Summary

**Introduction.** Today, there are new approaches to assessing the potential impact of alternative nicotine delivery systems, such as systemic toxicology and biomarker assessment. The modern development of science and technology, including laboratory research, allows for a detailed assessment of the biological effects of a substance or complex of substances on the human body as a whole.

**The aim of the study:** to compare and assess based on literature data possibility to broaden the standard approach for risk reduction assessment for lifestyle (potentially correctable) risk factors, especially tobacco smoking (TS). While epidemiology remains a golden standard for risk reduction assessment, novel approaches are based on preventive or system toxicology analysis and biomarkers of harm evaluation, thus it is crucial to understand both benefits and limitations of novel and standard approaches to complete risk reduction assessment for potentially correctable risk factors.

**Materials and methods.** The thematic scientific papers, published predominantly during the last decade, constituted the study material. The research methodology involved bibiosematic method and structural and logical analysis.

**Results and discussion.** Level of modern scientific development already can help us to assess the harm made by new/emerging products based on epidemiological, toxicological data and evaluation of biomarkers of potential harm for specific risk or disease. For TS biomarkers of harm are mostly well established and include 15 Harmful and Potentially Harmful Constituents (HPHCs) of tobacco smoke and their metabolites in the body. Reduction in Total-3-OH-B[a]P, S-PMA, COHb and other can show reduction in harm and risk caused by new/emerging product. So far most comprehensive analysis of reduction in HPHCs and biomarkers manifestation was concluded for tobacco heating system as TS alternative. Switching from cigarettes to THS for 5 days resulted in 56 % to 96 % reductions in 15 exposure biomarkers in the THS group compared to the TS group. These values approached the decrease in effect observed in the group of complete refusal of TS. Similar observations were made for the 90-day studies, where the reduction observed on day 5 was maintained until the end of the three-month studies and confirmed by other 3 clinical studies.

**Conclusions.** In general, the results of the risk reduction assessment based on novel approaches confirms that THS is an acceptable alternative to cigarettes for adult smokers, and based on the positive biological effects, the transition to THS represents a lower risk for the smoker’s body with regard to the effects of HPHCs.

**Key words:** biomarkers, tobacco smoking, THS, HPHCs, epidemiology, harm reduction

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**INTRODUCTION**

The facts of the negative/harmful impact of smoking on the development/progress of chronic non-communicable diseases (cardiovascular diseases, oncological, chronic respiratory diseases and diabetes) are well established and indisputable. According to the WHO, more than 7.2 million people die every year from the consequences of tobacco use (including the consequences of secondary exposure to tobacco smoke, known as «passive smoking»), and according to forecasts, this number will increase significantly in the coming years.
[1]. Smoking is a potentially modifiable risk factor, one whose impact can be reduced or eliminated altogether. At the same time, according to one of the leading specialists in the study of pathophysiological processes associated with tobacco smoking (TS) M. Fiore (2000), «it is difficult to identify any other condition that represents such a mixture of lethality, prevalence, and neglect...despite the possibility of effective and readily available interventions» [2]. Calculations by experts of the World Bank, which have already become a classic, showed that any anti-tobacco policy aimed solely at preventing new cases of TS will not have any effect on global smoking-related mortality for many decades [3]. This is due to the fact that most of the predicted deaths in the first half of the 21st century are deaths of current smokers. Therefore, according to WHO experts, governments of countries interested in improving health at the national level in the medium term should encourage the population to quit smoking (Fig. 1).

After all, this was confirmed in real life: the experience of the North Karelia project shows that one of the important factors is the decrease in mortality among men aged 35-64 by 82 % (during 40 years of observation — 1972-2012) there was a decrease in TS from 52.6 to 29.3 %. And in women of the same age category during the observation period, the decrease in the prevalence of TS from 19.4 to 11.4 % (combined with the correction of cholesterol and blood pressure) led to a decrease in total mortality by 84 % [4].

**Fig. 1 Estimated cumulative deaths from tobacco in 1950–2050 with different action strategies**

When considering the methodology of the tactics of giving up TS, first of all, the term «tobacco addiction» should be defined. Tobacco addiction is a set of behavioral, cognitive and physiological phenomena that are formed after repeated use of tobacco and usually include a strong desire to use tobacco, difficulties in controlling its use, constancy in using tobacco despite harmful consequences, a higher priority of using tobacco than other types of activities and obligations, increased tolerance and sometimes a physical state of abstinence [5].

Unfortunately, quitting smoking is a difficult process for most smokers. One of the main barriers that complicate the process of quitting is the factor of nicotine addiction. Nicotine acts directly on nicotinic cholinergic receptors, causing the release of dopamine. Its action consists not only in activation, but also in increasing the expression of a significant number of receptors in structures that secrete various mediators and are closely related to each other. Nicotine blocks receptors for a longer period than acetylcholine [6,7]. Already after a few weeks of regular TS, the body is restructured: the number of receptors and their structure changes, the body begins to produce less substances that regulate the synthesis of adrenaline and dopamine. Nicotine in tobacco smoke takes over these functions. If a person does not receive a portion of nicotine, his regulatory systems fail and a state of physical and mental discomfort, withdrawal syndrome occurs [5, 6, 7].

Withdrawal syndrome is the cause of failure when trying to stop smoking on your own in most attempts, its manifestations appear already within the first 1.5-2 hours after the last smoked cigarette. Most smokers lose the battle with the withdrawal syndrome, and only in 3-5 % (according to some data up to 10 %) self-quitting of TS is effective. It must be remembered that within 2 years after the refusal, the probability of relapse is very high, especially with a high level of social stress and low personal self-esteem. I would like to emphasize once again that the symptoms of the withdrawal syndrome of various degrees of severity are experienced by most smokers for a rather long period [5, 6, 7, 8].

So, addiction to TS had many names before — medicine, vice, pleasure, habit, freedom or lifestyle. Currently, tobacco addiction (TA) is considered as a complex combination of biochemical reactions, learned
behavior, social and genetic factors. In modern medicine, TA is classified as a disease, an independent nosological unit, which requires long-term systematic monitoring, drug treatment and repeated interventions to maintain persistent smoking cessation.

TA can be diagnosed according to WHO criteria. It is determined by the presence of at least 3 of the 7 criteria of this definition, if they are determined simultaneously during the last 12 months. In 1994, it was established that smoking 5 cigarettes is enough to develop TA. After 4 years (1998), the American Medical Association showed that this is the high value at which TA develops. Relapses in the treatment of TA are a phenomenon that reflects the chronic nature of addiction and does not mean the failure of the doctor and the patient [5, 6].

The classic assessment of the degree of TA in making a decision on the need for medical treatment is based on the Fagerström test [5]. In its absence, it is possible to use only three questions, which relate to the time of smoking the first cigarette, the average number of cigarettes per day, and the withdrawal symptoms that may have occurred during previous attempts to quit. The first cigarette within 30 minutes after waking up, 10 or more cigarettes smoked daily and symptoms of withdrawal syndrome during previous attempts entitle the doctor to offer the patient medical assistance in quitting smoking.

Nowadays, TA is considered as a mental and behavioral disorder due to the use of tobacco (IC code F17). It is a disease with a chronic course that recurs and requires long-term and systematic medical intervention and control. The latest scientific data convincingly prove that nicotine addiction is formed in 20% of psychological reasons (such smokers can quit smoking on their own, only some psychological help is needed), in 80% of cases — as a result of genetic predisposition (they cannot quit smoking on their own, special therapy is required) [9, 10].

Drugs the first lines for treatment tobacco dependencies:
- NRT drugs (patch, nasal spray, inhaler, chewing gum, sublingual tablets);
- antidepressant (bupropion);
- partial agonist/antagonist of nicotinic receptors (varenicline/champiks).

Second-line drugs for the treatment of tobacco addiction:
- tricyclic antidepressant nortriptyline;
- clonidine;
- selective serotonin reuptake inhibitor fluoxetine

Other drugs: partial agonist nicotine (cytisine); and the antagonist nicotine mecatylamine; antagonists opioids naloxone and naltrexone, and CYP 2A6 inhibitor methoxalen, vaccine [5, 6].

In the absence of motivation to quit other tactics are used to reduce the harm from, which is based on the understanding that «people smoke for nicotine, but die from the tar» [6].

Smokeless nicotine products are divided into two general categories: licensed medical devices — nicotine replacement therapy; unlicensed — chewing tobacco (snus) and electronic alternatives to cigarettes — electronic cigarettes (electronic nicotine delivery systems) and tobacco heating systems. It is the use of electronic nicotine delivery systems and tobacco heating systems during the last decade that has caused not only medical, but also political debates about the possibility of their use in different countries, which makes it necessary to express the attitude to this issue, first of all, by specialists [6].

One of the paradoxes of smoking is the fact that its prevalence is decreasing, while the absolute number of smokers worldwide is increasing. However, even where the frequency of TS has significantly decreased, there is a sufficiently large number of people who are unwilling or unable to give up TS [11]. In connection with the quantitative growth of smokers, the lack of effectiveness of existing drugs to help with smoking cessation, the lack of motivation of some smokers to quit or to use drugs for withdrawal, led to the fact that the «quit or die» position has increasingly become criticized by the international medical community. In recent years, new original approaches have been developed, the basis of which is the risk reduction strategy.

The essence of the strategy lies in the reformulation of treatment goals. If, according to the traditional therapy of nicotineism, the main task is a complete and unquestionable refusal of TS, then as part of the risk reduction strategy, it is the elimination of toxic substances that are formed during combustion and the satisfaction of addictive craving due to the intake of pure nicotine into the body [6].

The use of alternative nicotine delivery products potentially serves two purposes. The first, which is gaining more and more supporters among medical experts, is the reduction of negative health consequences when replacing traditional cigarette smoking with alternative sources of nicotine, and the second is a gradual reduction in smoking intensity (unlimited in time) with the potential for complete cessation from TS. It is assumed that this therapeutic approach should be applied to persons with the most pronounced and therapeutically resistant form of nicotinism [6].

«A drop of nicotine kills a horse» — this expression, in general did not help anyone to quit smoking, but firmly established in the minds of not only smokers, but also many doctors the firm belief that all the harm from smoking is related to nicotine. I would like to emphasize once again that nicotine is responsible for the mechanism of addiction and pleasure. Dr. Neil Benowitz, one of
the world’s leading experts on nicotine addiction from the University of California, concluded that long-term use of nicotine, although not completely harmless, is less dangerous than smoking cigarettes. Morbidity and mortality from smoking is caused by the toxicity of tobacco combustion products. Tobacco smoke contains 4-9 thousand harmful chemicals, which are the main factor of harm to the smoker’s health [12].

Currently, about 7,000 ingredients of tobacco smoke have been identified, of which only one third is formed directly from tobacco, the other 70% — from the ambient air that passes through the cigarette during smoking and interacts with tobacco during its combustion. From a physico-chemical point of view, burning tobacco is a combination of the processes of combustion, evaporation, simple sublimation, smoldering and pyrolysis. As a result of smoldering, which occurs with a lack of oxygen, many products of incomplete combustion are formed — carbon oxides, aldehydes, ketones, alcohols, ethers, etc. Many products of incomplete combustion are the result of pyrolysis [12]. The use of nicotine in ways that do not involve burning and smoke make it possible for a smoker to consume nicotine without or with a significantly lower proportion of harmful substances accompanying smoking, and thus achieve a significant reduction in harm to their health.

This suggests that alternative sources of nicotine delivery are not entirely safe, but are significantly better than traditional cigarettes.

After all, many legislative anti-tobacco acts are adopted without taking into account the presence of TA in a large number of people who smoke, and with a real disregard for their rights. The concept of «quitting smoking», which appears in legislative documents, assumes that smoking is conscious and voluntary in nature, in fact not being an addiction, but a habit that needs to be and can be easily given up.

The WHO policy statement emphasizes that «smokers get the maximum health benefits (only if) they completely stop using both tobacco and nicotine». This statement is indisputable, but disconnected from reality, since for many nicotine addicts this goal is not fully realized [11].

Every year, the arsenal of doctors is replenished with new knowledge about the possibilities of confronting the tobacco epidemic, and the strategy of harm reduction is becoming more and more popular.

THE AIM OF THE ARTICLE

Today, there are new approaches to assessing the potential impact of using alternative nicotine delivery systems — system toxicology and biomarker assessment. The modern development of science and technology, including laboratory research, allows a detailed assessment of the biological impact of a substance or complex of substances on the human body as a whole.

Most changes in our health — for better or worse — can be measured and quantified, but only if we know what signs to look for. Biomarkers are those signs. These are usually molecules that are found in the blood, other body fluids or tissues, and they are produced as a result of certain processes in the organism. Other measurements can also be biomarkers, for example, measuring how much air a person can forcefully exhale in one second.

MATERIALS AND METHODS

Based on the results of several observational clinical studies, key biomarkers of the effect of TS on pathophysiological changes in various organs and systems were determined (Fig. 2)

Thus, the proven effect of TS components on the occurrence/progression of cardiovascular diseases is due in particular to:

1. oxidizing chemicals and particles that increase the pathogenetic effect of inflammation on thrombus formation and endothelial dysfunction;
2. decrease in oxygen delivery due to hyperproduction of carbon monoxide;
3. volatile organic compounds, such as acrolein, which have a direct toxic effect on the cardiovascular system;
4. heavy metals that directly damage endothelial cells; and
5. nicotine, which is known to activate the sympathetic nervous system, leading to an increase in heart rate and blood pressure.

A biomarker of exposure is something that is measured in the body and indicates exposure to a particular stimulus. Biomarkers of exposure are usually found in blood, saliva, or urine, and are specific for the stimulus being studied. It can be a metabolite or the result of some other chemical reaction inside the body. Let’s give an example from tobacco research: the presence of a biomarker of nicotine exposure, cotinine, indicates that a person has been exposed to nicotine. This connection comes from the fact that nicotine is metabolized or converted into cotinine in the body. Cotinine is one of several metabolites of nicotine, which is an example of why multiple biomarkers of exposure can be used for the same chemical even within a single study. Another example: carbon monoxide exposure can be measured based on the presence of carboxyhemoglobin (COHb), i.e. carbon monoxide bound to hemoglobin. Hemoglobin is a protein that carries oxygen from the lungs to other parts of the body and carries carbon dioxide back to the lungs. But it binds more strongly to carbon monoxide, making COHb a useful biomarker of carbon monoxide exposure.
REVIEW AND DISCUSSION

It was the biomarkers for the effect of nicotine and carbon monoxide that were among the 15 components that were studied in 4 clinical studies on the effect of smoking regular cigarettes and the use of tobacco heating systems (THS). Data from these clinical observations were published in April 2023 [14].

TS exposes smokers to harmful and potentially harmful components (HPHCs). Tobacco Heating System 2.2 (THS 2.2) is a modified risk tobacco product that has been designed to reduce or eliminate the formation of harmful and potentially harmful components while preserving as much as possible the taste, feel, nicotine delivery profile and ritual characteristics of conventional cigarettes.

Two 5-day studies to determine reduced exposure THS were conducted in Japan (clinicaltrials.gov: NCT01970982) and Poland (clinicaltrials.gov: NCT01959932). Two 90-day reduced-dose trials used a menthol variant of THS and were conducted in Japan (clinicaltrials.gov: NCT01970995) and the United States (clinicaltrials.gov: NCT01989156) [14].

All these studies were conducted with 3 groups (160 participants). 80 participants were randomized to switch to THS for the duration of the study; the other 80 participants were randomized into two groups: 40 people each in the observation group with continued use of the usual brand of cigarettes and the group of TS abstinence quitted for the entire observation period. THS was provided to those randomized to the THS group, while those assigned to the cigarette group continued to purchase and smoke their usual brands of cigarettes. The abstinence status of the participants in the TS abstinence group was checked by the level of carbon monoxide in the exhaled air.

As for the first two studies, their design was the same: participants spent five days at the observation site. This restriction period resulted in strict control of participants’ use of the prescribed product, preventing them from using prohibited products.

These randomized, controlled, open-label trials at 5-day follow-up were designed to demonstrate a reduction in the exposure of selected HPHCs, to assess nicotine absorption and subjective effects in subjects who switched to THS 2.2 (n = 80) compared to a group that continued smoking regular cigarettes (HC (n = 40) and participants who abstain from smoking (n = 40). Subjects were randomized according to gender and intensity of daily cigarette consumption. Levels of HPHCs, determined after 5 days of observation, were significantly reduced in participants who switched to THS 2.2 compared to those who used cigarettes. More importantly, the magnitude of the observed reduction in biomarkers was close to that observed in participants who were completely abstinent from TS for 5 days. The reduction in cravings was comparable between the THS and TS groups, but the THS 2.2 group was slightly less satisfactory than the TS. The new TS alternative tobacco product was well tolerated.

However, because the retention period was only five days, this made it less likely that a decrease in biomarkers with longer half-lives, such as total NNAL (total 4 –
(methylnitrosamino)-1-(3-pyridyl)-1-butanol), for which the half-life varies from 10 to 18 days. NNAL itself is a tobacco-specific nitrosamine. Therefore, after 5 days of follow-up at the clinical center, the follow-up period lasted for 3 months: participants returned home with instructions to continue to follow the instructions of their study group: to continue smoking their own brand of cigarettes, to use THS, or to abstain from cigarettes. Participants returned for monthly follow-up visits and stayed overnight at the research center for 30, 60, and 90 days of follow-up. This longer study period made it more likely that a decrease in biomarkers for components with a longer half-life, such as NNAL, could be detected. In addition, the effects of reducing exposure to THS could be investigated in real-world settings. Participants self-reported product use during this outpatient period outside the clinical setting.

The characteristics of biomarkers of influence, which were analyzed in the studies, are presented in the table. 1. The list below shows the 15 HPHCs, their biomarkers of exposure and associated health concerns based on information available on the US FDA website. It is these HPHCs as markers recommended for the mandatory evaluation of the reduction of exposure to cigarette smoke, defined by the World Health Organization (WHO Study Group et al., 2008) and the draft guidelines of the Center for Tobacco Products (CTP) of the US Food and Drug Administration (FDA) «Notification of Harmful and Potentially Harmful Components in Tobacco Products and Tobacco Smoke» (US FDA, 2012) [15].

Table 1

<table>
<thead>
<tr>
<th>Characteristics of evaluated biomarker</th>
<th>Total-3-OH-B[a]P</th>
<th>3-hydroxy-benzo(a)pyrene</th>
<th>Benzo(a)pyrene</th>
<th>Carcinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total NNN</td>
<td>total N-nitrosornicotine</td>
<td>N-nitrosornicotine (NNN)</td>
<td>Carcinogen</td>
<td></td>
</tr>
<tr>
<td>Total NNAL</td>
<td>Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol</td>
<td>4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNK)</td>
<td>Carcinogen</td>
<td></td>
</tr>
<tr>
<td>Total 1-OHP</td>
<td>total 1-hydroxypyrene</td>
<td>Pyrene</td>
<td>Not classified</td>
<td></td>
</tr>
<tr>
<td>S-PMA</td>
<td>S-phenylmercapturic acid</td>
<td>Benzene</td>
<td>Carcinogen, a toxic effect on the reproductive system and cardiovascular system has been determined, which causes a delay in the development of the fetus</td>
<td></td>
</tr>
<tr>
<td>o-tol</td>
<td>o-toluidine</td>
<td>o-toluidine</td>
<td>Carcinogen</td>
<td></td>
</tr>
<tr>
<td>MHBMA</td>
<td>monohydroxybutenyl mercapturic acid</td>
<td>1,3-butadiene</td>
<td>Carcinogen, has a toxic effect on the reproductive system and the cardiovascular system, the respiratory system, causes a delay in the development of the fetus</td>
<td></td>
</tr>
<tr>
<td>HEMA</td>
<td>2-hydroxyethyl mercapturic acid</td>
<td>Ethylene oxide</td>
<td>Carcinogen, has a toxic effect on the reproductive system and the cardiovascular system, the respiratory system, causes a delay in the development of the fetus</td>
<td></td>
</tr>
<tr>
<td>COHb</td>
<td>carboxyhemoglobin</td>
<td>Carbon monoxide</td>
<td>A toxic effect on the reproductive system has been determined, causing a delay in the development of the fetus</td>
<td></td>
</tr>
<tr>
<td>CEMA</td>
<td>2-cyanoethylmercapturic acid</td>
<td>Acrylonitrile</td>
<td>Carcinogen, has a toxic effect on the respiratory system</td>
<td></td>
</tr>
<tr>
<td>4-ABP</td>
<td>4-aminobiphenyl (4-ABP)</td>
<td>4-aminobiphenyl</td>
<td>Carcinogen</td>
<td></td>
</tr>
<tr>
<td>3-HPMA</td>
<td>3-hydroxypropyl mercapturic acid</td>
<td>Acrolein</td>
<td>A toxic effect on the cardiovascular system and the respiratory system was determined</td>
<td></td>
</tr>
<tr>
<td>3-HMPMA</td>
<td>3-hydroxy-1-methylpropyl mercapturic acid</td>
<td>Crotonaldehyde</td>
<td>Carcinogen</td>
<td></td>
</tr>
<tr>
<td>2-NA</td>
<td>2-aminonaphthalene</td>
<td>2-aminonaphthalene</td>
<td>Carcinogen</td>
<td></td>
</tr>
<tr>
<td>1-NA</td>
<td>1-aminonaphthalene (1-NA)</td>
<td>1-aminonaphthalene</td>
<td>Carcinogen</td>
<td></td>
</tr>
</tbody>
</table>
Biomarker of the exposure to HPHCs is easy to detect with the help of proven, reliable, reproducible and accurate analytical methods. It is the level of a certain biomarker that reflects a specific toxic effect or is a reliable substitute for the effect of HPHC. The list of HPHCs includes HPHCs both from the gas phase and from the phase of solid particles formed at different temperature levels. The list of HPHCs includes a wide range of chemical classes and organ toxicity classes as defined by the US FDA (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive toxicant and developmental toxicant, addiction potential) (US FDA, 2012) [15]. The half-life of the HPHCs selected for measurement varies from a few hours to two weeks.

Additionally, levels of S-benzyl mercapturic acid, or S-BMA, a biomarker of toluene exposure, were measured, with only minor differences observed between smokers and nonsmokers. In addition to identifying biomarkers, several subjective effects were also measured in these studies.

Switching from cigarettes to THS for 5 days resulted in 56 % to 96 % reductions in 15 exposure biomarkers in the THS group compared to the TS group. These values approached the decrease in effect observed in the group of complete abstinence from TS. Similar observations were made for the 90-day studies, where the reduction observed on day 5 was maintained until the end of the three-month studies.

In a study conducted in Japan, indicators were analyzed in three groups. 160 Japanese adults (23-65 years old; smoking intensity ≥10 menthol cigarettes per day) were randomized as follows: 78 people to the mTHS group, 42 to the menthol cigarette smoking group, and 40 people to the TS abstinence group. Observation lasted for 5 days in the laboratory and 85 days in outpatient conditions. The endpoints included the determination of biomarkers of exposure to HPHCs, functional indicators of the respiratory system, safety assessment, and subjective effects. Results: After 5 days of mTHS use, the concentrations of carboxyhemoglobin, 3-hydroxypropylmercapturic acid, monohydroxybutenylmercapturic acid, and S-phenylmercapturic acid were 55 %, 49 %, 87 %, and 89 % lower (p < 0.001), respectively, in the mTHS group compared to the mC group. Other biomarkers of exposure (measured as secondary endpoints) were 50-94 % lower in the mTHS group than in the mC group at day 5. This reduction in the mTHS group was maintained at day 90, similar to the TS abstinence group. Switching to mTHS was associated with changes in respiratory function (shorter breathing intervals and more frequent breathing). Desire to smoke and level of satisfaction with smoking at day 90 were similar in the mTHS and mC groups. According to the obtained objective data, the researchers concluded that the transition from mC to mTHS significantly reduced the effect of HPHCs compared to those who continued to smoke mC.

The design of the US-based study on the effects of defined HPHCs (study registration: NCT01989156 (ClinicalTrials.gov)) was essentially similar to the observation of the Japanese cohort: it evaluated the reduction in exposure of selected HPHCs in smokers who switched to menthol tobacco heating system (mTHS) 2.2 compared to subjects who continued to smoke menthol cigarettes (mC) and were abstinent for 5 days at the study center, followed by an 86-day outpatient period. The sample cohort consisted of a total of 160 healthy adult smokers. Biomarkers of exposure to 15 HPHCs were measured in blood and 24-hour urine. Safety was monitored throughout the study. Information on product evaluation, use, subjective effects and clinical markers of risk were also collected (joint publication, Part 2) [14]. Results: Nicotine uptake was comparable in both exposure groups (ratio mTHS: mC 96 % at day 90.) At day 5, the exposure level of the other HPHCs was reduced by 51 %-96 % in the mTHS group compared to the mC group, and these reductions were maintained for most biomarkers throughout (up to 90 days) of the outpatient observation period. Switching to mTHS 2.2 resulted in significant reductions in exposure to total NNAL, total NNN, COHb, MHBMA, 3-HPMA, S-PMA, total 1-OHP, 4-ABP, 1-NA, 2-NA, o-tol, CEMA, HEMA, HMPMA. Decreases in the levels of these biomarkers were similar to those observed in the group of complete abstinence from TS. Moderate compliance in the mTHS group during the outpatient period indicated dual use of mTHS and mC. Therefore, mTHS is an acceptable alternative to mC for adult smokers. After 90 days of use, mTHS satisfaction and reduced cravings were comparable to mC. The researchers concluded that the switch from mC to mTHS significantly reduced the effects of HPHCs to levels close to those observed in subjects who abstained from smoking throughout the study.

For some of the HPHCs, data from the 90-day studies showed a slight increase in the levels of the relevant biomarkers at day 30 compared to day 5 for all groups. This fact is explained by the fact that all study participants were smokers at the time of enrollment in the study, and in their usual environment (outside the research center) they were exposed to environmental pollution, food, second-hand smoke, or other sources that were not present at the study site in the conditions of the research center.
According to the data of the 4 studies cited, it was noted that the reduction of exposure to HPHCs does not automatically mean a reduction in harm. To gain insight into the potential positive health effects of smokers switching from cigarettes to THS, data from a one-year exposure-response study was presented, that measured eight biomarkers of potential harm. The monitoring of eight biomarkers was chosen as the end point of the assessment because they indicate potential harm to the body and because they improve within six months of smoking cessation. This study (involving 984 adult US smokers) examined whether beneficial changes occurred in eight co-primary endpoints (HDL-C, white blood cells, forced expiratory volume (FEV), carboxyhemoglobin, total NNAL, sICAM-1, 11- DTX-B2, 8-epi-PGF2α), indicating biological and functional effects when smokers switch to the 2.2 tobacco heating system (THS). In addition, exposure biomarkers were quantified: MHBMA, 3-HPMA, Total NNN, CEMA, 3-OH-B[a]P, HMPMA, Total 1-OHP, NEQ and exhaled CO concentration.

Participants were randomized to continue smoking their preferred brand of cigarettes (n = 496) or to use THS (IQOS brand) (n = 488) for 6 months. The THS used in this study is characterized by a maximum heating temperature of 350 °C, delivering 1.21 mg of nicotine (using one stick) and 3.94 mg of glycerol according to Health Canada’s heavy smoking regime. The primary outcome was a favorable change at 6 months from baseline with statistically significant improvements in 5 of 8 biomarkers of exposure (HDL-C, leukocytes, FEV, carboxyhemoglobin levels, total NNAL) when smokers switched to THS compared with those who continued to smoke cigarettes. All eight biomarkers of potential harm in this study showed favorable changes in the same direction as smoking cessation, even though the THS group was allowed to continue smoking up to 30% cigarettes. [14] A full switch to THS significantly reduces harm compared to continuing to smoke. Although all eight biomarkers of potential harm showed favorable changes, five of the eight were statistically significant six months after switching to THS compared with continuing smoking. The lack of statistical significance for the other three biomarkers of potential harm means that it is not possible to draw an unequivocal conclusion as to what exactly the switch to THS caused these favorable changes.

In general, the results of the cited studies confirm that THS is an acceptable alternative to cigarettes for adult smokers, and based on the positive biological effects, the transition to THS represents a lower risk for the smoker’s body with regard to the effects of HPHCs.

In the context of the discussion of the reduction of the effect of HPHCs when giving up smoking traditional cigarettes and using alternative nicotine delivery systems, in particular, THS, we present the data of a 6-month observation conducted by researchers of the State University «Institute of Cardiology named after Acad. M. D. Strazheska» of the National Academy of Sciences of Ukraine in 2017: «Assessment of the impact of alternative nicotine delivery systems on the risk of cardiovascular diseases». In this observation, it was determined that the transition to the use of THS with the elimination of the effect of tobacco smoke allows to avoid violations of the oxygen transport function of the blood, the development and progression of endothelial dysfunction and proatherogenic changes in the metabolism of lipids and lipoproteins, which, in turn, leads to a reduction in the risk of the development/progression of CVD [16].

**CONCLUSIONS**

- Despite on decrease of smoking prevalence for the last 50 years, tobacco intoxication remains leading cause death, which can be eliminated. Help in quitting tobacco use is recognized as the most promising way to improve the health of the population, reduce mortality and increase life expectancy.
- It has been proven that the main harmful effect on health is caused by the products of tobacco combustion that are absorbed together with tobacco smoke.
- Tobacco addiction is a set of behavioral, cognitive and physiological phenomena that are formed after repeated use of tobacco, as a result of the combination of tobacco smoke: acetaldehyde, anabasine, nornicotine, anatabin, cotinine and myosmin.
- The main active substance of tobacco, which can cause addiction, is nicotine.
- The main direction of political efforts in the fight against tobacco is the Framework Convention of the World Health Organization with the prospect of minimizing harm to the health of the population by preventing the use of nicotine-containing products by people who have never smoked, and the complete cessation of smoking by heavy smokers. A harm reduction strategy plays an additional role and can serve as a road map for gradual cessation of smoking.
- A new tool for temporary abstinence from combustible cigarettes or complete tobacco smoking cessation — alternative sources of nicotine delivery, including THS systems — has gained great popularity all over the world.
- It has been proven that the pharmacokinetic profile of nicotine delivery plays an important role in the speed of its delivery and the satisfaction of nicotine craving when a smoker switches from using tobacco products to THS, increasing the probability of complete withdrawal from TS.
- Data from randomized controlled trials show that THS have a high therapeutic potential to help overcome tobacco addiction.
It has been proven that the overall toxicity of alternative nicotine delivery products is 90-95% less harmful than traditional smoking.

THS are not completely harmless. However, most of the results of toxicological, clinical and epidemiological studies indicate that the level of toxic exposure, assessed with indicators of changes in biomarkers, is less and lower than the levels observed under the influence of cigarette smoke and, as a rule, their use is well tolerated by consumers.

In general, the results of the risk reduction assessment based on novel approaches confirms that THS is an acceptable alternative to cigarettes for adult smokers, and based on the positive biological effects, the transition to THS represents a lower risk for the smoker’s body with regard to the effects of HPHCs.

FUTURE PERSPECTIVES

The harm reduction strategy is a pragmatic approach that aims to use safer alternative nicotine delivery products, especially in people with TA, thereby halting the pandemic of smoking-related diseases.

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Nothing to declare. The article is self-funded.

CONMPLIANCE WITH ETHICAL REQUIREMENTS

Ethical approval – not applicable (no animals or human subjects were used in this study).

REFERENCES

Вступ.
На сьогодні існують нові підходи щодо оцінки потенційного впливу застосування альтернативних систем доставки нікотину – системна токсикологія та оцінка біомаркерів. Сучасний розвиток науки і техніки, в тому числі лабораторних досліджень дозволяє детально оцінити біологічний вплив речовини або комплексу речовин на організм людини в цілому.

Мета дослідження: на основі літературних даних порівняти та оцінити можливе поновлення стандартного підходу до оцінки зниження ризику та факторів ризику, пов’язаних зі способом життя (які потенційно підаються корекції), зокрема тютюноокуріння (ТК). У той час як епідеміологія залишається золотим стандартом для оцінки зниження ризику, нові підходи базуються на превентивному або системному токсикологічному аналізі та оцінці біомаркерів шкоди, тому дуже важливо розуміти як переваги, так і обмеження нових і стандартних підходів для повноцінної оцінки зниження ризику для потенційно коригованих факторів ризику.

Матеріали та методи.
Матеріалом дослідження слугували тематичні наукові статті, опубліковані переважно впродовж останнього десятиліття. Методологія дослідження включала бібліосемантичний метод та структурно-логічний аналіз.

Результати та їх обговорення.
Рівень розвитку сучасної науки вже дозволяє оцінювати шкоду від нових (або тих, що знову з’являються) продуктів на основі епідеміологічних, токсикологічних даних та оцінки біомаркерів потенційної шкоди для конкретного ризику або захворювання. Для ТК біомаркери шкідливого добре відомі і включають 15 шкідливих і потенційно шкідливих складових (ШіПШК) тютюнового диму та їх метаболітів в організмі. Зменшення вмісту Total-3-OH-B[a]P, S-PMA, COHb та інших може свідчити про зменшення шкоди та ризику, спричиненого новим продуктом. Наразі найповніший аналіз зниження рівня ШіПШК та прояву біомаркерів було зроблено для системи нагрівання тютюну (THS) як альтернативи ТК. Перехід від сигарет до THS на 5 днів призвів до зниження рівня 15 біомаркерів впливу від 56 % до 96 % у групі THS порівняно з групою ТК. Ці значення наближалися до зниження ефекту, що спостерігалося в групі повної відмови від ТК. Аналогічні спостереження були зроблені в 90-денних дослідженнях, де зменшення, що спостерігалося на 5-й день, зберігалося до кінця тримісячних досліджень і було підтверджено іншими 3 клінічними дослідженнями.

Висновки.
Загалом, результати оцінки зниження ризику, проведеної на основі нових підходів, підтверджують, що THS є прийнятною альтернативою сигаретам для дорослих курців, з огляду на позитивні біологічні ефекти, перехід на THS становить менший ризик для організму курця щодо впливу ТК.

Ключові слова: біомаркери, тютюноокуріння, THS, шкідливі і потенційно шкідливі складові, епідеміологія, зменшення шкоди