INTRODUCTION

Cigarette smoking, an established etiological factor of mortality and morbidity around the globe, is a preventable epidemic. Development of a ‘smoking epidemic’ in a population can be defined in these stages: an initial rise of smoking prevalence and then a decline phase in its prevalence, followed by a similar trend in smoking-related diseases two to three decades later. The worldwide statistics projects that the number of smokers would rise to more than 1.6 billion by 2025. Numerous ill effects are reported both with active as well as passive smoking. Passive smoking, also called as involuntary smoking, otherwise known as secondhand smoke (SHS) occurs by the passive inhalation of environmental smoke which is a blend of the sidestream smoke (smoke released from the burning end of cigarette, pipe, or cigar) and the mainstream smoke exhaled from the lungs of smokers. Thirdhand smoke (THS) on the other hand is deposition and surface accretion of SHS, which gradually becomes more toxic with time.

Thirdhand smoke refers to the surface contamination produced by the emission of components in SHS and by products of their chemical transformations, and the off-gassing of volatile components into the atmosphere. It is defined by Matt et al. as residual tobacco smoke pollutants that remain on surfaces and in dust after tobacco has been smoked. Thus, THS, also called as aged tobacco smoke or residual SHS, could be either the tobacco residue or stale or aged secondhand smoke or both. This review gives an elaborated insight on the composition, sources, exposure and toxicity of THS along with its mitigation measures.
aromatic hydrocarbons (PAHs)\textsuperscript{12,13}. Incomplete pyrolysis of organic materials results in the production of PAHs\textsuperscript{10,14-16}. Around two-thirds of the PAHs in cigarette smoke are deposited onto surfaces in the environment\textsuperscript{16}. THS includes highly mutagenic and carcinogenic tobacco-specific nitrosamines (TSNAs) like nicotine-derived nitrosamine ketone (NNK), lethal metals, alkaloids like nicotine, general combustion products of organic materials (e.g. polycyclic aromatic hydrocarbons) and other unstable organic compounds (e.g. acrolein and other aldehydes). On chemical ageing, thirdhand smoke composition gets transformed with time and the compounds become more toxic. Moreover, nicotine, a contaminant in the original mixture of thirdhand smoke has the potential to react with general indoor contaminants to form supplementary lethal compounds. Additionally, nicotine reacts with nitrous acid, associated with outdoor or indoor sources, to produce NNK. When nicotine combines with ozone, the reaction generates secondary organic aerosols. Cotinine, formaldehyde, n-methyl-formamide, and nicotinaldehyde are other byproducts of this reaction. As the infusion of ozone into water (ozonation) is a common mode of management, organisms of THS mixture has the potential to react with general indoor contaminants to form supplementary lethal compounds.

Other than nicotine and tobacco specific nitrosamines, THS constituents identified include 3-ethenylpyridine (3- EP), phenol, cresols, formaldehyde, and naphthalene\textsuperscript{15}. The other constituents include hydrogen cyanide, toluene, butane, lethal metals like lead and arsenic, carbon monoxide gas, and traces of polonium-210 an extremely radioactive gas, and traces of polonium-210 an extremely radioactive carcinogen. The most troubling feature of TSNAs is their longevity once formed from burned cigarettes\textsuperscript{13}.

It is reported that there exists a close relationship between SHS and THS and are found to coexist in the initial period of THS formation in polluted indoors where smoking episodes take place\textsuperscript{5}. The primary exposure to SHS is inhalation whereas for THS it can be inhalation, dermal uptake or ingestion. In SHS, the exposure profile is high levels over short interval whereas that for THS is low levels over long periods\textsuperscript{14}. Total tobacco smoke exposure of an individual is the cumulative involuntary exposure to tobacco smoke pollutants during and after the time in which cigarettes are smoked\textsuperscript{4}.

The phrase ‘the four Rs’ provides a working definition of THS: tobacco chemicals (some toxic) remain, react, re-emit and/or are re-suspended long after active smoking ends\textsuperscript{7}. Another notable feature of THS is its potential for chemical ageing, wherein the residues adsorbed on the surface interact with atmospheric components leading to chemical transformations producing secondary toxic residues\textsuperscript{6}. The major factor influencing these aging processes and chemical reactions is the transport of pollutants between various indoor media. Tobacco smoke pollutants undergo simultaneous physicochemical transformations in a time span that varies from seconds to months, soon after their preliminary discharge during the smoking process\textsuperscript{5}.

**Sources of THS**

The prime source of THS exposure is indoor surfaces. This may include interiors of homes and apartments, buildings, office spaces and transportation systems. Even the cracks present in multi-unit residential plots transmit the pollutants, exposing non-smokers also to the ill-effects of these toxic components. This raises a considerable concern for those who are economically disadvantaged and dwell in low-cost public housing who smoke as a stress release mechanism\textsuperscript{6}. It is well noted that the indoor surfaces can represent an occult reservoir of THS ingredients that have the potential to be re-emitted long after the active smoking has ended\textsuperscript{5}.

In an enclosed environment, when cigarettes and similar tobacco products are repeatedly smoked over periods of months or years, a substantial mass of tobacco smoke pollutants emitted collects in dust, other available surfaces and in the materials of indoor areas. These pollutants react with oxidants and other composites in the environment, resulting in the production of secondary pollutants. The users/occupants of these contaminated spaces are exposed to unintentional and unnoticed tobacco smoke pollutants even after the cigarettes have been burnt out\textsuperscript{9}.

Apart from the indoor surfaces of house or closed rooms, the interiors of vehicles are a potential source of THS exposure. Even when the driver or passengers may not smoke inside a taxi, if they smoke before they enter the cab, the residual nicotine and chemicals from tobacco smoke might be introduced inside from their breath, skin or clothes. In spite of all the attempts to remove tobacco smoke by using fans or air conditioners or by opening windows, THS residue over time gathers on surfaces and resists normal cleansing activities. The relatively large surface areas of car interiors and the coverings used inside the cabs can absorb the pollutants, and remain as reservoirs of residual tobacco smoke pollutants\textsuperscript{17}.

Other than the enclosed environment, the hands, skin and clothes of a smoker can act as a potential source of THS pollutants. Studies have shown that PAH reservoir of one hand of a smoker represents 0.1% to 6% of that emitted from sidestream smoke\textsuperscript{18}. THS comprises smoke pollutants from tobacco products that remain in the environment and are re-emitted into the air or react with oxidants and other compounds from the environment to form secondary pollutants\textsuperscript{10,19}.

**Routes of exposure to THS**

The presence of THS in indoor surfaces and house hold items lead to multiple exposure routes. Inhalation, ingestion and dermal contact are the reported routes of exposure in human\textsuperscript{6,15}.

Young children may be extremely exposed through oral, dermal and nasal routes\textsuperscript{14,20,21}. The exposure through the
oral cavity is boosted in children by regular hand to mouth behaviors, dermal exposure by crawling and touching activities. Generally, the thickness of skin in children is less compared to adults so it paves a significant route. Inhalation exposures are boosted by their little stature and lively play close to the floor, where the house fine dust commonly accumulates, which later can be inhaled or absorbed through skin. Their close proximity with caregivers is yet another factor of concern. Younger children who stay close to caregivers who smoke are exposed both to SHS and THS.

Another factor that accounts for dermal absorption is the thin skin of children, which favors enhanced absorption of pollutants. The uptake levels of acrolein per unit of body mass is much higher than that of adults. The higher respiratory rate, presence of immature respiratory capacity and immune systems, and lower metabolic capacity are other factors enhancing absorption of THS constituents.

**Toxic effects of THS constituents on health**

Nicotine present in thirdhand smoke residue combines with common indoor air pollutants, like ozone and nitrous acid, to produce toxic and hazardous compounds. When it reacts nitrous acid, it forms carcinogenic tobacco-specific nitrosamines such as NNK and NNN. On reaction with ozone, additional harmful ultrafine particles are generated. The toxicity of THS is credited to its constituents like 4-(Methylnitrosamino)-4-(3-pyridyl)-butanal (NNN), and Tobacco Specific Nitrosamines (TSNA). These toxic compounds are responsible for multiple ill effects on health and well-being of the exposed individuals. The detrimental effects of THS on health are listed below.

**Increased risk of cancer**

The toxic constituents of THS pose an increased risk of carcinogenesis. The high-risk category includes infants who come in close contact with the skin of smokers or those who ingest 0.05 to 0.25 g of dust per day, including any PAHs adsorbed onto clothes or carpets. Various mechanisms have been attributed to the development of cancer. Chronic exposure of THS has been reported to cause DNA strand breaks and oxidative damage, leading to genetic damage and carcinogenic mutations. Another suggested cause is the production of DNA adducts, that play a pivotal role in smoking-induced mutagenesis and consequent carcinogenesis. In one study, it was found that NNK, a potent carcinogen, induced bulky DNA adducts in lungs of experimental animals rendering them prone to the development of pulmonary carcinoma. Oxidative stress to cells or organisms induced by the THS constituents is yet another suggested cause of disease-causing mutations and increased cancer risk.

**Effects on wound healing**

Animal studies have shown delayed wound healing in those who were exposed to THS. Also, the wounds were found to be conducive to reopening and more prone for heavy keratinization of epithelium. The associated reduction in wound strength was another notable feature. The possible explanations for impaired wound repair are listed below.

The high levels of oxidative stress and low levels of antioxidant activity in THS induced organisms could lead to tissue dysfunction by inducing protein nitration, lipid peroxidation and DNA damage. The THS exposed wounds showed higher levels of elastase enzyme suggesting degradation of elastin resulting in loss of wound plasticity and reopening of wounds.

**Effects on lungs**

Exposure of lungs to THS caused alveolar disruptions and presence of leucocyte infiltration especially macrophages, which is indicative of inflammation in respiratory bronchioles. NNAL components of THS could result in eventual damage to lung fibroblasts either due to cell death or reduced cell division, which could interrupt lung homeostasis leading to the development of pulmonary emphysema. NNAL, a metabolite of NNK, is considered as a risk indicator for pulmonary carcinogenesis.

**Effects on liver**

Animal studies showed disturbed liver functions with altered lipid profile and steatosis leading to increased risk of coronary thrombosis and stroke.

**Effects on brain**

It is also reported that higher concentrations of THS and acrolein affect neural stem adversely. A study has reported that THS extracts induced blebbing, vacuolization, cell fragmentation, severing of microfilaments and depolymerization of microtubules in mouse neural stem cells. It is also reported that higher concentrations of THS and acrolein result in dysfunction of melatonin secretion.

**Effects on metabolism**

Studies on animals showed elevated levels of fasting glucose which could be considered as a pre-diabetic condition.

**Effects on hormones**

In a study, THS-exposed mice showed multiple behavioral changes like increased anxiety, hyperactivity and stress. It was hypothesized that these changes could be induced due to the altered levels of hormones of the hypothalamus, pituitary, adrenal stress axis (HPA), and their precursors in THS exposed mice compared to their counterparts. These altered levels of hormones were associated with a secondary effect on insulin signaling and metabolism also, resulting in insulin resistance among exposed animals. It was also observed that THS exposure would induce abnormal DNA methylation, resulting in dysfunction of melatonin secretion.

**Effects on human behavior**

It is also likely that early age exposure to the nicotine could increase the risk of adopting smoking habit later in life.
Measurement of THS
Persistence of gas-phase nicotine levels serve as a good pool of sorbed nicotine in the contaminated settings. It is reported that levels of nicotine in dust and other surfaces are proportional to the persisting THS matter on indoor areas of the establishments. Also, nicotine present in dust signifies THS entrapped in house hold items like carpets, furniture, bed spreads, pillows, and curtains. The estimation of biomarkers of tobacco chemicals is of prime importance in identifying the health effects related to SHS and THS exposure. For a better estimation of the kind, degree and frequency of smoke exposure, biomonitoring of the chief nicotine biomarker, cotinine in urine, blood and saliva has been the suggested.

Generally, biomarker selection depends on available biological matrices and source of exposure. The gold standard biomarker of tobacco exposure is accepted to be cotinine. Simultaneous assessment of urinary cotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) permits a better characterization of SHS and THS exposure. The determination of NNK and NNN, the most concentrated TSNAs in the saliva and hairs biomatrices, can also be considered.

The 9-item tool, Beliefs About Third Hand Smoke (BATHS) scale, serves as an accepted valid and reliable tool to assess knowledge and beliefs about THS. It was developed based on the fact that beliefs about secondhand and thirdhand smoking influence the smoking behaviors and adoption of anti-smoking policies.

Management of THS
Public education and parental counselling
Creating awareness on the detrimental effects of THS among the public, especially parents and children, is one of the best methods to prevent the exposure to its toxic constituents. One of the recommendations put forward by the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) is to deliver healthcare education and counselling to parents on the ill effects of smoking, thereby reducing the exposure to SHS and THS. If the parents are well educated about the hazards of THS on children, they would definitely put efforts to establish smoke-free homes and cars for healthy upcoming generations. Healthcare professionals, especially those in pediatric settings could effectively deliver counselling to parents.

Public policy approaches
A legislative approach that can be undertaken in this regard is the formulation of a clear policy agenda that helps people protect themselves and their surroundings free of exposure to SHS and THS. Child healthcare professionals are the best suitable personnel to advocate for these legislative actions.

Healthcare settings
It is advised to screen for tobacco smoke exposure in healthcare settings to avoid unnecessary exposure to tobacco smoke by the patients. The development and implementation of electronic medical record systems which permit documentation of the smoking status of household members and screening facilities, will help to address the issue to a certain extent.

Topic incorporation in academic curricula
As this topic is a burning issue, it needs to be informed to all sections of the society. As a basic step, it is recommended to incorporate from grassroots level, by including in school curriculum its adverse effects and consequences. Also, since health professionals are in a better position to deliver counselling on SHS and THS, implementation of continuing medical education programs for health professionals and e-learning courses in medical education could be more effective.

Preventing the exposure
The first and foremost measure to prevent exposure is to quit the habit and encourage others also to follow a healthy lifestyle. In this regard, motivating the smokers to quit the habit to create smoke-free environments should be adopted. There exist no safe levels for SHS and THS. The various practices employed by smokers, like smoking in a different room, using fans to draw out the smoke, or utilizing ventilation, do not help to prevent the exposure to THS by those visiting these spaces.

Remediation, the removal of THS residue from surfaces in indoor environments or the safe containment of THS, is an important aspect to be considered. Remediation methods are based on the degree of contamination as well as the type of reservoir material. The adsorption, absorption, retention and re-emission capacity of materials commonly found indoors vary widely. Removal of TSNAs from contaminated surfaces such as human skin and hairs as well as indoor surfaces is more difficult than simply cleaning or washing with detergent and water. It is a fact that getting rid of THS pollutants accumulated on carpets is nearly impossible. The ventilation and air cleaning systems are found to be ineffective in averting exposure to THS pollutants. In this scenario, the only possible practical method to avoid non-smokers’ exposure to passive smoking is to stick to the policy of overall prevention of active smoking in enclosed spaces and encouraging people to adopt healthy life styles.

In certain countries, restoration services are provided by companies for spaces affected by tobacco smoke. Generally, the measures taken include removal of grossly affected materials like carpets and clothes or use of liquid cleaners especially ammonia-based cleaners to remove tobacco odors in rooms. Certain restoration companies make use of ozone generators to get rid of intense tobacco odors.

CONCLUSION
Thirdhand smoke could pose potential health risks to continuously exposed individuals. The best practical way to save ourselves and the next generation from its side...
effects is to adopt the policy of total ban on smoking in indoor places. Even though active and passive smoking is well known to all, a majority of the general population is unaware of the concept and consequence of thirdhand smoke. Education of the public utilizing social media could help us to serve the purpose to an extent. As its ill effects pose grave consequences to all age groups, the topic needs to be considered with much more gravity by the authorities.

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