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## Journal

Nicotine and Tobacco Research

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## Publication Date

2026-11-02

Peer reviewed

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# Dermal Uptake of Thirdhand Cigarette Smoke from Clothing

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**ABSTRACT**

**Introduction:** Smoking leads to the accumulation of smoke chemicals on indoor materials like furniture, bedding and clothing. Little is known about the uptake of nicotine and nitrosamines from clothing and other indoor materials.

**Methods:** We exposed cotton clothing to cigarette smoke under controlled conditions. Using a crossover study design, healthy nonsmokers who were not normally exposed to smoke wore the smoked clothing and clean clothing for three hours at separate study visits. We compared urinary concentrations of cotinine and 3-hydroxycotinine, which are metabolites of nicotine, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) which is a metabolite of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).

**Results:** One three-hour dermal exposure to thirdhand smoke on clothing led to statistically significant increases in the concentrations of nicotine and NNK metabolites in the urine of all participants (p-values < 0.001). Normalized to creatinine, the peak median cotinine concentration after THS exposure was 62 times that seen after the control exposure. Likewise, peak 3-hydroxycotinine was 51 times higher than control and NNAL 46 times higher.

**Conclusions:** This is the first demonstration of dermal uptake of NNK in a controlled human exposure study. The concentrations of nicotine and NNK metabolites were like those of people with chronic high exposure to secondhand smoke. Clearance of nicotine was slower than in inhalation exposure studies, suggesting a dermal reservoir for nicotine. Dermal uptake from

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clothing and other surfaces can be a significant source of exposure to nicotine, NNK and other toxicants in tobacco smoke.

## IMPLICATIONS

Dermal uptake is an important route of exposure to nicotine, NNK and other smoke toxicants and contributes substantially to total exposure. Nicotine and the tobacco-specific carcinogen, NNK, are both absorbed readily through the skin when people wear clothing that has been exposed to tobacco smoke. Since these chemicals are known to persist for months and years on indoor surfaces, nonsmoking policies and disclosure of prior smoking are important policies to protect the public health.

## INTRODUCTION

Thirdhand smoke is the residual tobacco smoke chemicals that remain in the environment after tobacco has been smoked[1, 2]. Air exchange rates in most homes and many public buildings are low (0.2-2 air change per hour[3, 4]), so many of the chemicals released when people smoke indoors stick to surfaces before they can be removed by ventilation. In an experimental chamber with 2 air changes per hour, ~50% of the total particulate material, 62% of the polycyclic aromatic hydrocarbons, 72% of the nicotine and ~80% of the tobacco-specific nitrosamines in cigarettes smoke deposited on the surfaces of the chamber[5, 6]. Research has shown that once a building is contaminated with thirdhand smoke, the contamination can persist for months and years[7-9] and cannot be removed using standard cleaning methods[10, 11]. In a casino that was heavily contaminated with thirdhand smoke, the air concentrations of nicotine were 9 $\mu g/m^3$, while the surfaces of the casino (walls, furniture, woodwork) yielded 651 $\mu g/m^2$ when wiped and dust vacuumed from the floors yielded 158 µg nicotine per gram of dust[8]. This means that dermal contact with surfaces is likely to be the primary route for human exposure to thirdhand smoke indoors.



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Skin is permeable to nicotine. This serves as the basis for the transdermal nicotine patch. Two prior studies have shown that nicotine can be absorbed directly from air through the skin[12, 13] and one study has shown that it can be absorbed from clothing[13]. However, the pharmacokinetics of uptake of nicotine from materials like clothing, bedding and furniture has not been well studied. To assess dermal uptake of nicotine and the tobacco-specific nitrosamine NNK, we exposed clothing to cigarette smoke under controlled conditions, had healthy nonsmokers wear it for 3 hours with intermittent exercise and then measured the metabolites of nicotine and NNK in their urine.

## METHODS

### Study Design

This study used a cross-over design where each participant had a smoke exposure (wearing smoke-exposed clothing for three hours) and a control exposure (wearing clean clothing for three hours). The order of the exposures was randomized and the exposures were separated by 21 or more days to eliminate cross-over health effects between the two exposures (Figure S1). This study was approved by the University of California Institutional Review Board (protocol #15-17009) and the study protocol is available on clinicaltrials.gov.

### Study Participants

21 healthy, adults (18-50) were recruited using advertisements in the San Francisco Bay area. Exclusion criteria included smoking, ongoing or recent exposure to secondhand smoke, occupational exposure to smoke, dust or fumes, eczema, rosacea and other skin diseases, allergies, pregnancy, recreational drug use, and use of prescription medications for acne, diabetes, blood pressure, cholesterol, autoimmune disorders, tendonitis and arthritis. Nonsmokers were defined as having smoked no more than 50 packs of cigarettes in their life and not smoking cigarettes in the past 3 years. Marijuana smokers were excluded if they had



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ever smoked daily and if they had smoked in the preceding three months. After the screening visit, low-level exposure to tobacco smoke was tested by quantifying salivary cotinine by gas chromatography/mass spectroscopy using an assay with a limit of detection of 10 ng/ml so that we did not study participants who were consistently exposed to tobacco in their daily lives. At screening and exposure visits, urine samples were tested using over-the-counter competitive ELISA assays for cotinine (positive test at 200 ng/ml) and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (positive test at 50 ng/ml), to screen for active use of tobacco or cannabis.

**Study Procedures**

On the day of the exposure visit, the participant donned the test clothing and entered the exposure chamber. The exposure chamber had 0.85 air changes per minute of HEPA and charcoal-filtered, conditioned air, at 70° F/21° C and 50% relative humidity. During the three-hour exposure, participants exercised on a treadmill or exercise bike for 15 minutes out of each hour, vigorously enough to induce perspiration. Participants were seated for the remainder of each hour. After three hours, participants changed back into their own clothing. Spot urine samples were collected before exposure and at three, six, nine and 13 hours after exposure, at waking the next day and in the laboratory that morning. The final sample was collected 22-23 hours after the start of exposure. Urine samples were centrifuged, aliquoted and stored at -20° C.

**Test Clothing**

The test clothing comprised long-sleeved shirts and pants made of knit fabric with 88-100% cotton and the balance elastane. Before use, clothing was washed four times in hot water with an unscented detergent. Control garments were sealed in clean polypropylene bags and stored at room temperature.

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THS garments were exposed to diluted smoke from Marlboro Red cigarettes, in a 6 $m^3$ stainless steel aging chamber. The smoke was generated according to Schick et al.[5]. Briefly, the cigarettes were machine-smoked, according to ISO method #15592-2:2001. The smoke was diluted with conditioned, filtered air to a final concentration of 350-1,200 µg/$m^3$ and routed through a stainless-steel chamber at 200 l/min (air exchange rate = 2 per hour). Particle concentration was measured using a Sidepak aerosol particle monitor (model AM510, TSI Inc., Shoreview, MI). The clothing was exposed repeatedly until the cumulative mass of $PM_{2.5}$ that entered the aging chamber totaled three grams.

The exposure of the clothing was meant to reproduce the exposure of clothing stored for a month in the home of someone who smokes ~12 cigarettes a day.

$$3{,}000\ mg = 8.3\ mg \frac{PM}{cigarette} * 12 \frac{cigarettes}{day} * 30\ days$$

8.3 mg total particulate material per cigarette is the average sidestream smoke emission factor from Klepeis et al[14]. After exposure, the THS garments were heat-sealed in metalized 2.5 mil (63.5 µm) polyester food bags and stored at -20° C.

**Measuring Nicotine, NNK and other Nicotine-Related Compounds in Urine and Cloth Samples**

Urine samples were assayed for cotinine and 3'-hydroxycotinine by liquid chromatography–atmospheric pressure chemical ionization tandem mass spectrometry (LC-MS/MS) and for NNAL with LC-MS/MS with electrospray ionization, following the methods of Jacob et al[15, 16]. The limit of quantitation was 0.05 ng/ml for cotinine, 0.1 ng/ml for 3-hydroxycotinine, and 0.25 pg/ml for NNAL.

Two swatches, measuring 2 cm x 4 cm, were cut from the hem of each garment before it was donned. The swatches were weighed, placed in amber glass vials and stored at -20° C. For analysis, internal standards were added to the vials and the samples were extracted in 45:45:10



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dichloromethane/pentane/ethyl acetate and analyzed by LC-MS/MS by the method of Whitehead et al. [17]. The limits of quantitation per sample were 3 ng for nicotine, 25 ng for myosmine, 2.7 ng for bipyridine, 3 ng for 3-ethenylpyridine, 8 ng for N-formyl nornicotine, 8 ng for cotinine, 0.09 ng for nicotelline, 0.5 ng for NNK, 0.456 ng for NNN, 0.27 ng for NNA, 0.09 ng for NAT and 0.09 ng for NAB.

**Estimating Median Total Metabolite Excretion and Absorption in 22 Hours**

Typical 24-hour urine volumes vary between 800 and 2,000 ml. To compare the total amount of nicotine excreted in three different smoke exposure studies, we used 1000 ml as an estimated urine volume and calculated the total micrograms of nicotine excreted per sample as follows:

$$\mu g\ metabolite\ per\ day = \left[Sample\ metabolite\ \frac{ng}{ml} * fraction\ of\ elapsed\ day/sample * \frac{1000\ ml}{1\ day} * \frac{1\ \mu g}{1000\ ng}\right]$$

Then the mass of each metabolite for each sample (3 h, 12 h, 20 h, 22 h) was summed and the 25$^{th}$ percentile, median and 75$^{th}$ percentile were calculated. The total mass of nicotine and NNK absorbed was estimated by multiplying the mass of the metabolites by their fraction of the total metabolites excreted in urine: 0.67 for cotinine + 3-hydroxycotinine[18] and 0.12 for NNAL[19].

**Statistical Analyses of Metabolite Concentrations**

We normalized the urinary metabolite concentrations to creatinine to reduce the variation due to urine osmolarity. Values below the limits of quantitation (LOQ) were set to LOQ/$\sqrt{2}$. Because the urinary metabolite data were highly skewed at all timepoints, we transformed them with the natural log, yielding near-linear data distributions. We fitted separate linear mixed effects models to each of the log-transformed outcomes, including the variables of smoke exposure, time point, order of exposure and all two- and three-way interactions of these three variables.

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All data from all participants were included in the linear mixed effects models. Analyses were done in Stata, v16.1. Descriptive statistics were calculated using Excel.

### Total Nicotine and NNK in Garments and Mass per Surface Area Skin

To determine how much nicotine and NNK were available for dermal uptake by the participants, we weighed the garments and multiplied the average nicotine and NNK concentrations per gram of cloth by the garment mass. To determine the dosage per $m^2$ skin, we used the Du Bois equation ($BSA = 0.007184 \times W^{0.425} \times H^{0.725}$) to calculate each person's body surface area (BSA) and multiplied by 0.8 since the clothing covered ~80% of the body. Then, we divided the average mass of each chemical in the clothing by the average body surface area covered by clothing for each participant.

### Laundering Frequency

To assess how long clothing and bedding may be exposed to secondhand smoke between washings in average households, we asked the participants the following questions: "The next questions are about the clothing you are wearing now. How many days have you worn each of the following since they were last washed: Pants, Shirt, Bra, Sweater or Jacket" The potential responses were "It was just washed, 1, 2, 3, 4, or 5 or more days." For bedding, the question was "How often do you wash your (name of item)? The response options were: "Weekly, Every 2 Weeks, Monthly, Every 2-4 Months, Twice a Year, Once a Year, and Once Every 2 Years.

## RESULTS

### Study Participants

We consented and screened 42 people, who completed the personal care questionnaire and are included in the analysis of laundering frequency. 21 participants were eligible, available and completed at least one exposure (13 female, 8 male) and are included in analyses of



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biomarkers. 18 completed a clean garment exposure, 19 completed a THS exposure and 17 completed both exposures (10 female, 7 male). The participants ranged in age from 21 to 49 and their mean age was 31.3. Six participants identified as White, six as Asian, five as of more than one race, two as African American, one as Native American and two participants declined to state their race. Of the 21 participants, four identified as Latino or Hispanic. Participant BMI ranged from 17 to 31, with an average of 24.4 for women and 25.2 for men.

**Nicotine, NNK and Nicotine-Related Chemicals in the Test Clothing**

The THS clothing was exposed to smoke in two lots. The first lot had 63.32 ± 36.96 µg nicotine per gram of fabric and 29.6 ± 15.87 ng NNK per gram of fabric. The second lot had 59.14 ± 18.07 µg nicotine per gram of fabric and 42.18 ± 25.65 ng NNK per gram of fabric. A subset of twelve swatches from smoke-exposed shirts were subjected to more detailed chemical analysis to determine the concentration of twelve chemicals related to and/or derived from nicotine. The data are normalized to a 300-gram garment, similar to a pair of men's athletic pants. Nicotine was present in the highest concentration, at nearly 19 milligrams per garment, followed by 3-ethenylpyridine, myosmine, bipyridine, N-formyl nornicotine, cotinine and nicotelline at 2.43, 1.36, 0.33, 0.14, 0.14 and 0.08 mgs respectively. The concentrations of the tobacco-specific nitrosamines were NNK, 8.89 µg, NNN, 2.65 µg, NNA, 11.42 µg, NAT, 1.44 µg and NAB, 0.53 µg (Figure 1).

To determine how much nicotine and NNK the participants were exposed to, we weighed representative garments. The average combination of shirt and pants contained 35.34 mg nicotine and 25.21 µg NNK for the male participants and 30.03 mg nicotine and 21.42 µg NNK for the female participants (Table 1). To assess whether the dosage was similar for men and women, we compared the average mass of chemicals in the clothing to average body surface area and volume for men and women, calculated using the Du Bois equation[20]. The average body surface area was 1.73 ± 0.117 $m^2$ for the women in this study and 1.90 ± 0.131



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$m^2$ for the men. The ratios between nicotine and NNK masses and body surface area were higher for men than women.

**Frequency of Laundering**

Most participants (71%) reported donning a clean shirt on the day of the survey. However, 39% reported that their sweater or jacket had been worn 6 or more days since it was last washed. 21% reported washing their sheets weekly, 40% every two weeks, 31% once a month and 7% every two to four months. For blankets, comforters and duvets, 5% reported washing weekly, 26% every 2 weeks, 69% reported washing every month or less frequently.

**Urinary Metabolites of Nicotine and NNK**

From a total of 259 urinary metabolite results possible ([17 participants x 7 time points x 2 exposures] + [3 participants x 7 time points x 1 exposure]), there were 256 results available for cotinine, 248 for 3-hydroxycotinine and 256 for NNAL. Many participants had concentrations of tobacco smoke metabolites in their urine that were below the limits of quantitation at baseline (Table 2) and for one or more of the control exposure samples. 17.3% of cotinine results, 7.1% of 3-hydroxycotinine results and 23.8% of NNAL results were below the limit of quantitation (Table S2). However, none of the samples collected after the initiation of THS exposure were below the limit of quantitation.

Two of the participants had metabolite levels indicating that they had been exposed to tobacco products prior to one of their two exposure visits. They had baseline cotinine concentrations of 9.8 and 9.3 ng/ml (6.9 and 3.6 ng/mg creatinine). However, all participants had values below the cut off points for active use (27- 29 ng/ml)[21]. The participant with the highest baseline values was excluded from the calculation of the time of peak concentration. With this one exception, all urinary metabolite data was included in all analyses.

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**Urinary Metabolites of Nicotine and NNK After Exposure**

Urinary concentrations of cotinine, 3-hydroxycotinine and NNAL were consistently higher after the THS clothing exposure than after the control clean clothing exposure (Figure 2 and Table S1). The exposure effects were tested by fitting separate linear mixed effects models to each log-transformed outcome that included time point, exposure, order and the 2-way interaction of time point and exposure. Likelihood ratio tests showed that the time point by exposure interactions were statistically significant for each outcome. Time-specific order effects were calculated using results from the mixed effects models and the estimated exposure effects at all timepoints after baseline were statistically significant, with z statistics greater than 4.0 and corresponding p-values <0.001, for all three metabolites (Table 3). The effects of exposure order, gender and age were not statistically significant.

The highest median urinary concentrations of cotinine (9.25 ng/mg creatinine [Table S1]) and 3-hydroxycotinine (40.18 ng/mg creatinine [Table S1]) were in the samples collected in the laboratory at 22 hours after the start of exposure. Likewise, the highest ratios of the THS metabolite concentration to control metabolite concentration (88 for cotinine, 76 for 3-hydroxycotinine) were at 22 hours (Table S3). The highest median NNAL concentration (12.82 pg/mg creatinine [Table S1]), was at 6 hours and the highest ratio of THS to control concentration was at 9 hours (Table S3).

**Comparison of Dermal and Inhalation Exposure**

The nicotine metabolite excretion kinetics in this dermal exposure study are different from two prior inhalational exposure studies with similar protocols from our laboratory[22, 23] (Figure 3). In Schick et al.[22], the inhalational smoke exposure lasted 30 minutes, the smoke was aged for 30 minutes (SHS) and the $PM_{2.5}$ concentration was 1,000 $\mu g/m^3$. The peak cotinine concentration in this study was observed at 12 hours (Table 4). The peak NNAL concentration was at 3 hours. In Pratt et al.[23], the inhalational smoke exposure lasted 3 hours, the smoke was aged 20 hours



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(THS) and the $PM_{2.5}$ concentration started at 350 $\mu g/m^3$ and declined over time. The highest cotinine concentration in this study was observed at 22 hours and the differences in the concentrations of NNAL were not statistically significant from baseline.

The arithmetic median metabolite concentrations for the three studies are shown in Table 4. We did not have the participants collect their total urinary output in these studies, so we can only estimate the total mass of nicotine and NNK metabolites that they excreted. For simplicity, we used 1000 mL as an estimated urine volume and calculated the total mass of nicotine and NNK metabolites excreted in the 22 hours of the study as measured at the common timepoints of baseline, 3 h, 12 h, 20 h and 22 h (Table 4). The estimates of nicotine and NNK absorbed were calculated by dividing the metabolite concentrations by their urinary excretion fractions[1, 18, 19]. Clearly the dermal exposure was higher than the inhalational exposures in the two prior studies.

## DISCUSSION

These experiments show that dermal uptake can be an important route of exposure to tobacco smoke chemicals. Wearing THS-contaminated clothing for three hours led to roughly 50-fold increases in urinary cotinine, 3-hydroxycotinine and NNAL, even without direct respiratory exposure. Research, in laboratory settings[5, 6], private homes[10, 24, 25], hotels[26], casinos[8] and in rental cars[27-29], has demonstrated that most of the THS in the indoor environment is sorbed to surfaces. Thus, skin contact with surfaces is likely to be the primary exposure route for THS in the home and a significant route in public spaces[30]. This is of particular concern for young children, who have thinner skin and explore their environment actively through touch. Children who live with smokers have approximately 10 times more nicotine on their hands than children who live in smokefree homes[31] and hand wipe nicotine correlates well with urinary cotinine[32].

The two lots of THS clothing used in this study had similar amounts of nicotine (63.32 and 59.14 µg/gram), which demonstrates that our smoke exposure protocol was reproducible.



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The difference in the concentrations of NNK (29.6 ng/g in lot 1 and 42.18 ± 25.65 ng/g in lot 2) is probably because NNK forms from nicotine over time[33, 34] and the second lot of clothing took 161 days to expose, while the first lot took 84 days. We exposed the clothing by hanging it in a stainless-steel chamber and piping through diluted tobacco smoke at an air exchange rate of 0.5 per hour, similar to residential air exchange rates in the US. We chose three grams total cigarette smoke particulate material because three grams is equal to the emissions from ~360 cigarettes with an average emission factor of 8.3 mgs smoke particles each[14]. 65.8% smokers in the US smoke 15 or fewer cigarettes per day [35]. 360 cigarettes is 24 days at 15 cigarettes/day or 72 days at 5 cigarettes/day. Our exposure protocol is like how clothing and bedding and furniture are exposed in the homes of smokers, except that the exposure chamber is not ventilated between smoking sessions and it took us longer to expose the garments because we did not operate the system every day. This exposure protocol has also been used to generate cloth used in animal exposure studies[36-45] allowing comparisons between the acute exposures of human participants in this study and chronic exposures in laboratory animals. [33, 34]

There are few publications in the literature that report the amount of nicotine absorbed by clothing or cloth to compare our data to. The best comparator available is a study showing that clean cotton pillows placed in the homes of active smokers for 9 days absorbed 4.3 µg nicotine[46], the majority of which was found in the pillowcase. Most published measurements of nicotine in the indoor environment are done by wiping solid surfaces or by extracting house dust. Dust is a better comparator for clothing than surface wipes because dust and cloth are both extracted in their entirety during chemical quantitation. Jacob et al. found an average nicotine concentration of 98.2 µg/g and an average NNK concentration of 84 ng/g in dust from two smokers' homes[47]. Aquilina et al. found an average concentration of 11.2 µg/g nicotine in dust collected from 16 smokers' homes[48], and the highest sample was 18.9 µg/g. The median NNK was 9.4 ng/g and the maximum was 216 ng/g. A longitudinal study of household dust in



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the homes of smokers and users of smokeless tobacco found median nicotine concentrations of 7-15 µg/g and median NNK concentrations of 3.4-6.3 ng/g[17]. In experiments conducted in a casino, median concentrations of nicotine in dust were 116-158 µg/g[8]. These data suggest that the nicotine and NNK concentrations in the clothing in our experiments (~60 ug/g nicotine) are within the range of values observed in dust from smoke-polluted indoor spaces. The laundry survey findings indicate that 84-161 days is within range of the exposure of bedding in many households.

The average combination of shirt and pants contained 35.34 mg nicotine and 25.21 µg NNK for the male participants and 30.03 mg nicotine and 21.42 µg NNK for the female participants (Table 1). For comparison, the tobacco in an average Marlboro Red cigarette contains 12-18 mgs nicotine and nicotine patches contain between 7 and 21 mgs of nicotine. The amount of nicotine delivered to the smoker from a single cigarette varies from 0.8 mg to over 3 mg[49]. In the first 22 hours after the start of the THS exposures, we estimate that the median amount of total nicotine metabolites excreted by the participants was 0.065 mg (Table 4) and the total nicotine absorbed was ~0.1 mg which suggests either that the participants either absorbed only a small fraction of the nicotine from the clothing or that the nicotine they absorbed had not yet been fully metabolized at 22 hours.

The ratios between body surface area and the amounts of nicotine and NNK present in the clothing were higher for men than for women (Table 2). Men's clothing is often thicker and heavier than women's, so exposure through clothing may be higher for men. However, men have slightly thicker skin than women, which may reduce the rate at which they absorb nicotine[50]. We did not detect differences in uptake between men and women.

This study focused on nicotine and NNK, because there are sensitive methods available to detect their metabolites in biofluids. However, the data on nicotine-derived chemicals in the THS clothing (Table 1) are a reminder that THS is a complex mixture. NNK and NNN are known human carcinogens, while there is too little evidence to determine whether NAB and NAT are



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carcinogenic to humans[33]. 3-Ethenylpyridine[51], myosmine[52], bipyridine[53], N-formylnornicotine[54] and nicotelline are toxic or probably toxic at high concentrations, but their toxicity at low concentrations has not been sufficiently studied. Using nontargeted methods, Hoh et al. detected 140 unique compounds in house dust from smokers' homes that were not found in dust from nonsmokers' homes[55], emphasizing that THS exposures are chemically complex.

The participants in this study had low baseline exposure to nicotine and NNK (Table 1). The median baseline cotinine concentration was 0.08 ng/ml and a number of participants had baseline nicotine or NNK urinary metabolite concentrations below the limits of quantitation. The highest baseline cotinine concentration was 9.8 ng/ml which suggests secondhand exposure. The optimal cutpoints for distinguishing smokers from nonsmokers, derived from the analysis of 8,333 participants in Wave 4 of the Population Assessment of Tobacco and Health study in 2017, are 29.9 ng/ml urinary cotinine for cigarette smokers and 27.3 ng/ml for users of multiple forms of tobacco[21].

**NNK Uptake and Metabolism**

This is the first controlled human exposure study we are aware of to show dermal uptake of NNK in humans. However, dermal uptake of NNK has been demonstrated in animal studies[56]. The apparently rapid clearance of NNAL, with peak metabolite concentrations observed at 6-9 hours (Figures 2 and 3, Tables 3 and S1) was surprising, because estimates of the half-life of NNK range from 10 to 45 days [57, 58]. This could be due to rapid metabolism of NNK to NNAL, excretion, and distribution into tissues, followed by a slower terminal elimination phase. The literature on the metabolism of NNK is based on studies of active tobacco users[57, 58] and of nonsmokers who are chronically exposed[59]. NNK is believed to accumulate in tissues and disperse back into the bloodstream slowly[57]. Our data suggest that, in nonsmokers with low baseline exposure to NNK, the half-life of the first phase of elimination is between 12 and 24

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hours. Collection of samples at later timepoints may reveal a more complex pharmacokinetic pattern with slow elimination from deeper tissue compartments.

**Dermal Reservoir**

Our data also suggests that there is a difference in nicotine uptake kinetics between dermal and inhalational exposures (Figure 3). The median urinary cotinine concentrations reached their maxima at 12 hours after exposure in the inhalational SHS and THS experiments and then either declined (SHS) or plateaued (THS). After dermal exposures, the median urinary cotinine concentrations were still increasing at 22 hours. Dermal exposures are subject to a phenomena known as “dermal reservoir” whereby the skin appears to absorb a chemical and then release it into circulation over time[60]. Two findings in the literature suggest this is true for nicotine. In pharmacokinetic studies of the transdermal nicotine patch, plasma concentrations of nicotine typically take several hours to begin to decline after transdermal patches are removed[61, 62]. In green-tobacco sickness, an occupational disease of tobacco pickers caused by dermal uptake of nicotine from dew-soaked tobacco leaves, the symptoms of headache, dizziness, nausea and vomiting typically begin in the afternoon, hours after first contact with the plants. In pickers who started work shortly after dawn, urinary cotinine concentrations were barely elevated at noon and reached concentrations 10-fold above baseline at 24 hours[63].The dermal exposure studies by Beko et al. found that urinary concentrations of cotinine and 3-hydroxycotinine were highest in the 36-60 hour pooled sample in some participants and in the 12-36 hour pooled sample in others[12, 13].

The dermal reservoir may increase the effective exposure period to THS because the nicotine and possibly other chemicals will continue to release from the skin into the bloodstream after exposure to THS ends.

**Limitations**



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The participants in this study did not wear respiratory protection to limit the amount of nicotine and NNK they may have inhaled after it evaporated from their clothing. However, the air exchange rate in the exposure chamber was 0.85 per minute, approximately 100 times higher than the normal air exchange rate in homes[3, 64], which minimized the inhalational exposure to chemicals evaporating from the clothing. The fact that the chamber in which the clothing was exposed was not ventilated between smoke generation periods means that there was less opportunity for THS to desorb from the clothing than in a normal home. The strengths of the study include consistent, well-controlled exposures, the quantification of nicotine, NNK and other nicotine-derived chemicals on the clothing, and the crossover study design which allowed us to confidently identify significant effects with a small sample size.

## CONCLUSIONS

Our data show that both nicotine and NNK pass readily from smoke-contaminated clothing, through the skin and into the body. This means that dermal contact with any smoke-contaminated surface, including bedding, furniture and vehicle interiors, can lead to exposure. Because most of the nicotine, nitrosamines and polycyclic aromatic hydrocarbons released when people smoke indoors remain on indoor surfaces and materials, the skin is the greatest source of exposure to thirdhand smoke in many indoor environments. Further research is required to identify the exact mechanisms of dermal uptake of THS, the metabolic half-life of the constituent chemicals and the health effects of dermal exposure to thirdhand tobacco smoke.

## DATA AVAILABILITY STATEMENT

Urinary metabolite and nicotine related compounds in cloth are available on Dryad (https://doi.org/10.5061/dryad.h70rxwdz5). Other data are available upon request to the lead author.

## CONFLICTS



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The authors have no conflicts of interest to acknowledge.

**ACKNOWLEDGEMENTS**

The authors thank John Neuhaus, PhD for his statistical analyses, Adam Whitlatch, Morgan Murphy, Keith Cheung, and Fabiola Quiroz for their assistance with the conduct of the study, Lawrence Chan for urine NNAL analyses, Trisha Mao for urine cotinine and 3'-hydroxycotinine analyses, and Kristina Bello and Lisa Yu for analytical laboratory supervision.

Funding for the study came from the California Tobacco-Related Disease Research Program grants #24RT-0039, 28PT-0081, T32PT6041, and T32PT6244. Laboratory infrastructure in the Division of Cardiology was supported by the National Institutes of Health by grant DA012393.

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**Figure 1: Nicotine and Related Chemicals in Test Clothing**

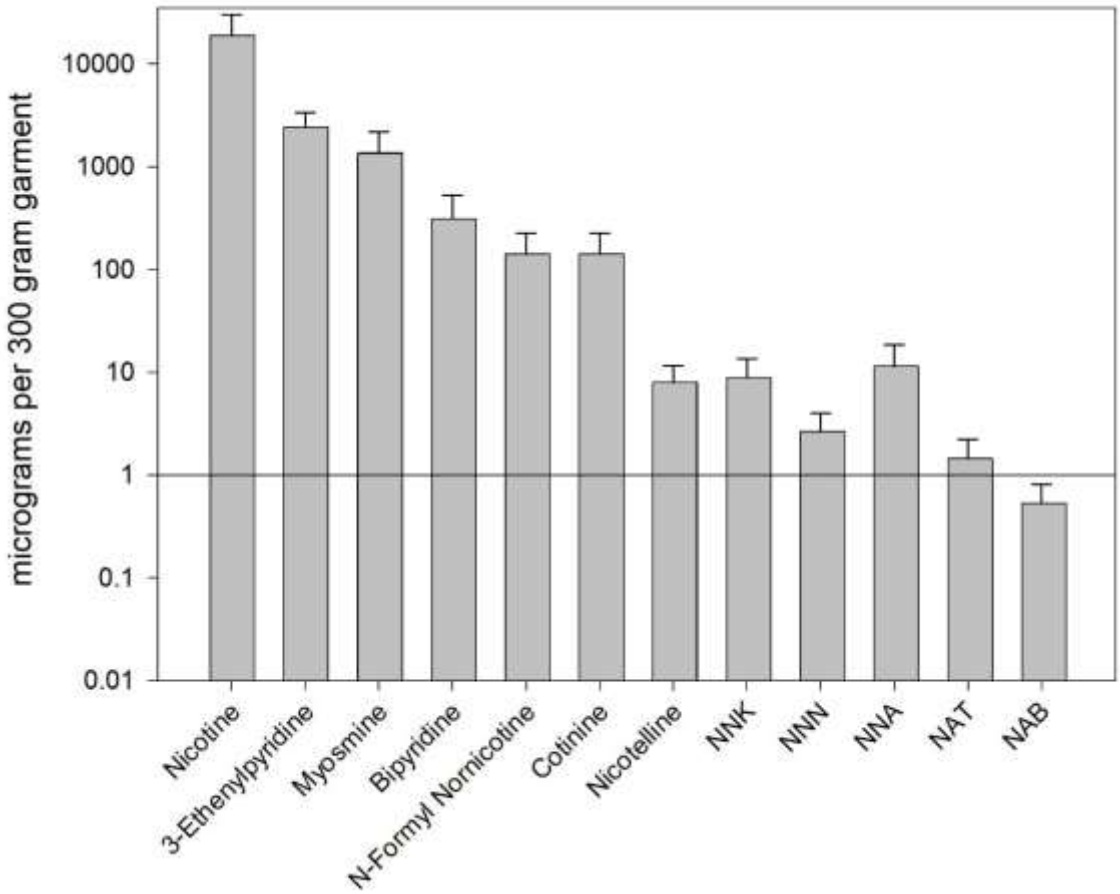



**Table 1: Nicotine and NNK Content of THS Clothing, Relative to Body Surface Area**

| | Men | | Women | |
|---|---|---|---|---|

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| | nicotine mg | NNK µg | nicotine mg | NNK µg |
|---|---|---|---|---|
| Shirt | 17.12 | 12.21 | 14.97 | 10.67 |
| Pants | 18.22 | 12.99 | 15.06 | 10.74 |
| Total | 35.34 | 25.21 | 30.03 | 21.42 |
| Mass/BSAC* | 23.2 mg/m$^2$ | 16.6 µg/m$^2$ | 21.7 mg/m$^2$ | 15.5 µg/m$^2$ |
| *BSAC = body surface area covered by clothing (BSA X 0.8) | | | | |

**Table 2: Baseline Urinary Tobacco Metabolite and Creatinine Concentrations**

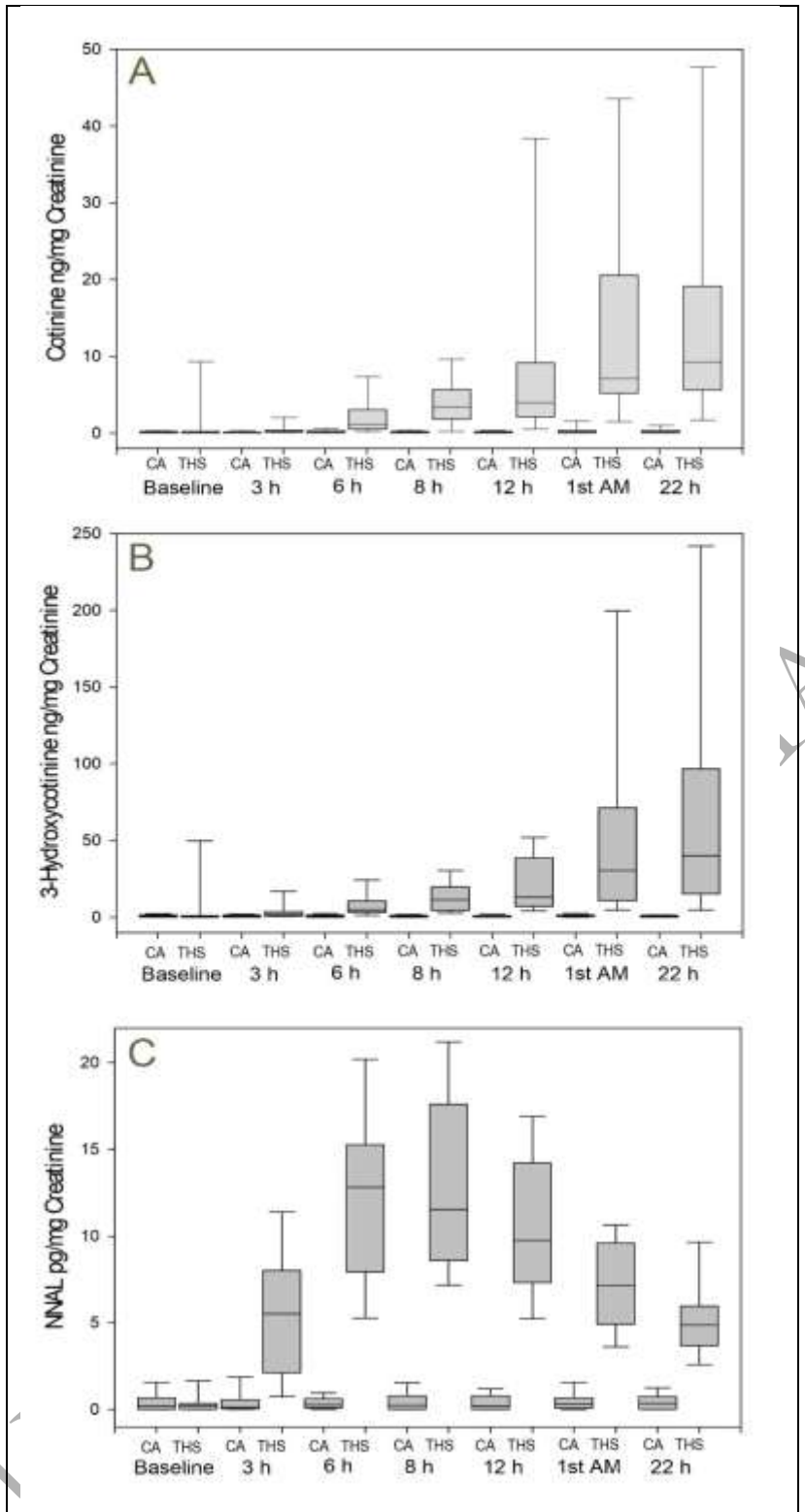
| | Cotinine ng/ml | 3-HC ng/ml | NNAL pg/ml | Creatinine mg/ml |
|---|---|---|---|---|
| Minimum | BLOQ | BLOQ | BLOQ | 0.10 |
| 25$^{th}$ Percentile | BLOQ | 0.2 | BLOQ | 0.57 |
| Median | 0.07 | 0.6 | 0.270 | 1.41 |
| 75$^{th}$ Percentile | 0.16 | 1.4 | 0.707 | 2.07 |
| Maximum | 9.84 | 260.1 | 7.638 | 4.14 |
| Skewness | 4.08 | 5.8 | 3.733 | 0.72 |
| Kurtosis | 15.65 | 34.3 | 16.235 | 0.30 |
| N | 37 | 36 | 37 | 37 |

Limits of quantitation (LOQ): cotinine = 0.05 ng/ml, 3-hydroxycotinine = 0.1 ng/ml, NNAL = 0.025 pg/ml, creatinine, = 0.05 mg/ml.

**Figure 2: Urinary Cotinine, 3-Hydroxycotine and NNAL after THS and Clean Clothing Exposures**

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CA is control clean clothing exposure, THS is thirdhand smoke-exposed clothing exposure

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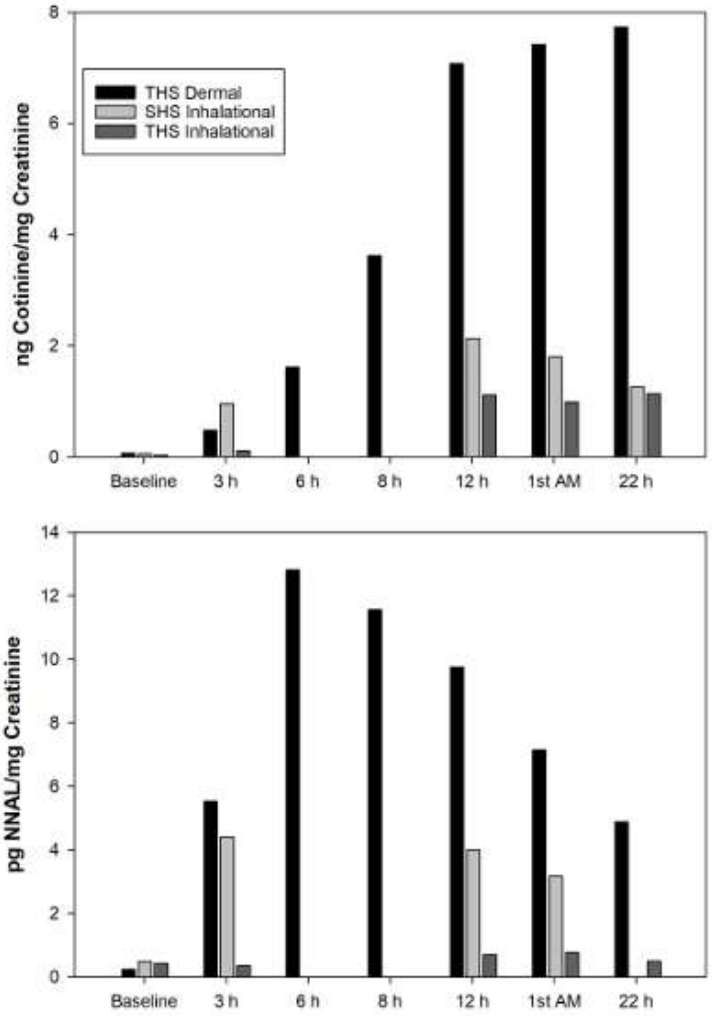



Figure 3: Urinary Cotinine, 3-Hydroxycotine and NNAL after THS and Clean Clothing Exposures

| **Table 3: Estimated Time-Specific Exposure Effects: THS Clothing vs Clean Clothing** | | | | |
|---|---|---|---|---|
| | Mean | Standard Error | z | 95% Confidence Interval |
| | **Cotinine/Creatinine*** | | | |
| Baseline | 0.19 | 0.30 | 0.64 | -0.40 - 0.78 |
| 3 h | 1.28 | 0.30 | 4.25 | 0.69 - 1.87 |
| 6 h | 2.55 | 0.30 | 8.38 | 1.95 -3.15 |
| 9 h | 3.54 | 0.30 | 11.79 | 2.95 - 4.13 |
| 12 h | 4.18 | 0.30 | 13.91 | 3.59 - 4.77 |
| 1st AM | 4.31 | 0.31 | 13.99 | 3.71 - 4.92 |
| 22 h | 4.48 | 0.30 | 14.89 | 3.89 - 5.06 |

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| | | | | |
|---|---|---|---|---|
| | **3HC/Creatinine** | | | |
| Baseline | 0.38 | 0.22 | 1.55 | -0.10 - 0.85 |
| 3 h | 1.12 | 0.24 | 4.60 | 0.65 - 1.60 |
| 6 h | 2.42 | 0.26 | 9.39 | 1.91 - 2.92 |
| 9 h | 3.08 | 0.24 | 12.96 | 2.62 - 3.55 |
| 12 h | 3.55 | 0.24 | 14.66 | 2.08 - 4.03 |
| 1st AM | 3.99 | 0.24 | 16.38 | 3.52 - 4.47 |
| 22 h | 4.33 | 0.24 | 18.22 | 3.87 - 4.80 |
| | **NNAL/Creatinine** | | | |
| Baseline | -0.01 | 0.35 | -0.03 | -0.69 - 0.68 |
| 3 h | 3.22 | 0.35 | 9.21 | 2.53 - 3.90 |
| 6 h | 3.93 | 0.35 | 11.25 | 3.35 - 4.62 |
| 9 h | 4.44 | 0.35 | 12.70 | 3.75 - 5.12 |
| 12 h | 4.43 | 0.35 | 12.68 | 3.74 - 5.12 |
| 1st AM | 3.60 | 0.36 | 10.06 | 2.90 - 4.30 |
| 22 h | 3.34 | 0.35 | 9.56 | 2.66 - 4.03 |
| *Urinary metabolite data normalized to creatinine were converted with the natural log and the data shown as “mean” and “95% confidence interval” = THS/Clean. | | | | |

| **Table 4: Interstudy Comparison of Nicotine and NNK Metabolites** | | | | |
|---|---|---|---|---|
| Smoke type | | SHS[22] | THS[23] | THS |
| Exposure route | | Respiratory | Respiratory | Dermal |
| Exposure duration | | 0.5 h | 3 h | 3 h |
| | | **Median Values** | | |
| **Cotinine ng/mg Creatinine** | Baseline | 0.06 | 0.03 | 0.07 |
| | Post-exposure | 0.96 | 0.12 | 0.48 |
| | 12 h | 2.13 | 1.11 | 7.08 |
| | 1st AM | 1.80 | 0.99 | 7.42 |
| | 22 h | 1.26 | 1.13 | 7.73 |
| **3-Hydroxycotinine ng/mg Creatinine** | Baseline | 0.44 | 0.34 | 0.44 |
| | Post-exposure | 1.31 | 0.41 | 1.65 |
| | 12 h | 6.29 | 2.66 | 13.10 |
| | 1st AM | 7.56 | 3.76 | 30.44 |
| | 22 h | 7.743 | 3.939 | 40.182 |
| **NNAL pg/mg Creatinine** | Baseline | 0.47 | 0.59 | 0.23 |
| | Post-exposure | 4.396 | 0.935 | 5.54 |
| | 12 h | 3.99 | 0.91 | 9.76 |
| | 1st AM | 3.17 | 0.77 | 7.14 |
| | 22 h | 2.59 | 0.61 | 4.87 |
| **Estimated[#] total µg nicotine excreted[@]** | | **13.6** | **7.45** | **64.59** |

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| | | | |
|---|---|---|---|
| **Estimated total µg nicotine absorbed*[(18)]** | **20.30** | **11.12** | **96.40** |
| **Estimated[#] total ng NNK excreted** | **3.28** | | **7.91** |
| **Estimated total ng NNK absorbed*[(19)]** | **27.33** | | **65.92** |

[#]Assuming 1 liter urine/day.
[@]Sum of total cotinine and total 3HC
*Estimates of absorbed nicotine and NNK are calculated by dividing the excreted metabolites by their fraction of the total urinary metabolites for the chemical: 0.67 for cotinine + 3-hydroxycotinine[(18)] and 0.12 for NNAL[(19)].

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