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## Forms of Tobacco Consumption and the Associated Toxicity Risk

C Dan Piperea-Șianu<sup>1</sup>, Monica Găgiu<sup>2</sup>, Alice Piperea-Șianu<sup>3\*</sup>, Adela-Maria Ceau<sup>4</sup>, Daniela Bălan<sup>5</sup>

<sup>1</sup>DDS; PhD student; General Medicine Teacher; Assistant lecturer, Department of Physiology, Faculty of Dental Medicine, "Carol Davila" University of Medicine of Pharmacy, Bucharest; Romania

<sup>2</sup>Pharmacist;

<sup>3</sup>PhD; Senior Pharmacist; Lecturer, Department of Toxicology, Faculty of Pharmacy, Titu Maiorescu University, Bucharest;

<sup>4</sup>DDS; PhD student, Politehnica University of Bucharest; Resident physician in Endodontics,

<sup>5</sup>MD; PhD; Lecturer, Department of Physiology, Faculty of Dental Medicine, "Carol Davila" University of Medicine of Pharmacy, Bucharest

**Abstract** Smoking is a risk factor for many pathologies, including cardiovascular disease, pulmonary disease and cancer. New nicotine release products have a lower health risk compared to classical cigarettes. The purpose of this review is to present the most popular forms of tobacco consumption as well as the health risks they imply, based on chemical analyzes conducted by both producers and independent studies.

**Keyword:** tobacco, nicotin, electronic cigarette, HNB, cancer

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### 1. Introduction

Tobacco is a plant grown for its leaves. It contains nicotine, a xenobiotic with addiction potential and increased carcinogenic risk. Besides nicotine, there are also many other potentially harmful chemicals found in tobacco or that are created by burning it [1].

According to the current situation where a large number of young adults start to smoke but few give up, it is estimated that smoking will account for approximately one billion deaths in the 21st century. Tobacco use is the main risk factor for non-communicable diseases [2].

However, smoking and other forms of tobacco consumption rates are still very high and some populations are disproportionately affected by the health consequences of smoking. In particular, people with mental disorders, including substance abuse disorders, smoke more than the general population [3-7].

In addition, people living below the poverty threshold and those with a low level of education are more likely to smoke than those in the general population. Tobacco use is the leading cause of preventable mortality in the United States [8].

In the United States, about 40 million smokers currently use the cigarette, which is the most dangerous form of tobacco consumption. Cigarette smoking is the leading cause of preventable disease in the US, causing more than 480,000 deaths each year and over 16 million cases of disease each year [9].

Each year, nearly 70% of these smokers express their desire to quit smoking and almost 40% will try to quit that year. An attempt to quit smoking is usually done by ceasing consumption suddenly or by administering over-the-counter medications such as nicotine replacement products (as a patch or gum) or medication that is released on



prescription (eg varenicline or bupropion). Despite the high rate of smoking cessation attempts, the overall success rate of smoking cessation is low, around 6% over a 12-month period since the initiation of these measures for most smokers. Given that most current smokers will not give up smoking, there is a continuing need to explore alternative ways of reducing harm to those tens of millions of smokers, their families and society as a whole [10].

Many smokers have tried new forms of nicotine consumption, such as electronic cigarettes. These products have prompted many smokers to switch from classic cigarettes to new forms of nicotine consumption that are less likely to be unhealthy. A recent study published in the British Medical Journal concluded that smokers using electronic cigarettes are more likely to quit smoking and gave a greater likelihood of success compared to classical cigarette users. Overall, the authors conclude that increasing the use of electronic cigarettes among adult smokers in the US has been associated with a statistically significant increase in smoking cessation rates in the population. However, electronic cigarettes have not been found to be popular with adult smokers and are rejected by most adult smokers trying them because they lack the basic sensory attributes of classic cigarettes, such as tobacco flavor, enough nicotine and the familiar sense of the tobacco bath [11].

### **Tabacco Consumption in Numbers**

Approximately one quarter of the population uses tobacco products, 19.4% using classic cigarettes. According to the National Survey on Drug Use and Health, conducted in 2017 in the United States, about 63.4 million people aged at least 12 years had consumed a tobacco product during the previous month, 51.3 million of them being classic cigarette smokers [12].

According to the Centers for Disease Control and Prevention (CDC), the percentage of smokers continues to decline from year to year. The percentage of people over the age of 18 who smoke classic cigarettes has fallen from 20.9% in 2005 to 15.8% in 2016, according to the International Health Survey in 2017 [13].

However, the percentage of smokers is substantially higher among vulnerable people in this regard. Thus, 25% of Americans with mental disorders, including addiction, consume 40% of the total of cigarettes smoked in the United States. People living in rural areas, especially in the South Atlantic, also use all forms of tobacco more frequently than people living in urban areas [14].

According to Singh T *et al*, smoking among young people is at historically low levels. According to a survey sponsored by the National Institute on Drug Abuse (NIDA), also known as Monitoring the Future, in 2015, about 4.7 million gymnasium and high school students used tobacco products in the previous month. Electronic cigarettes were the most commonly used tobacco products among pupils in general school (5.3%) and high school (16.0%) in 2015 [15].

Electronic cigarettes release synthetic nicotine and do not contain tobacco; however, they are classified as tobacco products for regulatory purposes. The fact that electronic cigarettes release synthetic nicotine and do not contain tobacco has been confirmed by other studies, including the Monitoring the Future. Scientists have not yet determined the medical consequences of the long-term use of electronic cigarettes or the side effects of their vapors concerning one's health [16-20].

Between 1964 and 2012, in the US, about 17.7 million deaths were related to smoking, which led to more than 480,000 deaths annually [8].

If the proportion of smokers will remain constant at today's levels, it is estimated that about 5.6 million americans who are currently younger than 18 will die prematurely due to smoking-related illnesses [15].

In addition to the extraordinary impact of premature tobacco-related deaths, economic costs are high. Experts estimate that between 2009 and 2012, the society's annual smoking assigned costs in the United States is between 289 and 332.5 billion dollars, of which \$132.5 billion to \$175.9 billion for direct medical care for adults and \$151 billion for lost productivity due to premature deaths. In 2006, loss of productivity due to passive smoking cost the United States \$5.6 billion. Approximately 70% of current healthcare costs with smokers could be reduced by giving up smoking [21].



## **Tobacco Consumption Patterns**

### **Classic Cigarette (Tobacco)**

Using tobacco cigarettes is a highly addictive habit, which makes quitting smoking an exhausting and difficult task. One reason for this is related to the rate and amount of nicotine released during smoking. Quitting smoking without requesting specialists' help is the most common method of smoking cessation, but it is also the least effective, with a success rate of less than 5% in a year [22].

Because of these limitations, reducing tobacco harm has been advocated as an additional option for smokers who are incapable of giving up smoking or who do not want to give up alone or with medicines. This approach is based on the principle of nicotine delivery through less harmful, non-combustion products [23].

Development of nicotine products like New Generation Products (NGP) is currently focusing on new low-risk products for health, including tobacco heating products and electronic cigarettes. In many countries, including the US and European countries, the marketing of NGP is subjected to strict regulations. Such approval must be obtained by presenting details of the design, performance and impact of a new product to users and non-users. In the US, the FDS has highlighted the requirements for introducing a new type of tobacco on the market through the Application for Substantial Equivalence or Premarket Tobacco Applications approach [24].

### **Electronic Cigarettes**

Electronic cigarettes (electronic nicotine release systems) appeared on the US market in 2007 and their popularity increased rapidly [25].

Electronic cigarettes or e-vaporizers are devices that heat a liquid containing solvents, flavors and often nicotine. Users inhale the resulting vapors [26].

A variety of models are available, some imitating the look of traditional cigarettes. More than 7,000 flavors are available for electronic cigarettes, some of which are particularly appealing to young people [27].

In 2013, more than a third of the classic cigarette smokers said they had used electronic cigarettes at least once. According to the Tobacco Products and Risk Perceptions Survey data from 2014, current cigarette smokers were more likely to use electronic cigarettes. This analysis found that half of the classic cigarette smokers used at least once an electronic cigarette and that 20.7% of them are currently using these devices. However, about 10% of adults using electronic cigarettes were not smokers before their consumption began [28].

Data from the 2014 National Health Survey showed that 0.4% of smokers and 0.8% of former smokers (abstinent 4 years or more) are currently using electronic cigarettes. The study also found that 13% of daily electronic cigarette users were former smokers who had quit smoking in the past year [29].

As with classical cigarettes, the use of electronic cigarettes is higher among people with mental illness, 3.1% currently compared with 1.1% of those without mental illness [30].

It is also worrying that pregnant women use electronic cigarettes, because exposure to nicotine during vulnerable fetal development periods has negative consequences on their health. [31].

Users are convinced that electronic cigarettes are less harmful than traditional cigarettes and many report that they use them as an adjuvant to quit smoking traditional cigarettes. Although it is not yet clear whether electronic cigarettes are effective smoking cessation products, these devices are sometimes marketed for this purpose [32,33].

Some research suggests that older adults use these devices as substitutes for tobacco, although not always as a method of giving up nicotine [34].

Users also mention comfort and consciousness toward others as a reason for using these products [35].

Electronic cigarettes are currently the most popular products for reducing the harmful effects of smoking, yet not all smokers consider them to be effective or sufficiently satisfactory for complete smoking substitution. Studies conducted on electronic cigarette users have shown that the levels of nicotine used are initially high, some of them having to increase nicotine concentration in order to successfully quit smoking [36].

Nicotine release studies in first-generation electronic cigarettes have demonstrated minimal and slow absorption of nicotine [37-38].

This is due to the low release of nicotine in the aerosol of such products [39,40].



Laboratory studies of new generation devices have shown a more efficient distribution of nicotine in the aerosol, while some studies have shown that nicotine absorption following the use of electronic cigarettes can be as effective and fast as smoking, but not for all products [39,41-43].

The FDA, which regulates, among others, cigarettes, tobacco and smokeless tobacco, has acquired the authority in 2016 to also regulate electronic nicotine release systems (such as electronic cigarettes and pens), all types of cigarettes, hookah, pipe tobacco and nicotine gels, among other tobacco products. Under the new regulations, manufacturers of electronic cigarettes must indicate their ingredients on the packaging, and sellers can not sell electronic cigarettes to people under the age of 18 [44].

### HNB devices

A new nicotine release product, developed by two independent manufacturers, was recently introduced on the market. It has been characterized as a non-burning product (HNB-Heat Not Burn) and is in fact an electrically heated tobacco product. Tobacco products that do not burn are electronic devices that heat the tobacco leaf and resemble cigarettes with regard to the production of aerosols [45].

Unlike electronic cigarettes that aerosolize a nicotine-containing liquid, the HNB heats a specially designed tobacco stick, provides an aerosol with similar nicotine-like characteristics to a traditional cigarette, and has flavor that are more familiar to smokers. The HNB consists of a device that heats, but does not burn, a tobacco stick ("HeatSticks") [46].

This device consists of a battery that contains a metal plate that acts as a heater, a short tab of tobacco introduced into the battery system, and a battery that acts as a battery charger. According to the manufacturer's information, it operates at a maximum temperature of 350°C, much lower than the temperature of 900°C measured in the burning area of a traditional tobacco cigarette and there is no combustion [46,47,48].

HNB devices are made up of three main components:

- **Tobacco stick**, a new tobacco product containing tobacco strips processed from tobacco powder. It is specifically designed to work with the holder to produce an aerosol. To meet the different consumer preferences, the manufacturers created three different HeatSticks, one normal and two menthol (with menthol in the concentration of 1.25 mg and 2.5 mg per stick).
- The **holder**, in which the tobacco stick is inserted, which heats the tobacco material by means of an electronically controlled heating blade.
- The **charger** is recharged by the user after each use. The charger stores a sufficient amount of energy to use about 20 tobacco sticks and can be recharged from domestic energy [46].

The tobacco stick differs from traditional cigarettes significantly. Unlike a cigarette containing tobacco filler (tobacco leaf cut into small pieces found in cigarettes), the tobacco stick contains special processed tobacco which was reconstituted into sheets ("cast leaves") after the addition of water, glycerin, guar gum (hemicellulose) and cellulose fibers. The tobacco stick contains much smaller amounts of tobacco compared to a traditional cigarette (approximately 320 mg compared to 550-700 mg in the traditional cigarette). Unlike a cigarette, the tobacco stick contains two unique and independent filters: a polymer film for cooling the aerosol and a small-density cellulose filter (which is inserted into the oral cavity) to mimic the appearance of a traditional cigarette. An empty acetate tube separates the tobacco plug and the polymer film filter.

To operate the HNB, the user inserts a tobacco stick into the holder and switches the device on with a switch. This action initiates the heating of the tobacco by means of the heating blade inserted into the tobacco plug. Electronically controlled heating, combined with uniquely processed tobacco, prevents burning.

The holder provides heat to the tobacco rod by means of the heating blade for about six minutes and allows for up to 14 smokes to be generated during that time.

The temperature of the heating blade is carefully controlled and the blade energy supply is interrupted if the operating temperature exceeds 350°C. The temperature measured in the tobacco never reaches this limit and, in fact, most of the tobacco remains below 250°C.



The tight blade temperature control, combined with its limitations during operation and the number of puffs, ensures that HNB devices generate a reproducible aerosol over a wide range of conditions of use (including extreme ones), resulting in a consistent reduction in the formation of harmful and potentially harmful xenobiotics.

Since the HNB was designed to heat the tobacco below the combustion level, HNB produces an aerosol that has a very different composition from cigarette smoke. The IQOS aerosol contains significantly reduced levels of harmful and potentially harmful xenobiotics compared to cigarette smoke and is mainly composed of water, glycerine and nicotine. According to the manufacturer, cigarette smoke has a brownish color when captured on a laboratory filter, unlike the HNB aerosol [45,46].

Studies by the manufacturer of the product showed low levels of toxic chemicals, low *in vitro* and *in vivo* (animal) adverse effects, and lower exposure of the human body to harmful and potentially harmful substances, which are probably related to low temperature heating the product [49-51].

### **Manufacturer's Assertions About The Hnb System**

The first assertion by the manufacturer is that the HNB system heats the tobacco but does not burn it, which significantly reduces the production of harmful and potentially harmful substances. The manufacturer warns that low risk does not mean absence of risk and that the best way to reduce the risk of tobacco-related diseases is to give up tobacco consumption altogether, that HNB devices contain nicotine that causes dependence and that use of the HNB system can affect the health of the user.

The second assertion of the manufacturer refers to the fact that full replacement of classic HBI cigarettes reduces the risk of classical smoking.

The third assertion of the manufacturer refers to the fact that the complete replacement of the classic HBI cigarette significantly reduces the production of harmful and potentially harmful substances. The manufacturer points out that it has not been demonstrated that switching to the HNB system reduces the risk of developing tobacco-related diseases compared to classical cigarettes [46].

Health aspects related to new products, such as "low exposure" and "low risk", should be justified by a comprehensive scientific-based approach. The FDA has provided a guidance project outlining a framework for the assessment of new products as Modified Risk Tobacco Product (MRTP) [52].

### **Conclusions concerning the chemical analysis of HNB aerosol vs. the classical aerosol**

**Conclusions of the manufacturer's study** The scientific evaluation program of the manufacturer has shown that the HNB will significantly reduce the harm and risk of tobacco-related illnesses for smokers who switch from regular cigarette smoking to IQOS use, as according to the manufacturer's studies:

- HNB produces significantly lower concentrations of harmful and potentially harmful substances as compared to cigarette smoke;
- HNB aerosol does not contain ultra-fine solid carbon based particles, unlike cigarette smoke;
- HNB aerosol is significantly less toxic than cigarette smoke;
- HNB aerosol causes to a lesser extent emphysema and atherosclerotic plaque according to animal studies;
- clinical studies have shown that switching from smoking classical cigarettes to HNB involves a significantly reduced exposure to harmful and potentially harmful substances;
- clinical studies have shown that the transition from conventional cigarette smoking results in a change in the HNB positive clinical risk markers, which are similar to those changes that are observed early after giving up smoking [46].

### **Conclusions of independent studies**

In the independent study by Mitova *et al.*, it has been shown that levels of concentrations of toxic compounds in aerosols of HNB are much lower than those in conventional cigarettes. Although in low concentration, the compounds exist in the HNB aerosol. Mitova *et al.* have shown that aerosol expiration from HNB users has increased the background levels of compounds such as acetaldehyde and nicotine in a closed space so that the



adverse effects of these compounds can easily spread to a non-smoking population (passive smoking) especially in crowded indoor places such as restaurants. Various other dangerous compounds, such as volatile organic compounds, are also included in both the solid phase and the gas phase of the HNB aerosol [49,53,54].

In view of these issues, additional chemical assessment and studies on the effects of these substances on health are needed to support future HNB regulation [55].

### Conclusions

Clinical trials should compare the different products in terms of their ability to deliver nicotine and replace the consumption of traditional cigarettes with tobacco among smokers. These studies should also assess the difference between toxin emissions and the safety risk profile so that smokers are properly informed about the continuity of the risk posed by different tobacco substitutes. Of course, it is also necessary to examine the responsibility regarding abuse and the potential for addiction to non-smokers.

Quitting smoking is the most effective way to reduce the risk of having harmful tobacco substances. Cessation of smoking involves, by definition, the complete elimination of exposure to harmful and potentially harmful substances and, therefore, the elimination of their negative impact on molecular, cellular and tissue function. Smoking cessation is accompanied by a predictable and favorable restoration of cellular and normal tissue function that can be measured in *in vivo* and *in vitro* experimental systems using standard and systemic toxicological approaches. Human subjects who quit smoking show favorable changes in clinical risk objectives and, over time, improve their physiological functions.

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