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REVIEW

Physico-Chemical Aspects of the Processes During the Combustion and Heating of Tobacco under Different Conditions

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Smoking cigarettes causes lung cancer, heart disease, chronic obstructive pulmonary disease (COPD) and other serious diseases. The damage caused by cigarette smoking is multifaceted and complex. Exposure to harmful and potentially harmful constituents (HPHCs), created during the process of burning tobacco, is the main reason for the development of smoking-related diseases. An alternative way to reduce the generation of toxicants from tobacco product is to heat rather than burn tobacco. Modified risk tobacco product (MRTP) are designed to significantly reduce or eliminate the release of harmful and potentially harmful chemicals while preserving, as much as possible, taste, sensory experience, nicotine delivery profile, and the ritual component of smoking cigarettes. In this review, the chemical composition of the smoke generated by conventional cigarettes to the composition of the aerosol generated by devices for controlled tobacco heating is compared. Also, critically assess the current knowledge in the field, aiming towards an objective assessment of the alternative tobacco products.

Keywords: Tobacco smoke, Modified risk tobacco products, Combustion, Heated tobacco products.

INTRODUCTION

In order to thoroughly understand the chemical processes that take place during the combustion of tobacco, as well as during its controlled heating at significantly lower temperatures than those at which combustion takes place, it is necessary to know its chemical composition in as much detail as possible.

The term "tobacco" actually covers a relatively heterogeneous category of processed complex plant material [1,2]. Heterogeneity is particularly induced through the series of processes to which tobacco is subjected immediately after harvest [3]. There is a clear relationship between the chemical composition of tobacco and the chemical composition of the smoke and aerosol produced when it is burned or heated under controlled conditions. Cigarette smoke is reported to contain more than 6000 chemical constituents [1], which are formed during distillation, pyrolysis, and combustion reactions when tobacco is burned [4]. Various scientific and regulatory bodies have also acknowledged the presence of more than 100 harmful and potentially harmful constituents (HPHC) in tobacco and cigarette smoke [5-7].

First, the tobacco is subjected to dehydration, which can be carried out in an atmosphere of heated air, or in a stream of air at ambient temperature. After dehydration and fermentation of different types of cigarettes follow (which usually take place for a longer time in conditions of low or increased atmospheric humidity, at ambient or elevated temperature) and before the finalization of the product,various additives with a specific purpose are added to the tobacco. The specific way of treating the tobacco as well as the type of additive that will be applied depends on the type of product for which it is intended, as well as on the manufacturer of the final product.

Chemistry of nicotine: Nicotine as a substance has been known since the middle of 16th century, while in a purified form since the first half of the nineteenth century. Nicotine is a pyridine alkaloid that is widely distributed in the plant world. The weight share of nicotine in dry tobacco leaves (from the species *Nicotiana tabacum, Solanaceae)* is about 5%. In certain other types of tobacco, this value can reach up to 14% [8,9]. Nicotine is also present in other plants of the family such as potatoes, tomatoes and eggplants. Its role in these plants is not entirely clear, but it is thought to serve as a natural defense against insects, fungi and bacteria. To some extent, in some parts of the world nicotine is also used as an insecticide, so it can also be found in food as a contaminant. In fact, it is estimated that humans ingest about 1.4 μg of nicotine per day through the usual diet [8,9].

Nicotine is the main constituent of tobacco, which is crucial in terms of causing addiction. When a person inhales cigarette smoke, nicotine is transferred through the smoke particles to the lungs, where it is quickly absorbed into the pulmonary venous circulation. From there, nicotine passes into the arterial circulation and enters the brain, where it binds to nicotinic acetylcholine receptors (nAChRs-ligand-dependent ion channels), which leads to the entry of sodium and calcium cations into the cell [10]. The end effect is the release of neurotransmitters from the cell.

The nAChRs receptor complex is made up of five subunits, the $\alpha4\beta2$ subtype is dominant in the human brain and assumed to play a key role in the behavioral effects of nicotine that contribute to the development of addiction [11]. The pharmacology of nicotine is complex and its binding to the receptors results in the release of a wide range of neurotransmitters, responsible for complex mechanisms in tobacco users [12]. Some of them are dopamine, which is known to cause pleasure and its level in the body increases under the influence of almost all substances that are subject to abuse; norepinephrine and acetylcholine, which improve alertness and cognitive function; glutamate, which improves memory and learning; serotonin, which affects mood; γ-aminobutyric acid (GABA) and endorphin, which relieve stress and anxiety [9].

Study shows that the nicotine has the potential for an analgesic effect that can be mild to moderate. Acute analgesia induced by nicotine is likely mediated by nicotinic cholinergic receptors, more precise the $\alpha4\beta2$ subtype [11]. There is also evidence to suggest that the analgesic effects also mediated by activation of the endogenous opioid system and the release of β-endorphins. Nicotine can regulate pain through pressor actions on the cardiovascular system [12]. Smoking also reduces appetite and understanding the neurobiological mechanisms underlying this effect could help facilitate the process of smoking cessation in terms of preventing weight gain in individuals trying to quit smoking [13].

Pharmacological, molecular genetic and electrophysiological studies have linked this effect to the activation of hypothalamic $\alpha3\beta4$ nicotinic cholinergic receptors. This leads to activation of proopiomelanocortin (POMC) neurons and subsequent activation of melanocortin 4 receptors [14]. This influence on the hypothalamic melanocortin system is responsible for the effect of reducing appetite and body weight as a result of smoking cigarettes [15]. Nicotine is metabolized by the hepatic enzymes CYP2A6, UDP-glucuronosyl transferase (UGT) and flavin monooxygenases (FMO) [16].

The main metabolite is cotinine, which is often used as a biomarker of nicotine exposure. Cotinine levels can be monitored in blood, urine, saliva, hair or nails. Nicotine metabolism is strongly influenced by genetic factors, but also by other factors such as age, gender, diet, use of oral contraceptives, pregnancy, use of drugs [16,17]. It is significant that nicotine passes through the hemoplacental barrier and accumulates in breast milk, where it can reach high concentrations which are sufficient for intoxication, including cessation of breathing in the child [18].

Standard textbooks and databases consistently state that the lethal dose of nicotine for adults is 60 mg. However, numerous cases of intoxication with significantly higher doses of nicotine, which did not have a fatal outcome, are found throughout the literature. Perhaps the most drastic example is a suicide attempt by administering 4 g of pure nicotine. Undoubtedly, there is a discrepancy between the generally accepted lethal dose and documented cases of nicotine intoxication [19].

According to the literature reports of fatal nicotine intoxications, the lower limit lethal concentration of nicotine in the blood is about 2 mg/L. This concentration is about 20 times higher than the one resulting from the intake of 60 mg of nicotine. According to this data, it can be observed that the lower limit dose of nicotine has a fatal outcome is 0.5-1 g of nicotine, which corresponds to an oral median lethal dose (LD_{50}) of 6.5-13 mg/kg [19,20].

Molecular structure of nicotine: L-(–)-nicotine belongs to the group of alkaloids, *i.e.* natural compounds that contain nitrogen atoms in their molecule and have a strong pharmacological effect (so-called compounds with a strong effect) [21, 22]. The composition of the molecule of this compound includes two nitrogen atoms. Nicotine is actually in a certain sense an unusual alkaloid because its molecule contains two heterocyclic rings that have a nitrogen atom - pyridine and pyrrolidine. The nicotine molecule has characteristics of bases [23,24]. Because of its greater basicity, the nitrogen atom in the five-membered ring is the first to be protonated. In some modern tobacco inhalation products (especially electronic cigarettes), nicotine is present in protonated form rather than in "free base" form (Fig. 1). According to the latest research in the field [1], protonated nicotine is much easier to inhale.

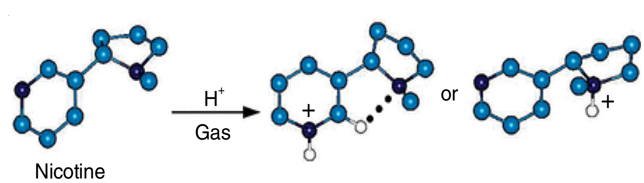

Fig. 1. Simplified schematic representation of the protonation process of the nicotine molecule. The nitrogen center in the nicotine molecule-on which the protonation is performed in the first stage is highlighted red

Physico-chemical properties of nicotine: Nicotine, as a pure substance under ambient conditions (atmospheric pressure of about 105 Pa and room temperature of about 25 ºC) is a hygroscopic oily liquid, volatile, which either be colourless or yellowish-brown, soluble in alcohol or ether [21,22]. The basic (non-protonated) form of nicotine is miscible with water in any ratio in the temperature interval from about 60 ºC to about 210 ºC. With acids it forms ammonium salts, which are usually solids under ambient conditions and usually well soluble in water.

Chemistry of tobacco combustion: Combustion processes, from a chemical point of view, represent the self-sustaining reactions with oxygen, for which three components are necessary *viz.* (i) fuel, *i.e.* material that burns (*e.g.* tobacco); (ii) oxygen (atmosphere); and (iii) enough heat to initiate the combustion process. The combustion process is exothermic, so after its initialization, due to the continuous release of heat during its development, the reaction will become "self-sustaining" [25]. During the process of tobacco combustion in the conventional cigarettes, oxygen is not available in sufficient quantities so that the combustion does not take place completely in all segments of the cigarette. Under idealized conditions in which combustion would occur with a sufficient excess of oxygen in all segments of the cigarette, hydrocarbons (compounds made only of carbon and hydrogen) would undergo complete oxidation, giving only carbon dioxide and water. More complex organic compounds (such as those containing other elements besides carbon and hydrogen) would also give other oxides. During incomplete combustion of tobacco, however, a complex mixture is generated in which more than 6000 compounds have been identified, covering almost all known classes of organic compounds.

Within this complex mixture, about 100 components are associated with smoking-related diseases in smokers. These include aromatic amines, aldehydes, ketones, some metals, oxygen free radicals, polycyclic aromatic hydrocarbons, tobacco specific N-nitrosamines, toxic gases such as carbon monoxide, hydrogen cyanide, butane, toluene and ammonia. Some of these compounds (arsenic, benzene, formaldehyde, lead, nitrosamines, polonium-210) have been proven or are suspected to be carcinogenic substances [26]. Certain products that are formed during the reactions of incomplete combustion of tobacco form solid micro- or nanoparticles or liquid micro- or nanodroplets [27, 28]. Cigarette smoke is made up of these components and other products of combustion.

Smoke is a multi-phase system that represents an aerosol in reality. It is dangerous to breathe in since it contains toxic materials. The harmfulness of the aerosol is determined by the technique of production as well as its chemical composition. Among the other components, various metals are found in the smoke from conventional cigarettes *e.g.* arsenic, beryllium, chromium, nickel and cadmium. All these metals are on the list of human carcinogens issued by the International Agency for Research on Cancer (IARC), since 1985 [29].

Tobacco combustion in traditional cigarettes involves a number of different processes and knowing the temperature profile of the reactor or the section of the cigarette where this process occurs, is incredibly helpful [30,31]. A typical temperature profile of this type, obtained through the experimental measurements of the temperature field, is shown in Fig. 2 [30]. As can be seen from the measured temperature profile, the temperature at which tobacco burns in conventional cigarettes ranges between 600 and 800 ºC. Due to such high temperatures, there are constituents generated during the range of processes such as distillation, pyrolysis, as well as combustion in the presence of oxygen (not always present in excess).

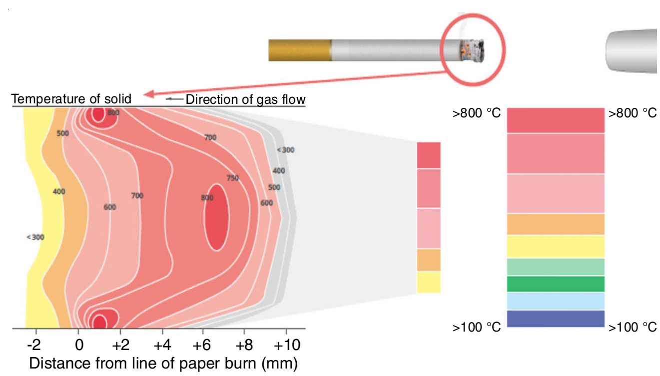

Fig. 2. Temperature profile of a conventional cigarette as a "reactor" in which the tobacco combustion process takes place, obtained through experimental measurements of the temperature field (taken from PMI Scientific Update April 2020, Issue 09)

Non-combustible tobacco products seriously reduced harm with using non-combustible tobacco products *versus* the harm from burning tobacco. Data from scientific analyzes indicating/presenting reduced toxicity in the aerosol generated with this new product category: Non-combustible tobacco products, as electrically heated tobacco products (EHTPs) represent a newer category of products that have been developed in order to reduce the risk associated with cigarette smoking among adult smokers who do not intend to quit smoking. These products heat the tobacco to temperatures well below the limit required for combustion to occur, thus generating an aerosol containing nicotine but significantly lower levels of harmful and potentially harmful chemicals (HPHC) than cigarette smoke [32]. On July 7, 2020, the US Food and Drug Administration (FDA) announced its decision classifying non-combustible tobacco products as a modified risk tobacco product (MRTP). Modified risk tobacco products are designed to significantly reduce or eliminate the release of HPHCs.

The device for controlled heating of tobacco is a system consisting of three different components *viz.* (i) a tobacco stick made of processed tobacco, (ii) an electronically controlled holder in which the tobacco stick is inserted and (iii) charger for filling the holder. The electronic holder contains a heater that directly heats the tobacco, but at the same time monitors and controls the temperature of the tobacco, ensuring that it does not exceed 350 ºC [22,33]. Given that the tobacco is heated to a maximum temperature of 350 ºC, significantly lower than 400 ºC (temperature required to start the combustion process), the composition of the aerosol which is generated is fundamentally different from cigarette smoke in terms of origin, physical properties and chemical composition.

In principle, the formation of aerosol occurs during the processes of evaporation, distillation and low-temperature pyrolysis of the tobacco substrate. Although the temperature of the heater reaches a maximum of 350 ºC, even the tobacco closest to the heater never reaches this temperature. In fact, most of the tobacco is exposed to a temperature below 250 ºC. Thus, nicotine is one of many examples of evidence demonstrating that these items do not produce smoke from burning tobacco but rather an aerosol of liquid droplets and gas [22,33,34].

Aerosols: Aerosols are the product of the regulated heating and vaporisation of nicotine, and it is important to know what they are in order to fully understand the differences between cigarette smoke and this aerosol. The term aerosol itself is a kind of "coinage" that comes from the English words aero-solution [35,36]. An aerosol is actually a suspension of solid particles (usually very small in size, on the micrometer or even nanometer scale) or liquid droplets (extremely small in size) in air or some other gas. What makes aerosols visible is the scattering of light by the particles present in these dispersed systems. It is the presence of submicron particles in aerosols that is the primary reason for the reduced visibility in large industrialized cities with a significant concentration of smog in the atmosphere. Generating of aerosols includes evaporation, distillation, as well as low-temperature pyrolysis of the tobacco substrate, (in which the agents introduced during the previous tobacco treatment, as well as the additives, *i.e.* the various flavours) [31,37] are present. All this indicates that the aerosol produced under these conditions will contain significantly reduced amounts of constituents that have a proven harmful or potentially harmful effect on human health (which are regularly found in the smoke of conventional cigarettes in relatively large quantities). These intuitive assumptions based on previous knowledge of the processes of combustion of organic constituents of tobacco in the absence of a sufficient excess of oxygen were confirmed by thorough research of the chemical composition of the aerosol generated by such devices [38-41].

Chemistry of tobacco during thermal treatment (combustion, *i.e.* evaporation and pyrolysis): In general, given the requirements set forth in the US Family Smoking Prevention and Tobacco Control Act (FSPTCA, 2009) in the USA [42], which also define the conditions that a product must meet in order to be included in the category of tobacco products with modified risk tobacco products (MRTP) and therefore to allow its sale and distribution. It is necessary for companies to perform a thorough scientific assessment consisting of non-clinical and clinical evaluation of the product.

Chemical composition of smoke generated during the combustion of tobacco and aerosol generated by devices for controlled heating of tobacco: The studies, conducted at Philip Morris Products (PMP) research centers, include a list of 54 harmful or potentially harmful constituents that are routinely measured during the development of heat-treated tobacco products. These scientific studies have shown significant reductions in the concentrations of all prioritized toxic substances, from the previously mentioned, in the aerosol generated by the THS2.2 system, compared to a smoke from the reference 3R4F cigarettes [40-45]. In most of the studies the reduction of harmful or potentially harmful constituents was more than 90% compared to reference conventional cigarettes with tobacco combustion. A decrease in concentration of the mentioned substances in the aerosol is also accompanied by a decrease of toxicity in *in vitro* conditions, again compared to the reference cigarettes 3R4F [46]. However, despite this scientifically supported argumentation, skepticism remained among the scientific community regarding the possibility of generating other toxico-logically relevant substances under the conditions of controlled heating of tobacco.

One of the most recent studies involves a detailed non-targeted analytical characterization of the aerosol generated by the Tobacco Heating System 2.2 [47]. The analysis in this study follows the non-targeted strategy that was previously discussed. The intent of the non-targeted approach is to identify all analytes that are relevant for a certain specific chemical area, as opposed to the conventional quantitative analysis, where only the chemical constituents of interest for a specific purpose are analyzed, effectively excluding the rest of the constituents that are not of interest.

Tobacco-related aerosols are studied by using analytical methods that cover the most ground possible in terms of the chemicals of interest. From an analytical point of view, it is mainly about the techniques of 2D chromatography in the gas phase coupled with time-of-flight mass spectrometry (GC x GC-TOFMS) as well as liquid chromatography coupled with high-resolution accurate mass spectrometry (LC-HRAM-MS– liquid chromatography with high-resolution accurate mass spectrometry). It is important to observe that in this study each analytical signal is analyzed in detail in order to do exact and in-depth determination and assignment, to a particular analyte.

The *in silico* techniques applied in this study are based on the advanced molecular modeling methods using mostly high-performance computing systems. Although every analytical technique is not absolutely correct and precise, still the reliability of the results obtained in the mentioned study can be considered as a good scientific approach in modern analytics. In this detailed study, 529 individual chemical constituents were detected in the aerosol generated by the THS 2.2 tobacco heating system, whose amounts were greater than 100 ng (excluding water, glycerine and nicotine) [47]. Based on these results, it has been demonstrated that the aerosol generated by tobacco heating systems does not contain a significantly different range of toxicologically relevant substances compared to the smoke generated by conventional cigarettes.

Air quality in closed spaces where conventional cigarettes and devices for controlled tobacco heating are used: A second important aspect that can be used for comparison of the potential harm of reduced-risk products, in relation to conventional cigarettes is the issue of air quality in closed and especially residential spaces where these products are used. In assessing the potential harm of reduced-risk products (*e.g.*, tobacco heating systems), of course, in addition to the direct impact on the user of the product, it is essential to assess the impact of product use on those in close proximity to direct user. The smoke generated in the environment, known as environmental tobacco smoke), is already recognized as a serious contributor to indoor air pollution, with a very substantial negative impact on its quality [48].

In fact, environmental tobacco smoke (ETS) is already recognized as a serious contributor to indoor air pollution, with a very substantial negative impact on its quality [48]. In fact, ETS is a diluted complex and time-evolved, *i.e.* aged mixture of the smoke emitted directly from the burning end of the cigarette where the process of slow combustion takes place (this smoke is usually called sideburn, *i.e.* sidestream), as well as the smoke inhaled by the cigarette user (the so-called main-stream *i.e.* the main part of the total smoke). Schematically, the difference between the main *i.e.* the sidestream smoke is shown in Fig. 3.

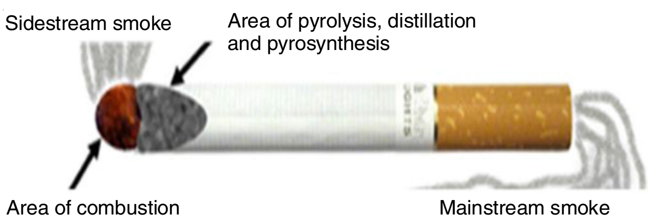

Fig. 3. Schematic representation of the parts of a conventional cigarette where different processes take place, with an indication of the areas of sidestream or mainstream smoke generation

Exhaled smoke has been found to contribute a about 3- 11% of the total carbon monoxide (CO) concentration, 15-43% of the total particulate matter concentration and 1-9% of the total nicotine concentration in ETS. The side component of the smoke is more alkaline compared to the main component and contains higher amounts of ammonia and bases [40-45]. The concentrations of nicotine and other volatile elements in ETS are much lower than those in inhaled cigarette smoke since there is much less nicotine and other volatile constituents in ETS.This is in accordance with the fact that a large part of these substances are retained in the body of the cigarette user after inhalation. A number of publications have shown that aerosols emitted/ generated byproducts that use tobacco heating have significantly lower impact on the composition of indoor air in which these products are used compared to ETS generated by conventional cigarettes [43-45]. Tobacco-based aerosol products do not use combustion or high-temperature pyrolysis to produce their aerosols, which is not quite expected. When these two steps are taken out of the aerosol formation process, the number of hazardous and possibly harmful components is drastically reduced [43].

Out of a total of 24 constituents whose concentrations were monitored in air, only in the case of three of them (nicotine, acetaldehyde and glycerin) concentrations increased above background concentrations in all studied simulations with THS 2.2. Accordingly, using the THS2.2 system indoors does not reduce air quality compared to when a conventional cigarettes are used. The re-emitted nicotine is subject to reactions with numerous oxidizing agents present indoors. The most relevant oxidizing agents are ozone, hydroxyl radicals and nitrate radicals [33,40]. Chemical reactions of nicotine with oxidizing agents can lead to the production of even more toxic and carcinogenic compounds, such as nitrosamines.

It was found that nicotine that is secondarily desorbed from indoor surfaces undergoes oxidation by OH radicals [49]. As products of this process, a number of toxic compounds are obtained, such as formamide, acetaldehyde, acetonitrile and others. The rate constant of the reaction at ambient temperature *i.e.* 298 K between nicotine and OH radicals was found to be 8.38×10^{-11} cm^3 mol^{-1} s^{-1}. It was concluded that the elimination of nicotine by oxidation with OH radicals is competitive with the processes of surface adsorption of nicotine, as well as with other processes that include the so-called "heterogeneous chemistry" of nicotine.This term refers to all the processes that take place at the interface (gas - solid phase), that is, during the adsorption of nicotine. The value given for the rate constant of nicotine oxidation is cumulative, indicating it accounts for all possible transformation processes.

Generation of free radicals during the use of conventional cigarettes and devices for controlled heating of tobacco: Aerosols from traditional cigarettes, electronic cigarettes and heat-not-burn tobacco products have all been studied for their potential to contain free radicals and recent independent scientific comparisons have provided a new light on this topic. Namely, in the scientific studies analyzed so far, the focus of research is mainly on the detection of substances *i.e.* compounds that are on the list of harmful or potentially harmful constituents. All these molecular species are stable *i.e.* they do not have the character of radicals.

Recently Shein & Jesche [50], the focus is on the presence of free radicals in the mainstream aerosol of 3R4F conventional cigarettes, two types of electronic cigarettes, as well as a tobacco heating product. In this work, the type and amount of free radicals in the mainstream aerosol is compared between the tobacco products. The quantification of free radicals as well as nitrogen monoxide (NO) in the gas phase of these aerosols was performed with the electron paramagnetic resonance (EPR) technique using a so-called spin trap. The solid phase from the aerosols was previously separated (Cambridge filter) and then subjected to extraction. Final analysis of persistent free radicals was again performed by electron paramagnetic resonance. In the overall study, a standardized aerosol generation machine (*i.e.* simulated smoking) was used to generate the aerosols.

The levels of organic radicals in tobacco heating products (as well as electronic cigarettes) did not exceed 1% of levels observed in conventional cigarettes. In fact, they were very close to the levels observed in the blank air samples. It was discovered that the spin density of the radicals found in regular cigarette smoke is concentrated on the oxygen atoms. Therefore, it was concluded that they are most likely alkoxy radicals. A very weak signal was, on the other hand, observed in aerosols generated by electronic cigarettes as well as by the tobacco heating product, which corresponds to free radicals where the electron (spin) density is localized on a carbon atom. Numerous questions related to the presence of free radicals, primarily in the smoke generated by conventional cigarettes, are still unsolved. These questions are primarily related to the chemical identity of these highly reactive and harmful species.

Quantum studies: Using quantum theoretical chemistry, Chavarrio-Cañas *et al.* [33] investigated the mechanism and kinetics of low-temperature nicotine degradation under conditions analogous to those of tobacco heating devices. The study concluded that, in general, several different initiation mechanisms can participate in the oxidation and pyrolysis processes of nicotine. At temperatures lower than 800 K, it is expected that the reactions of hydrogen subtraction from the nicotine molecule, which take place through the mediation of OH radicals, play a key role in the process of its oxidation. This happens due to the fact that at low temperatures, it is impossible to achieve the high activation energy of the dissociation reactions of other chemical bonds in the nicotine molecule. Reactions of the latter type, on the other hand, would be expected to be dominant and to control the degradation of nicotine at higher temperatures.

A particularly interesting finding in the study is the so-called non-Arrhenius kinetics of transformation at temperatures lower than 873 K. Such kinetics conditions result with an increase in the rate of hydrogen removal reactions from the nicotine molecule by means of OH radicals, when the temperature is lowered below the mentioned value. As a consequence of this, the calculated average lifetime of nicotine in closed spaces is longer with the decrease of the reactor temperature. The validity of theoretical approach implemented in the study is demonstrated by comparing the calculated rate constant of the nicotine oxidation process at 298 K (ambient conditions). In this context, it is significant to emphasize that quantum theoretical chemistry is increasingly used as a tool for a more thorough interpretation of experimental results and in a series of other studies, where the focus is primarily on the experimental measurements.

Conclusion

Finding alternative ways of satisfying the need for nicotine, based on products that would be less harmful compared to conventional cigarettes, is undoubtedly an important branch of modern science and technology. Solving this task requires a subtle combination of modern scientific knowledge and appropriate engineering innovation. Given the fact that it is about the health of individuals who are users or potential users of these products, a thorough characterization of all chemical entities generated by such products and an evaluation of their potential harm is necessary. In this study, a literature review was performed with a focus on efforts to characterize in detail the aerosols generated by the products based on heating tobacco and to compare their composition and properties with those of smoke generated by conventional cigarettes (and in some cases also by electronic cigarettes). The analysis was made impartially and exclusively based on the available scientific literature, primarily from the primary sources of information, that is, the original scientific papers.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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