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Thirdhand Tobacco Smoke: Emerging Evidence and Arguments for a Multidisciplinary Research Agenda

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Abstract

Background: While there is broad consensus regarding the health impact of tobacco use and secondhand smoke exposure, considerable ambiguity exists about the nature and consequences of thirdhand smoke (THS).

Objectives: We introduce definitions of THS and THS exposure and review recent findings about (a) constituents, indoor sorption-desorption dynamics, and transformations of THS, (b) distribution and persistence of THS in residential settings, (c) implications for pathways of exposure, (d) potential clinical significance and health effects, and (e) behavioral and policy issues that affect and are affected by THS.

Discussion: Physical and chemical transformations of tobacco smoke pollutants take place over timescales ranging from seconds to months and include the creation of secondary pollutants (e.g., tobacco-specific nitrosamines). THS persists in real-world residential settings in the air, dust, and surfaces, and is associated with elevated levels of nicotine on hands and cotinine in urine of nonsmokers residing in former smoker homes. Much still needs to be learned about the chemistry, exposure, toxicology, health risks, and policy implications.

Conclusion: The existing evidence provides strong support for pursuing a programmatic research agenda on THS to close gaps in our current understanding of the chemistry, exposure, toxicology, health effects, as well as behavioral, economic, and socio-cultural considerations and consequences of THS. Such a research agenda is necessary to illuminate the role of THS in existing and future tobacco control efforts to decrease smoking initiation and smoking levels, to increase cessation attempts and sustained

cessation, and to reduce the cumulative effects of tobacco use on morbidity and mortality.

Short running title:

Thirdhand Tobacco Smoke

Key words:

Aggregate exposures, biomarkers, cumulative exposure, exposure, housing, nicotine, policy, secondhand smoke, tobacco smoke

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Abbreviations:

THS	Thirdhand smoke
SHS	Secondhand smoke
PAH	polycyclic aromatic hydrocarbon
3-EP	3-ethenylpyridine
VOC	volatile organic compound
SVOC	semivolatile organic compound
TSNA	tobacco specific nitrosamine

NNA	1-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridinyl)-4-butanal
NNK	4-(methylnitrosamino)-1-(3-pyridinyl)-1-butanone
NNN	*N*-nitroso nornicotine

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Introduction

This manuscript aims to clarify ambiguities and misunderstandings in the scientific community regarding thirdhand smoke (THS), also known as residual or aged tobacco smoke. The significance of THS in the broader context of tobacco control efforts and its specific role in causing, contributing, moderating, or mediating tobacco-related illnesses has been questioned. To paraphrase one anonymous reviewer of an earlier manuscript on THS: "THS is probably no more than a trivial nuisance, no worse than spilled coffee." This skepticism is in contrast to the positions taken by the public health community on issues of tobacco control in general and involuntary exposure to tobacco smoke in particular. The 2006 U.S. Surgeon General Report on the health consequences of involuntary exposure to tobacco smoke concluded: "The scientific evidence indicates that there is no risk-free level of exposure to secondhand smoke." (p. 11)(U.S. Department of Health and Human Services 2006). If decades of scientific research support the conclusion that there is no risk-free level of exposure to the potent mixture of carcinogens, irritants, and other toxins in secondhand smoke (SHS), the composition, prevalence, and distribution of THS and the acute and cumulative exposure to those compounds among nonsmokers should be examined before we declare THS pollution and exposure a mere nuisance. We must better understand the role of THS exposure of people, particularly children, to tobacco smoke components and the implications of this exposure for disease mechanisms and their moderators and the THS-related acute and long-term risks of disease and premature mortality. Finally, we should consider the degree to which such understanding can inform and perhaps transform tobacco control policies, allowing nonsmokers, their families, and the public generally to make more

informed decisions about living in THS polluted environments, and to help smokers to more fully understand the risks their smoking brings to others. Perhaps, improved understanding of THS, the associated risks to nonsmokers, stricter norms and attitudes, and economic and social contingencies will motivate nonsmokers not to start and prompt addicted smokers to quit. We propose that the "bench to bedside to population" approach of translational research will be useful in guiding research on THS and in fostering translation of findings to protect public health (National Institutes of Health 2009).

This paper reviews the emerging evidence on THS and outlines the case for an interdisciplinary research effort. The existing evidence provides strong support for pursuing a programmatic research agenda on THS to fill important gaps in our current understanding of the short and long-term effects of involuntary exposure to tobacco smoke. We begin with brief definitions of THS and THS exposure. We then present a review of recent findings on the chemistry of THS, its persistence in indoor environments, implications for pathways of exposure and health effects, and behavioral and policy issues that affect and are affected by THS. We conclude with recommendations for interdisciplinary research efforts to address the gap in knowledge of the biological mechanisms of toxicity on cellular and molecular levels, as well as relevant behavioral, economic, and socio-cultural considerations and consequences.

What is Thirdhand Smoke and how is it different from Secondhand Smoke?

SHS is a mixture of the sidestream smoke (i.e., smoke emitted from the burning cigarette, pipe, or cigar) and the mainstream smoke exhaled from the lungs of smokers. SHS contains more than 4,000 chemicals, many of which are known or suspected to

contribute to adverse health effects. These include ammonia, acrolein, carbon monoxide, formaldehyde, hydrogen cyanide, nicotine, nitrogen oxides, polycyclic aromatic hydrocarbons (PAHs), sulfur dioxide and more that are eye and respiratory irritants, mutagens, carcinogens, cardiovascular and reproductive toxicants. (U.S. Department of Health and Human Services 2006)

THS consists of residual tobacco smoke pollutants that (1) ***remain*** on surfaces and in dust after tobacco has been smoked, or (2) are ***re-emitted*** back into the gas phase, or (3) ***react*** with oxidants and other compounds in the environment to yield secondary pollutants. The processes of formation of THS are illustrated in Figure 1. The constituents of THS that have been identified so far include nicotine, 3-ethenylpyridine (3-EP), phenol, cresols, naphthalene, formaldehyde, and tobacco-specific nitrosamines (some absent in freshly emitted tobacco smoke). (Destaillats et al. 2006; Sleiman et al. 2010a; Singer et al. 2002; Singer et al. 2003; Singer et al. 2004)

SHS exposure results from the involuntary inhalation of sidestream and exhaled mainstream smoke. In contrast, *THS exposure* results from the involuntary inhalation, ingestion, or dermal uptake of THS pollutants in the air, in dust, and on surfaces. It includes inhalation exposure to compounds re-emitted into the air from indoor surfaces and particles re-suspended from deposits, and dermal and ingestion exposure to compounds partially derived from cigarette smoke and resulting particles that have settled, deposited, and accumulated on surfaces.

Although the term THS is relatively new (Szabo 2006; New York Times 2009), the chemical aging of tobacco smoke, evidence it leaves behind in indoor environments (e.g., cigarette butts, unpleasant odor, smelly clothes), and its aversive impact on

nonsmokers have long been recognized. We favor the term thirdhand smoke compared to alternative terms, such as aged tobacco smoke or residual secondhand smoke, to stress that THS is the legacy of tobacco smoke, evolves from SHS, and – similar to SHS – leads to involuntary exposure to tobacco smoke pollutants. While it is important to distinguish SHS from THS because of significant chemical, toxicological, and behavioral differences, SHS and THS are closely related and co-exist during the early period of THS formation and in contaminated environments in which smoking takes place episodically.

Based on our definitions of SHS and THS, *total tobacco smoke exposure* is the cumulative involuntary exposure to tobacco smoke pollutants during and after the time in which cigarettes are smoked. The exposure risk does not end when a cigarette has been extinguished and may persist in the absence of further smoking, because THS pollutants, trapped and deposited on surfaces and in dust, persist in environments in which smoking took place at some earlier points in time.

Constituents, Sorption-Desorption Dynamics, and Transformations of THS

Some of the pollutants present in SHS remain principally in the gas phase and can be removed by ventilation, but a significant fraction associates with indoor surfaces and has much longer residence times. Complex physicochemical transformations of those compounds take place after smoking (i.e., aging*)* that impact both short and long term exposure patterns of nonsmokers. Aging processes include chemical reactions of residual components of tobacco smoke deposited on indoor surfaces. They also include pollutant transport between different indoor media, for example the deposition into "deep" reservoirs such as the gypsum core of wallboard panels. Physical and chemical

transformations of tobacco smoke pollutants take place simultaneously, over timescales that range from a few seconds to several weeks or months after their initial release during smoking. During an initial period of up to a few hours immediately after smoking, SHS and THS exposure co-exist, with the latter becoming predominant once SHS is removed by ventilation.

Indoor sorption and desorption dynamics

Indoor surface-to-volume ratios are often in the range 1 – 10 m^2/m^3, which are much larger than typical outdoor ratios (Knutson et al. 1992). Partitioning of volatile and semivolatile organic compounds (VOCs and SVOCs) to surfaces is a key mediator of human exposure to indoor pollutants. Building materials and furnishings often operate as sinks, reservoirs or sources for these chemicals. The affinity of a VOC to building products (such as carpet, gypsum board, upholstery, flooring material and acoustic tiles), is inversely proportional to the compound's vapor pressure and is affected by specific molecular interactions and competition with water vapor (Won et al. 2001). Tobacco smoke contains both VOCs and SVOCs; the latter partition between aerosol particles and the gas phase according to Junge-Pankow model predictions (Liang and Pankow 1996; Pankow et al. 1994). Partitioning must include the indoor materials, as described by Weschler and Nazaroff (Weschler and Nazaroff 2010; Weschler and Nazaroff 2008). Nicotine is one of the major SVOCs, released in large amounts during smoking (1 – 3 mg/cigarette) (Singer et al. 2003). Other authors have reported higher amounts; e.g., the 1999 Massachusetts Benchmark Study reported nicotine levels in sidestream smoke ranging from 2.2-5.3 mg/cigarette depending on cigarette brand (Borgerding et al. 2000). Nicotine room-temperature vapor pressure (0.04 mmHg) is

between three and four orders of magnitude lower than that of indoor VOCs such as toluene (22 mmHg) or benzene (100 mmHg).

Sorption and desorption have been monitored in realistic settings by carrying out experiments in real indoor environments or in room-sized environmental chambers. In studies performed in a room-sized 50-m^3 chamber furnished with typical materials (wallboard, carpet, draperies and furniture), tobacco smoke was generated by machine-smoking following regular smoking (Singer et al. 2002; Singer et al. 2003). Emission factors have been determined for short term (1 day) and long term (1 month) periods for 26 gas-phase organic compounds present in tobacco smoke. The analytes included volatile aldehydes (formaldehyde, acrolein), aromatic hydrocarbons (benzene, toluene, naphthalene), nicotine and tobacco-related amines (pyridine, 3-ethenylpyridine). The emission factor of each individual compound was influenced by sorption and re-emission from indoor surfaces and materials. For each analyte, sorptive losses were found to be highest at the highest level of furnishing (i.e., when more effective surface area was available) and for lower ventilation rates (i.e., higher residence times). Losses were more marked for the less volatile chemicals, and they were particularly remarkable for nicotine. In a month-long cyclic smoking study, after an initial accumulation period of ~10 days, re-emission of accumulated nicotine in indoor surfaces became a source of equal strength to smoking (Singer et al. 2003). In subsequent experiments using the same chamber (Singer et al. 2004), pure chemicals were released by flash-evaporation and allowed to partition between gas phase and indoor surfaces. Several tobacco smoke constituents (nicotine, ethenylpyridine, methyl naphthalenes, *o*-cresol) exhibited largely sorptive behavior, and nicotine had the highest affinity for surfaces. Nicotine was

almost completely removed from the gas phase and deposited on indoor surfaces, while most other chemicals showed more moderate partitioning behavior. The extreme sorptive tendency of nicotine implies that indoor surfaces in environments where smoking is habitual can be loaded with large amounts of this alkaloid. As a direct consequence of its sorptivity, re-emission of nicotine from indoor surfaces continues long after smoking ceases.

Spectroscopic evidence suggests that amines adsorb predominantly in a protonated state in the presence of moisture (Destaillats et al. 2007; Ongwandee et al. 2007). Sorptive interactions of nicotine and other tobacco alkaloids are strongly influenced by the presence of other common airborne acids and bases, such as CO_2 and NH_3, respectively, that are often present at high concentrations indoors. In bench-scale studies, the sorptive capacity of common materials such as carpet and wallboard towards trimethylamine, a model amine, increased in the presence of CO_2, and decreased in the presence of NH_3 as a consequence of the enhancing protonation capacity of CO_2 (acid) and the competition with NH_3 (base) (Ongwandee and Morrison 2008; Ongwandee et al. 2005).

Indoor chemical transformations

Reactions driven by oxygenated and nitrogenated atmospheric species are the source of indoor secondary pollutants of potential toxicological relevance (Morrison 2008). A recent study identified the formation of carcinogenic tobacco specific nitrosamines (TSNAs) from the reaction of adsorbed nicotine with nitrous acid (HONO) (Sleiman et al. 2010a). HONO is typically produced indoors by combustion sources and heterogeneous conversion of atmospheric nitrogen oxides. Nicotine adsorbed to a

model surface showed high reactivity towards HONO, leading to the formation of three TSNAs: 1-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridinyl)-4-butanal (NNA), 4-(methylnitrosamino)-1-(3-pyridinyl)-1-butanone (NNK) and *N*-nitroso nornicotine (NNN). The structures of these compounds as well as their mechanisms of formation are shown in Figure 2. NNA, which is not present in freshly emitted tobacco smoke, was the most predominant TSNA. Due to their low vapor pressures, these TSNAs are likely associated with indoor surfaces and dust. In addition to TSNAs, nitrosation of nicotine generated low levels of *N*-nitrosopyrrolidine (a carcinogenic volatile nitrosamine) and various other multifunctional byproducts.

Ozone and related atmospheric oxidants (hydroxyl radical and H_2O_2) may generate oxidized products by reaction with some of the tobacco smoke components that remain sorbed to indoor surfaces. Thus, some of the respiratory symptoms associated with tobacco smoke may originate, not from directly emitted air pollutants, but from volatile byproducts that have low thresholds for eye, skin, and upper respiratory tract irritation (Destaillats et al. 2006; Singer et al. 2006).

The atmospheric lifetime of ozone is long enough to allow for its transport to the indoor environment, where it reacts at rates that are often higher than typical ventilation removal rates leading to typical indoor/outdoor (I/O) ratios between 0.2 and 0.7 (Weschler 2000). Typical indoor ozone levels in most settings are ≤ 20 ppbv. However, much higher ozone levels may be generated using devices marketed as “air purifiers” often used to remove tobacco odors (Hubbard et al. 2005; Boeniger 1995).

The reaction of ozone with VOCs emitted during smoking was studied in a room-sized chamber (Shaughnesy et al. 2001). Ozone reacted rapidly with unsaturated

VOCs, such as isoprene, pyrrole and styrene, but was relatively inert towards aromatic hydrocarbons. The main byproducts were volatile aldehydes, which included formaldehyde, acetaldehyde and benzaldehyde. While amine ozonation is typically slow in the gas phase, sorption of nicotine to indoor surfaces can extend its indoor residence time and make it more available for ozonation(Petrick et al. 2010). The reactivity of nicotine sorbed to model surfaces towards ozone was evaluated in laboratory experiments, observing the formation of formaldehyde, N-methyl formamide, myosmine, ethyl pyridyl ketone, nicotinaldehyde and cotinine, which were re-emitted into the gas phase (Destaillats et al. 2006). Ozone reactions with nicotine or with SHS also formed ultrafine particles as shown in Figure 3, in which several multifunctional oxidized species with high asthma hazard index (AHI) values were identified (Sleiman et al. 2010b). Figure 4 illustrates the molecular structures of the identified nicotine oxidation byproducts and their pathways of formation.

Prevalence and Persistence of THS in Real-World Indoor Environments

The chemistry and physics of tobacco combustion in indoor environments suggest that some gas- and particle-phase THS compounds can remain for extended periods in all indoor environments in which tobacco smoke has been produced (Destaillats et al. 2006; Singer et al. 2002; Singer et al. 2004; Destaillats et al. 2007; Matt et al. 2004; Matt et al. 2008a; Matt et al. 2011). The persistence of THS in real-world residential settings has been demonstrated based on nicotine concentrations in air, dust, and surfaces, in the days, weeks, and months after the last smoking has taken place. Further support comes from quantitative measurements of ultrafine tobacco smoke

particles that were resuspended after their deposition on household surfaces (Becquemin et al. 2010).

Increased and/or persistent gas-phase air nicotine levels are indicative of a reservoir of sorbed nicotine in these environments. Nicotine levels in dust and on surfaces are proportional to THS matter that has deposited and accumulated on indoor surfaces, including coffee tables, bed frames, cabinets, doors, and walls. Nicotine in dust also represents THS that is trapped in carpets, upholstery, curtains, pillows, mattresses, and the like. In addition, PAHs, known human carcinogens associated with tobacco smoke and other combustion sources, have been demonstrated to pollute house dust from homes of smokers (Wittry et al. 2010). Hein et al. (1991) were the first to report elevated levels of nicotine house dust collected in homes of smokers and its positive association with smoking level. Nicotine has also been found to contaminate private homes of smokers with home smoking bans (Matt et al. 2004) and homes of nonsmokers formerly occupied by smokers (Matt et al. 2011).

The automobile cabin is another enclosed microenvironment with a high surface-to-volume ratio, where sorption of tobacco pollutants may lead to long-term contamination and substantial exposure of nonsmokers. In a recent study, cars of smokers who did not impose smoking bans exhibited high levels of nicotine on surfaces such as dashboards, in dust and in cabin air, with mean values of 8.6 μg m^{-2}, 19.5 μg g^{-1} and 740 ng m^{-3}, respectively. These values were measured several hours or days after smoking took place, and were significantly higher than those from cars where smoking bans were implemented, and from cars belonging to non-smokers (Matt et al. 2008a). Nicotine also remained in used cars sold by smokers with and without car smoking

bans, and rental cars (Matt et al. 2008a). Fortmann et al. (2010) found that smokers can lower THS contamination of their cars by reducing or ceasing smoking; however, commonly used cleaning and ventilation methods were unsuccessful.

Implications for Exposure

The presence of THS compounds in the air, in dust, and on surfaces of indoor environments creates potential exposure routes through inhalation, ingestion, and dermal transfer. These pathways are likely to be relevant for children living in homes in which adults smoke, even if smoking occurs at times or in rooms when no children are present. Infants and young children are likely to be more at risk of THS exposure than adults because they typically spend more time indoors, are in closer proximity to and engage in greater activity in areas where dust collects and may be resuspended (e.g., carpets on the floor), and they insert nonfood items in their mouths more frequently than adults (U.S. Environmental Protection Agency 2008). Infants and young children have been estimated to be 100 times more sensitive than adults to pollutants in house dust due to such factors as increased respiration relative to body size and immature metabolic capacity (Roberts et al. 2009). For other environmental toxicants such as lead, pesticides, allergens, endotoxins and flame retardants, house dust has been reported to be the main route of exposure for infants and young children (U.S. Environmental Protection Agency 2008, 1997). Homes of smokers that contain young children present an on-going risk of THS exposure to the children, and the risk adds to SHS exposure they already receive when around a smoking adult. In addition, involuntary exposure of children of non-smokers may occur when they unknowingly come in contact with THS in a polluted environment.

Indoor environments that frequently change ownership or occupancy present the highest risk of involuntary exposure to THS pollution for occupants. Such environments include rental apartments, condominiums and houses, hotel rooms, and rental and used cars. The increased risk of THS exposure in these environments is the result of two factors. First, these environments are often private spaces in which public smoking bans do not apply or private smoking bans are poorly implemented or monitored. Second, because smoking prevalence among adults is 10-25% in the U.S. (Utah: 9.8%; Kentucky, West Virginia: 25.6%; (Centers for Disease Control and Prevention 2010)), the probability that one or more smokers occupied and smoked in these environments is high. After only 5 occupancies, the probability that among those were one or more smokers is 41% given a smoking prevalence of 0.10 and 76% given a prevalence of 0.25.

Although much THS appears to be stored in dust and on surfaces in a polluted environment, THS is not constrained to the physical space in which tobacco was smoked. Recognizable as stale tobacco smoke, THS is trapped on the clothes on smokers and nonsmokers who were exposed to SHS. Most importantly, THS is detectable on the hands of smokers beyond the environment in which they smoked (Matt et al. 2004; Matt et al. 2011), and they may spread THS pollutants to other persons (e.g., their infants) and other objects (e.g., toys, food).

When nonsmokers touch polluted surfaces in smoking environments, they sample pollutants via their hands. Matt and colleagues recently demonstrated that THS is detectable in dust and on surfaces of former smoker apartments and on the hands of

nonsmokers who moved into former smoker apartment more than two months after smokers moved out (Matt et al. 2011).

THS is a special concern in multi-unit housing where smoking is permitted (Kraev et al. 2009). Tobacco smoke can move along air ducts, through wall and floor cracks, through elevator shafts, and along plumbing and electrical routes to contaminate units on other floors far removed from the smoking area (Spengler 1999). Tobacco smoke exposure in public housing is particularly troubling because it afflicts disadvantaged and vulnerable populations (Winickoff et al. 2009). In 2008-09, 32% of households in public housing included elderly persons, 35% disabled persons, and 41% children (U.S. Department of Housing and Urban Development 2010). Children who live in multi-unit housing apartments where their parents do not allow smoking have 140% higher blood cotinine levels than children who live in detached housing (Wilson et al. 2011).

In summary, the available evidence on THS pollution of indoor environments shows that it is ubiquitous and pervasive wherever tobacco has been smoked. Its presence in air, dust, and surfaces allows for multiple exposure routes, and THS creates special risks for nonsmokers spending time indoors in environments in proximity to polluted surfaces, especially infants and children, due to their increased exposure and increased sensitivity, persons with limited mobility, and populations spending time in multi-unit housing and spaces with frequent changes in occupancy.

Potential Clinical Significance and Public Health Implications of THS

It is currently premature to assess the independent health risks of THS because of the lack of evidence on clinical outcomes. Characterization of the health risks attributable to THS will depend on applying new knowledge from cell and molecular

biology, conducting clinical trials (e.g. randomized trials of health outcomes as a consequence of reduced exposure) and gathering objective evidence of THS contamination and biomarkers confirming individual exposure and relating these data to outcomes (e.g., morbidity or premature mortality associated with THS). Clinical significance, however, must take into account the impact of THS in the broader context of tobacco control efforts to prevent and reduce smoking behavior.

Potential Health Risks

THS exposes people to mixtures of chemical compounds in gas- and particulate-phase that are similar to those contained in mainstream smoke and SHS, as well as to additional products of surface reactions involving tobacco smoke constituents. Because THS and SHS differ in the composition and distribution of pollutants and in exposure profiles, a simple quantitative comparison of pollutant concentrations is not possible. For instance, air nicotine levels of indoor environments in which active smoking takes place are excellent markers of SHS pollution and correlate well with SHS exposure as measured by urine cotinine levels (Jaakkola and Jaakkola 1997). Air nicotine levels, however, are likely to be not the best indicator of THS pollution, and pollutant levels of nicotine and other compounds on surfaces and in dust must also be considered. Urine cotinine levels are likely to underestimate exposure to THS from sources other than nicotine, including those that deposit on surfaces and in dust in proportions independent of or negatively correlated with nicotine.

Compared to SHS and active smoking, the existing evidence suggests that exposure to THS involves very different time profiles of exposure (i.e., low-level, long periods, cumulative vs. repeated, short intervals, peak levels), different pollutant

concentrations in different media (i.e., surfaces and dust vs. primarily air), and different relative contributions of exposure routes (i.e., inhalation vs. dermal vs. ingestion) (Jaakkola and Jaakkola 1997). Consequently, health risks of THS may include some of those of SHS and active smoking as well as new ones not yet directly associated with tobacco smoke.

Human exposure to constituents of THS has not been well characterized, and it is, therefore, premature to assess the health risk of THS. Given this caveat, one can consider how some of the known THS components could affect human health. The chemicals that mediate adverse health consequences can be considered in categories such as particles, volatile organic chemicals, oxidants, carcinogens (e.g., TSNAs, PAHs), and nicotine.

Nicotine is known to play multiple roles in carcinogenesis through inhibition of apoptosis and cell proliferation (Wright et al. 1993; Zhou et al. 2010; Catassi et al. 2008). It is known to affect oxidative stress and to have adverse effects on brain and lung development in children (Zhou et al. 2010). Nicotine may have adverse effects on vascular function and might promote inflammation (Wittebole et al. 2007). As discussed earlier, a major concern is now how nicotine and other compounds are transformed into new toxicants (Sleiman et al. 2010a; Sleiman et al. 2010b).

An important question is how many of the known carcinogens identified by IARC that are found in mainstream and sidestream smoke are continuously and intermittently present in THS (International Agency for Research on Cancer 2004). TSNAs, such as NNK, are potent lung carcinogens, and some TSNAs form from nicotine on indoor surfaces through chemical reactions with ambient nitrous acid (Hecht 2003). See Burton

(2011) for an initial effort to quantify the potential exposure to NNA and NNK via dermal transfer. PAHs in tobacco smoke, particularly benzo[*a*]pyrene, are also carcinogenic (International Agency for Research on Cancer 2004). Particles and oxidant gases produce free radical species (ROS) and oxidant injury that can promote inflammation, affect immune function and can activate thrombotic mechanisms (van Eeden et al. 2005; Hamade et al. 2008). Oxidant and irritant gases can trigger allergic symptoms and asthma (Dworski 2000).

Comprehensive assessment of risks of THS will require characterization of levels of THS constituents in the environment, analysis of their cytotoxicity and genotoxicity in vitro and in animal models, measurement of human exposure based on validated biomarkers, and, eventually, epidemiologic studies of the association of THS exposure with morbidity and mortality.

Risk assessment will require the development of biomarkers of THS exposure. A logical initial focus for a selective biomarker might be metabolites of NNA, because it is the major TSNA formed from the reaction of nicotine and nitrous acid, and has not been found in tobacco smoke. Likely metabolites are *iso*-NNAL (1-(N-methyl-N-nitrosamino)-1-(3-pyridinyl)-4-butanol) and iso-NNAC (4-(N-methyl-N-nitrosamino)-4-(3-pyridinyl)-butanoic acid) which might be measurable in urine. NNA or other substances derived from it might be suitable as markers of THS in dust or surfaces.

Risk assessments will benefit from careful consideration of sensitive populations (e.g., young children, medically compromised persons) and at-risk environments (e.g., low-income housing and used cars). Because of the immature stage of their biological and behavioral development, the level of exposure and health risks are likely to be

greatest for young children who are in direct contact with polluted surfaces and house dust.

Broader Clinical and Public Health Consequences of THS on Tobacco Control Efforts

Even though THS is a dynamic mixture of chemical compounds, it is important to remember that it is a consequence of smoking behavior, a modifiable human activity with well-understood harmful health outcomes. It is in this context that public awareness of THS, aversion to stale tobacco odor, and beliefs about THS take on clinical significance beyond any specific health effects of THS still to be demonstrated. For instance, knowledge about THS could be used clinically to increase smoke-free home and car policies and to promote cessation. In the first study on attitudes about THS, controlling for known confounders including SHS beliefs, respondents were asked whether they agreed that "smoking in a room today could cause harm to infants and children tomorrow". Those who agreed were more than twice as likely to have a strict home smoking ban than those who disagreed with that statement. Importantly, those who had uncertainty about the harm were also more likely to have a strict home smoking ban (Winickoff et al. 2009).

Policy implications of THS for Overall Tobacco Control

While it is premature to formulate public policies in response to potential THS health risks, it is important to note that numerous voluntary private policies have emerged over the past 10 years targeting THS. Major international, national, and local hotels (e.g., Marriot, Westin) and car rental companies (e.g., Avis, Hertz, Enterprise) have adopted complete or partial nonsmoking bans to protect nonsmokers from the effects of lingering tobacco smoke. These policies grew out of complaints and concerns

about unpleasant odor, respiratory symptoms, and eye irritation among hotel guests and customers of rental cars. Similar consumer preferences for smoke-free environments are also noticeable in the used car and real estate markets. Research conducted in Southern California markets has shown that used cars of smokers were valued at 8-9% less than equivalent nonsmoker cars (Matt et al. 2008b), and rental apartments remained vacant longer and required higher maintenance costs (Matt et al. 2011) when they were occupied by smokers rather than nonsmokers.

In the absence of definitive scientific evidence on health risks of THS, how did these policies and consumer preferences develop? We believe that the distinct unpleasant odor of stale tobacco smoke and acute respiratory and eye symptoms played a critical role, alerting consumers to a tobacco-polluted environment. This explanation is consistent with Junker et al's findings (Junker et al. 2001), demonstrating odor detection thresholds lower by three or more orders of magnitude than previously suggested for acceptable indoor conditions (>19,000 m^3/cigarette). Eye and nasal irritations were observed at levels one order of magnitude lower than previously thought, corresponding to a fresh air dilution volume of >3,000 m^3/cigarette. For comparison, a 1,000 sq ft apartment in the U.S. has a volume of less than 300 m^3. The practical significance of odor thresholds is captured by a popular saying in the real estate and use car markets: "If you can smell it, you can't sell it".

Odor thresholds and health symptoms by themselves, however, do not explain the recent emergence of THS policies and market place responses. We believe that consumer knowledge of the health effects of tobacco use, changing norms, expectations, and attitudes to tobacco smoke exposure empowered consumers to

express their dislike, request a nonsmoking hotel room, ask for repairs and cleaning, and negotiate a lower price. Such a market place response to consumer demands shows that when the norm and expectation are a smoke-free apartment, hotel room, or car, it is not only desirable but also profitable for private businesses to establish smoke-free policies.

While the emergence of smoke-free policies in the private sector appears to be a response to consumer demand, norms, and expectations, their success in protecting nonsmokers is not at all certain. Whereas voluntary policies do not follow common standards for detecting THS pollutants, training employees, monitoring implementation, and enforcing compliance, public policies can introduce shared standards and direct attention to the neediest instead of the noisiest. While consumer complaints about THS and demand for smoke-free environments provide an excellent starting point, we currently lack full understanding of how to promote or temper cultural demands for protection from THS exposure. We lack coordinated efforts to educate, reinforce, and strengthen norms toward establishing and maintaining 100% smoke-free environments, should the toxicology and epidemiology justify such action. This is where public health policies regarding THS can emerge as an extension of current efforts to protect vulnerable nonsmokers from SHS as part of a coordinating tobacco control strategy toward completely smoke-free environments.

Recommendations for an interdisciplinary research agenda on THS

The following summarizes directions and recommendations for an interdisciplinary research agenda on THS. Consistent with the risk assessment framework introduced by the National Research Council(National Research Council 2009), the proposed

agenda addresses issues surrounding hazard identification, dose-response assessment, exposure assessment, and risk characterization. We propose, however, to go beyond assessing the unique adverse health effects of THS components and to consider the role of THS as part of a broader tobacco control strategy. The goal of this programmatic agenda is to connect basic and applied research on risk assessment with research to prevent and reduce tobacco use, exposure to tobacco smoke pollutants, and tobacco-induced diseases.

Chemistry of THS

While there is a considerable body of research on the chemistry of main and side-stream tobacco smoke and the agents that cause tobacco-induced diseases, there is, however, much to be learned about the formation of new compounds by THS components through aging and interaction with environmental oxidants such as ozone, oxides of nitrogen and related compounds from both outdoor and indoor sources, and their relative proportion over the aging period. Importantly, these processes need to be studied over the time scale of days, weeks, and months in the presence and the absence of further smoking. The following research needs arise from the work to date: seem particularly relevant to us.

- Characterize as completely as possible the chemistry of THS; identify toxic and potentially toxic substances; examine how THS differs from SHS.
- Identify mechanisms of THS formation, reactive species, and reaction pathways.
- Examine how THS deposits and accumulates in dust, surfaces, and air, and how chemical mechanisms compare in these different media.

- Explore the interaction of THS with environmental oxidants such as air pollution, and continued smoking through controlled lab studies and observational field studies of THS in actual indoor environments with typical smoking, cleaning, ventilation, and use patterns.
- Develop, test, and validate tracers of THS pollutants at different stages of aging (e.g., NNA) and for different media (dust, surface, air).

Exposure Assessment

The assessment of exposure to THS has to consider (a) smoking behavior that generates tobacco smoke, (b) the environment that becomes contaminated with tobacco smoke pollutants, (c) the behavior of smokers and nonsmokers in a polluted environment that brings them in contact with the pollutants, (d) multiple pathways and time profiles over which exposure takes place, (e) and efforts to protect an environment from pollutants and behaviors to prevent exposure to occur. Due to the importance of dust and surfaces in the accumulation of THS, infants and children are most at risk of higher THS exposures due to their increased contact with dusts and surfaces and their close association with adults. While there is a considerable body of literature on the exposure to tobacco smoke pollutants among active and passive smokers, little is currently known, for instance, about (a) how different smoking patterns contribute to the accumulation of THS pollutants, (b) how pollutants accumulate in different media, (c) the relative effectiveness of different strategies to protect an environment from the accumulation of THS, and (d) relative importance of different pathways and profiles of exposure in different populations. We believe that the following topics require special attention. Future experimental and epidemiological research should:

- Develop, test, validate biomarkers of exposure to different THS pollutants and different stages of THS aging, especially biomarkers suitable for use in children.
- Investigate association between smoking behavior, tracers for THS pollutants in air, dust, surface, and biomarkers of THS exposure.
- Compare (a) indoor spaces with ongoing active smoking (SHS+THS) and (b) indoor spaces that transitioned from smoker to smoke-free (aging THS).
- Examine occupational exposure risks (e.g., hospitality, delivery truck drivers).
- Conduct controlled human exposure experiments as a way of testing and validating biomarkers of exposure to THS.
- Evaluate the relative contribution of different exposure pathways in different settings and different populations, such as in young children and in low-income households with other concomitant exposures such as traffic-related pollutants.
- Survey indoor environments (home, car, hotels, etc) for THS tracers when exposed to environmental oxidants, and investigate whether surrogate measure of oxidant levels (presence of gas stove in home, proximity to a busy street) can predict formation of more toxic THS components.
- Investigate THS pollution levels as a function of smoking behavior, cleaning, ventilation, activity patterns, household appliance, environments by season (outdoor temp, weather, climate), income/SES.
- Investigate effectiveness of different efforts to prevent THS pollution and exposure (e.g., smoking restrictions, clean-up/remediation).

Toxicology and Health Effects

While there is a growing body of research on the toxicology and health effects of tobacco smoke and SHS (i.e., dose-response assessment and risk characterization), very little is currently known about the potential and actual health effects attributable to THS. To achieve a better understanding of health effects attributable to THS, future experimental and epidemiological research should:

- Develop biomarkers for disease or tissue damage caused by THS components.
- Study *in vitro* metabolism, toxicology and genotoxic potential of THS components, especially compounds formed through aging and oxidant reactions.
- Carry out *in vivo* metabolism and toxicology studies of the most toxic compounds.
- Evaluate the toxicology of different exposure pathways (inhalation, dermal transfer, ingestion), and exposure profiles (acute/chronic, cumulative/single) and during sensitive periods, such as infancy.
- Evaluate risk in medically compromised populations: respiratory/pulmonary; immune system; prenatal, neonates; at risk groups by environment: non-smokers living with smokers; children cared for by smokers and in smoker homes; effects of exposure reduction in high risk populations
- Discriminate effects attributable to THS from those of SHS exposure and active smoking.
- Identify smoking behaviors and environments that are particularly hazardous to different population.

Tobacco-Related Norms, Preferences, and Behaviors

Our review suggests that concerns associated with THS shape behaviors and attitudes of individuals, local policies, and marketing strategies targeting consumers.

Little is currently know how concerns about THS emerge and evolve, how they shape behaviors of smokers and nonsmokers, and how they can be leveraged to reduce smoking behavior and SHS and THS exposure. The following topics seem particularly worthwhile:

- Research on the nature, origins, and pervasiveness of THS awareness, concerns, attitudes, and norms.
- Quasi-experimental and observational research on the evolution of tobacco-related norms and the gradual change in cultures affecting smoking, SHS, THS practices and policies.
- Research on the relationship between THS awareness, attitudes, norms, and their expression in consumer preferences and behavior.
- Intervention trials on how best to conduct health education and promotion campaigns to influence norms and expectations to adopt stricter bans and to reduce smoking behavior.
- Focused THS education campaigns and interventions to affect the valuation of smoke-free environments: real-estate; cars; child home care.
- Develop counseling and coaching interventions for medically vulnerable populations to address disparities issues and to provide a more sensitive and immediate tests of possible health benefits from intervention.

Tobacco Control Policies: Protecting Nonsmokers from Tobacco Smoke Pollutants

Our review indicates that public awareness and consumer preference have given rise to a range of policies at the local levels and in private enterprises. While they are evidence for interest in and demand for further control of smoking behavior, the impact

and limitations of these emerging policies are not well understood. The following research areas can help contribute important evidence for developing and implementing effective public and private policies to protect nonsmokers from THS and to reduce tobacco use overall.

- Studying the effectiveness of emerging local ordinances, corporate policies, private bans and rules.
- Examining policy loopholes, vulnerable population, and critical environments informed by basic and clinical research.
- Investigate need for better occupational exposure protection (e.g., hospitality industries, delivery truck drivers).
- Connecting policy efforts at the local, regional, state levels and in personal, public, work, school, and business domains.
- Working with consumer organizations to incorporate preferences about smoke-free environments in informal and formal norms, property valuation, standards for monitoring and compliance.

Conclusion

The emerging evidence on THS suggests important new directions for understanding the long-term consequences of tobacco use and for preventing and reducing tobacco use. While it is premature to trivialize or dramatize the significance of THS, the existing evidence provides strong support for pursuing a programmatic research agenda to fill important gaps in our current understanding of the chemistry, toxicology, pollution, exposure, clinical significance, and policy implications of THS. Such a programmatic research program is necessary to illuminate the role of THS in

existing and future tobacco control efforts to decrease smoking initiation and smoking levels, to increase cessation attempts and sustained cessation, and to reduce the cumulative effects of tobacco use on morbidity and mortality.

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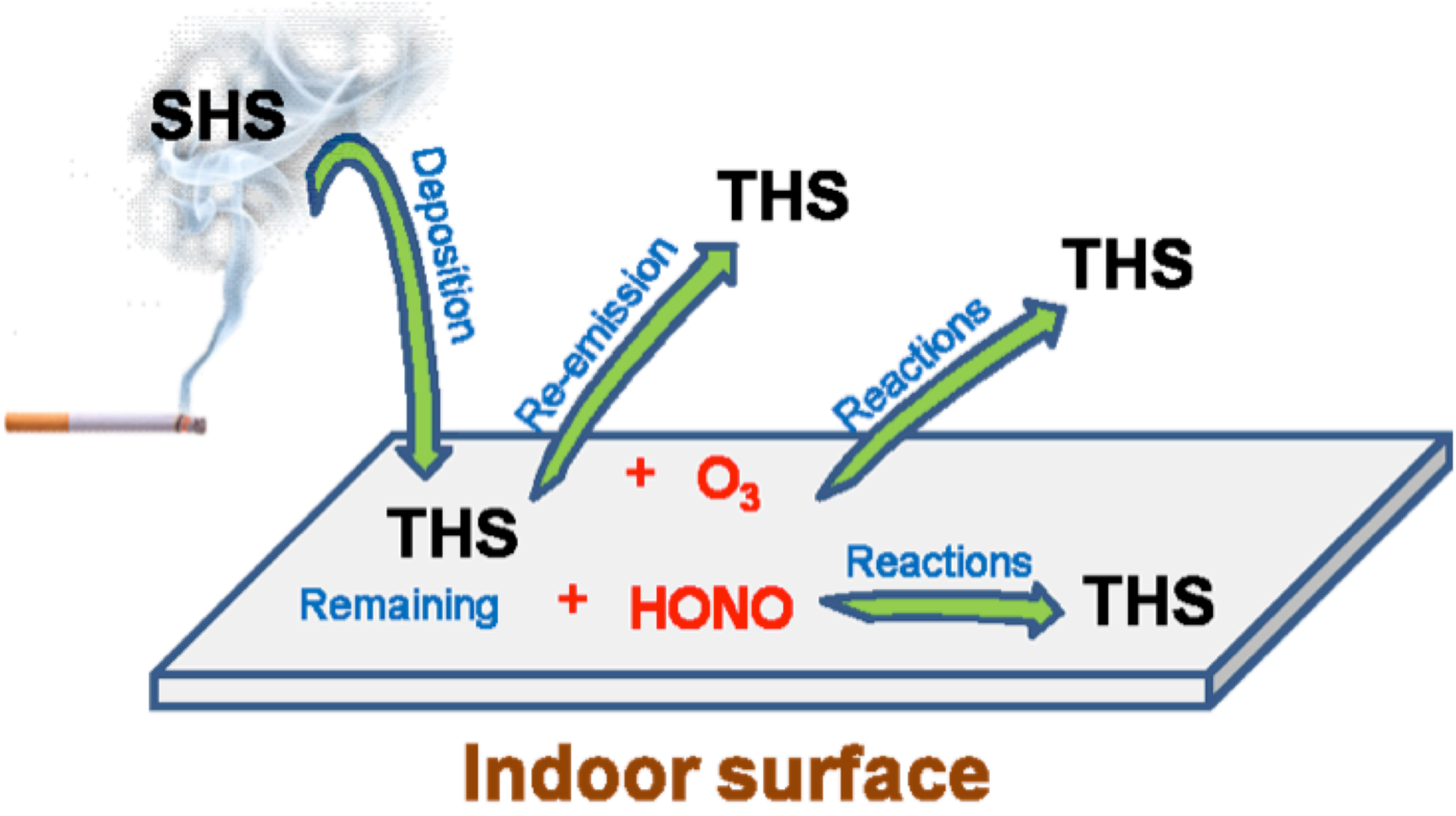
Figure Legends

Figure 1. General schematic of thirdhand smoke (THS) formation and reactions on indoor surfaces

Figure 2. Physical-chemical processes of nicotine reactions with nitrous acid on indoor surfaces. (A) Illustration of surface-mediated nitrosation of nicotine. (B) Proposed mechanism for the formation of TSNAs. (adapted from(Destaillats et al. 2006))

Figure 3. Mass spectrum and size distribution of secondary organic aerosol generated during nicotine reaction with ozone. (adapted from(Singer et al. 2006))

Figure 4. Reaction products and proposed pathways for nicotine reactions with ozone. (adapted from (Singer et al. 2006))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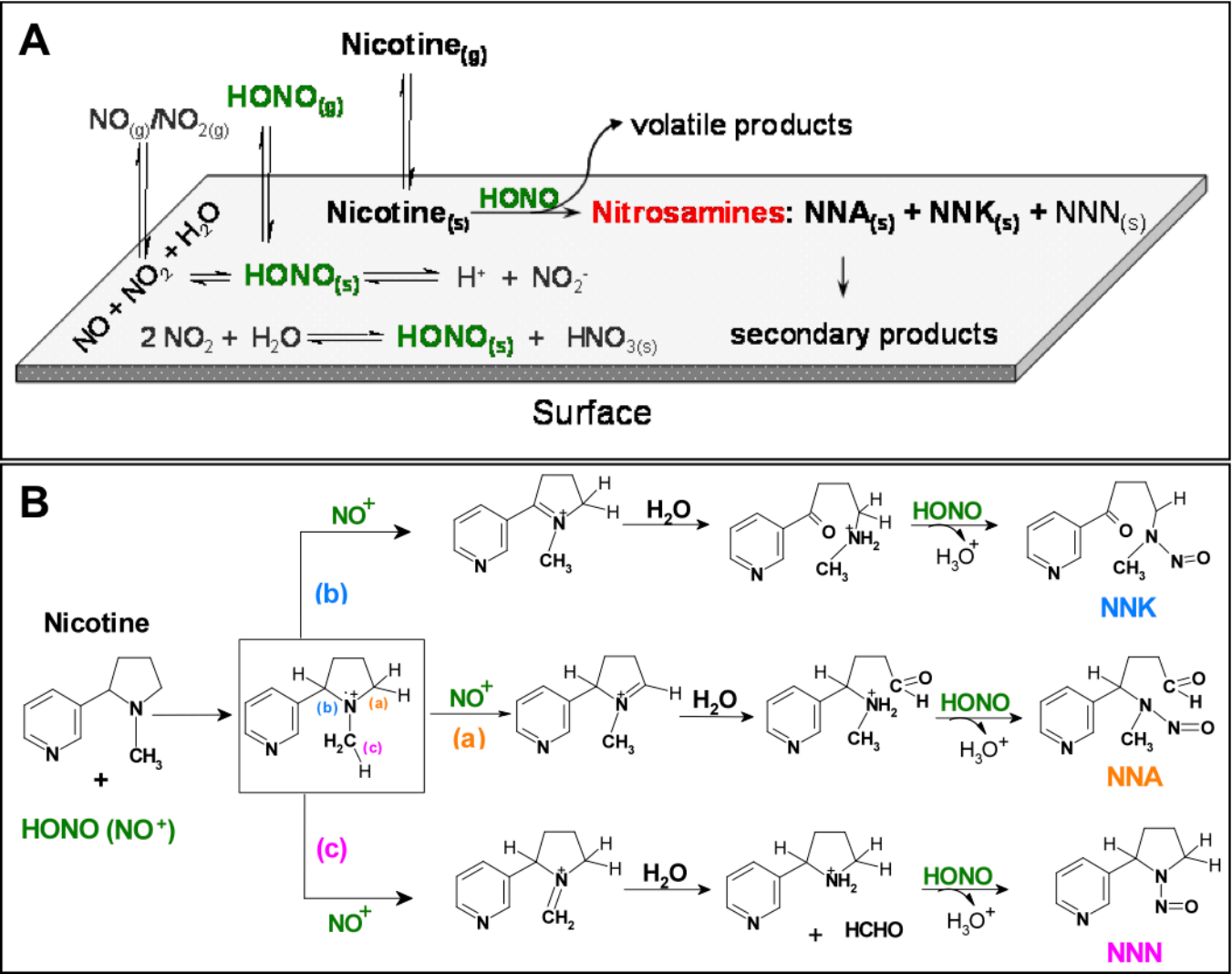
+ O_3
THS
Remaining
+ HONO
Reactions
THS
Indoor surface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Nicotine(g)
HONO(g)
NO(g)/NO2(g)
volatile products
Nicotine(s)
HONO
Nitrosamines: NNA(s) + NNK(s) + NNN(s)
NO + NO2 + H2O
HONO(s)
H+ + NO2-
2 NO2 + H2O
HONO(s) + HNO3(s)
secondary products
Surface
B
Nicotine
+
HONO (NO+)
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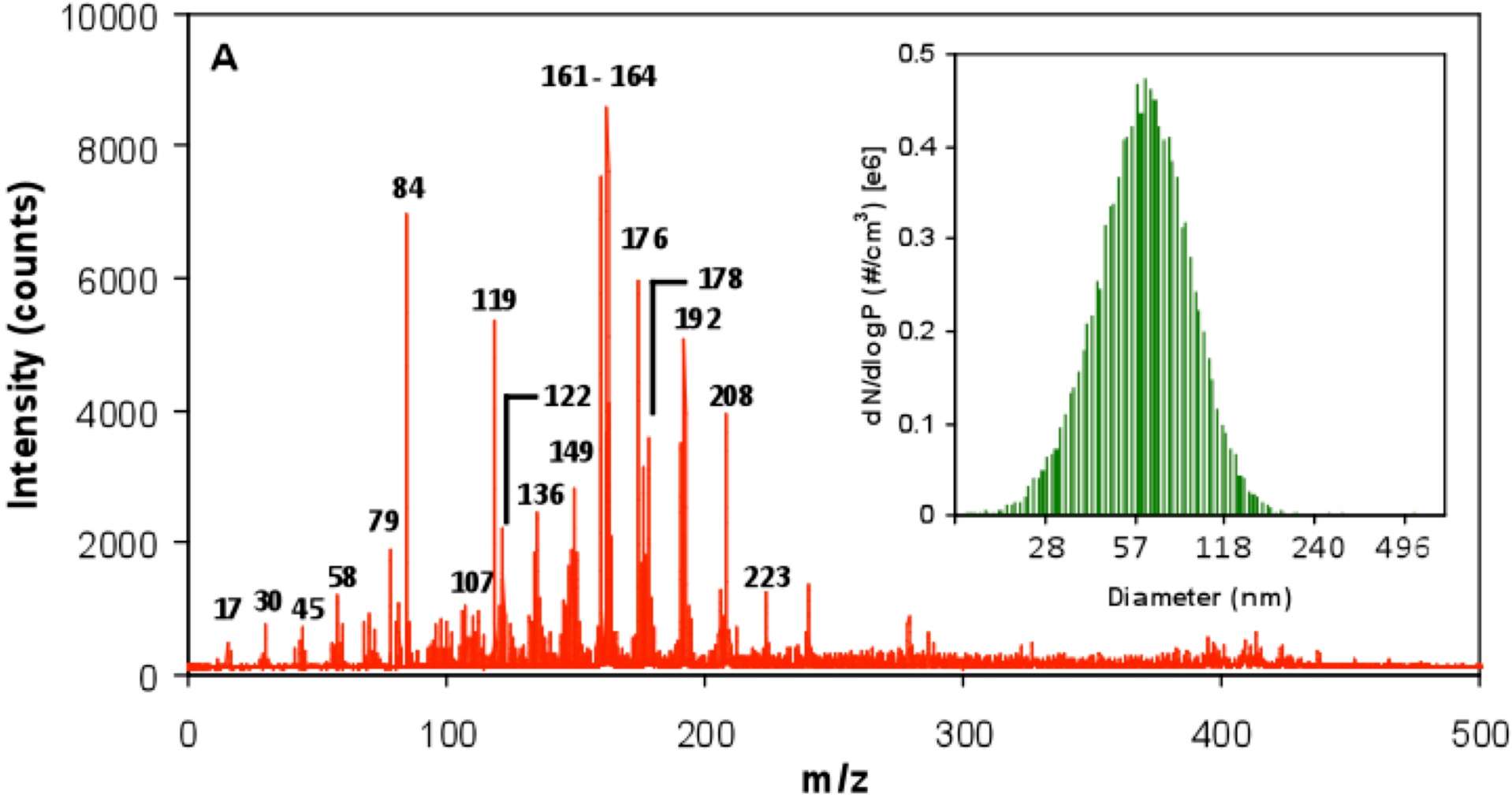
NNA
NNN
+ HCHO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4000
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100
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300
400
500
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58
79
84
107
119
122
136
149
161 - 164
176
178
192
208
223
dN/dlogP (#/cm3) [e6]
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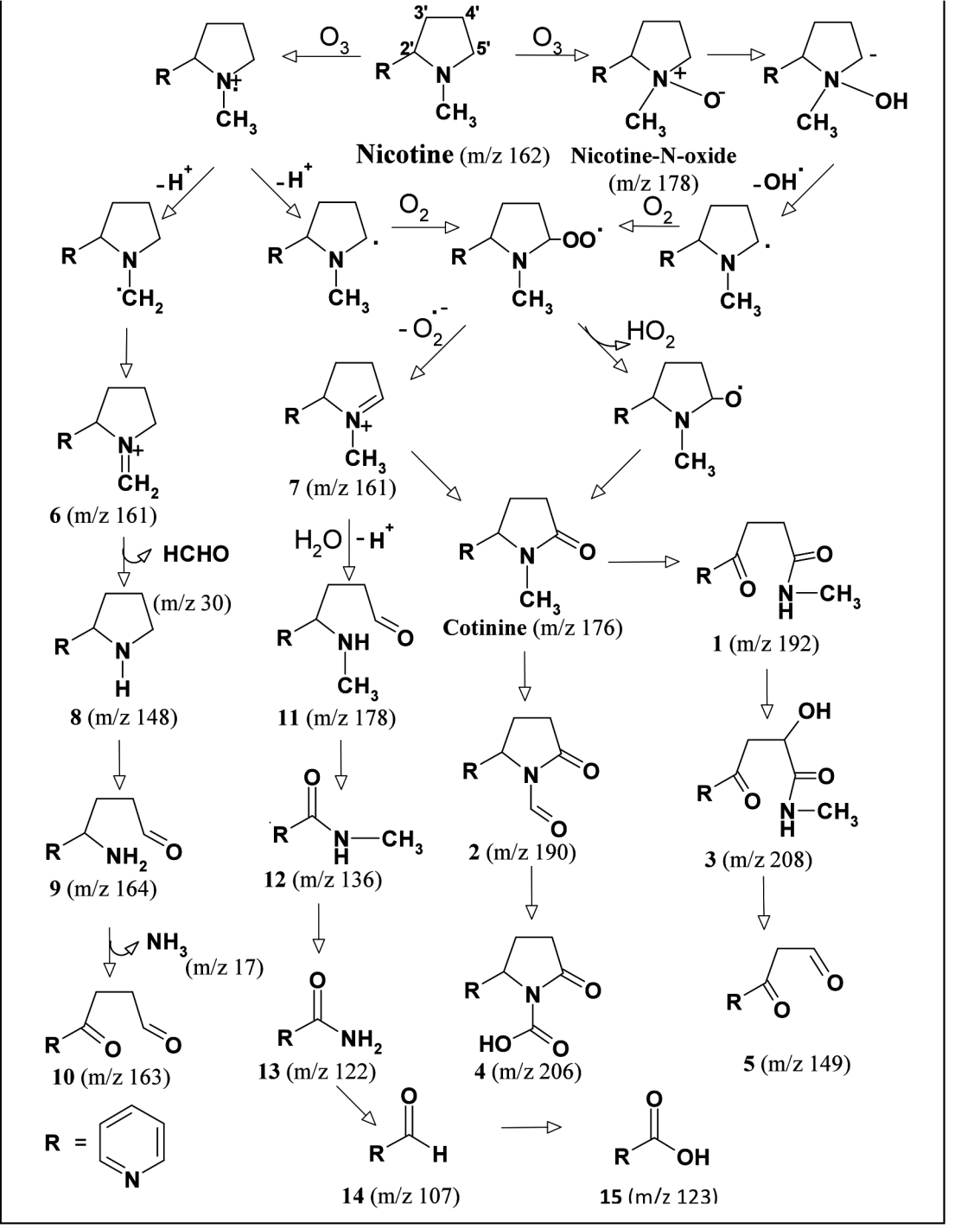
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