, by satisfying addiction to tobacco. It is a moot point, because this is complying with the pharmaceutical industry thesis, which argues that nicotine is the only cause of tobacco dependence, in order to substitute the "dirty nicotine" of tobacco for the "clean nicotine" of NRT (Nicotine Replacement Therapy).. I disputed this notion on this same site [27]. A molecule can have effects judged as favorable without creating dependency, as caffeine does. Nicotine is a stimulant, keeps awake, and at the same time gives a sensation of muscle relaxation. In addition, it raises the blood sugar quickly. It irritates the throat, and certainly contributes to the feeling of hit that can remind the vaper his tobacco cigarette without creating a lasting dependence to vaping. But it is unlikely that these effects may be felt if the limits of the EU proposal were to be adopted.

Some vapers are really hooked to their e -cig . They say that on forums, even the 1-3 % that use e -cigs without nicotine. Clinical studies comparing the long-term dependency on cigarettes with or without nicotine could clarify this potential role of nicotine. In fact, many vapers, having begun with nicotine-rich e-cigs, diminish their content little by little, and succeed in eliminating it eventually. An e-cigarette without nicotine as well as a 18 mg e -cig similarly mitigate the desire to smoke, compared to handle simply a cigarette. Nicotine would be more effective in men only [28]. Acids in e-liquids ionize nicotine, altering its bioavailability. In this ionized form, it is less vaporized by atomizers and less absorbed by mucous membranes. This may explain why one of the Eissenberg's studies did not find any rise of blood nicotine. Anyway, nicotine is only an accessory factor of the vaping habit, perhaps partly psychological, considering the role that advertising has given to it in the collective unconscious.

Italy prohibits the sale of e-cigs under 18 years, for fear of creating nicotine addiction. Professor Martinet, president of the National Committee Against Tobacco defends the opinion that electronic cigarettes could make children nicotine-dependent and get them to smoke. This notion is not confirmed by a recent survey [29]. To lighten a cigarette directly is more exciting for a child generally. Apart from the normal curiosity at this age, those who use electronic cigarettes permanently are always already addicted smokers. Yet a certain attachment to e -cigs seems clear, although many will quit it easily. Possible factors are numerous. Issue of pseudo-smoke, manipulation of this object, sensation of heat, both from inhaled vapor and from e-cig in the fingers, the behavioral side is obvious. The mere repetition of the same gestures, of the same situations is reassuring, reduces stress. But it is innate. We already observed it in the childhood games, when you have to repeat to children a hundred times the same story.

Propylene glycol and glycerol are sugars. They have their sweet flavor and meet the metabolic pathway of glucose. This distinguishes them from sweeteners, which cause pre- absorptive insulin release, but are not satiating, because they do not raise blood glucose level, on the contrary. Sugars can also explain part of tobacco dependence, like part of the triumph of the American-style tobaccos over the brown, very fermented tobaccos, which do not have any added honey and molasses. The *hit* is a peripheral sensation that vapers are seeking highly, as well as smokers, for whom this feeling related to inhalation is part of the fun to smoke. Among its factors, one can imagine the mucosal dryness by propylene glycol, irritation related to nicotine, alcohol, aggressive acidity of some vapors, some aromas. A brand offers an acid-free e -liquid without nicotine, with only 2% of aromas. It presents it as giving a very strong hit. Some flavors as pepper, jalapeno pepper, menthol could explain.it.

Menthol deserves a special place. It makes quitting more difficult, especially by blacks and Hispanics, but not by Caucasians [30]. It seems desirable to initiate a vigilant monitoring of long-term toxicity of vaping. But for now the harmful effects are minor, merely respiratory irritation, incommensurate with those of tobacco. Thus, even if dependence was to occur, it is unlikely to give health problems as serious as those of tobacco dependence.

6.3 - Effects on tobacco addiction

Electronic cigarette is such widespread because it interests smokers, almost exclusively. To vape where smoking is prohibited is one aspect of the question only. Many say they try to at least reduce their consumption of tobacco, often after many failed attempts, where failure of medications is frequent. In forums, one is impressed by the number of vapers who say how much vaping is helping them, unlike NRT. Most studies aiming to assess the percentage of quitters or of smoking reduction do not cover sufficient a number of subjects and a long lasting follow-up. It would be necessary to develop them. An ambitious protocol is proposed in Australia in an attempt to answer this question. Some surveys have been made *on-line*. However, they are subject to a clear bias, because they concern only vapers motivated enough to respond, and do not control their alveolar CO, only measurement able to confirm reduction or quitting. Anyway, a number of vapers adopt electronic cigarette permanently and are satisfied regarding the evolution of their smoking. It has none of the drawbacks of combustion. No production of carbon monoxide, which bears a large responsibility in cardiovascular diseases. No tar, no carcinogenic hydrocarbons, no nitrosamines, although you can find some traces, like everywhere when you are looking for. That would be a step forward for the society to succeed in reducing the number of smokers and their cancers. One does not set fire to the forest or to one's bed while vaping . A vaper does not bother neighbors. For sure, traces of nicotine, oxidation derivatives of propylene glycol, fine and ultrafine particles and metal nanoparticles from atomizers may be found after vaping in the environmental air of a closed room, but passive vaping seems a view of the mind [31]. A sign announces the irresistible rise of e- cigarette: It becomes a formidable competitor for large multinational tobacco firms . They feel the wind and are already thinking about their redeployment. It is a huge potential market. *Imperial Tobacco* , *Philip Morris* , *BAT*, *Altadis*, have already bought e-cigarette companies, or will make them themselves. But electronic cigarette is also a formidable competitor for pharmaceutical companies. On forums, many vapers who stopped smoking had already unsuccessfully tried NRT. A study on the popularity of e -cigs , based on Google connections followed for two years, comparing them to NRT, snus and varenicline shows the rise of the e -cig which eventually surpass widely other means which are in decline [32]. Tobacconists would like to have a monopoly on its sale to compensate for the lost sales of cigarettes because of smuggling that follows price increases. Limitations that seek to enact the European Commission, both on nicotine and aromas, are intended to eliminate a obvious competitor of gums and patches. The market is huge. Multinational pharmaceutical companies might be tempted to propose medicinal electronic cigarettes. Subjecting them to strict control of their composition and quality of the components, free to offer high nicotine content, they could continue advertising the so successful myth of nicotine addiction. Certified by an AMM [33], these e-cigs would crush competitors corseted by regulatory limits, and thus would get a monopoly. The change in tone of some opinion leaders such as B. Dautzenberg, which hitherto decried the electronic cigarette, inclines me to think so. "*These events are beyond me, do pretend to be their instigator*" . [34]

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7 – Conclusion

The electronic cigarette is always a gimmick. But without any noisy advertisement, only by word of mouth advertising and spontaneous forums, it is poised to overtake all other ways to stop smoking, doing so without obvious risk. This does not make of it a drug, nor of antidepressants such as chocolate or coffee. Its possible antibacterial and antiviral properties could be explored and exploited. Its drawbacks are minor, merely irritation of the airways, far below that of tobacco smoke, and problems of fluid leaks or battery problems that increasing

technical progress should make exceptional. The price is already quite competitive compared to tobacco cigarettes and is expected to decline, according to competition if the market keeps on growing. It is unlikely that the rearguard fight waged by its detractors, puritans or lobbyists of financial interest would succeed in blocking its development. A list of criteria of quality regarding components and hazardous ingredients seems necessary, with a Fraud Control Service, without any medicalization to be needed. The electronic cigarette has a bright future, and I think will be beneficial to public health.

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Post-scriptum

Conflicts of interests

In my statement of lack of links of interest with the tobacco and the pharmaceutical industry visible on the Formindep site, I add that I also have no link with the manufacturers and sellers of electronic cigarettes. For those who want to know more about my activities, see http://fr.wikipedia.org/wiki/Robert_Molimard

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