Heated Tobacco Cigarettes: Definition, Type of Tobacco Used and Nicotine Levels Achieved

https://doi.org/10.32635/2176-9745.RBC.2025v71n3.5224EN

Cigarros de Tabaco Aquecido: Definição, Tipo de Tabaco Utilizado e Níveis de Nicotina Atingidos

Cigarrillos de Tabaco Calentado: Definición, Tipo de Tabaco Utilizado y Niveles de Nicotina Alcanzados

Paulo César Rodrigues Pinto Corrêa[1]; Mariana Coutinho Marques de Pinho[2]

INTRODUCTION

Electronic nicotine delivery systems (ENDS) include electronic cigarettes – the most common products. In Brazil, electronic smoking devices (*dispositivos eletrônicos para fumar* – DEF) include ENDS and heated tobacco products (HTP). The basic difference is that HTP "heats" the tobacco, instead of having a liquid nicotine solution to release nicotine to its users. It must be noted that the World Health Organization (WHO) does not consider ENDS as tobacco products[1].

The 8th Session of the Conference of the Parties (COP8) of the Framework Convention on Tobacco Control (FCTC) recognized that HTPs are subject to the treaty's rules[2]. However, since HTPs are being promoted by companies, they can impose regulatory challenges regarding their definition and classification, and represent challenges for broadly enforcing FCTC[2].

In Brazil, the National Health Surveillance Agency (Anvisa) has regulated ENDS[3] since 2009 (Resolution N. 46/2009[4]) and more recently through Resolution N. 855/2024[5]. The latter determines the prohibition on manufacturing, commercialization, importation, advertising, distribution, storage, and importation of these products, including their accessories, pieces, parts, and refills designed to be used with/on ENDS, which include electronic cigarettes and HTPs[5]. Additionally, the Resolution forbids their consumption in closed environments[5].

As will be discussed further in the text, HTPs are a reemerging category of tobacco products. The promotion of these products is globally done through the communication that they are "less harmful alternatives" to conventional combustible cigarettes (CC). A significant number of studies on the health hazards of HTP were conducted or financed by the tobacco industry, and, as a result, present conflicts of interest.

Cigarette companies also produce HTP. Moreover, they use the same strategies from the 20th century. Health professionals have been co-opted by these corporations to endorse these "new products" and the fallacy of harm reduction[6]. Companies push decision-makers, the press, and the public opinion to get authorization to sell their products, recruit new users through deceitful messages, which lead people to believe these products can be innocuous or bring benefits for smokers who switch to them.

A recently published Japanese study shows how the image of HTP was successfully "sold": among the 3,420 participants, 40.3% of tobacco users and 18.3% of non-users considered HTP less harmful. For participants aged 20-39 years, these proportions rose to 49.9% and 30.4%, respectively. Among the 1,160 respondents who were non-smokers, familiarized with HTP, factors such as being male, under 39 years old, and with fewer years of education, were associated with the perception of HTP being less harmful[7].

Therefore, understanding these products from solid scientific evidence is essential to doctors, other health professionals, and the whole Public Health community, especially those working in tobacco/nicotine addiction control and those working in cancer screening, prevention, control, and treatment. This whole body of specialists is responsible for protecting public policies formulated by Anvisa and by the National Cancer Institute (INCA) so that HTPs remain classified as ENDS in the country and, therefore, within the scope of Anvisa's Resolution N. 855/2024[5].

HTPs are a reemerging class of consumption products, created by the tobacco industry originally in the 1980s[8]. The first devices heated tobacco through a carbon tip. Most recent products have been promoted by manufacturers as "tobacco cessation instruments", when actually they are not.

[1]Universidade Federal de Ouro Preto, Escola de Medicina. Ouro Preto (MG), Brasil. Universidade Federal de Minas Gerais (UFMG). Belo Horizonte (MG), Brasil. E-mail: paulocrpcorrea@yahoo.com.br. Orcid iD: http://orcid.org/0000-0001-7108-0640
[2]ACT Promoção da Saúde. Rio de Janeiro (RJ), Brasil. E-mail: mariana.pinho@actbr.org.br. Orcid iD: https://orcid.org/0000-0002-8372-9272
Corresponding author: Paulo César Rodrigues Pinto Corrêa. Universidade Federal de Ouro Preto, Escola de Medicina. Sala 113 B, Campus Morro do Cruzeiro. Ouro Preto (MG), Brasil. CEP 35400-000. E-mail: paulocrpcorrea@yahoo.com.br

DEVELOPMENT

1. DEFINITION OF HTP

There are several definitions for HTP.

a) Definition by the campaign for tobacco free kids (CTFK)

— HTPs are tobacco products that require the use of an electronic device to heat a stick or pod of compressed tobacco[9]. The stick (by definition, a cigarette) or the tobacco pod is heated to a temperature high enough to produce an inhalable aerosol, but the temperature is below that which is required for full combustion[9]. HTP systems are fully integrated so that the heating device and cigarettes or pods for each system must be used together[9]. The systems are exclusive to each manufacturer in that the components are not interchangeable[9].

Although that is a good definition, it does not encompass a particular and important aspect of HTPs: they use only reconstituted tobacco[10]. While combustible cigarettes usually include tobacco leaves (cured in a greenhouse, for instance, burley, Asian tobacco), expanded tobacco, and reconstituted tobacco.

b) Definition by Upadhyay et al.[10]

— HTPs are novel products that allow users to inhale nicotine by heating (350 °C) reconstituted tobacco rather than combustion (900 °C) as in conventional cigarettes.[10].

Using the defined temperatures is troublesome for several reasons. Firstly, each product has a temperature at which tobacco is heated, according to manufacturers. Moreover, temperatures reported by the industry may not be precise: some HTP products have recorded temperatures up to 550 °C[11]. Secondly, there are hybrid products like "Ploom TECH" and "lil Hybrid", which first heat the liquid, which then heats the tobacco (see further ahead, item d, type 4 devices). These hybrid devices heat tobacco around 30-40 °C[9]. It must be highlighted that tobacco combustion exists in HTPs: an article on the iQOS brand product showed evidence of pyrolysis[12]. Pyrolysis is a synonym for incomplete combustion, as elegantly and eloquently discussed in a publication by the Karolinska Institute[13]. Therefore, there is tobacco combustion in HTPs.

c) Definition by an HTP manufacturing company

— Heat-not-burn products[14]

By far, the worst and most inadequate definition. In addition to not characterizing tobacco, it claims that there is no tobacco combustion in HTPs, which is incorrect, as previously discussed[12,13].

d) 2020 Definition by the WHO

— HTPs produce aerosols containing nicotine and toxic chemicals when tobacco is heated or when a device containing tobacco is activated. These aerosols are inhaled by users during a process of sucking or smoking involving a device. They contain the highly addictive substance nicotine as well as non-tobacco additives, and are often flavored. The tobacco may be in the form of specially designed cigarettes (e.g. "heat sticks" and "Neo sticks") or pods or plugs[15]. Newer HTPs include lower-and higher-temperature variants, hybrid electronic devices with both tobacco and liquid, carbon-tipped devices, devices using a metallic mesh punctured with tiny holes to heat a pre-filled, pre-sealed liquid cap, and others which allow users to customize the temperature and manage the aerosol and flavor output. Additionally, several products in this category are under development, some of which are based on new technology[15].

This is an excellent definition and characterization, which highlights the broad array of existing and in-development products. It only failed to mention that they use reconstituted tobacco.

In Brazil, INCA defines heated cigarettes or HTP as "ENDS that hit pressed tobacco sticks, tobacco pods or, in the case of hybrid products, pressed tobacco sticks together with a liquid. When heated to a high temperature, they generate an aerosol"[16].

2. TYPES OF HTP

a) Type 1 – device resembling a cigarette (Figure 1)

The heat is provided by a pressed carbon tip located in the product's extremity, which must be lit like a traditional cigarette, that is, with a standard match or lighter. Premier and Eclipse are examples of this type of cigarette (see ahead).

In 1988, RJ Reynolds (RJR) was the first tobacco company to sell HTP to consumers by launching Premier in the United States. Its functioning was thus described in its press release: "warm air passes through a tobacco roll; through a capsule containing beads coated with spray-dried tobacco, flavors and glycerol; through a tobacco

Figure 1. Drawing of a device that heats through a carbon tip
Source: Nova Online[17].

paper filter and a standard cigarette filter"[18]. Glycerol (VG) was used as an aerosol-generator agent (see the section on humectants), with mentions in internal documents of the potential risk of lung cancer in mice[19]. It was made available in two versions: regular and menthol. Inhaling nicotine using Premier promoted blood level increase to 13 ng/ml[20], lower than a CC cigarette.

Premier was withdrawn from the market in 1989. The failure of RJR's "smokeless cigarette" was due, partly, to the generalized negative word-of-mouth about the flavor, smell, quality, and difficulty of keeping the product lit[21].

British American Tobacco (BAT) acquired RJR in 2017 and continued producing carbon-tip HTPs[22], with the release of Neocore.

Philip Morris International (PMI) also developed and finished in 2016 a "platform" with carbon tip heating called TEEPS[23]. It was released in 2017[24].

b) Type 2 – device that uses an external heat source to turn the nicotine from specially-projected sticks into aerosol

Although distinct, this is the basic project of iQOS (PMI) and Glo (BAT) (Figure 2). The iQOS tobacco stick is called HeatStick, and Glo's is called Neostick. There is also Pulze, produced by British Imperial Tobacco, whose stick was called ID[25].

Glo is BAT's flagship heating tobacco product. It is a battery-powered device that heats specially-designed tobacco sticks at approximately 240 °C[26]. The company claims on its website that Glo was "designed in the UK through a process that involved more than 100 experts across five continents, including scientists, engineers, product designers, tobacco specialists and toxicologists"[26]. It was launched in December 2016 in the Japanese city of Sendai[26].

When a Neostick (also called Neo, for short) is introduced into the device, the single control button on the device activates the heating system[26]. It takes 40 seconds to reach operational temperature. The user knows the device is ready to use when the control button is completely lit up[26]. When the user puts the product in their mouth and inhales it, the air goes through the lower part of Glo, through the tobacco (heated at around 240 °C). This creates an aerosol with nicotine, which is inhaled by the user[26]. At the end of the session, the Neostick is removed and discarded[26]. Each use "session" lasts around three and a half minutes[26]. According to a Portuguese website, there is also a supplementary period of 10-15 seconds on Glo Hyper+, in which the individual can inhale once or twice after the device signals (through vibration) that the time has ended[27]. The device's power allows for up to 30 sessions[26].

The product has undergone several modifications since its introduction in 2016[28].

The main HTP being sold by PMI in many companies is iQOS. The pilot launch was in Milan, Italy, and Nagoya, Japan, in November 2014[11]. Portugal was the third market in which the product was commercialized. For a sequential list of release dates by country, the interested reader can check the University of Bath's web page[11].

To operate iQOS, the user inserts a tobacco stick into the holder and powers on the device through a switch. This initiates the tobacco heating through a heating blade inserted into the tobacco plug. The device heats the tobacco stick through the heating blade for an approximate period of six minutes and allows for up to 14 inhalations within that period[29].

Figure 2. Illustration of the tobacco stick insertion into the heating system of the first iQOS devices
Source: Wikipedia[30].

The iQOS sticks (HEETS) include a variety of flavors, such as tobacco, menthol, bubble gum, and lime[31].

c) Type 3 – device that uses a sealed heated chamber like a micro-oven

The use of this device requires the user to fill the "micro-oven" with ground tobacco leaves to aerosolize the nicotine[11]. There is a battery to provide energy to heat the chamber, which transfers heat through physical contact to any material the user has put inside it[11]. Smoke is then inhaled by the user through the mouthpiece[11]. This is how Pax 2 (Figure 3) and Pax 3 products, designed to be used with dry herbs or dry tobacco leaves, work[32].

d) Type 4 – hybrid devices, mix between ENDS and HTP

They combine characteristics from both products: ENDS and HTP. They work by heating a liquid, which subsequently heats small amounts of tobacco, which is then inhaled by the user. Examples of these products are "Ploom TECH" (Japan Tobacco International, JTI), "iFuse" (BAT), and "lil Hybrid" (The Korea Tobacco

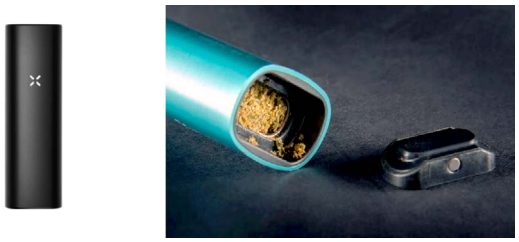

Figure 3. Pax 2, closed device to the left and open to the right; can be used for tobacco or marijuana
Source: Bourque[33].

and Ginseng Corporation, KT&G). The word "lil" is an acronym meaning "a Little Is a Lot"[31].

3. TOBACCO AND HTP

After all, what is reconstituted tobacco? After the leaves are processed, about 4% of this amount becomes a residue constituted basically of stems (central ribs of the leaves) and dust from processing[34].

These stems, which correspond to approximately 20% of the total weight of the leaves, present a higher amount of cellulose than the blade, up to 23% of mass, making it impossible to directly use them to manufacture cigarettes, since cellulose creates a displeasing taste when it burns[34].

iQOS and Glo products contain exclusively reconstituted tobacco[10,11].

In the secret documents of the tobacco/nicotine industry, housed in the virtual library of the University of California, San Francisco (UCSF), it is possible to find information on reconstituted tobacco. Philip Morris produces two forms of reconstituted tobacco, RL (Reconstituted Leaf) and BL (Blended Leaf)[35]. This industry produces both RL and BL as a way of using tobacco components, like tobacco stems, small fragments of tobacco leaves, and tobacco powder, which are byproducts of their manufacturing process. Before the advent of reconstituted tobacco, these materials were usually discarded[35]. To use these residues (reconstituted tobacco), there is a process in which stems are laminated, forming a structure similar to a sheet of paper (called cast-leaf), which can receive flavorizing additives and humectants (see ahead) to make their intake viable[34]. The iQOS manufacturer admits to adding water, glycerin, and guar gum[36]. The reconstituted tobacco leaf, cast-leaf, is then cast into a small plug through a patented process known as "crimping"[36], only mentioned, but never explained in the company's several publications.

An aspect that should be highlighted is that the tobacco stick contains much less tobacco compared to a combustible cigarette[36]. The weight of the tobacco plug on the tobacco stick is approximately 320 mg on iQOS, compared to the 550-700 mg found in conventional cigarettes[36].

4. UNDERSTANDING THE RECONSTITUTED TOBACCO HUMECTANTS AND THE CHEMICAL COMPLEXITY OF HTP BURN PROCESS

An essential aspect to understand is that the final composition of the aerosol inhaled by the HTP user depends on the device used, the device settings (for instance, use of high mode on the "with 2" device), and the tobacco stick ingredients.

Humectants are hygroscopic substances that retain humidity (water)[37]. 1.2-propanodiol (PG) and/or vegetable glycerin (or glycerol – VG) are the humectants used on iQOS (to keep the tobacco moist) and the e-liquids of electronic cigarettes[37,38]. Humectants are also added to tobacco to facilitate the formation of the aerosol ("atomization")[8]. This aerosol acts as a nicotine vehicle, which is absorbed by the lungs[8].

The iQOS product sticks (HeatSticks) contain the vegetable glycerin humectants – also called VG (52.3 mg/stick) – and propylene glycol (PG, 2.04-2.57 mg/HeatStick)[38]. This amount is greater on the HeatSticks than on conventional cigarettes.

A study clarified the proportions of VG and PG in the characteristics of the smoke released by HTPs[39]. This study showed that thermal release of tobacco and its humectants includes three steps[39]:

- Step 1: evaporation of the tobacco water;
- Step 2: release of humectants ("atomizing agents" in some texts); this is the highest peak of weight loss in tobacco samples;
- Step 3: thermal decomposition of tobacco at around 330 °C.

As elegantly demonstrated in the study by Tong et al.[39], in the actual smoking process, the release temperature of the atomizing agents (VG and PG) should be compatible with the temperature of thermal decomposition of tobacco (above 300 °C) to maximize the "atomization" ability and transportation of atomizing agents (VG and PG)[39].

Tong et al.[39] also elucidate why the greatest VG proportion in comparison to PG on iQOS. The use of thermogravimetry (TG) of the samples with atomizing agents VG and PG in different proportions showed that as the proportion of VG in the atomizing agent increases, the residual mass of residues on TG decreases. When the proportion of VG among atomizing agents is greater than 90% in weight, the residue mass decreases to about 3% in weight when compared to the sample that uses pure PG as an atomizing agent. Results showed that VG can promote

the thermal decomposition of tobacco and smoke release more effectively than PG[40]. The attentive reader will notice that the VG/PG ratio in iQOS is 95%.

5. NICOTINE SERUM LEVELS ACHIEVED WITH THE USE OF HTP

The most studied device is iQOS. Thus, this discussion will be restricted to the nicotine content in that device. A preliminary study in animals presented at the Scientific Sessions of the American Heart Association Congress in 2017,[40], and later published in full by Nabavizadeh et al.[41], brought forth information both necessary and concerning. Researchers exposed rats (n=8/group) via nasal cone to the iQOS aerosol, the main smoke of a Marlboro cigarette, or clean air (as control), ten times over five minutes, to get an approximate understanding of the intake of a single iQOS HeatStick. The nicotine serum levels immediately after exposure to the Marlboro cigarette reached typical values similar to those when a human smokes a cigarette: 15 ng/ml[40,41]. Therefore, the authors validated their exposure system to study iQOS. The nicotine serum levels immediately after exposure to the iQOS aerosol were 4.5 times greater than those of the combustible cigarette: 70.3 ng/ml[40,41].

This information is critical due to the large number of studies that minimize the nicotine dosage distributed by HTPs, most of them related to the industry. Papers on the subject often claim that "nicotine levels contained in the aerosol released by HTPs (regular and menthol versions) were 70-80% of the recorded for a CC"[42-45]. Even the excellent paper by Auer repeats this equivocated information[46], but one must consider that it was published in July 2017; that is, one year before Nabavizadeh's publication (June 2018)[40].

6. HTP AND CANCER

HTPs contain tobacco. It is no surprise that studies on the emissions produced by HTPs have shown a variety of chemical species, such as carbon monoxide[47-49], volatile organic compounds (VOC)[49], carbonyls[50,51], polycyclic aromatic hydrocarbons (PAH)[52,53], metals[54], aromatic amines[55], n-alkanes[56], organic acids[57], and particulate material[57-59].

The carcinogenesis of a conventional cigarette comes from its carcinogenic constituents (for instance, tobacco-specific nitrosamine carcinogens)[60-62]. The mechanisms follow a well-established sequence, from repeated exposure to carcinogens, due to nicotine addiction, to metabolic activation of carcinogens, through the formation of DNA adducts and consequent critical mutations in growth control genes that result in cancer[60-62].

Users of heated tobacco "smoke" their tobacco sticks differently from a conventional cigarette. There is an increase in the intensity of inhalations after the change to HTP, in addition to the fact that its users are forced to smoke more quickly (there is a time frame for the device to power off), which can lead to an increase in the inhalation of carbonyls and nicotine, bringing risks to respiratory health and inducing a greater level of nicotine addiction[12]. The same study revealed that there is formaldehyde cyanohydrin release at 90 °C, well below the maximum temperature reached during normal use. This is very concerning, since formaldehyde cyanohydrin is extremely toxic in very low concentrations[12]. Another study made the quantification of toxic volatile carbonylic compounds originating from the pyrolysis of PG and VG under precisely controlled temperatures in the absence of nicotine and flavor additives[63]. Significant amounts of formaldehyde (class 1 carcinogenic according to the International Agency for Research on Cancer – IARC) and acetaldehyde were generated at ≥215 °C temperatures for both PG and VG, and the heating of VG at temperatures higher than 270 °C resulted in the formation of acrolein[63]. VG produces much more formaldehyde than PG[63]. Exposure to these reactive carbonyls (formaldehyde, acetaldehyde, and acrolein) is related to the pathogenesis (causes an inflammatory process, leading to the increase in eosinophils, collagen production, and remodeling of airways, in addition to changes in mitochondrial function, oxidative stress induction, and limitation of air flow)[64] and asthma exacerbation[65].

In a comparison of biomarkers in HTP users *versus* non-smokers, three other biomarkers (in addition to 3-HPMA) were significantly high among HTP users: 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanol (NNAL), n-nitrosonornicotine (NNN), and total nicotine equivalents (TNeq)[13]. NNAL and NNN are two tobacco-specific nitrosamines (TSNA) that are generated in the process of tobacco curing (and not through combustion), being transferred from HTP to the aerosol it generates when used[66]. They are classified as class 1 by IARC (proven to be carcinogenic to humans). Leigh et al. showed that iQOS emits substantial levels of both, in addition to two other TSNA, just like other combustible tobacco products[66]. Exposure to tobacco-specific nitrosamines is associated with lung, nose, esophagus, liver, pancreas, and cervical cancer[67].

A necessary explanation: the Food and Drug Administration (FDA) published a preliminary list of 93 harmful and potentially harmful constituents (HPHC) of tobacco products in April 2012[67]. This HPHC list focuses on chemical products tied to the five most severe effects of the use of tobacco on health (cancer, cardiovascular

diseases, respiratory effects, reproductive issues, and addiction)[67]. In October 2019, the FDA updated the HPHC list, with the inclusion of glycidol and ethylene glycol[68]. Glycidol is a thermal byproduct of glycerol[68], which has been classified as possibly carcinogenic by IARC (group 2A). St. Helen et al. emphasized that PMI reported levels of only 40 of the 93 HPHCs from the FDA HPHC list in their mainstream iQOS aerosol[69]. The levels of the other 56 constituents, which are not included in the manufacturer's list (called PMI-58) or the FDA HPHC list, were higher in the iQOS emissions: 22 were at least 200% higher, and seven were at least 1000% higher than in the 3R4F reference cigarette smoke[69].

VOCs, such as benzene, toluene, and isoprene, are also harmful when inhaled; many cause cancer, and some affect the respiratory, cardiovascular, and reproductive systems[67].

Considering acenaphthene specifically, which is a PAH present in the HTP smoke, the substance is generated from the incomplete combustion of tobacco, constituting a hydrocarbon derived from naphthalene[70]. Levels almost three times higher of acenaphthene were reported in the HTP smoke in comparison to conventional cigarettes[46]. The Environmental Protection Agency (EPA) considers that "information is inappropriate to assess the carcinogenic potential" of the substance, since there are no long-term oral or inhalation studies in animals, nor epidemiological studies available[70]. Similarly, IARC categorizes the carcinogenic potential of acenaphthene as Group 3, "non-classifiable regarding carcinogenicity in human beings"[71].

HTP products with pods (FC-HTP) deserve special attention. The pod embedded in the filter includes several flavors, like menthol and fruits (mango, cherry, grape, and orange, for instance)[72]. The flavor pods can make smokers inhale more deeply, due to their cooling, paralytic, and analgesic effects[73]. Moreover, menthol increases the absorption of tobacco smoke components, pulmonary permeability, nicotine, and carcinogen intake, and slows nicotine/cotinine metabolism[73].

Lim et al.[72] assessed the VOC amounts generated by FC-HTP[72]. When the FC-HTP cigarette pods were broken, the total VOC concentrations increased up to eight times[72]. The main VOCs released after breaking the flavored pods were ethyl butyrate (lil), isoamyl acetate (lil), and limonene (Glo)[73]. Exposure to 2.3-butanodinone (or diacetyl[74]) exceeds around three times the maximum daily intake limit established by the National Institute for Occupational Safety & Health (NIOSH) guidelines[72]. Diacetyl is related to a pulmonary disease called bronchiolitis obliterans, popularly known in the United States as "popcorn lung". Exposures through inhalation of the diacetyl flavorizing agent in its production location caused an irreversible obstructive disease of the airways of previously healthy workers. And that is not all: diacetyl can be carcinogenic after exposure through inhalation[75]. Sustained cytotoxicity and cellular proliferation resulting from chronic exposure to diacetyl, in combination with the reported formation of DNA adducts, probably contribute to the induction of respiratory tumors[75]. Data is still insufficient to classify this chemical product as to its carcinogenicity[75].

In line with the literature not produced by the tobacco/nicotine industry, another analysis of the chemical components of the iQOS product confirmed that, in terms of disease clinical biomarkers, iQOS is not significantly different from conventional cigarettes[77]. Popova et al. highlighted that the request by PMI to the FDA in the United States to register iQOS as a modified risk tobacco product has no scientific grounds[72]. The reduced risk and reduced exposure claims are perceived by people as an indication of reduced risk[76]. The authors contested the agency's decision, which allowed PMI to promote their iQOS product as a "reduced exposure product". They emphasized that this permission is a legally sanctioned repetition of the 20th century "light" cigarettes fraud[76].

Research on biomarkers for assessment of tobacco and nicotine products has flourished over the last 15 years[77]. But exposure biomarkers have a limited ability to predict changes in the risk of diseases[77]. This article does not intend to list all the tobacco substances that may be involved in cancer genesis. For readers interested in this perspective, we recommend reading the review by Bjurlin et al.[78], which presents a didactic chart and classification of each substance by IARC, in users of electronic cigarettes, with a focus on bladder cancer biomarkers. There is a specific systematic review to identify exposure biomarkers present in the urine of HTP users associated with bladder cancer that compared quantitative biomarkers' levels with those observed in combustible cigarettes[79]. Svendsen et al.[79] obtained 561 articles and 30 clinical trials. Of those, 11 studies met the inclusion criteria. The authors identified 29 exposure biomarkers present in the urine of HTP users, which reflect the exposure to 21 original compounds, of which 14 are carcinogenic and ten have a known connection with bladder cancer[79]. The attentive reader will verify that Table 1 by Svendsen et al. lists 11 class 1 biomarkers from IARC[79]. To this class, lower biomarker levels do not ensure the absence or lower risk of cancer, as there are no safe levels of exposure/intake. In other words, biomarkers of this class cannot be present in any amount; if they are, there is an increased risk of cancer. WHO highlights in one of its publications the lack of independent studies on biomarkers in HTP

users[77]. Anyhow, chronic urothelial exposure to bladder carcinogens is concerning[79] and the magnitude of risk of bladder cancer remains currently unknown. Further long-term studies are needed to elucidate the risk of bladder cancer from the use of HTP[79].

Lung cancer is the most common type and the main cause of death by cancer worldwide - 2.09 million new cases (11.6% of the total cancer cases) and 1.76 million deaths (18.4% of the total deaths by cancer) were estimated in 2018[80].

Lung cancer originates in cancer stem cells (CSC), which constitute a minor population of cells in tumors and contribute to resistance to medication and its recurrence[81]. Hirata et al[81]. investigated the effects of HTP smoke extract (CSE) on lung CSC in lung cancer cellular lines. The authors found that CSE induced the proliferation of lung CSC and increased the expression levels of stem-cell markers[77]. Moreover, CSE induced the expression of epithelial-mesenchymal transition (EMT) and the production of cytokines[81]. These results suggest that HTP can induce lung CSC *in vitro*[81].

Braznell et al.[80] examined the existing biomarker data to assess the risk of lung cancer caused by HTP. The group identified all the exposure biomarkers and possible damage measured in studies with HTP and assessed their adequacy based on the ideal characteristics to measure the risk of lung cancer and the use of tobacco. A synthesis of the effects of HTP on the most appropriate biomarkers was made in cigarette smokers who started using HTP and compared it with the continuation of regular cigarette intake or intake interruption[81]. A total of 16 of the 82 biomarkers (7 exposure and 9 potential damage) measured in clinical trials were associated with tobacco intake and lung cancer, dose-dependently correlated with smoking, modifiable after cessation, measured within an appropriate period, and with published results[81]. Three of the exposure biomarkers improved significantly in smokers who switched to HTP and were not significantly different from cessation[81]. The remaining 13 biomarkers did not improve – and, in some cases, worsened with the switch to HTP – or were inconsistently affected in the studies[81]. There was no appropriate data to estimate the risk of lung cancer of HTP in non-smokers[81]. Thus, the study concludes that most of the existing biomarkers' data on HTP are inappropriate to determine the risk of lung cancer caused by HTP[81]. Particularly, there is a data shortage on the absolute risk of lung cancer in HTP. This risk may be estimated in the future through comparisons (epidemiological studies) of smokers who quit smoking, individuals who have never smoked but were exposed to HTP smoke, and individuals who never smoked and started using HTP.

CONCLUSION

HTP are tobacco products that require the use of an electronic device to heat a stick, pod, or plug of compressed tobacco. They produce aerosols containing, simply put, high concentrations of nicotine, additives, and toxic chemical substances that are inhaled by users through a sucking or smoking process involving this type of electronic smoking device. The long-term adverse effects on health from the use of HTP, especially the magnitude of risks of several types of cancer, are currently unknown, due to the lack of reliable long-term studies. However, when assessing clinical disease biomarkers, HTPs are not significantly different from conventional cigarettes and, therefore, diverse negative clinical outcomes are expected, including several cancers.

The tobacco/nicotine control and cancer prevention, control, and treatment communities should stay vigilant with law proposals in the National Congress. Anvisa's Resolution N. 855/2024[5] must be enforced. This resolution protects public health by regulating smoking products (tobacco or other), forbidding electronic smoking devices in the country (this category includes electronic cigarettes and HTP).

CONTRIBUTIONS

Both authors have substantially contributed to the study design and/or planning, acquisition, analysis and interpretation of the data, wording, and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All the contents associated with the article are included in the manuscript.

FUNDING SOURCES

ACT Promoção da Saúde

REFERENCES

1. Neal D. Freedman MJ, et al. Chapter 2.1 Tobacco products: massive and still growing causes of cancer worldwide. In: Wild CP, Weiderpass E, Stewart BW, editores. World cancer report: cancer research for cancer prevention [Internet]. Lyon: International Agency

for Research on Cancer; 2020. [acesso 2025 jan 25]. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK606449/

2. World Health Organization. WHO report on the global tobacco epidemic, 2023: protect people from tobacco smoke [Internet]. Geneva: WHO; 2023. [Disponível em: 2025 jan 20]. Disponível em: https://iris.who.int/bitstream/handle/10665/372043/9789240077164-eng.pdf?sequence=1
3. Agência Nacional de Vigilância Sanitária [Internet]. Brasília, DF: ANVISA; [sem data]. Cigarro eletrônico - Dispositivos Eletrônicos para Fumar (DEFs), 2016. [acesso 2025 jun 10]. Disponível em: https://www.gov.br/anvisa/pt-br/assuntos/tabaco/cigarro-eletronico
4. Minitério da Saúde (BR). Resolução nº 46, de 28 de agosto de 2009. Proíbe a comercialização, a importação e a propaganda de quaisquer dispositivos eletrônicos para fumar, conhecidos como cigarro eletrônico. Diário Oficial da União, Brasília, DF. 2009 ago 31; Edição 166; Seção 1:45.
5. Agência Nacional de Vigilância Sanitária (BR). Resolução da Diretoria Colegiada RDC no 855, de 23 de abril de 2024. Proíbe a fabricação, a importação, a comercialização, a distribuição, o armazenamento, o transporte e a propaganda de dispositivos eletrônicos para fumar. Diário Oficial da União, Brasília, DF. 2024 abr 24; Edição 79; Seção 1:110.
6. University of Bath. Tobacco companies targeting health professionals: the tactics. Tobacco Tactics [Internet]. 2025 abr 15. [acesso 2025 jun 5]. Disponível em: https://www.tobaccotactics.org/article/targeting-health-professionals-the-tactics/
7. Momosaka T, Saito J, Otsuki A, et al. Associations of individual characteristics and socioeconomic status with heated tobacco product harmfulness perceptions in Japan: a nationwide cross-sectional study (inform Study 2020). J Epidemiol. 2024;34(9):JE20230177. doi: https://doi.org/10.2188/jea.je202301778
8. World Health Organization. Heated tobacco products: summary of research and evidence of health impacts [Internet]. Geneva: WHO; 2023. [acesso 2025 jan 25]. Disponível em: https://www.drugsandalcohol.ie/39268/1/Heated tobacco products.pdf
9. Heated tobacco products: definition and global market [Internet]. Tobacco Free Kids. 2020 out. [Acesso 2025 jan 25]. Disponível em: https://assets.tobaccofreekids.org/global/pdfs/en/HTP_definition_en.pdf
10. Upadhyay S, Rahman M, Johanson G, et al. Heated Tobacco products: insights into composition and toxicity. Toxics. 2023;11(8):667. doi: https://doi.org/10.3390/toxics11080667
11. World Health Organization Regional Office for Europe. Heated tobacco products:a brief. Genebra: WHO; 2020. [Acesso 2025 jan 25]. Disponível em: https://iris.who.int/bitstream/handle/10665/350470/WHO-EURO-2020-4571-44334-64934-eng.pdf?sequence=3
12. Davis B, Williams M, Talbot P. IQOS: evidence of pyrolysis and release of a toxicant from plastic. Tob Control. 2019;28(1):34-41. doi: https://doi.org/10.1136/tobaccocontrol-2017-054104
13. Ganguly K, Upadhyay S, Rahman M, et al. Expert opinion on heated tobacco products [Internet]. Paris: Institute of Environmental Medicine; 2023. https://ki.se/media/259069/download
14. Philip Morris International [Internet]. Berna: PMI; [sem data]. Heat-not-burn products explained-glossary, 2023. [acesso 2025 jan 25]. Disponível em: https://www.pmi.com/glossary-section/glossary/heated-tobacco-products#:~:text=Heat-not-burn products%2C,reduced compared to cigarette smoke*
15. World Health Organization. Heated tobacco products information sheet [Internet]. 2. ed. Genebra: WHO; 2020. [acesso 2025 jan 25]. Disponível em: https://www.who.int/publications/i/item/WHO-HEP-HPR-2020.2
16. Instituto Nacional de Câncer. Impacto do uso de produtos de tabaco aquecido na qualidade do ar em ambientes fechados [Internet]. Rio de Janeiro: INCA; 2023. [Acesso 2025 jan 25]. Disponível em: https://ninho.inca.gov.br/jspui/bitstream/123456789/15141/1/3_Sumário Executivo 3.pdf
17. Anatomia de um Cigarro [Internet]. Nova Online. 2001 out. [acesso 2025 jan 25]. Disponível em: https://www.pbs.org/wgbh/nova/cigarette/anat_text.html
18. Reynolds RJ. Press release. Winston-Salem, n.c. when smoker light the carbon heat source in the tip of r.j. Reynolds tobacco co.'s new premier cigarette, warm air passes through a tobacco roll; press release [Internet]. Winston-Salem: Reynolds Building; 1988. [acesso 2025 jan 25]. Disponível em: https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=slny0078
19. Hayes JR, Steele RH. A review of the toxicology of glycerol. To review the biological activity of selected smoke components from premier prototypes [Internet]. Winston-Salem: Reynolds Building; 1994. [acesso 2025 jan 25]. Disponível em: https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=nkkb0079
20. Stapleton JA, Russell MAH, Sutherland G, et al. Nicotine availability from eclipse tobacco-heating cigarette. Psychopharmacology (Berl). 1998;139(3):288-90. doi: https://doi.org/10.1007/s002130050719
21. Anderson SJ, Ling PM. "And they told two friends... and so on": RJ Reynolds' viral marketing of eclipse and its potential to mislead the public. Tob Control. 2008;17(4):222-9. doi: https://doi.org/10.1136/tc.2007.024273
22. Tobacco Control Legal Consortium. Heated cigarettes: how states can avoid getting burned. Public Health

Law Center [Internet] 2018 ago. [acesso 2025 jan 25]. Disponível em: https://publichealthlawcenter.org/sites/default/files/resources/Heated-Cigarettes-2018.pdf

23. Philip Morris International. Sustainability report communication on progress 2016: United Nations Global Compact [Internet]. Lausanne: PMI; 2016. [acesso 2025 jan 25]. Disponível em: https://www.pmi.com/resources/docs/default-source/pmi-sustainability/pmi_sustainability_report_2016.pdf?sfvrsn=143382b5_2
24. Philip Morris International. Sustainability Report 2017 [Internet]. Lausanne: PMI; 2017. [acesso 2025 jan 25]. Disponível em: https://www.pmi.com/resources/docs/default-source/sustainability-reports-and-publications/pmi-sustainability-report-2017.pdf?sfvrsn=7aef95b5_4
25. Pulze Portugal – Preço 19 EUR [Internet]. YouTube. Publicado em 2025 jul 10 [acesso 2025 jul 11]. Disponível em: https://www.youtube.com/watch?v=Ezq7PqLqBjk
26. British American Tobacco [Internet]. Londres: BAT; 2020. British American tobacco website, tobacco heating products, 2020 fev 6. [acesso 2025 jan 25]. Disponível em: https://web.archive.org/web/20200206085143/https:/www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOAWUGNJ#
27. Trendy Report [Internet]. Lisboa: FIDEMO; [2011]. Durand R. BAT Glo Hyper+. Experimentámos a nova máquina de tabaco aquecido que quer ser a concorrente da IQOS, 2022 maio 27 [acesso em 2024 dez 15]. https://trendy.pt/2022/05/bat-glo-hyper-testamos-a-nova-maquina-de-tabaco-aquecido-que-quer-ser-a-concorrente-da-iqos/
28. British American Tobacco [Internet]. Londres: BAT; 2020. British American Tobacco website,2013-2023 new categories-a decade of reduced-risk products and portfolio transformation, 2023. [acesso 2025 jan 25]. Disponível em: https://www.bat.com/group/sites/UK__CRHJSY.nsf/vwPagesWebLive/DOCS4JKT#
29. Elias J, Dutra LM, Helen G, et al. Revolution or redux? Assessing IQOS through a precursor product. Tob Control. 2018;27(Supl 1):s102-10. doi: https://doi.org/10.1136/tobaccocontrol-2018-054327
30. Iqos [Internet]. São Francisco: Wikipédia; 2024. [Acesso 2025 jul 9, Atualizado 2025 jun 4]. Disponível em: https://en.wikipedia.org/wiki/Iqos
31. Cho YJ, Thrasher JF. Flavour capsule heat-sticks for heated tobacco products. Tob Control. 2019;28(e2):e158-9. doi: https://doi.org/10.1136/tobaccocontrol-2018-054472
32. Ramamurthi D, Chau C, Jackler RK. JUUL and other stealth vaporisers: hiding the habit from parents and teachers. Tob Control. 2019;28(6):610-16. doi: https://doi.org/10.1136/tobaccocontrol-2018-054455
33. Bourque B. Pax 2 review: the pax 2 is truly the ipod of vaporizers. Digitaltrends [Internet]. 2019 ago 23. [acesso 2025 jun 30]. Disponível em: https://www.digitaltrends.com/cool-tech/ploom-pax-2-review/
34. Tuzzin G, Godinho M, Dettmer A, et al. Análise estatística da polpação de talos de tabaco por explosão a vapor. O Pap. 2015;76(9):61-70.
35. Lenzi JC. N393: reconstituted tobaccos [Internet]. Lausanne: PMI; 1995. [acesso 2025 jun 30]. Disponível em: https://www.industrydocuments.ucsf.edu/docs/nlhx0093
36. Smith MR, Clark B, Lüdicke F, et al. Evaluation of the tobacco heating system 2.2. part 1: description of the system and the scientific assessment program. Regul Toxicol Pharmacol. 2016;81:S17-26. doi: https://doi.org/10.1016/j.yrtph.2016.07.006
37. Stefaniak AB, Ranpara AC, Virji MA, et al. Influence of e-liquid humectants, nicotine, and flavorings on aerosol particle size distribution and implications for modeling respiratory deposition. Front Public Heal. 2022;10:1-13. doi: https://doi.org/10.3389/fpubh.2022.782068
38. Zuck KC. Evidence Related to the health risk of IQOS use [Internet]. 2018 jan 25. [acesso 2025 jun 30]. Disponível em: https://www.fda.gov/media/110744/download
39. Tong Y, Xiong Y, Yan Q, et al. Effects of glycerol and propylene glycol on smoke release of heat-not-burn tobacco products. J Phys Conf Ser. 2021;1802:022025. doi: https://doi.org/10.1088/1742-6596/1802/2/022025
40. Nabavizadeh P, Liu J, Ibrahim S, et al. Impairment of endothelial function by inhalation of heat-not-burn tobacco aerosol. Circulation [Internet]. 2018[acesso 2025 jun 30];136(Supl 1):A16035. https://www.ahajournals.org/doi/10.1161/circ.136.suppl_1.16035
41. Nabavizadeh P, Liu J, Havel CM, et al. Vascular endothelial function is impaired by aerosol from a single IQOS heatstick to the same extent as by cigarette smoke. Tob Control. 2018;27(Supl 1):s13-9. doi: https://doi.org/10.1136/tobaccocontrol-2018-054325
42. Jaccard G, Tafin Djoko D, Moennikes O, et al. Comparative assessment of HPHC yields in the tobacco heating system THS2.2 and commercial cigarettes. Regul Toxicol Pharmacol. 2017;90:1-8. doi: https://doi.org/10.1016/j.yrtph.2017.08.006
43. Li X, Luo Y, Jiang X, et al. Chemical analysis and simulated pyrolysis of tobacco heating system 2.2 compared to conventional cigarettes. Nicotine Tob Res. 2019;21(1):111-8. doi: https://doi.org/10.1093/ntr/nty005
44. Mallock N, Böss L, Burk R, et al. Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. Arch Toxicol. 2018;92(6):2145-9. doi: https://doi.org/10.1007/s00204-018-2215-y
45. Brossard P, Weitkunat R, Poux V, et al. Nicotine pharmacokinetic profiles of the Tobacco Heating System 2.2, cigarettes and nicotine gum in Japanese smokers.

Regul Toxicol Pharmacol. 2017;89:193-9. doi: https://doi.org/10.1016/j.yrtph.2017.07.032

46. Auer R, Concha-Lozano N, Jacot-Sadowski I, et al. Heat-not-burn tobacco cigarettes: smoke by any other name. JAMA Intern Med. 2017;177(7):1050-2. doi: https://doi.org/10.1001/jamainternmed.2017.1419
47. Nga JDL, Hakim SL, Bilal S. Comparison of end tidal carbon monoxide levels between conventional cigarette, electronic cigarette and heated tobacco product among Asiatic smokers. Subst Use Misuse. 2020;55(12):1943-8. doi: https://doi.org/10.1080/10826084.2020.1781180
48. Caponnetto P, Maglia M, Prosperini G, et al. Carbon monoxide levels after inhalation from new generation heated tobacco products. Respir Res. 2018;19(1):164. doi: https://doi.org/10.1186/s12931-018-0867-z
49. Lu F, Yu M, Chen C, et al. The emission of VOCs and CO from heated tobacco products, electronic cigarettes, and conventional cigarettes, and their health risk. Toxics. 2022;10(1):8. doi: https://doi.org/10.3390/toxics10010008
50. Wang HT, Wang PH, Chen CY, et al. Comparison of carbonyls and tobacco-specific nitrosamines in aerosols of heated tobacco products and conventional cigarette smoke using both targeted and untargeted analytical methods. Regul Toxicol Pharmacol. 2025;157:105786. doi: https://doi.org/10.1016/j.yrtph.2025.105786
51. Sussman RA, Sipala F, Emma R, et al. Aerosol emissions from heated tobacco products: a review focusing on carbonyls, analytical methods, and experimental quality. Toxics. 2023;11(12):947. doi: https://doi.org/10.3390/toxics11120947
52. Solomou N, Fernández E, Szafnauer R, et al. Total and bioavailable polycyclic aromatic hydrocarbons in unused and operated heat-not-burn tobacco products and conventional cigarettes. Chemosphere. 2023;335:139050. doi: https://doi.org/10.1016/j.chemosphere.2023.139050
53. Dusautoir R, Zarcone G, Verriele M, et al. Comparison of the chemical composition of aerosols from heated tobacco products, electronic cigarettes and tobacco cigarettes and their toxic impacts on the human bronchial epithelial BEAS-2B cells. J Hazard Mater. 2021;401:123417. doi: https://doi.org/10.1016/j.jhazmat.2020.123417
54. Świsłowski P, Śmiechowicz B, Rajfur M. Effects of tobacco smoke on indoor air quality: the use of mosses in biomonitoring. J Environ Heal Sci Eng. 2022;20(1):485-93. doi: https://doi.org/10.1007/s40201-022-00794-2
55. Scherer G, Riedel K, Pluym N, et al. Assessment of the exposure to aromatic amines in users of various tobacco/nicotine products. ACS Omega. 2022;7(45):41775-82. doi: https://doi.org/10.1021/acsomega.2c06130
56. Ruprecht AA, Marco C, Saffari A, et al. Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products, and conventional cigarettes. Aerosol Sci Technol. 2017;51(6):674-84. doi: https://doi.org/10.1080/02786826.2017.1300231
57. Zervas EN, Matsouki NE, Tsipa CF, et al. Particle emissions from heated tobacco products. Tob Prev Cessat. 2024;10(abril):15. doi: https://doi.org/10.18332/tpc/185870
58. Protano C, Manigrasso M, Avino P, et al. Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system. Ann di Ig Med Prev e di Comunita. 2016;28(2):109-12. doi: https://doi.org/10.7416/ai.2016.2089
59. Protano C, Manigrasso M, Avino P, et al. Second-hand smoke generated by combustion and electronic smoking devices used in real scenarios: ultrafine particle pollution and age-related dose assessment. Environ Int. 2017;107:190-5. doi: https://doi.org/10.1016/j.envint.2017.07.014
60. Hecht SS, Hatsukami DK. Smokeless tobacco and cigarette smoking: chemical mechanisms and cancer prevention. Nat Rev Cancer. 2022;22(3):143-55. doi: https://doi.org/10.1038/s41568-021-00423-4
61. Hecht SS, Stepanov I, Carmella SG. Exposure and metabolic activation biomarkers of carcinogenic tobacco-specific nitrosamines. Acc Chem Res. 2016;49(1):106-14. doi: https://doi.org/10.1021/acs.accounts.5b00472
62. Hecht SS. Tobacco carcinogens, their biomarkers and tobacco-induced cancer. Nat Rev Cancer. 2003;3(10):733-44. doi: https://doi.org/10.1038/nrc1190
63. Wang P, Chen W, Liao J, et al. A device-independent evaluation of carbonyl emissions from heated electronic cigarette solvents. PLoS One. 2017;12(1):e0169811. doi: https://doi.org/10.1371/journal.pone.0169811
64. Lee A, Lee SY, Lee K-S. The use of heated tobacco products is associated with asthma, allergic rhinitis, and atopic dermatitis in Korean adolescents. Sci Rep. 2019;9(1):17699. doi: https://doi.org/10.1038/s41598-019-54102-4
65. Clapp PW, Jaspers I. Electronic cigarettes: their constituents and potential links to asthma. Curr Allergy Asthma Rep. 2017;17(79). doi: https://doi.org/10.1007/s11882-017-0747-5
66. Leigh NJ, Palumbo MN, Marino AM, et al. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. Tob Control. 2018;27(Supl 1):s37-8. doi: https://doi.org/10.1136/tobaccocontrol-2018-054318
67. U.S. Food and Drug Administration [Internet]. Silver Spring: FDA; [sem data]. Harmful and potentially harmful constituents in tobacco products and tobacco smoke: established list. 2012 abr [Acesso 2020 dez

8, atualizado em 2019 out]. Disponível em: https://www.fda.gov/tobacco-products/rules-regulations-and-guidance-related-tobacco-products/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list

68. U.S. Food and Drug Administration. Harmful and potentially harmful constituents in tobacco products; established list; proposed additions. Fed Regist. 2019;84(150):38032-5.
69. St.Helen G, Jacob III P, Nardone N, et al. IQOS: examination of Philip Morris International's claim of reduced exposure. Tob Control. 2018;27(Supl 1):s30-6. doi: https://doi.org/10.1136/tobaccocontrol-2018-054321
70. U.S. Environmental Protection Agency. Peer-Reviewed Provisional Toxicity Value for Acenaphthene (CASRN 83-32-9) [Internet]. 2011 jun 4. [acesso 2025 jun 30]. Disponível em: https://cfpub.epa.gov/ncea/pprtv/documents/Acenaphthene.pdf
71. International Agency for Research on Cancer. Monograph 92: some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures [Internet]. Lyon: IARC; 2010. [acesso 2025 jun 30]. Disponível em: http://monographs.iarc.fr/ENG/Monographs/vol92/mono92-14.pdf
72. Lim D-H, Ahmadi Y, Kim Y-H, et al. The extent of harmful volatile organic compounds released when smoking after breaking the flavor capsules of heat-not-burn (HNB) cigarette products. Environ Res. 2023;216:114501. doi: https://doi.org/10.1016/j.envres.2022.114501
73. Kim HS, Pack EC, Koo YJ, et al. Quantitative analysis of menthol and identification of other flavoring ingredients in capsule cigarettes marketed in Korea. Regul Toxicol Pharmacol. 2018;92:420-8. doi: https://doi.org/10.1016/j.yrtph.2018.01.002
74. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004. PubChem Compound Summary for CID 650, Diacetyl. [acesso 2025 jul 9]. Disponível em: https://pubchem.ncbi.nlm.nih.gov/compound/Diacetyl
75. Australian Government Department of Health. Acetylpropionyl and Diacetyl. Evaluation Statement [EVA00033] [Internet]. Sidney: Governo da Australia; 2022. [acesso 2025 jul 9]. Disponível em: https://cdnservices.industrialchemicals.gov.au/statements/EVA00033%20-%20Evaluation%20Statement%20-%2014%20January%202022.pdf
76. Popova L, Lempert LK, Glantz SA. Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims. Tob Control. 2018;27(Supl 1):s87-95. doi: https://doi.org/10.1136/tobaccocontrol-2018-054324
77. World Health Organization. WHO study group on tobacco product regulation: report on the scientific basis of tobacco product regulation: ninth report of a WHO study group [Internet]. Geneva: World Health Organization; 2008. [acesso 2025 jul 9]. Disponível em: https://www.who.int/tobacco/global_interaction/tobreg/en
78. Bjurlin MA, Matulewicz RS, Roberts TR, et al. Carcinogen biomarkers in the urine of electronic cigarette users and implications for the development of bladder cancer: a systematic review. Eur Urol Oncol. 2021;4(5):766-83. doi: https://doi.org/10.1016/j.euo.2020.02.004
79. Svendsen C, James A, Matulewicz RS, et al. Carcinogenic biomarkers of exposure in the urine of heated tobacco product users associated with bladder cancer: a systematic review. Urol Oncol Semin Orig Investig. 2022;40(4):149-60. doi: https://doi.org/10.1016/j.urolonc.2021.11.018
80. Braznell S, Campbell J, Gilmore AB. What can current biomarker data tell us about the risks of lung cancer posed by heated tobacco products? Nicotine Tob Res. 2023;26(3):270-80. doi: https://doi.org/10.1093/ntr/ntad081
81. Hirata N, Horinouchi T, Kanda Y. Effects of cigarette smoke extract derived from heated tobacco products on the proliferation of lung cancer stem cells. Toxicol Reports. 2022;9:1273-80. doi: https://doi.org/10.1016/j.toxrep.2022.06.001

Recebido em 30/4/2025
Aprovado em 25/6/2025

Scientific-editor: Anke Bergmann. Orcid iD: https://orcid.org/0000-0002-1972-8777