*FABAD J. Pharm. Sci., 48, 2, 303-318, 2023*
*Doi: 10.55262/fabadeczacilik.1144926*
*REVIEW ARTICLE*

# Thirdhand Smoke Exposure and Its Toxicological Impacts: A Review on Target Organ-Based Studies

Kübra KOLCİ[*], Sena Nur GARİPKUŞ[**], Rengin REİS[***°]

***Thirdhand Smoke Exposure and Its Toxicological Impacts: A Review on Target Organ-Based Studies***

***SUMMARY***

*Thirdhand smoke (THS) is a newly described environmental health hazard that might be defined as residual cigarette smoke that occurs due to the accumulation of toxins of second-hand smoke (SHS) in the smoking environment. In addition, the chemicodynamic of THS may alter due to the interaction with other gases and chemicals in the environment. THS may cause serious health outcomes in the lungs, liver, skin, heart, and nervous system as well. Hence, it is thought to represent a major health hazard for people, particularly children, who are exposed to THS, where they interact more frequently with these surfaces exposed to THS via hand-to-mouth transfer. In the present study, it was aimed to summarize the proposed toxicity mechanisms based on in vitro and in vivo studies based on target organ toxicity. In this study, it is aimed to review the toxicity mechanisms of THS based on in vitro and in vivo studies on target organ toxicity. Recent studies reported that THS might induce unwanted effects in the respiratory, cardiovascular, nervous, hematopoietic, and skeletal systems and skin. Literature data indicated that THS-mediated oxidative damage and an increase in inflammatory response may play an important role in the pathogenesis of cardiovascular and neurobehavioral diseases, especially the target organ lung. In the future, THS might be defined as a preventable environmental risk factor. Therefore, further studies on THS are needed to define its toxicity mechanism as well as increase social awareness and legal regulations.*

***Key Words:*** *Thirdhand smoke, cigarette, oxidative stress, lung, nicotine*

***Üçüncü El Dumanı Maruziyeti ve Toksikolojik Etkileri: Hedef Organa Yönelik Çalışmalara İlişkin Bir Derleme***

***ÖZ***

*Üçüncü el duman (THS), sigara içilen ortamda ikinci el dumanının (SHS) toksinlerinin birikmesi nedeniyle oluşan "artık sigara dumanı" olarak tanımlanabilecek kısmen yeni bir çevresel sağlık tehlikesidir. Ayrıca, THS'nin kimyasal dinamiği, çevrede bulunan diğer gazlar ve kimyasallarla etkileşime bağlı olarak değişebilmektedir. THS akciğer, karaciğer, cilt, kalp ve sinir sisteminde de ciddi sağlık sorunlarına neden olabilmektedir. Bu nedenle, el-ağız transferi yoluyla THS'ye maruz kalan, bu yüzeylerle daha sık etkileşime girerek THS'ye maruz kalan insanlar ve özellikle çocuklar için büyük bir sağlık tehlikesi oluşturduğu düşünülmektedir. Bu çalışmada, hedef organ toksisitesine dayalı in vitro ve in vivo çalışmalara dayalı olarak söz konusu toksisite mekanizmalarının özetlenmesi amaçlanmıştır. Son zamanlarda yapılan çalışmalar THS'nin solunum, kardiyovasküler, sinir, hematopoietik ve iskelet sistemi ve cilt üzerinde olumsuz etkileri olduğuna yönelik bulgular rapor etmektedir. Literatür verileri, özellikle THS aracılı oksidatif hasarın tetiklenmesinin ve inflamatuvar yanıtın artışının gelecekte başta hedef organ akciğer olmak üzere, kardiyovasküler ve nörodavranışsal hastalıkların patojenezinde önemli rol oynayabileceği ve THS'nin önlenebilir bir çevresel risk faktörü olarak tanımlanabileceğine işaret etmektedir. Bu nedenle THS'nin toksisite mekanizmasının belirlenmesi, toplumsal farkındalığın ve yasal düzenlemelerin artırılması için daha kapsamlı ileri çalışmalara ihtiyaç duyulmaktadır.*

***Anahtar Kelimeler:*** *Üçüncü el duman, sigara, oksidatif stres, akciğer, nikotin*

*Received: 18.07.2022*
*Revised: 21.02.2023*
*Accepted: 22.02.2023*

[*] ORCID: 0000-0003-4228-6564, Acıbadem Mehmet Ali Aydınlar University, Faculty of Pharmacy, Department of Toxicology, Atasehir/ Istanbul, Turkey
[**] ORCID: 0000-0002-8110-0112, Acıbadem Mehmet Ali Aydınlar University, Faculty of Pharmacy, Department of Toxicology, Atasehir/ Istanbul, Turkey
[***] ORCID: 0000-0002-3484-2201, Acıbadem Mehmet Ali Aydınlar University, Faculty of Pharmacy, Department of Toxicology, Atasehir/ Istanbul, Turkey

[°] Corresponding Author; Rengin Reis
e-mail: rengin.reis@acibadem.edu.tr
Phone number: +90 216 500 42 59

## INTRODUCTION

Cigarette smoke (CS) is one of the most common and preventable health hazard for public health; that causes more than 8 million deaths annually. More than 1 million of those are passive smokers exposed to second-hand smoke (SHS) (WHO, 2021). Even if it has not resulted in death, severe health outcomes such as cancer, heart diseases, diabetes, chronic obstructive pulmonary disease (COPD), eye disorders, and tuberculosis might be seen in people who smoke. Thus, it contributes to a decrease in life quality gradually. The toxicity of CS in numerous target organs has been well-studied previously both *in vivo* and *in vitro* (Guan et al., 2012; Zong et al., 2019; Reis et al., 2021.) In addition to active smoke and SHS, a new toxicological concept, thirdhand smoke (THS) has arisen due to cigarette smoke's environmental residue. Basically, THS can be described as the 'residual tobacco smoke' or 'aged tobacco smoke', which is formed due to the accumulation of SHS toxins on surfaces of environments where smoking has occurred, such as carpets, tabletops, utensils, foods, household dust and cloths of smokers after the smoking was finished. The pollution of THS may remain in the environment for more than a month, depending on the degree of absorption or adhesion rates (Moon et al., 2019). Even though the public awareness of the health impacts of direct exposure to CS and SHS is well-acknowledged, people still do not have consciousness of the negative health impacts of THS as well as its concept. According to several studies on people from different age groups, education levels, and health professions, people were asked what THS is and which health problems it may cause. The results implicated that more than half of them did not know about it (Roberts et al., 2017; Moon et al., 2019; Lidón-Moyano et al., 2021). Today, smoking is prohibited in public places such as restaurants, cafes, and playgrounds due to various health outcomes, particularly lung diseases; however, according to the most recent World Health Organization (WHO) report, smoking in outdoor places is still not prohibited in many countries, including Turkey (WHO, 2020). According to the latest published information, public awareness of the concept of THS was highest in the United States (U.S.) and several prohibitions have been applied based on the published articles in the U.S. (Delgado-Rendon, et al., 2017). The majority of the studies on THS have shown that THS exposure might represent a public health concern, especially for children, due to the different exposure routes and children's developing organ-body system (Martins-Green et al., 2014; Mahabee-Gittens, et al., 2018; Myers, et al., 2018). Therefore, the toxicological profile of THS in the aspect of both public and environmental health should be elucidated to define its possible effects on human health. Although THS is a great risk to human health, very few people have awareness of its potential danger (Winickoff et al., 2009). In most countries, smoke-free laws are becoming widespread recently. In 2006, half of the states of the U.S. restricted smoking in workplaces and public areas (Delgado-Rendon et al., 2017). By keeping the value of smoke-free homes and cars higher, it is planned to prevent indoor smoking and involuntary exposure to THS. Studies show that this sanction implemented in the U.S. is successful in reducing exposure (Bundy et al., 2018). Based on the content of THS, nicotine is the main constituent of THS. It might be accumulated on surfaces for weeks to months, which can also react with oxidant gases (e.g., ozone and nitrous acid) to form carcinogenic nitrosamines such as 1-(N-methyl-N-nitrosamino)-1-(3-pyridinyl)-4-butanal (NNA), 4-(methylnitrosamino)-1-(3-pyridinyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN). These carcinogens may persist for a long time due to their low volatility property, and people can be exposed to these carcinogens for a while by involuntary ingestion, inhalation, and dermal contact (Ferrante et al., 2013). THS, which contains many different chemicals such as nicotine, phenol, cresols, acetaldehyde, formaldehyde, polycyclic aromatic hydrocarbons, isocyanic acid (HNCO), and TSNAs, has the potential to ad-

here and accumulate on many surfaces (Matt et al., 2011). People are chronically exposed to this because it can remain on indoor surfaces for weeks to months and can be re-emitted in the air (Acuff et al., 2016). According to several literature data, lung diseases, cardiovascular diseases, chronic depression, and poor wound healing were seen in people exposed to THS (Martins-Green et al., 2014; Karim et al., 2015; Dhall et al., 2016a; Adhami et al., 2018). In addition, abnormal melatonin catabolism through hypo-methylation of CYP1A2-promoter is another outcome of exposure to THS (Jiang et al., 2021). Besides its harmful effects on human health, THS might be a leading cause of an economic burden with estimated hundreds of billions of dollars in costs annually (Martins-Green et al., 2014). Hence, as a new toxicological concept, the present study is aimed to review the recent findings on THS exposure and possible health impacts on public health, primarily on children and people who are suffering from chronic diseases.

## THE CONCEPT OF THS

CS is a serious health risk for both smokers and non-smokers, with almost 7000 toxin content (Centers for Disease Control and Prevention (U.S.); National Center for Chronic Disease Prevention and Health Promotion (U.S.); Office on Smoking and Health (U.S.), 2010). Therefore, THS might be classified as an involuntary exposure route to these toxins due to its accumulation and aging capacity (Acuff, et al., 2016). It was first described in 2006; however, thoroughly investigated in 2009 by pediatrician Winickoff (Ganjre et al., 2016). In the study of Winickoff et al. (2009), it was mentioned that was no safe exposure level to THS and, the children were uniquely susceptible to exposure. In addition, the SHS can be removed from the indoor environment by ventilation. However, the THS may persist for several days, weeks, or even months after cigarettes have been smoked (Ferrante et al., 2013; Chen, et al., 2018). The differences between SHS and THS exposure and chemical content are described in Table 1.

**Table 1.** Main differences between SHS and THS based on their chemical content, exposure frequency and accumulation capacity.

| | SHS | THS |
|---|---|---|
| Route of exposure | Inhalation of both side-stream and main-stream smoke (Hang et al., 2013) | Inhalation, ingestion, and dermal absorption of pollution (Acuff et al., 2016) |
| Exposure frequency | High levels over a short time (Ferrante et al., 2013) | Low levels over a long time (Ferrante et al., 2013) |
| Physical characteristics | Removal through ventilation (Acuff et al., 2016) | Persistence on indoor surfaces and above humans (Acuff et al., 2016) |
| Accumulation | — | Walls, doors, carpets, pillows, curtains, furniture, clothes, skin, and hair (Acuff et al., 2016; Dhall et al., 2016a) |
| Chemical content | Carbon dioxide, carbon monoxide, nicotine, carbonyls (acetaldehyde, formaldehyde, acrolein), hydrocarbons (benzene, toluene, PAHs), nitrogen oxides, pyridine, ammonia, nitrosamines, and hydrogen cyanide (CalEPA, 2005) | Nicotine, 3-ethenylpyridine, phenol, cresols, naphthalene, formaldehyde, and TSNAs (NNN, NNK, NNA) (Northrup et al., 2016) |

The pollution of SHS that accumulates on surfaces reacts with dust, other chemicals, or gases in the environment, and this reaction produces THS, as depicted in Figure 1. By this conversion, aged THS becomes more toxic and harmful than SHS (Dhall et al., 2016a).


**Figure 1.** Illustration of THS and its exposure in the environmental system

People might be exposed to THS via involuntary inhalation, contact with the surfaces, or ingestion, as shown in Figure 2 (Ferrante et al., 2013). Especially children tend to be exposed to dust ingestion because of close interaction with household surfaces and frequent hand-to-mouth transmission. Therefore, it has been seen that the effects of THS are mostly seen in infants and children, and negative health impacts have been reported by several studies (Ferrante et al., 2013; Mahabee-Gittens et al., 2018). In addition, exposure to THS by dermal intake and inhalation may occur when non-smokers are present in a previously smoked environment (Acuff et al., 2016; Chen et al., 2018).

There are three common pathways for exposure to THS: inhalation of gaseous chemicals, dermal absorption, and oral ingestion by hand-to-mouth transfer of chemicals (Li et al., 2021). Since THS is an involuntary source of exposure by individuals, it is an issue with public health implications (Matt et al., 2011). The most commonly investigated target organs were the lungs, skin, heart, and brain (Escoffery et al., 2013; Ferrante et al., 2013; Martins-Green et al., 2014; Acuff et al., 2016). According to the results of *in vitro* and *in vivo* studies (Bahl et al., 2016; Hang, et al., 2018), it was shown that THS has negative impacts on the primary target, the respiratory system, by increasing oxidative damage (Hang et al., 2013), inflammatory response (Jacob et al., 2017), and fibrosis (Martins-Green et al., 2014). On the other hand, dermal and systemic exposure to THS has exerted its toxicity via several mechanisms. In the skin, THS deteriorates the wound-healing process which, involves hemostasis, inflammation, cell proliferation, and tissue remodeling. While carbon monoxide (CO) affects wound healing by binding to hemoglobin to form carboxyhemoglobin and preventing oxygen supply to tissues, hydrogen cyanide (HCN) disrupts oxidative metabolism and oxygen transport, creating a hypoxic effect (Silverstein, 1992; Dhall et al., 2016b). Since the inflammatory response, collagen deposition, and angiogenesis are decreased; clot formation and blood vessel leakage are increased (Dhall et al., 2016a). The wound healing delays, because of the decrease in the level of fibrillar collagen, resulted in a reduction in the strength of tissue (Martins-Green et al., 2014). In the cardiovascular system, THS has exerted its toxicity via stimulation of high levels of inflammatory cytokines and increased lipid levels (Martins-Green et al., 2014). Tail bleeding time assay revealed that bleeding times had been significantly shortened in THS-exposed mice, which poses a

great risk for thrombosis (Karim et al., 2015). Besides thrombosis, atherosclerosis, hyperlipidemia, and hypertension are the other health consequences of THS exposure (Deivanayagi et al., 2021). Some of the neurotoxic effects of THS are anxiety, memory loss, attention deficit hyperactivity disorder, and learning disorders, and these are the consequences of elevated nitro tyrosine levels causing oxidative stress and decreased ATP levels with THS exposure (Martins-Green et al., 2014; Chen et al., 2018; He et al., 2021).

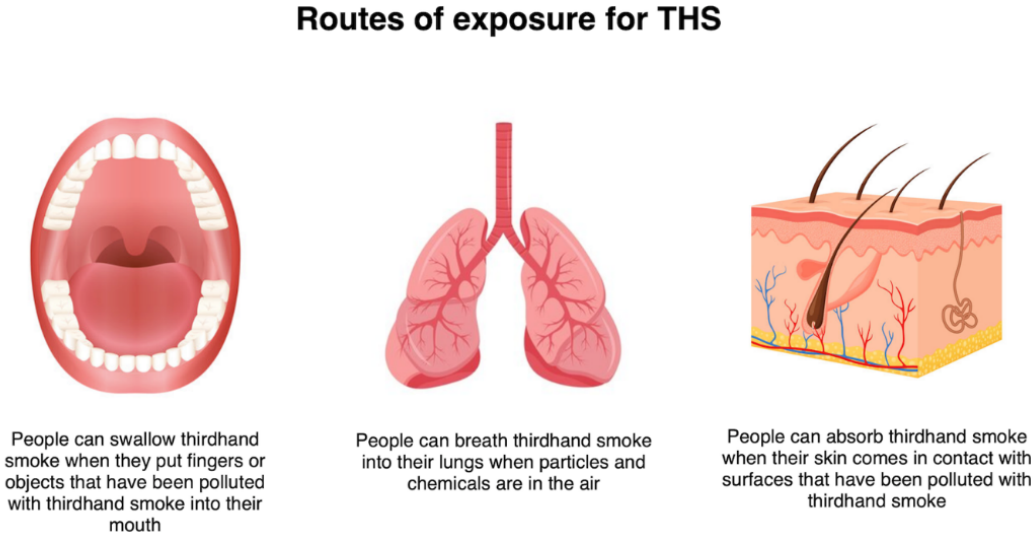


**Figure 2.** Illustration of the route of exposure to THS

Apart from the exposure differences compared to the SHS, the THS consists of mainly nicotine, tobacco-specific nitrosamines (TSNAs), phenol, cresols, naphthalene, formaldehyde, and 3-ethenylpyridine. After the release of smoke from a smoker several physical, and chemical transformations occur in the environment and it can continue at different levels just after the smoke is released. The most abundant disseminated constituent, nicotine, has the majority of accumulation potential among the other components, which persists for weeks to months (Matt et al., 2011). It might easily react with ozone and nitrous acid that, are oxidant gases present in indoor environments, and form TSNAs, such as NNK, NNN, and NNA, which are classified as group 1 lung carcinogens by the International Agency for Research on Cancer (IARC) (Burton, 2011; Stepanov, et al., 2013). These TSNAs, even in low doses, might lead to long-term health problem for infants since they are in close contact with surfaces, and have a higher respiration rate, and a lower body weight (Ferrante et al., 2013). Moreover, nicotine can form other volatile compounds such as formaldehydes, phenols, carbon monoxide, benzene, etc. are available to be exposed via inhalation due to their lower volatility and classified as human carcinogens with no safe level of exposure (Bogdanovica, et al., 2011). In addition, heavy metals such as chromium (Cr), lead (Pb), cadmium (Cd), copper (Cu), aluminum (Al), and nickel (Ni) are released during CS release and accumulate on surfaces (Yaprak et al., 2017). In a study conducted in an area exposed to THS, it has been proven that Pb and Cd, in particular, are highly mixed with house dust and accumulate for a long time (Matt et al., 2021). These heavy metals have lifelong health effects on humans. According to the studies, adverse cognitive and behavioral outcomes, increase in the risk of cardiovascular diseases, cancer and COPD thought to be related to the THS may be due to the accumulation of these heavy metals (Richter, et al., 2008; Obeng-Gyasi, et al., 2018; Zeng et al., 2018).

## GENERAL HEALTH IMPACTS OF THS

### Respiratory system

CS poses a great risk to the respiratory system due to its potential to induce target organ toxicity. Nicotine, the main content of CS, is also might be oxidized and produces several nitrosamines, the TSNAs, in the presence of ozone and nitrous acid (Rehan, et al., 2011). In addition to active smoke, the harmful effects of passive smoke on the lungs and several other organs are well acknowledged according to previous studies (Wannamethee et al., 2001; Fujii et al., 2012; Vani et al., 2015; Akhavan Rezayat et al., 2018; Reis et al., 2021). Cigarette smoke serves hazards especially for the human being exposed to passive smoke. Over the last decades, the effects of natural compounds on smoking-mediated respiratory diseases such as COPD, asthma, and lung cancer have been under investigation, as well as the mechanistic aspects of disease progression. In the present study, the protective mechanism of eucalyptol SHS causes a significant increase in hospitalizations and health expenditures of children each year due to pneumonia, bronchiolitis, or severe asthma (Cook et al., 1999; Li, et al., 1999). Although cough and nasal symptoms are more severe in SHS groups, THS also have a great impact on children's respiratory system (Ferrante et al., 2013).

In an *in vitro* study conducted by Bahl et al. (2015), the effects of acrolein, a toxic residue of THS, on human health revealed that acrolein killed lung fibroblasts. In another study conducted by Yu et al. (2018), even low levels of exposure to residual THS nitric oxide cause severe airway inflammation. In this study, the relationship between epicutaneous exposure to NNK, an important component of THS, and asthma was demonstrated by using a cockroach antigen (CRA) induced model of asthma in mice. As an adverse effect of this exposure, exacerbations in airway hyperreactivity, airflow inflammation, and airway remodeling were observed in mice (Yu, et al., 2018) which are the features of asthma (Busse et al., 2001; Umetsu, et al., 2002). Disruptions and thickening in the walls of the alveoli of mice were observed under THS exposure (Martins-Green et al., 2014). Besides, in the respiratory bronchioles, leukocyte infiltration, especially macrophages which indicate inflammation and highly disorganized collagen fibers, were observed in the interstitial tissue. All these observations and the pro-inflammatory environment in the lungs suggested an increased risk for the development of lung fibrosis in people who have been chronically exposed to THS (Martins-Green et al., 2014; Jacob et al., 2017). It is known that children might be exposed to THS easier because of both physiological, and behavioral reasons (Jacob et al., 2017). Hang et al. (2018) investigated how early exposure affects lung cancer by using 4 to 7 weeks age mice. In this study, the mice were exposed to THS at measured concentrations that a small child would be exposed to, and their lungs were observed after forty weeks. According to this study, a significant increase in the incidence of lung cancer was observed in mice exposed to THS compared to the control group. Also, *in vitro* studies conducted by Hang et al. (2018) using human cancer cell lines suggested an increase in lung cancer risk. It was concluded that THS might induce tumorigenic phenotypes, including cell proliferation and colony formation, in cells exposed to THS. The data confirmed that THS increases the cancer risk due to the induction of DNA double-strand breaks (Hang et al., 2013). As a result, the risk of lung cancer in children most exposed to THS for physiological and behavioral reasons increases continuously depending on the exposure time (Hang, et al., 2019). Our previous *in vitro* study (Reis et al. 2022) has also shown that THS might be led to an increase in oxidative stress, IL-6 level, and intracellular ROS level in A549 human lung adenocarcinoma cells. Based on the studies conducted with THS and its impact on the respiratory system, it might be concluded that repeated exposure to THS might induce fibrosis, oxidative and pro-inflammatory responses in the airway epithelia and lung fibroblast thus, THS might contribute to the symptoms of people with chronic pulmonary diseases.

**Skin**

Skin is one of the most important barriers to environmental exposures and to chemical substances that are embedded on the surfaces where people contact physically. Since THS differs from SHS and direct CS exposure, one of the main important exposure routes for THS is dermal exposure (Dhall et al., 2016b). Limited studies have shown the effects of active and passive smoking and their possible effects on the dermal system such as aging, wrinkle forming, atopic dermatitis, skin darkening, and thickening of the skin on the cheek (Knuutinen et al., 2002; Bernhard et al., 2007; Norman et al., 2010; Ishiwata et al., 2013; Yazdanparast et al., 2019). However, dermal side effects of THS are not elucidated clearly in the literature. According to the limited data on dermal exposure to THS, it was shown that the greatest known impact of THS on the skin was a delay in wound healing (Martins-Green et al., 2014; Acuff et al., 2016; Jacob et al., 2017). Wound healing is a dynamic process that involves four stages as hemostasis (blood clotting), inflammation, cell proliferation (tissue growth), and tissue remodeling. Delays, imbalances, and external factors occurring in these stages may disrupt the normal recovery period and cause adverse effects on human health (Sen et al., 2009). According to studies and tests carried out on mice, THS is one of the factors that cause a delay in wound healing. Mainly, nicotine, CO, and HCN in THS are suggested to be responsible for the aforementioned healing delay (Martins-Green et al., 2014). Since the affinity of CO to hemoglobin is greater than that of oxygen, it binds to hemoglobin to form carboxyhemoglobin and prevents adequate oxygen supply to the tissue. On the other hand, HCN disrupts oxidative metabolism, and oxygen transport, creates a hypoxic effect in the tissue, and delays healing (Nolan et al., 1985; Silverstein, 1992). The main active ingredient of THS, nicotine, is also known to cause tissue ischemia as a result of vasoconstriction in the peripheral vascular system, increases the tendency to thrombus and causes deterioration of the wound healing process due to its negative effects on blood cells (Mosely et al., 1978). Another study by Dhall et al. (2016), mice were placed in cages containing materials that had been smoked for several days and exposed to THS for one week. Full-thickness excision wounds were performed on the shaved skins of mice 24 h after exposure. The same procedure was performed on a group of mice not exposed to THS for comparison at the end of the study. Then wound tissues were collected from each group at various times to measure superoxide dismutase, hydrogen peroxide ($H_2O_2$), catalase, glutathione peroxidase (GPx), and lipid peroxidase activities, nitrotyrosine, cytokine and chemokine levels. According to the results, while the wounds of the mice were healed in 12 days, the wounds of the mice exposed to THS were healed on the 14$^{th}$ day, which showed that THS-exposed wounds took approximately 25% more time to heal compared to the control. Although the cellular and molecular mechanism underlying the delay of wound healing due to THS is unknown, it has been observed that increased oxidative stress, and related tissue damage cause an imbalance in chemokines and cytokines. As evidenced by the tests performed as a result of this imbalance, the inflammatory response, collagen deposition and angiogenesis are decreased; clot formation and blood vessel leakage are increased (Dhall et al., 2016). The decrease in the level of fibrillar collagen in THS-exposed mice is the main reason of delaying wound closure since it results in a notable reduction of the strength of wound tissue (Martins-Green et al., 2014). Another critical factor in impaired wound healing associated with THS is the imbalance of reactive oxygen species (ROS) levels (Nolan et al., 1985) and elevated superoxide dismutase activity, which causes an increase in $H_2O_2$. When $H_2O_2$ cannot be broken down to $H_2O$ and $O_2$ by the oxidant enzymes, GPx, and catalase, it leads to an increase in oxidative stress. As a consequence of the increment of oxidative stress, DNA damage in tissues might be seen and negatively affects wound healing (Buettner, 2011). Hence, the overall literature data points that THS-induced ROS production and imbalances in the collagen deposition

of skin might be the leading causes of delay in wound healing, but further studies are needed, though.

**Cardiovascular system**

As it is known, although CS is one of the most obvious causes of coronary heart disease (CHD), it is a preventable risk factor compared to other factors such as age, gender, family history of CHD, diabetes mellitus (DM), hypertension, dyslipidemia, and ethnicity (Kitamura et al., 2013).

There are limited studies are elucidating the effects of THS in the cardiovascular system (Martins-Green et al., 2014; Karim et al., 2015). Although it is known that both active and passive smoking is a major risk factor for the cardiovascular system, especially acute coronary thrombosis, the risk of THS on this system has been newly started to be investigated in recent years (Karim et al., 2015). According to a study conducted by Martins-Green et al. (2014), THS has a negative effect on the cardiovascular system by causing stimulation of high levels of inflammatory cytokines and increased lipid levels. In another study, Karim et al. (2015) suggested that enhanced platelet aggregation, glycoprotein IIb-IIIa activation and platelet secretion were observed in platelets of mice that were exposed to THS. Based on the performed tail bleeding time assay to evaluate hemostasis, it was revealed that bleeding times had been significantly shortened in THS-exposed mice. In the same study, platelet aggregation and secretion were also evaluated in $FeCl_3$-induced carotid artery injury in mice exposed to THS. According to their findings, the occlusion time was observed to be almost 10-fold shorter in mice exposed to THS (Karim et al., 2015). All these data showed that THS may pose a preventable risk factor for the progression of thrombosis, particularly for people at the risk of CVD.

Besides the aforementioned studies, several findings conducted the effects of chemical constituents of CS. Among them, nicotine, the major content of THS, is a sympathomimetic chemical, that acts peripherally and centrally by increasing the release of catecholamine and other neurotransmitters. Apart from its cardiovascular effects, such as elevation in the heart rate, high cardiac output, and increased arterial blood pressure (Ambrose et al., 2004), it also has metabolic effects, such as increased lipolysis. Lipolysis increases the amount of free fatty acids and glycerol in the blood and increased fat metabolism increases the oxygen demand of the whole system. Thus, nicotine-induced sympathetic activity increases the myocardium's oxygen demand without an increase in blood flow to the myocardium. On the contrary, vasoconstriction occurs in the coronary arteries, and all these effects cause symptoms of ischemia (Pur Özyiğit, 2019). On the other hand, the hemodynamic effects of nicotine are thought to increase atherosclerosis by causing endothelial damage (Beere et al., 1984). In addition, nicotine acts on nicotinic cholinergic receptors on endothelial cells, causing increased blood pressure, which causes the highest death rate (Arima et al., 2011) from cardiovascular diseases. These receptors lead to hypertension by arrangement in a barrel-like configuration forming a channel in the cell membrane, and increasing cation permeability from this channel (Lee et al., 2011). Another important mechanism is lipid peroxidation, which defines the oxidation of lipids, proteins, and DNA, which leads to cell damage and forms the basis of atherogenesis. CS is rich in oxidant chemicals such as hydrogen peroxide, peroxynitrite and superoxide. It also contributes to oxidant production *in vivo* (Burke et al., 2003). It is well acknowledged that reduced nitric oxide levels in smokers may cause acute cardiovascular events, and accelerated atherogenesis (Kiowski et al., 1994). Therefore, further studies are needed to conduct the possible health impacts of THS in the cardiovascular system based on exposure frequency, exposure level, age and cardiovascular health status.

**Nervous system**

Neurotoxicity can be defined as the alteration of the normal activity of the nervous system by disruption or death of neurons due to exposure to toxic

substances. Since the children might be exposed to THS via hand-to-mouth transfer as well, one of the expected target organs might be defined as the central nervous system (CNS). According to the data of the National Survey on Children's Health in 2007, among approximately fifty-five thousand children under the age of twelve that were exposed to SHS and relatively THS, 6% of them had attention-deficit/hyperactivity disorder, 9% had learning disabilities, and 4% had other behavioral disorders (Yolton et al., 2005; Kabir et al., 2011). Some studies have shown that CS causes many behavioral health problems, especially increasing depressive symptoms (Prokhorov et al., 2016). On the other hand, there are many studies reveal the effects of THS on human behavioral health (Martins-Green et al., 2014; Adhami et al., 2018; He et al., 2021).

In the tests conducted by Martins-Green et al. (2014) on mice, it was concluded that mice exposed to THS were hyperactive and anxious compared to non-exposed. It was observed that THS exposure caused elevated nitrotyrosine level. Consequently, oxidative stress increased in the brains of mice which caused penetration of the blood-brain barrier damaging many molecular structures in brain tissue. At the same time, ATP levels decreased in the brain tissues of mice exposed to THS (Chen et al., 2018). In another study, anxiety-like behavior in six strains exposed to THS was measured in the light/dark box, and one strain, the anxiety level was detected to be increased. They also measured the memory potential using the passive avoidance assay, and again, one strain displayed significant memory loss in mice that were exposed to THS from 4 to 9 weeks. This data showed that THS exposure may negatively affect anxiety-like behavior and memory in a strain-dependent manner (He et al., 2021). According to the aforementioned studies, THS might be important environmental pollutant, particularly for crawling babies and children exposed to accumulated THS on surfaces via hand-to-mouth transfer. However, to define the exact neurotoxicity mechanisms, its capacity to pass the blood-brain barrier, and the physicochemical dynamics of THS content have a major role and need to be elucidated with further studies.

**Hematopoietic system**

The hematopoietic system is the other suggested target for THS exposure. According to the limited data, an *in vivo* study showed that complete blood count values of neonatal and adult mice exposed to THS were elevated. Moreover, the number of neutrophils in female mice and the amount of basophils in male mice were higher than that of the non-exposed control (Hang et al., 2017). In the same study, it was also reported that THS exposure permanently affected the presence of B cells, and myeloid cells. Although there was no significant difference in blood lymphocyte counts between control mice and THS-exposed mice, significant differences were reported in the lymphocyte subpopulations and a significant decrease was observed in the myeloid/NK cell fraction, while the B cell fraction of neonatal and adult mice was increased. In another recent study in pregnant Cdkn2a/ dams exposed to THS, THS-exposed and control Cdkn2a/ mice bone marrow samples were transplanted into wild-type recipient mice with bone marrow ablation (irradiated) and then observed for one year to determine the effect of THS exposure in leukemia/ lymphoma risk. According to the measured cytokines above thirty types, twenty of them in THS-exposed pups were found to be less than that of control mice. Moreover, the β-subunit of basic fibroblast growth factor and platelet-derived growth factor was found to be higher in mice exposed to THS, and plasma cytokine differences were elevated in both genders exposed to THS (Snijders et al. 2021). Based on the literature findings, it might be suggested that repeated exposure to THS might affect complete blood counts as well as cytokine levels.

**CONCLUSION**

THS might be defined as important and preventable environmental pollution. Thus, exposure to THS might contribute to adverse health outcomes in many

systems, particularly in the respiratory and cardiovascular systems, by inducing oxidative stress and inflammatory responses. Hence, it might be suggested that repeated exposure to THS may cause serious health problems, especially in children, due to their involuntary contact with the surfaces. Therefore, further experimental, and clinical studies should conduct to determine the risk level of THS exposure and to raise public awareness. In addition, the legal sanctions that restrict smoking, especially indoors, should be brought to the agenda, and it should be ensured that these negative health effects related to THS could be minimized. As a result, it might be suggested that repeated exposure to THS may constitute a risk factor not only for public health but also for the environment.

**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

**AUTHOR CONTRIBUTION STATEMENT**

Literature research(KK, NG, RR), preparing the study text (KK, NG, RR), reviewing the text (KK, RR); developing hypothesis (RR)

**REFERENCES**

Acuff, L., Fristoe, K., Hamblen, J., Smith, M., & Chen, J. (2016). Third-hand smoke: Old smoke, new concerns. *Journal of Community Health, 41*(3), 680–687. doi: 10.1007/s10900-015-0114-1

Adhami, N., Chen, Y., & Martins-Green, M. (2018). Correction: Biomarkers of disease can be detected in mice as early as 4 weeks after initiation of exposure to third-hand smoke levels equivalent to those found in homes of smokers. *Clinical Science, 132*(12), 1365–1366. doi: 10.1042/CS20171053

Akhavan Rezayat, A., Dadgar Moghadam, M., Ghasemi Nour, M., Shirazinia, M., Ghodsi, H., Rouhbakhsh Zahmatkesh, M. R., … Akhavan Rezayat, K. (2018). Association between smoking and non-alcoholic fatty liver disease: A systematic review and meta-analysis. *SAGE Open Medicine, 6,* 2050312117745223. doi: 10.1177/2050312117745223

Ambrose, J. A., & Barua, R. S. (2004). The pathophysiology of cigarette smoking and cardiovascular disease: An update. *Journal of the American College of Cardiology, 43*(10), 1731–1737. doi: 10.1016/j.jacc.2003.12.047

Arima, H., Barzi, F., & Chalmers, J. (2011). Mortality patterns in hypertension. *Journal of Hypertension, 29*(1), S3–S7. doi: 10.1097/01.hjh.0000410246.59221.b1

Bahl, V., Weng, N. J., Schick, S. F., Sleiman, M., Whitehead, J., Ibarra, A., & Talbot, P. (2016). Cytotoxicity of thirdhand smoke and identification of acrolein as a volatile thirdhand smoke chemical that inhibits cell proliferation. *Toxicological Sciences: An Official Journal of the Society of Toxicology, 150*(1), 234–246. doi: 10.1093/toxsci/kfv327

Beere, P. A., Glagov, S., & Zarins, C. K. (1984). Retarding effect of lowered heart rate on coronary atherosclerosis. *Science, 226,* 4671, 180–182. doi: 10.1126/science.6484569

Bernhard, D., Moser, C., Backovic, A., & Wick, G. (2007). Cigarette smoke- an aging accelerator? *Experimental Gerontology, 42*(3), 160–165. doi: 10.1016/j.exger.2006.09.016

Bogdanovica, I., Godfrey, F., McNeill, A., & Britton, J. (2011). Smoking prevalence in the European Union: a comparison of national and transnational prevalence survey methods and results. *Tobacco Control, 20*(1), e4. doi: 10.1136/tc.2010.036103

Buettner, G. R. (2011). Superoxide dismutase in redox biology: The roles of superoxide and hydrogen peroxide. *Anti-Cancer Agents in Medicinal Chemistry, 11*(4), 341–346. doi: 10.2174/187152011795677544

Bundy, Ł. T., Haardörfer, R., Kegler, M. C., Owolabi, S., Berg, C. J., Escoffery, … Kreuter, M. W. (2020). Disseminating a smoke-free homes program to low socioeconomic status households in the United States through 2-1-1: Results of a national impact evaluation. *Nicotine & Tobacco Research: Official Journal of The Society for Research on Nicotine and Tobacco, 22*(4), 498–505. doi: 10.1093/ntr/nty256

Burke, A., & Fitzgerald, G. A. (2003). Oxidative stress and smoking-induced vascular injury. *Progress in Cardiovascular Diseases, 46*(1), 79–90. doi:10.1016/S0033-0620(03)00076-8

Burton, A. (2011). Does the smoke ever really clear? Thirdhand smoke exposure raises new concerns, *Environmental Health Perspectives, 119*(2), A70–A74. doi: 10.1289/ehp.119-a70

Busse, W. W., & Lemanske, R. F. Jr. (2001). Asthma. *The New England Journal of Medicine, 344*(5), 350–362. doi: 10.1056/NEJM200102013440507

California Environmental Protection Agency: Air Resources Board. (2005). *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant.* Retrieved from https://escholarship.org/uc/item/8hk6960q

Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US). (2010). *How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General, Atlanta (USA): Centers for Disease Control and Prevention.* https://www.ncbi.nlm.nih.gov/books/NBK53017/

Chen, Y., Adhami, N., & Martins-Green, M. (2018). Biological markers of harm can be detected in mice exposed for two months to low doses of third-hand smoke under conditions that mimic human exposure. *Food and Chemical Toxicology, 122,* 95–103. doi: 10.1016/j.fct.2018.09.048

Cook, D. G., & Strachan, D. P. (1999). Health effects of passive smoking 10: Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax, 54*(4), 357–366. doi: 10.1136/thx.54.4.357

Deivanayagi, M., Shakila, K. R., Massillamani, F., & Nayanaa, S. (2021). The exigency of third eye for third hand smoke exposure in cardiovascular system. *Natural Volatiles & Essential Oils, 8*(5), 71–76. Retrived from https://www.nveo.org/index.php/journal/article/view/326

Delgado-Rendon, A., Cruz, T. B., Soto, D., Baez-conde-Garbanati, L., & Unger, J. B. (2017). Second and thirdhand smoke exposure, attitudes and protective practices: Results from a survey of hispanic residents in multi-unit housing. *Journal of Immigrant and Minority Health, 19*(5), 1148–1155. doi: 10.1007/s10903-016-0540-x

Dhall, S., Alamat, R., Castro, A., Sarker, A. H., Mao, J. H., Chan, A., … Martins-Green, M. (2016). Tobacco toxins deposited on surfaces (third-hand smoke) impair wound healing. *Clinical Science, 130*(14), 1269–1284. doi: 10.1042/CS20160236

Escoffery, C., Bundy, L., Carvalho, M., Yembra, D., Haardorfer, R., Berg, C., & Kegler, M. C. (2013). Third-hand smoke as a potential intervention message for promoting smoke-free homes in low-income communities. *Health Education Research, 28*(5), 923–930. doi:10.1093/her/cyt056

Ferrante, G., Simoni, M., Cibella, F., Ferrara, F., Liotta, G., Malizia, V., & Grutta, S. la. (2013). Third-hand smoke exposure and health hazards in children. *Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace, 79*(1), 38–43. doi: 10.4081/monaldi.2013.108

Fujii, S., Hara, H., Araya, J., Takasaka, N., Kojima, J., Ito, S., … Kuwano, K. (2012). Insufficient autophagy promotes bronchial epithelial cell senescence in chronic obstructive pulmonary disease. *Oncoimmunology 1*(5), 630–641. doi: 10.4161/onci.20297

Ganjre, A. P., & Sarode, G. S. (2016). Third hand smoke- a hidden demon. *Oral Oncology, 54,* e3-e4. doi: 10.1016/j.oraloncology.2016.01.007

Guan, Y., Li, F.F., Hong, L., Yan, X.F., Tan, G.L., He, J.S., … Xie, Q.M. (2012). Protective effects of liquiritin apioside on cigarette smoke-induced lung epithelial cell injury. *Fundamental & Clinical Pharmacology, 26*(4), 473–483. doi: 10.1111/j.1472-8206.2011.00956.x

Hang, B., Sarker, A. H., Havel, C., Saha, S., Hazra, T. K., Schick, S., … Gundel, L. A. (2013). Thirdhand smoke causes DNA damage in human cells. *Mutagenesis, 28*(4), 381–391. doi: 10.1093/mutage/get013

Hang, B., Snijders, A. M., Huang, Y., Schick, S. F., Wang, P., Xia, Y., … Mao, J. H. (2017). Early exposure to thirdhand cigarette smoke affects body mass and the development of immunity in mice. *Scientific Reports, 7*(1), 41915. doi: 10.1038/srep41915

Hang, B., Wang, Y., Huang, Y., Wang, P., Langley, S. A., Bi, L., … Snijders, A. M. (2018). Short-term early exposure to thirdhand cigarette smoke increases lung cancer incidence in mice. *Clinical Science, 132*(4), 475–488. doi: 10.1042/CS20171521

Hang, B., Mao, J. H., & Snijders, A. M. (2019). Genetic susceptibility to thirdhand-smoke-induced lung cancer development. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco, 21*(9), 1294–1296. doi: 10.1093/ntr/nty127/5039570

He, L., Wang, P., Schick, S. F., Huang, A., Jacob, P., 3rd, Yang, X., … Hang, B. (2021). Genetic background influences the effect of thirdhand smoke exposure on anxiety and memory in collaborative cross mice. *Scientific Reports, 11*(1), 13285. doi: 10.1038/s41598-021-92702-1

Ishiwata, T., Seyama, K., Hirao, T., Shimada, K., Morio, Y., Miura, K., … Takahashi, K. (2013). Improvement in skin color achieved by smoking cessation. *International Journal of Cosmetic Science, 35*(2), 191–195. doi: 10.1111/ics.12025

Jacob, P., 3rd, Benowitz, N. L., Destaillats, H., Gundel, L., Hang, B., Martins-Green, M., … Whitehead, T. P. (2017). Thirdhand smoke: New evidence, challenges, and future directions. *Chemical Research in Toxicology, 30*(1), 270–294. doi: 10.1021/acs.chemrestox.6b00343

Jiang, W., Wu, H., Yu, X., Wang, Y., Gu, W., Wei, W., … Han, T. (2021). Third-hand smoke exposure is associated with abnormal serum melatonin level via hypomethylation of CYP1A2 promoter: Evidence from human and animal studies. *Environmental Pollution, 277,* 116669. doi: 10.1016/j.envpol.2021.116669

Kabir, Z., Connolly, G. N., & Alpert, H. R. (2011). Secondhand smoke exposure and neurobehavioral disorders among children in the United States. *Pediatrics, 128*(2), 263–270. doi: 10.1542/peds.2011-0023

Karim, Z. A., Alshbool, F. Z., Vemana, H. P., Adhami, N., Dhall, S., Espinosa, E. V., … Khasawneh, F. T. (2015). Third-hand smoke: Impact on hemostasis and thrombogenesis. *Journal of Cardiovascular Pharmacology, 66*(2), 177–182. doi: 10.1097/FJC.0000000000000260

Kiowski, W., Linder, L., Stoschitzky, K., Pfisterer, M., Burckhardt, D., Burkart, F., & Bühler, F. R. (1994). Diminished vascular response to inhibition of endothelium-derived nitric oxide and enhanced vasoconstriction to exogenously administered endothelin-1 in clinically healthy smokers. *Circulation, 90*(1), 27-34. doi: 10.1161/01.cir.90.1.27

Kitamura, T., Obara, H., Takashima, Y., Takahashi, K., Inaoka, K., Nagai, M., … Sugiura, Y. (2013). World Health Assembly agendas and trends of international health issues for the last 43 years: analysis of World Health Assembly agendas between 1970 and 2012. *Health Policy, 110*(2-3), 198–206. doi: 10.1016/j.healthpol.2012.12.008

Knuutinen, A., Kallioinen, M., Vähäkangas, K., & Oikarinen, A. (2002). Smoking and skin: A study of the physical qualities and histology of skin in smokers and non-smokers. *Acta Dermato-Venereologica, 82*(1), 36–40. doi: 10.1080/000155502753600867

Lee, J., & Cooke, J. P. (2011). The role of nicotine in the pathogenesis of atherosclerosis. *Atherosclerosis, 215*(2), 281–283. doi: 10.1016/j.atherosclerosis.2011.01.003

Li, J. S., Peat, J. K., Xuan, W., & Berry, G. (1999). Meta-analysis on the association between Environmental Tobacco Smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. *Pediatric Pulmonology, 27*(1), 5–13. doi: 10.1002/(sici)1099-0496(199901)27:1<5::aid-ppul3>3.0.co;2-5

Li, L., Hughes, L., & Arnot, J. A. (2021). Addressing uncertainty in mouthing-mediated ingestion of chemicals on indoor surfaces, objects, and dust. *Environment International, 146,* 106266. doi: 10.1016/j.envint.2020.106266

Lidón-Moyano, C., Fu, M., Pérez-Ortuño, R., Ballbè, M., Garcia, E., Martín-Sánchez, J. C., … Martínez-Sánchez, J. M. (2021). Third-hand exposure at homes: Assessment using salivary cotinine. *Environmental Research, 196,* 110393. doi: 10.1016/j.envres.2020.110393

Mahabee-Gittens, E. M., Merianos, A. L., & Matt, G. E. (2018). Preliminary evidence that high levels of nicotine on children's hands may contribute to overall tobacco smoke exposure. *Tobacco Control, 27*(2), 217–219. doi: 10.1136/tobaccocontrol-2016-053602

Martins-Green, M., Adhami, N., Frankos, M., Valdez, M., Goodwin, B., Lyubovitsky, J., … Curras-Collazo, M. (2014). Cigarette smoke toxins deposited on surfaces: Implications for human health. *PloS one, 9*(1), e86391. doi: 10.1371/journal.pone.0086391

Matt, G. E., Quintana, P. J., Destaillats, H., Gundel, L. A., Sleiman, M., Singer, B. C., … Hovell, M. F. (2011). Thirdhand tobacco smoke: Emerging evidence and arguments for a multidisciplinary. *Environmental Health Perspectives, 119*(9), 1218–1226. doi: 10.1289/ehp.1103500

Matt, G. E., Quintana, P. J. E., Hoh, E., Dodder, N. G., Mahabee-Gittens, E. M., Padilla, S., … Watanabe, K. (2021). Tobacco smoke is a likely source of lead and cadmium in settled house dust. *Journal of Trace Elements in Medicine and Biology: Organ of the Society for Minerals and Trace Elements (GMS), 63,* 126656. doi: 10.1016/j.jtemb.2020.126656

Moon, S. Y., Kim, T. W., Kim, Y. J., Kim, Y., Kim, S. Y., & Kang, D. (2019). Public facility utility and third-hand smoking exposure without first and second-hand smoking according to urinary cotinine level. *International Journal of Environmental Research and Public Health, 16*(5), 855. doi: 10.3390/ijerph16050855

Mosely, L. H., Finseth, F., & Goody, M. (1978). Nicotine and its effect on wound healing. *Plastic and Reconstructive Surgery, 61*(4), 570–575. doi: 10.1097/00006534-197804000-00013.

Myers, V., Shiloh, S., & Rosen, L. (2018). Parental perceptions of children's exposure to tobacco smoke: Development and validation of a new measure. *BMC Public Health, 18,* 1031. doi: 10.1186/s12889-018-5928-1

Nolan, J., Jenkins, R. A., Kurihara, K., & Schultz, R. C. (1985). The acute effects of cigarette smoke exposure on experimental skin flaps. *Plastic and Reconstructive Surgery, 75*(4), 544–551. doi: 10.1097/00006534-198504000-00018

Norman, R. A., & Rappaport, M. (2010). Smoking, obesity/nutrition, sun, and the skin. *Preventive Dermatology,* 17-20. doi: 10.1007/978-1-84996-021-2_2

Northrup, T. F., Jacob, P., 3rd, Benowitz, N. L., Hoh, E., Quintana, P. J., Hovell, M. F., … Stotts, A. L. (2016). Thirdhand smoke: State of the science and a call for policy expansion. *Public Health Reports, 131*(2), 233–238. doi: 10.1177/003335491613100206

Obeng-Gyasi, E., Armijos, R. X., Weigel, M. M., Filippelli, G. M., & Sayegh, M. A. (2018). Cardiovascular-related outcomes in U.S. adults exposed to lead. *International Journal of Environmental Research and Public Health, 15*(4), 759. doi: 10.3390/ijerph15040759

Prokhorov, A. V., Calabro, K. S., & Tamí-Maury, I. (2016). Nicotine and tobacco use prevention among youth and families. *Seminars in Oncology Nursing, 32*(3), 197–205. doi: 10.1016/j.soncn.2016.05.003

Pur Özyiğit, S. L., & Kılıçaslan. Z. (2009). *Sigara bırakmanın kalp hızı değişkenliği ve koroner akım üzerindeki etkileri.* Retrieved from http://nek.istanbul.edu.tr:4444/ekos/TEZ/45907.pdf

Rehan, V. K., Sakurai, R., & Torday, J. S. (2011). Thirdhand smoke: A new dimension to the effects of cigarette smoke on the developing lung. *American Journal of Physiology Lung Cellular and Molecular Physiology, 301*(1), L1–L8. doi: 10.1152/ajplung.00393.2010

Reis, R., Orak, D., Yilmaz, D., Cimen, H., & Sipahi, H. (2021). Modulation of cigarette smoke extract-induced human bronchial epithelial damage by eucalyptol and curcumin. *Human & Experimental Toxicology, 40*(9), 1445–1462. doi: 10.1177/0960327121997986

Reis, R., Kolci, K., Ozhan, Y., & Sipahi, H. (2022). Thirdhand smoke exacerbates $H_2O_2$ induced-oxidative response in human airway epithelial cells. *Society of Toxicology 61st Annual Meeting and ToxExpo, 343,* 27- 31 March 2022, San Diego, USA.

Richter, P., Pechacek, T., Swahn, M., & Wagman, V. (2008). Reducing levels of toxic chemicals in cigarette smoke: a new healthy people 2010 objective. *Public Health Reports, 123*(1), 30–38. doi: 10.1177/003335490812300105

Roberts, C., Wagler, G., & Carr, M. M. (2017). Environmental tobacco smoke: Public perception of risks of exposing children to second- and third-hand tobacco smoke. *Journal of Pediatric Health Care, 31*(1), e7–e13. doi: 10.1016/j.pedhc.2016.08.008

Sen, C. K., Gordillo, G. M., Roy, S., Kirsner, R., Lambert, L., Hunt, T. K., … Longaker, M. T. (2009). Human skin wounds: A major and snowballing threat to public health and the economy. *Wound Repair and Regeneration, 17*(6), 763–771. doi: 10.1111/j.1524-475X.2009.00543.x

Silverstein, P. (1992). Smoking and wound healing. *The American Journal of Medicine, 93*(1A), 22S–24S. doi: 10.1016/0002-9343(92)90623-j

Snijders, A. M., Zhou, M., Whitehead, T. P., Fitch, B., Pandey, P., Hechmer, A., … Kogan, S. C. (2021). *In utero* and early-life exposure to thirdhand smoke causes profound changes to the immune system. *Clinical Science, 135*(8), 1053–1063. doi: 10.1042/CS20201498

Stepanov, I., Yershova, K., Carmella, S., Upadhyaya, P., & Hecht, S. S. (2013). Levels of (S)-N′-nitrosonornicotine in U.S. tobacco products. *Nicotine and Tobacco Research, 15*(7), 1305–1310. doi: 10.1093/ntr/nts249

Umetsu, D. T., McIntire, J. J., Akbari, O., Macaubas, C., & DeKruyff, R. H. (2002). Asthma: An epidemic of dysregulated immunity. *Nature Immunology, 3*(8), 715–720. doi: 10.1038/ni0802-715

Vani, G., Anbarasi, K., & Shyamaladevi, C.S. (2015). Bacoside A: Role in cigarette smoking induced changes in brain. *Evidence-Based Complementary And Alternative Medicine (ECAM), 2015,* 286137. doi: 10.1155/2015/286137

Wannamethee, S. G., Shaper, A. G., Perry, I. J., & British Regional Heart Study. (2001). Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. *Diabetes Care, 24*(9), 1590–1595. doi: 10.2337/diacare.24.9.1590

Winickoff, J. P., Friebely, J., Tanski, S. E., Sherrod, C., Matt, G. E., Hovell, M. F., & McMillen, R. C. (2009). Beliefs about the health effects of "thirdhand" smoke and home smoking bans. *Pediatrics, 123*(1), e74–e79. doi: 10.1542/peds.2008-2184

Yaprak, E., Yolcubal, Sinanoğlu, A., Doğrul-Demiray, A., Guzeldemir-Akcakanat, E., & Marakoğlu, I. (2017). High levels of heavy metal accumulation in dental calculus of smokers: A pilot İnductively coupled plasma mass spectrometry study. *Journal of Periodontal Research, 52*(1), 83–88. doi: 10.1111/jre.12371

Yazdanparast, T., Hassanzadeh, H., Nasrollahi, S. A., Seyedmehdi, S. M., Jamaati, H., Naimian, A., … Firooz, A. (2019). Cigarettes smoking and skin: A comparison study of the biophysical properties of skin in smokers and non-smokers. *Tanaffos, 18*(2), 163–168. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32440305/

Yolton, K., Dietrich, K., Auinger, P., Lanphear, B. P., & Hornung, R. (2005). Exposure to environmental tobacco smoke and cognitive abilities among U.S. children and adolescents. *Environmental Health Perspectives, 113*(1), 98–103. doi: 10.1289/ehp.7210

Yu, M., Mukai, K., Tsai, M., & Galli, S. J. (2018). Thirdhand smoke component can exacerbate a mouse asthma model through mast cells. *Journal of Allergy and Clinical Immunology, 142*(5), 1618-1627.e9. doi: 10.1016/j.jaci.2018.04.001

Zeng, X., Xu, X., Qin, Q., Ye, K., Wu, W., & Huo, X. (2018). Heavy metal exposure has adverse effects on the growth and development of preschool children. *Environmental Geochemistry and Health, 41*(1), 309–321. doi: 10.1007/s10653-018-0114-z

Zong, D., Liu, X., Li, J., Ouyang, R., & Chen, P. (2019). The role of cigarette smoke-induced epigenetic alterations in inflammation. *Epigenetics and Chromatin, 12*(1), 65. doi: 10.1186/s13072-019-0311-8