SUPPORTING INFORMATION

Thirdhand exposures to tobacco-specific nitrosamines through inhalation, dust ingestion, dermal uptake, and epidermal chemistry.

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Table S1: Tobacco smoke constituents in IARC Group 1 (carcinogenic to humans)

	Vapor pressure (mm Hg)
Organic compounds	
Formaldehyde	gas
Vinyl chloride	gas
Ethylene oxide	gas
1,3-Butadiene	gas
Benzene	96
4-Aminobiphenyl	7.7×10^{-2}
2-Naphthylamine	2.6×10^{-4}
N'-Nitrosonornicotine (NNN)	5.1×10^{-4}
4-(Methylnitrosamino)- 1-(3-pyridyl)-1-butanone (NNK)	6.8×10^{-5}
Benzo[a]pyrene (BaP)	5.5×10^{-9}
Inorganic species	
Arsenic	N/A
Beryllium	N/A
Nickel	N/A
Chromium	N/A
Cadmium	N/A
Polonium-210	N/A

Section S1: TSNA mutagenicity and carcinogenicity

Both NNK and NNN are activated metabolically, with formation of DNA adducts being considered critical for their mutagenicity and carcinogenicity [1, 2]. The carcinogenicity of NNK was tested in mice, rats, hamsters and mink, with administration via drinking water, gavage, subcutaneous or intraperitoneal injection, and skin painting [3-6]. NNK causes lung, liver, pancreas and other types of cancers and is more carcinogenic than NNN for the induction of lung and liver tumors in F344 rats or A/J mice [5, 7]. DNA adduct formation by NNK and NNN, after activation by the cytochrome P450 system, is considered a central mechanism for tumorigenesis [8]. In addition, the binding of NNK and NNN to the nicotinic acetylcholine receptor promotes tumor growth by enhancing and deregulating cell proliferation, migration, and invasion [9], thereby creating a microenvironment for tumor growth. The tumorigenic activity of NNA, together with NNK and NNN, was studied in strain A/J mice, and found to cause tumors, though at a lower incidence than NNK and NNN, with 36% for NNA compared to 87% and 76% for NNK and NNN, respectively [10]. In a study using a HPRT locus mutagenicity assay, NNA exhibited a mutagenic activity comparable to that of NNK in a human B-lymphoblastoid cell line expressing P450 CYP2D6 cDNA [11]. Similarly, the DNA damage caused by NNA and NNK in a comet assay quantifying strand breaks in human HepG2 cells showed a similar damage and dose response, suggesting comparable genotoxicity for both compounds [12]. Several NNA adducts were identified *in vitro* from its reaction with deoxyguanosine [13].

Figure S1: Experimental setup

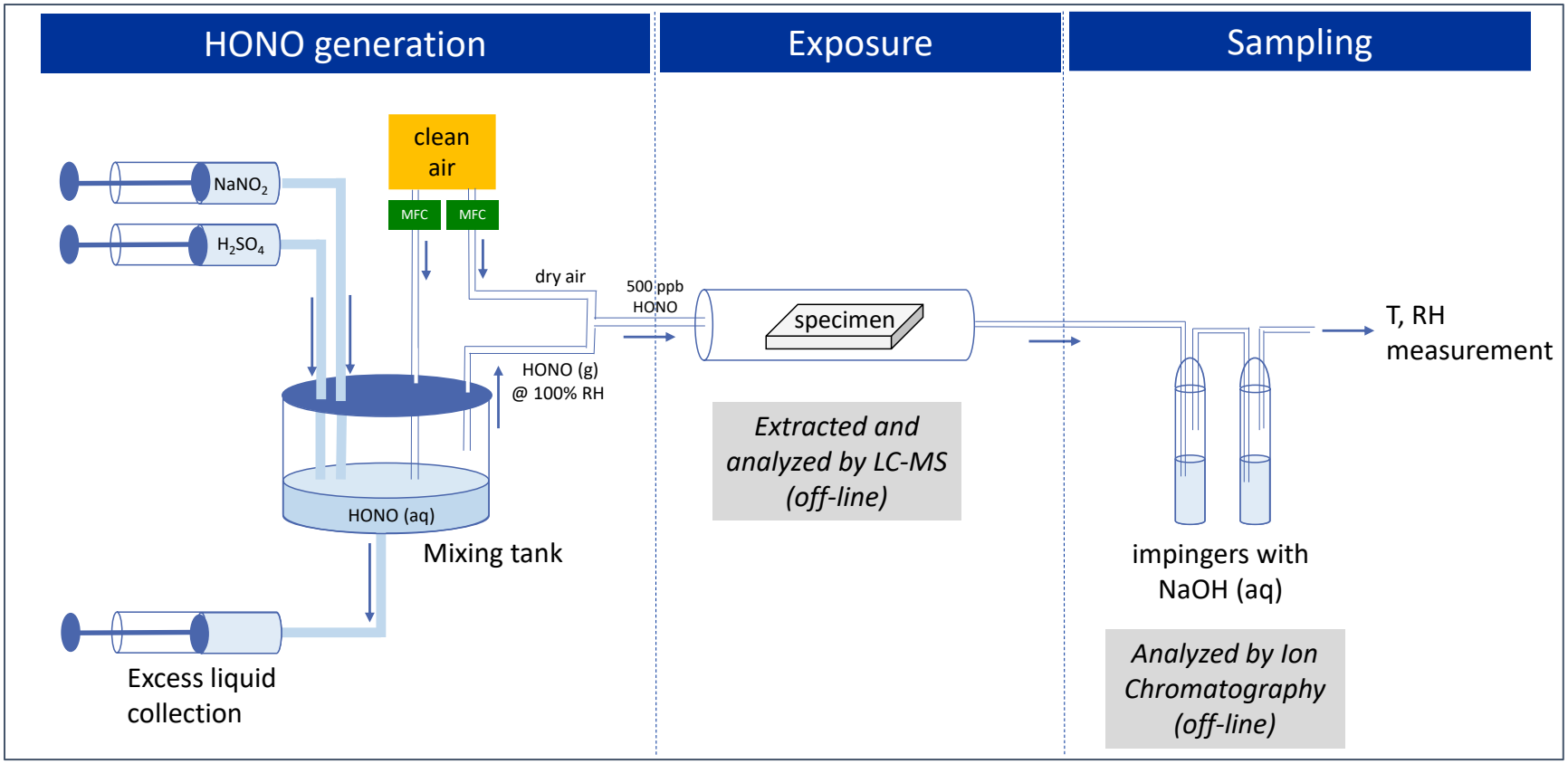
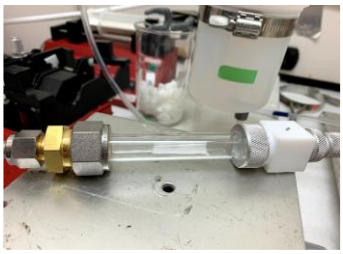


Table S2: Substrates and conditions used in the evaluation of the effects of skin liquids on the nitrosation of nicotine

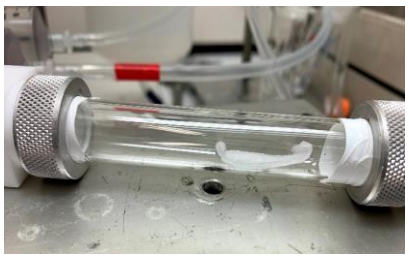
	Control (only HONO or nicotine)	Nicotine on clean substrate	Nicotine & skin liquids	Nicotine & artificial sweat, pH = 4	Nicotine & artificial sweat, pH = 7
Cellulose	×	×	×	×	×
Cotton	×	×	×	×	×

Figure S2: Specimens used in the experiments



Cellulose specimen (1 x 3 cm, 57 mg)

Cotton specimens on bandage applied to the skin (forearm) for 8 h prior to experiment



Cotton specimen (55 mg) with sweat surrogate mixture (250 mg)

Table S3: Sweat surrogate mixture composition*

Chemical	**Concentration (mM)**
NaCl	340
NH_4Cl	330
Urea	83
Lactic Acid	170
Acetic Acid	42

* adapted from Pavilonis et al, 2014 – *Risk Analysis* [14]

Section S2. Quantification of nicotine and TSNAs on cellulose and cotton substrates

The determination of nicotine and TSNAs is based on the method described by Whitehead et al. [28]

NNN and NNK: 200 µL of standards, QCs, or sample extracts and 100 µL internal standard solution were pipetted into a 13 × 100 mm glass culture tube. These were mixed with 0.75 mL of 1:1 saturated $NaHCO_3$/50% K_2CO_3 and 4 mL of 40:40:15:5 pentane/dichloromethane/ethyl acetate/isopropanol, added for the extraction of analytes. The tubes were vortexed, centrifuged, and placed in dry ice acetone bath to freeze the aqueous layers. The organic layers were poured into new tubes containing 200 µL 0.2N HCl in MeOH, and evaporated to dryness in a Thermo Speedvac centrifugal evaporator at (1.5h/45°C). The residues were reconstituted in 250 µL LC mobile phase and 10 µL were injected into the LC-MS/MS system. The LOQs were 0.05 ng/mL.

Nicotine: the same samples were diluted and analyzed by GC/MS to determine nicotine concentrations. The LOQ was 100 ng/mL.

NNA: A different aliquot from each sample was used. To 1 mL standards, QCs, and samples were added NNA-d_3 internal standard, followed by 750 µL 1:1 saturated $NaHCO_3$/50% K_2CO_3 and 4 mL 45:45:10 dichloromethane/pentane/ethyl acetate. The samples were vortexed, centrifuged, and placed in a dry ice/acetone bath to freeze the aqueous layers. The organic layers were poured to culture tubes containing 100 µL 0.1N HCl in methanol. The solvent was evaporated to dryness using a centrifugal vacuum evaporator (~1.5 hr at 45 deg C). To the tubes were added 200 µL of derivatizing agent, pentafluorophenylhydrazine (PFPH), 3 mg/mL in acetonitrile. The tubes were heated for 30 min at 60°. After cooling to room temperature, 0.5 mL of the base (1:1 saturated $NaHCO_3$/50% K_2CO_3) and 4 mL of extraction solvent (45:45:10 dichloromethane/pentane/ethyl acetate) was added. The samples were vortexed, centrifuged, and placed in a dry ice/acetone bath to freeze the aqueous layers. The organic layers were poured to culture tubes containing 0.5 mL of 1 M sulfuric acid, and the samples were vortexed, centrifuged, and placed in a dry ice/acetone bath to freeze the aqueous layers. The organic layers were poured off and discarded. The above base, 0.5 mL, and 4 mL of the above extraction solvent were added. The samples were vortexed, centrifuged, and placed in a dry ice/acetone bath to freeze the aqueous layers. The organic layers were poured to culture tubes and the solvent was evaporated at 55° with a stream of nitrogen. The evaporated samples were reconstituted in 50 µL mobile phase, 10 mM ammonium formate in 85:15 water/methanol. 20 µL were injected into the LC-MS/MS system, with a Phenomenex Phenyl-Hexyl 3 x 150 mm column, mass spectrometer with a heated ESI source (HESI), run in SRM mode, as described in Whitehead et al. The LOQ was 0.05 ng/mL.

Figure S3. DNA double strand breaks (DSBs) in lung epithelial cells in the presence of NNA.

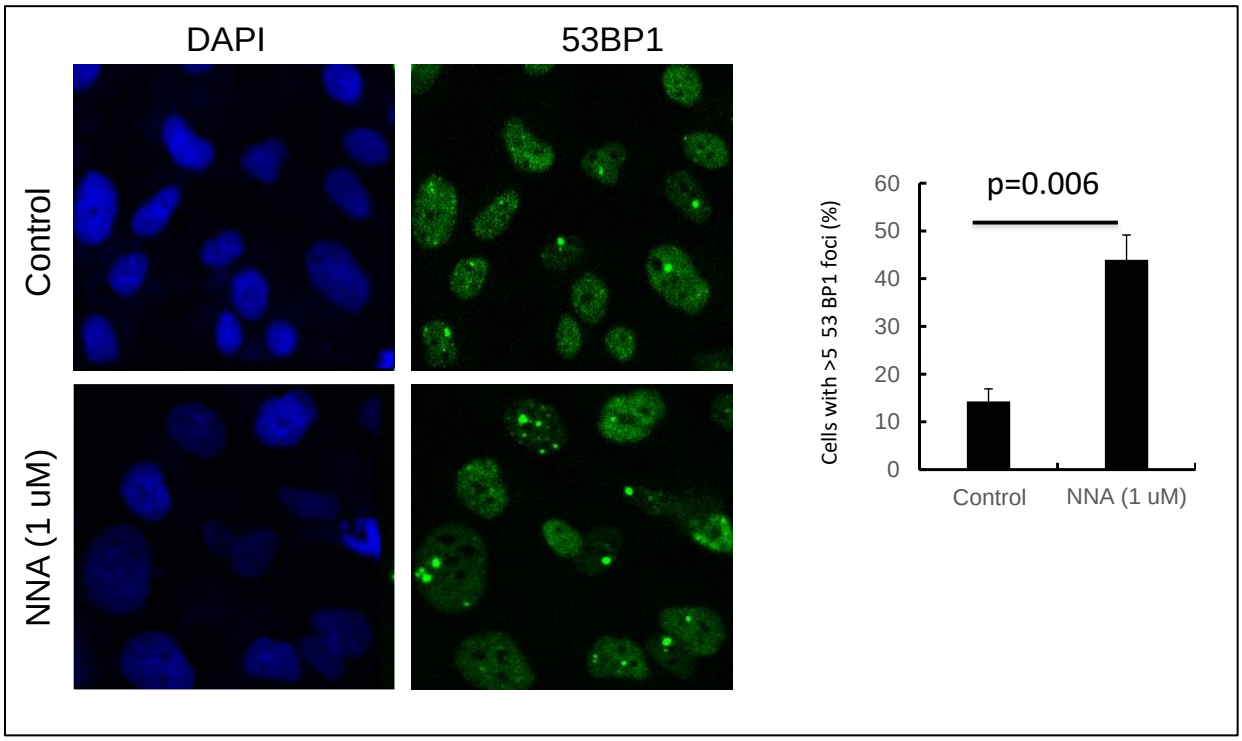
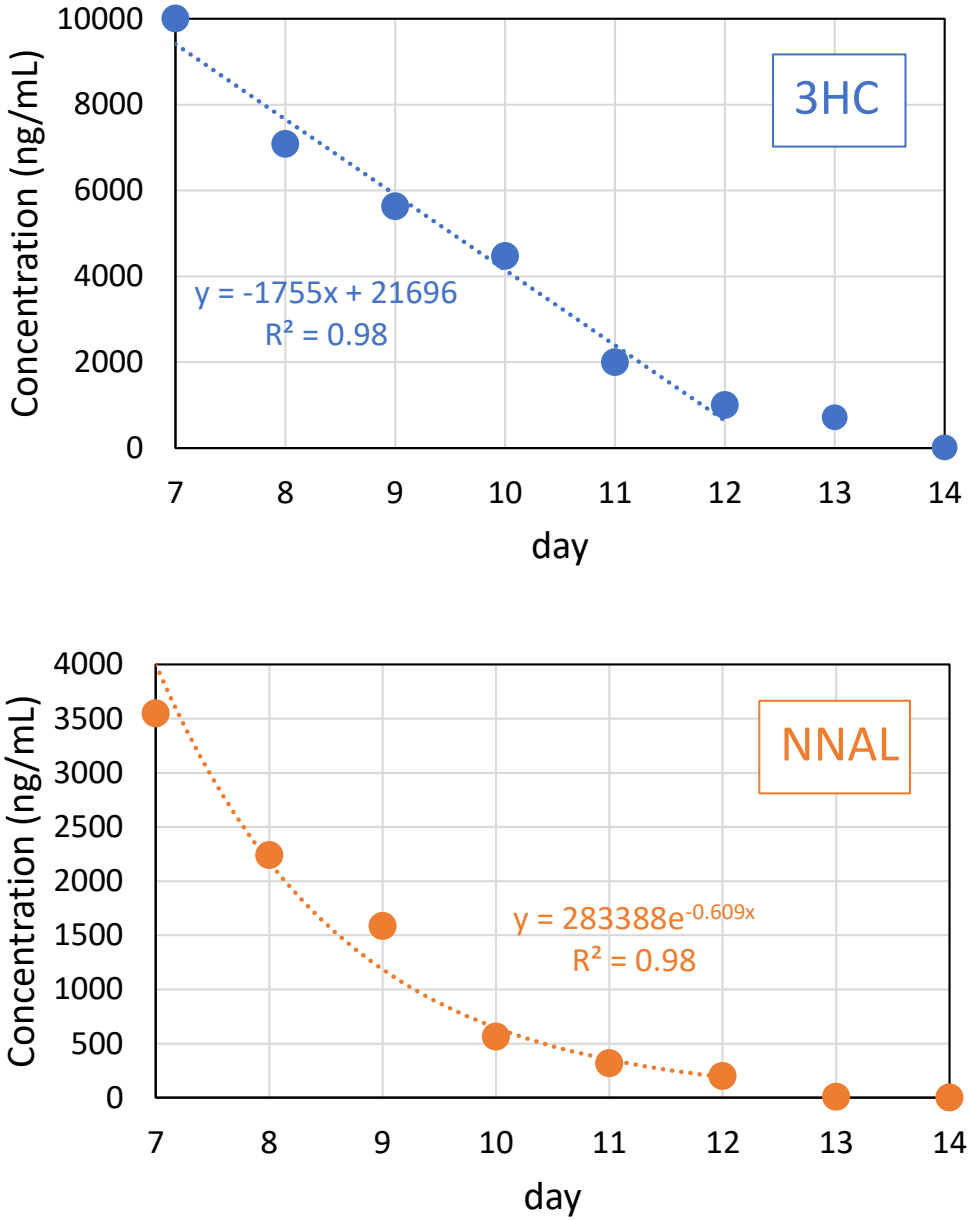


Figure S4. Loss kinetics for 3-HC (zero-order) and NNAL (first-order) in mice exposed dermally to nicotine and NNK, respectively.



Section S3: Human dermal uptake of nicotine and NNK from tobacco-laden clothing

Three volunteers wore tobacco-contaminated clothing inside an environmental chamber with nearly 0.85 air changes per minute. This is approximately 100 times more air exchange than is normally seen in homes in the US [15, 16]. Thus, dermal absorption, rather than inhalation, was the dominant form of exposure in this study. The clothing was long-sleeved shirts and full-length pants that had been exposed to cigarette smoke for 30 days, at concentrations similar to those found in the home of a pack-a-day smoker (3 mgs total particulate material). Each participant also completed a control exposure where they wore similar clothing that had not been exposed to smoke and the order of the exposures was randomized. The participants did not smoke tobacco or cannabis and were not exposed to smoke at home or work. They wore the clothing for three hours and exercised enough to perspire for thirty minutes out of each of hour. Urine specimens were collected prior to exposure, and at 8 hours after the start of exposure. Metabolites of nicotine (cotinine) and NNK (NNAL) were analyzed by published methods [17, 18].

The results show that both nicotine and NNK were absorbed through the human skin. Eight hours after the start of exposure, the urinary NNAL concentration was 86-fold higher than background levels, when the participants wore THS clothing, but remained at background levels when they wore clean clothing. The corresponding cotinine concentrations increased by a factor of 18 during the same period when tobacco-contaminated clothing was worn. These findings suggest that despite having a higher molecular weight than nicotine, NNK passes through the human dermis and into the bloodstream.

Table S4: Biomarkers of nicotine and NNK measured in urine before (background) and eight hours after exposure to tobacco-contaminated clothing.

	Cotinine (ng/mg creatinine)	**NNAL (pg/mg creatinine)**
Limit of quantification (LOQ)	0.04	0.02
Background	0.61	0.16
After exposure	11.1	13.8

Table S5: Measured formation rates and predicted rate constants for NNK, NNN and NNA resulting from the nitrosation of skin-bound nicotine

TSNA (*i*)	Formation rate, r_i	Rate constant, k_i	
	(nmol m^{-2} h^{-1})	(ppb^{-1} h^{-1})	(ppb^{-1} day^{-1})
NNK	24 – 72	$2.3 \times 10^{-8} – 6.9 \times 10^{-8}$	$5.5 \times 10^{-7} – 1.6 \times 10^{-6}$
NNN	17 – 73	$1.6 \times 10^{-8} – 7.0 \times 10^{-8}$	$3.9 \times 10^{-7} – 1.7 \times 10^{-6}$
NNA	53 - 179	$5.0 \times 10^{-8} – 1.7 \times 10^{-7}$	$1.2 \times 10^{-6} – 4.1 \times 10^{-6}$

Section S4: Determination of the NNK formation rate constant

The quantitative determination of nicotine, HONO and TSNA concentrations allowed for the estimation of the rate constant k_{NNK} for NNK formation through epidermal chemistry. The formation rate r_{NNK} on experiments carried out on cellulose and cotton was between 24 and 72 nmol m^{-2} h^{-1}. For these experiments, considering a nicotine skin surface concentration $C_N = 1.5 \times 10^3$ µmol m^{-2}, a HONO concentration [HONO] = 700 ppb, and a median NNK formation rate r_{NNK} = 37 nmol m^{-2} h^{-1}, a bimolecular reaction rate constant $k_{NNK} = 5.5 \times 10^{-7} – 1.6 \times 10^{-6}$ was determined as the ratio:

$$k_{NNK} = \frac{r_{NNK}}{[\mathrm{HONO}] \times C_N} \quad \text{(S1)}$$

Figure S5. NNA concentration on substrates modified with artificial sweat surrogate mixture at pH = 4 (light blue) and pH = 7 (dark blue)

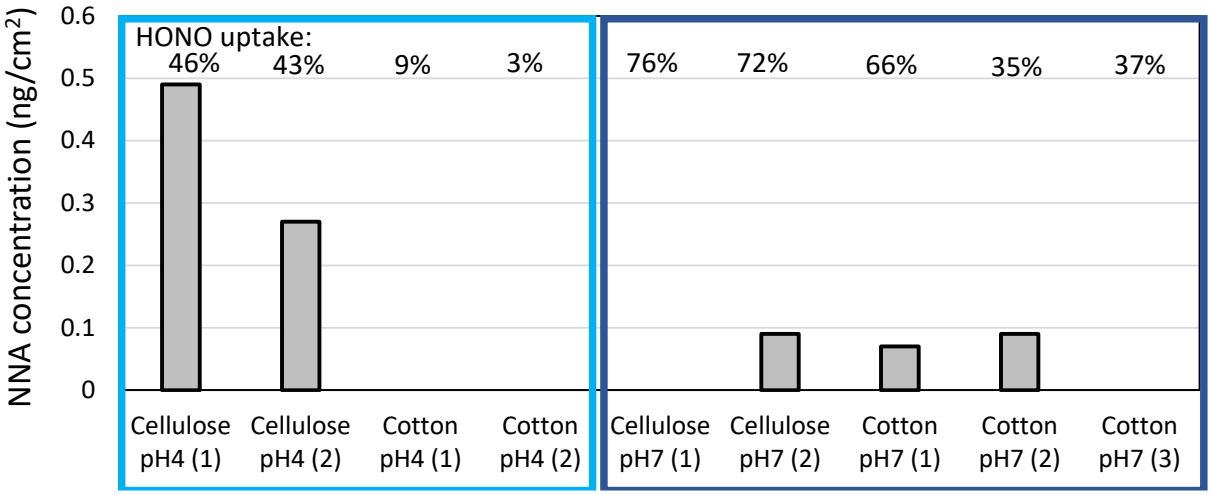


Table S6: TSNA and nicotine concentrations in indoor and outdoor air

AIR	Nicotine ($ng\ m^{-3}$)	$PM_{2.5}$ ($\mu g\ m^{-3}$)	TSNAs			NNK / nicotine ratio (x1000)	Reference
			NNN ($pg\ m^{-3}$)	NNK ($pg\ m^{-3}$)	NNA ($pg\ m^{-3}$)		
Indoor air							
16-m^3 room-sized chamber, secondhand smoke (SHS)	61,000	1,500	12,000	253,000	1000	4.1	[19]
16-m^3 room-sized chamber, 1-3 h post-smoking (SHS/THS)	21,000	500	5,500	10,900		0.5	
16-m^3 room-sized chamber, 4-18 h post-smoking (THS)	5,900	25	120	240	110	0.041	
16-m^3 room-sized chamber, 19-43 h post-smoking (THS>24h)	2,700	2	80	40	7	0.015	
Smoke aging chamber	5,000 – 70,000			3,000-100,000		0.60	[20]
Office of 72.3 m^3			810	4,130			[21]
Non-smoking homes with reported past smoking	70 – 400						[22]
Hookah bars Istanbul, Moscow, Cairo	700 – 1,400	82-213		500 – 1,900		0.71	[23]
Bars and restaurants, Germany (n=10)	2,200-33,500			7,000-50,000		3.2	[24]
Smoker homes, Germany (n=5)	3,600-28,500			4,100-23,000		1.1	
Smoker offices, Germany (n=4)	4,000-20,000			2,400-15,200		0.60	
Bars and restaurants, USA (n=5)			n.d.-22,800	1,400-23,800			[25]
Outdoor (urban) air							
London, UK			200	290			[26]
San Francisco, CA	3.4		0.17	0.63		0.19	[13]
California (five sites)	0.41 - 7.6			0.2 – 4.3			[27]
Birmingham, UK	0.54 - 5.5			4.3			
Hong Kong, China				4.2 – 9.9			
Msida, Malta	6.7 - 82	8		2.1 – 37			

Table S7: TSNA and nicotine concentrations in settled indoor dust

DUST	Nicotine ($\mu g\ g^{-1}$)	n	TSNAs					NNK / nicotine ratio (x1000)	Reference
			NNN ($ng\ g^{-1}$)	NNK ($ng\ g^{-1}$)	NNA ($ng\ g^{-1}$)	NAT	NAB		
CA - smokers' homes (2002-2007)	7	6	1.6	3.7	0.46			0.53	[28]
CA - non-smokers homes (2002-2007)	0.52	20	<LOQ	<LOQ	<LOQ				
CA - smokers' homes (2010)	7.8	6	2.9	5.8	0.6			0.74	
CA - non-smokers homes (2010)	0.51	20	<LOQ	0.51	<LOQ			1.00	
CA - homes - baseline	17.4	17/22/65	2.5	8.9		2.0	0.9	0.51	[29]
CA - homes - week 1 after quitting	10.5	7 and 13/22	1.5	11.2		3.4	<LOQ	1.07	
CA - homes - month 1 after quitting	5.2	4 and 9		9.9		<LOQ		1.90	
CA - homes - month 3 after quitting	2.8	7							
CA - homes - month 6 after quitting	3.8	5							
CA - casino bingo hall (smoking)	121		24	84		31	8.6	0.69	[30]
CA - casino slots (non-smoking)	145		23	53		13	6.4	0.37	
CA - casino central area (pit)	170		14	31		34	2.6	0.18	
Korea - government buildings		10		189					[31]
Korea - large buildings		10		198					
Korea - nurseries		5		15					
Korea - private educational institutions		7		45					
China – smoking hotel rooms		31	640 (230 – 1200)	1190 (320 – 3720)	40 (<LOQ – 130)				[32]
Europe - nonsmokers house dust	2.3			40				17.4	[33]
Europe - smokers house dust	26			540				20.8	

Table S8: TSNA and nicotine concentrations in indoor surfaces and skin

SURFACES AND SKIN	n	Nicotine (μg m^{-2})	TSNAs			Reference
			NNN (ng m^{-2})	NNK (ng m^{-2})	NNA (ng m^{-2})	
Homes - baseline	45	31.2				[29]
Homes - week 1 after quitting	35	10.8				
Homes - month 1 after quitting	17	4.3				
Homes - month 3 after quitting	11	2.6				
Homes - month 6 after quitting	7	3.2				
Apartments – multiunit housing	38	7.2 - 62				[34]
37 smoker homes	37			70		[35]
19 nonsmoker homes	19			<LOQ		
Nonsmoker homes (living room)	5	1.37				[36]
Hookah-only smoker homes	19	32				
NICU crib/incubator	5	0.18				[37]
NICU furniture	6	7.9				
Terrycloth stored 11 months		106	37	170	229	[38]
Terrycloth stored 16 months		113	46	219	219	
Terrycloth stored 19 months		70	31	132	88	
Polyester stored 11 months		0.56				
Polyester stored 19 months		1.79		3.2		
Smoker's finger	17	150 (a)				[39]
Finger of occupants in smoking homes	91	157 (a)				[22]
Finger of non-smoker new occupants	19	1.2 (a)				
Children's hands	276	9 (b)				[40]
Children's hands (protected from exposure to tobacco smoke)	311	0.3 (b)				[41]
Children's hands (exposed to smoke)	193	2.2 (b)				
Children's hands (THS-free home)	10	1.3				[42]
Children's hands (THS-polluted home)	19	32				
Silicone wristbands used as exposure monitors for 2 days	31	167				[43]

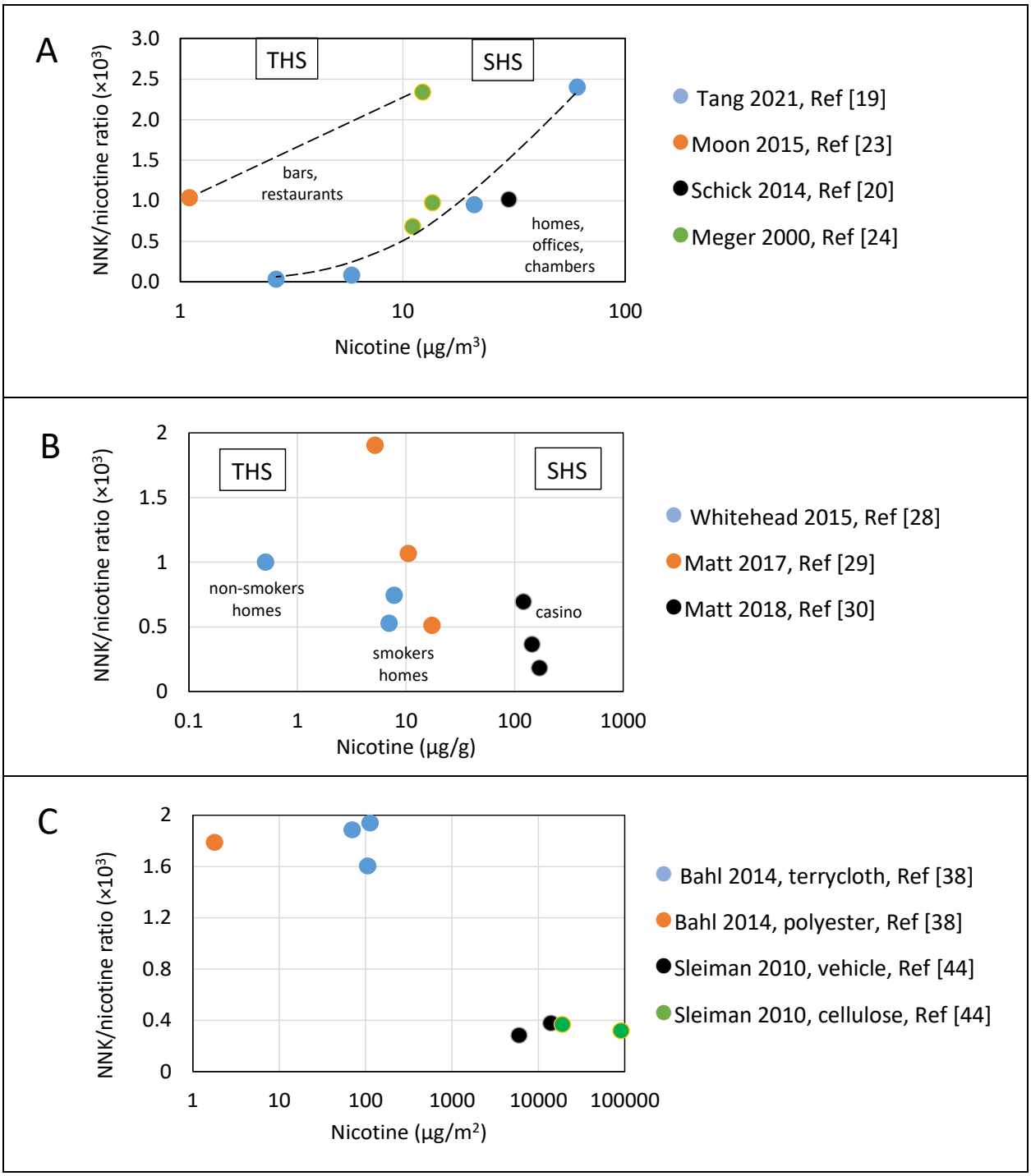
(a) assumes 42 cm^2 per wipe

(b) assumes 100 cm^2 per wipe

Table S9: TSNA concentrations measured simultaneously in the gas phase and particle phase at different times after smoking ended, and fraction of each compound in the gas phase (results published in Tang et al, 2021 [19], Figure 2)

Compound	Blank chamber	SHS (fresh smoke)	SHS/THS (1-3 h post smoking)	THS (4-18 h post smoking)	THS>24h (19-43 h post smoking)
Denuder (gas phase), ng m^{-3}					
NNN	0.01	0.9	0.5	0.02	0.06
NNA	n.d.	n.d.	n.d.	0.07	0.01
NNK	n.d.	2.4	0.41	0.19	0.04
Filter (particle phase), ng m^{-3}					
NNN	0.06	15.2	4.89	0.098	n.d.
NNA	0.036	1.28	n.d.	n.d.	n.d.
NNK	0.031	245	12.8	0.039	n.d.
Fraction in gas phase, f_g					
NNN		6%	9%	21%	100%
NNA		0%	0%	100%	100%
NNK		1%	3%	96%	100%

Figure S6. NNK/nicotine ratio from different studies reported in the literature in A) indoor air, B) indoor settled dust, and C) indoor surfaces. Labels "SHS" and "THS" indicate samples that are more typically associated with secondhand and thirdhand smoke, respectively.



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