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Are heated tobacco products (HTPs) a public health opportunity?

Da li proizvodi za zagrevanje duvana (HTP) predstavljaju priliku za javno zdravlje?

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Abstract
Heated tobacco products (HTPs) are a new, rapidly emerging category of tobacco products that are designed to heat the tobacco instead of burning it, thus substantially reducing the emission of harmful chemicals.
Currently there is a debate about whether HTPs provide an opportunity for public health, to accelerate the decline in cigarette smoking prevalence and thereby smoking-related population harm. To answer this question, HTPs have to be scientifically substantiated to reduce the harm to the individual smoker, but they also have to be satisfying for adult smokers to maximize the number of adult smokers who switch, while minimizing the number of youths and non-smokers who initiate or relapse to these products, as well as minimizing the number of smokers who intend to quit who may use those products instead.
In this article we present the evidence showing that switching to the THS reduces the negative health effects that are triggered by chronic exposure to the toxic substances generated during tobacco combustion and that lead to disease, compared to continuing smoking.

Key words: heated tobacco products, HTPs, tobacco heating system, THS, public health, tobacco harm reduction

Apstrakt
Proizvodi za zagrevanje duvana (HTP, heated tobacco products) su nova, brzo razvijajuća kategorija duvanskih proizvoda koji su dizajnirani da zagreju duvan umesto da ga sagorevaju, čime se znatno smanjuje emisija štetnih materija.
Trenutno se vodi debata o tome da li HTP pruža mogućnost javnom zdravlju da ubrza smanjenje prevalencije pušenja i na taj način utiče na smanjenje štetnosti kod populacije koja nastaje kao posledica pušenja. Da bi odgovorili na ovo pitanje, proizvodi za zagrevanje duvana treba da budu naučno potkrepljeni kako bi se smanjila štetnost za pojedinačnog pušača, ali isto tako treba da budu zadovoljavajući za odrasle pušače kako bi se maksimalno povećao broj odraslih pušača koji bi prešao sa cigareta na ove proizvode, uz istovremeno smanjenje broja mladih i nepušača koji počinju ili se vraćaju na ove proizvode, kao i smanjenje broja pušača koji nameravaju da odustanu od pušenja a mogli bi da predju na ove proizvode.
U ovom članku predstavljamo dokaze koji pokazuju da prelazak na Sistem za zagrevanje duvana (THS, tobacco heating system) smanjuje negativne zdravstvene efekte koji su izazvani hroničnim izlaganjem toksičnim supstancama generisanim tokom sagorevanja duvana koji dovode do bolesti, u poređenju sa kontinuiranim pušenjem.

Ključne reči: zagrejani duvanski proizvodi, HTP, sistem za grejanje duvana, THS, javno zdravlje, smanjenje štetnosti duvana

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Smoking causes a number of serious diseases (including cardiovascular diseases, lung cancer and chronic obstructive pulmonary disease (COPD)) and increases the risk of early death. According to the report from the World Health Organization, annually eight million deaths are attributed to cigarette smoke in the world (1). Quitting tobacco and nicotine use altogether is clearly the most effective strategy for smokers to reduce their risk of harm and disease, but many won't quit.

Tobacco control measures aimed at preventing smoking and supporting quitting play a key role in reducing the harm caused by smoking. However, the WHO estimates that more than 1 billion men and women still smoke worldwide (1) and that this number is unlikely to decline in the foreseeable future (2). Therefore, as a complementary measure for adult smokers, who would otherwise continue to smoke cigarettes, providing them with the opportunity to switch to scientifically substantiated, less harmful products has the potential to accelerate the decline in the prevalence of people smoking cigarettes.

What are HTPs?

Heated tobacco products (HTPs) are a newer type of tobacco product that were developed with the aim to reduce the harm associated with smoking for adult smokers who would otherwise continue to smoke cigarettes. Unlike cigarettes, HTPs heat the tobacco to temperatures well below combustion (burning), in order to generate an aerosol that contains nicotine, but far lower levels of harmful chemicals than cigarette smoke.

The term HTPs refers to an ever-evolving range of different products, based on innovative technologies that are continually developing and improving. Within this category the products vary in temperature (i.e., generally <400°C), heating sources (e.g., embedded; external; or a heated sealed chamber), the way the tobacco is processed (e.g., dry, moist, or liquid tobacco ingredients, including hybrid devices that combine tobacco and liquid), the flavors used. The final design can take variety of shapes and sizes to satisfy as wide a range of adult nicotine users as possible. Although HTPs are a class of products, each specific product must be assessed separately.

HTPs heat tobacco (sometimes together with a liquid), below the ignition temperature of tobacco (~400°C). As mentioned above, the heating source can vary from one product to another, but in all cases the heat aerosolizes nicotine directly from the tobacco. The user draws on the mouthpiece to inhale the aerosol, which is then taken into the body. It is because the tobacco is heated and not burned, that the aerosol that is inhaled by the user is not smoke.

Unlike e-cigarettes, which vaporize an e-liquid containing nicotine (generally derived from tobacco) and flavors, HTPs contain real tobacco, and therefore can provide a taste and nicotine delivery similar to those of cigarettes.

How does cigarette smoking cause disease?

When a cigarette is lit, the tobacco burns at temperatures that reach over 850 °C at the lit end when a puff is taken (3). The heat released by the combustion process breaks down the tobacco leaf components, generating smoke, light and ash. Cigarette smoke contains more than 6,000 chemicals (4), with around 100 being classified by public health authorities as likely causes of smoking-related diseases, such as lung cancer, heart disease, and emphysema.

The harm induced by cigarette smoking is multifaceted and complex. The exposure to harmful and potentially harmful constituents (HPHCs) can simultaneously affect different organs in the body and may interfere with the mechanisms regulating inflammation, oxidative stress, platelet activation, and lipid metabolism.

It is widely recognized that the adverse health effects that are caused by cigarette smoking are primarily triggered by chronic exposure to toxic substances generated during tobacco combustion, not from nicotine (5). While nicotine is not risk free and addictive, it is not the primary cause of smoking related diseases.

It is important to highlight that diseases manifest after a chain of events that occurs following exposure to cigarette smoke. Cigarette smoke triggers subsequent downstream events such as molecular changes, disruptions of biological mechanisms, and cellular/tissue changes that may over time accumulate and manifest as disease.

Epidemiology shows that smoking cessation ends the causal chain of events because it eliminates the exposure to toxic emissions from cigarettes which starts to reverse the disruptions at each step of the chain and over time reduces the excess risk for a smoker to develop smoking-related disease. Quitting tobacco and nicotine use altogether is therefore the most effective strategy for smokers to reduce the harms of smoking and the risk of suffering from a smoking-related disease.

By avoiding combustion, HTP reduces the number and levels of toxicants being emitted thereby lowering adult users' exposure, which has the potential to lower their risk of developing smoking-related diseases compared with continued smoking.

Figure 1. Chain of events that leads from smoke exposure to disease manifestation

How is HTP different from cigarettes?

Unlike cigarettes, HTP heats the tobacco to a maximum temperature of 350°C, well below the 400°C that are required for combustion processes to begin. Figure 2 shows the tobacco temperature at different distances from the surface of the heating blade. Although the temperature of the heating blade reaches 350°C even the tobacco that is closest to the blade never reaches this temperature. In fact, most of the tobacco remains below 250°C.

This is just one of the many pieces of evidence demonstrating that combustion doesn't occur in HTP. The absence of combustion in HTP, has been verified by scientific experts in numerous countries, including Italy, the United Kingdom, Japan, Poland, the United States, Australia, and Germany, as well as by an independent research organization in New Zealand (6).

Heating the tobacco without burning it generates a nicotine-containing aerosol that is fundamentally different from cigarette smoke in origin, physical properties and chemical composition. Cigarette smoke is a complex mixture of gas, liquid droplets and carbon-based solid particles that are the hallmark of combustion. Inhalation of carbon-based solid particles is known to have detrimental effects on human health. On the contrary, laboratory studies show that HTP generates a liquid-based inhalable aerosol that consists of liquid droplets and gas and does not contain carbon-based solid particles. As a result, in case of HTP, the levels of HPHCs (as defined and listed by different regulatory bodies) are on average 90-95% reduced compared to the smoke of a standard reference cigarette (3R4F) (7). The exact reduction varies depending on the different lists and which variant is being tested.

Does switching completely to HTP reduce the negative health effects compared to continuing smoking?

To demonstrate that switching completely to HTP reduces the harm caused by smoking, we compare the effects of switching to HTP with the effects of continued smoking at each step of the causal chain of events that leads from smoke exposure to disease manifestation. Quitting smoking is the best way for smokers to reduce the harm from smoking and therefore the risk profile of smoking cessation is the aspirational goal for a less harmful alternative product to cigarettes (8). For this, in our studies, we also assess the effects of switching completely to HTP against quitting altogether.

This includes:

- Assessing if the reduction of the toxic emissions in the aerosol translates to a reduction in exposure to the toxicants in smokers who switch completely to HTP as compared to smokers who continue to smoke cigarettes.

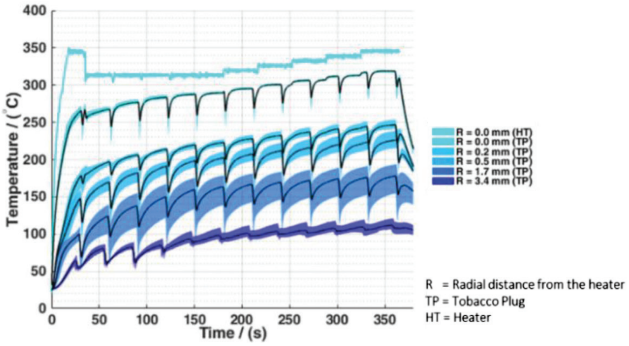

Figure 2. HTP: tobacco temperature at different distances from the surface of the heating blade

- Assessing the effects on molecular pathways and biological networks that are known to play a role in the development of smoking related diseases.
- Assessing if the reduction in exposure results in favorable changes in a set of biomarkers of potential harm that are negatively impacted by smoking and linked to the development of smoking related diseases.
- Assessing all the steps in the causal chain of events linking exposure to disease in animal models of disease for cardiovascular disease, respiratory disease and lung cancer.

To assess if the reduced emission of harmful chemicals reduces the body exposure to these chemicals, we measured a set of biomarkers of exposure to HPHCs in adult smokers who switched to HTP for three months and compared them with adult smokers who continued to smoke cigarettes and with adult smokers that quit smoking altogether for the duration of the study. A substantial reduction was observed in the group of smokers who switched completely to IQOS as compared with those who continued smoking and the observed reduction was similar to the effects observed in adult smokers who quit smoking altogether for the duration of the study (9, 10).

With systems toxicology studies, we assess the biological changes that occur at molecular level, often well before disease symptoms appear, in response to exposure to harmful chemicals. Our studies show reduced modifications in the expression of genes involved in the initiation and development of smoking-related disease, such as cardiovascular and respiratory disease, as well as those involved in the inflammatory response, which is the underlying mechanism of every disease (11–13).

We also conduct studies to assess the effects of HTP exposure compared with cigarettes on the histology of tissues. A study conducted on human small airway epithelium cells, showed a pronounced damage when the tissue cultures were exposed to the highest concentration of cigarette smoke tested. In contrast, HTP aerosol-exposed samples did not exhibit any apparent morphological alterations compared with the air-exposed controls, even at much higher concentration

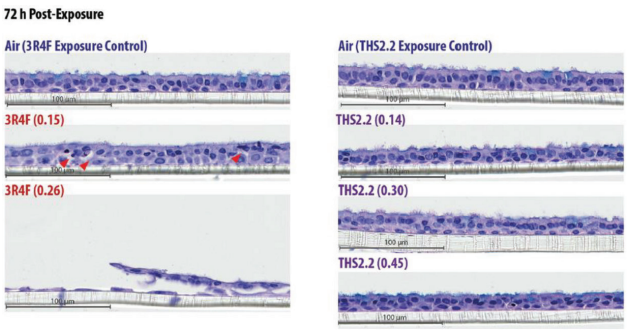

Figure 3. Culture morphology 72 h post-exposure.

than the highest concentration of cigarette smoke tested (Figure 3) (14).

To further investigate the progression of pathology, we investigated hallmarks of chronic obstructive pulmonary disease (COPD) and cardiovascular disease over an 8-month period in Apoe-/- mice exposed to IQOS aerosol compared with cigarette smoke. Exposure to cigarette smoke resulted in increased atherosclerotic plaque volume and pulmonary inflammation and emphysematous changes compared with controls (air). Exposure to HTP aerosol neither induced lung inflammation and emphysema nor did it consistently change the lipid profile or enhance the plaque area. The study also shows that switching from cigarette smoke exposure to fresh air and switching from cigarette smoke exposure to HTP exposure result in a reversal of the inflammatory responses and halt the progression of initial emphysematous changes and the aortic plaque area (11).

We also conducted a lifetime (18 month) inhalation study on AJ mice comparing lung tumor incidence and multiplicity in response to exposure to cigarette smoke from the reference cigarette (3R4F) and HTP aerosol. Clear effects were observed upon smoke exposure to cigarette smoke. No increased incidence and multiplicity in pre-neoplastic and neoplastic changes were observed in the lungs of HTP aerosol-exposed mice, even at twice the concentration of nicotine in the aerosol (15, 16).

Laboratory studies on animal models provide a very good indication of the potential reduced risk of switching to alternative products, but do not replace the need of human data to substantiate and quantify the reduction in the risk of disease. In circumstances where direct assessment of health outcomes is not feasible in the short-term, as it is the case for smoking-related diseases due to the duration of disease development, the impact of smoking history (both duration and intensity) and other life-style factors, looking at changes in biomarkers of potential harm (BoPH) that are reflective of pathways involved in the development of smoking related diseases is recognized as a valuable approach. Although BoPH are in itself not direct predictors of disease outcome and therefore cannot provide direct evidence of disease risk, BoPH are indicators of pathomechanistic dysregulations and clinical risk factors that have been strongly associated with disease. Using a combination of BoPH that together are indicative of various disease pathways leading to clinical outcomes, is therefore a valuable strategy to substantiate a subsequent reduction in risk (8).

We conducted a six month study with 984 adult American smokers to examine whether favorable changes occur in a set of eight co-primary BoPH reflective of pathways involved in the development of smoking related diseases when cigarette smokers switch to HTP. A systematic literature review of over 250 BoPH looking at the associations of smoking and smoking cessation on smoking-related diseases was performed. From this, eight BoPH were found covering multiple pathways related to a number of smoking-related diseases, being negatively affected by smoking and being reversible upon cessation within a

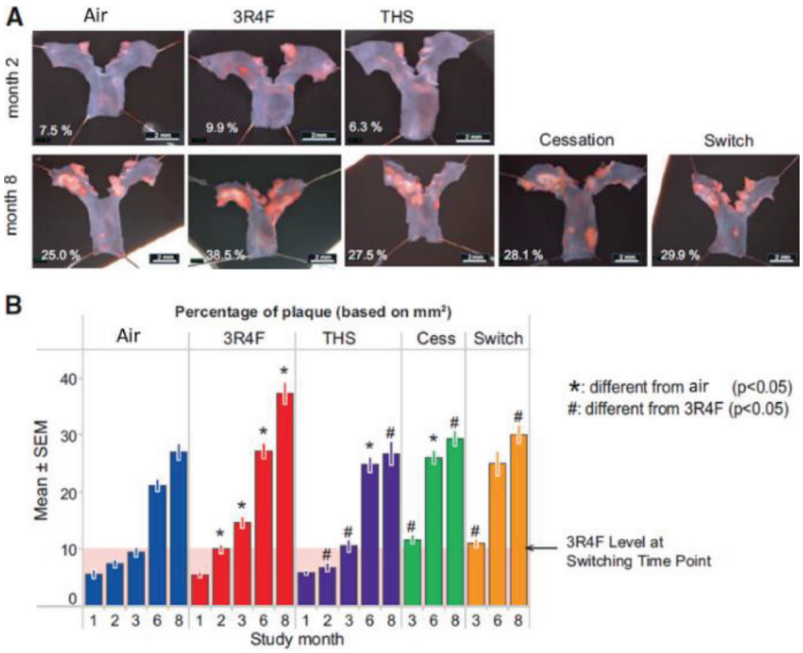

Figure 4. Atherosclerotic plaque area measurements

six-month timeframe. These eight BoPH were therefore selected as endpoints that can therefore provide evidence on the potential of HTP to reduce the harm and risk to the individual if they would change favorably after switching completely to HTP. In smokers who switched predominantly to HTP (i.e. ≥70% of tobacco products used daily) all of the BoPH moved in the same direction as with smoking cessation (improved biological effects) and for the majority of them the changes were statistically significant in comparison with cigarette smoke. The nicotine levels were similar in the group that switched to HTP and in the group that continued to smoke cigarettes (17).

To summarize, PMI used a totality of evidence based approach, leveraging BoPH, to ensure that adult smokers get access to and information about product(s) that have the potential to reduce the harm/risk of tobacco-related diseases as soon as possible.

Our data show that switching completely to HTP reduces the negative health effects along the chain of events that lead from exposure to disease compared to continuing smoking.

Can switching completely toHTP reduce population harm?

To positively impact the population, not only do novel products have to be scientifically substantiated to reduce the individual risk, they also have to be satisfying for adult smokers in order for them to switch in scale, while at the same time minimizing the risk that youth, non-smokers or smokers that successfully quit would not initiate or relapse to those products.

As smoking is both an addiction to nicotine and a conditioned habit triggered by various environmental cues, with smokers enjoying the rituals associated with smoking (18), it is imperative that alternative products to cigarettes are comparable to cigarettes in nicotine delivery, ritual, sensory characteristics and taste to enable a full transition away from cigarette.

Our clinical studies show that, after an adaptation period, adult users' satisfaction of HTP in terms of nicotine uptake and subjective effects is comparable to cigarettes, which is critical in adult smokers' acceptance of a substitute for their cigarettes.

Perception and behavior studies were also conducted to assess the effect of information provided on HTP. These studies consistently show that the way potential risks and benefits of HTP are communicated to consumers, generated substantial intent to use HTP among adult smokers with no intention to quit smoking, while only a negligible portion of adult never-smokers expressed an intention to use it. At the same time, for smokers who expressed an intention to quit smoking, the communication materials did not significantly alter their intention to quit nicotine and tobacco altogether (13).

These results have been confirmed in a number of countries in the post-market setting, were the results in Japan (19), Germany (20) and Switzerland (21) show that the rates of initiation in never smokers, including youth, are very low.

These findings support the potential of IQOS to contribute to tobacco harm reduction on a population level.

IQOS: the first electronic nicotine product ever to be authorized as Modified Risk Tobacco Product (MRTP)

Following the authorization to market a variant of the IQOS Tobacco Heating System in the US in April 2019, the U.S. Food and Drug Administration (FDA) further authorized the marketing of the IQOS Tobacco Heating System with reduced exposure information. This is the second set of products ever to be authorized as Modified Risk Tobacco Products (MRTPs), and the first electronic nicotine product to receive such authorization (22).

The following is the reduced exposure information that was authorized by the FDA:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

In particular, the agency determined that the evidence on the IQOS tobacco heating system heats tobacco and does not burn it, significantly reduces the production of harmful and potentially harmful chemicals compared to cigarettes. They also concluded that the totality of evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies (23).

The FDA's MRTP authorization establishes that IQOS is a fundamentally different product than combustible cigarettes, and creates a pathway for it to be regulated differently. The agency reached its conclusions even in the absence of long-term epidemiological evidence.

Despite the concerns that some unknowns may pose, the FDA concluded that the available scientific evidence demonstrates that the issuance of exposure modification orders for IQOS is appropriate to promote the public health and is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. In this respect, the FDA Modified Risk Order (MRO) also incorporates post-market requirements to determine the impact of these orders on consumer perception, behavior and health, and to enable the FDA to review the accuracy of the determinations upon which the orders were based. The key pillars of this post-market surveillance program

consists of monitoring risk comprehension and use behaviors amongst smokers and non-smokers, youth awareness, and an additional computational toxicology program studies to determine the impact of these orders on consumer understanding and perception, behavior and health, and to enable the FDA to review the accuracy of the determinations upon which the orders were based.

Conclusion

While HTPs are not risk free and contain nicotine which is addictive and also not risk free, scientifically substantiated and regulated, smoke-free products can represent a public health opportunity to accelerate the decline in smoking prevalence and smoking-related population harm.

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