

# 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol and its Glucuronides in the Urine of Infants Exposed to Environmental Tobacco Smoke

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## Abstract

Biomarkers of carcinogen uptake could provide important information pertinent to the question of exposure to environmental tobacco smoke (ETS) in childhood and cancer development later in life. Previous studies have focused on exposures before birth and during childhood, but carcinogen uptake from ETS in infants has not been reported. Exposures in infants could be higher than in children or adults because of their proximity to parents who smoke. Therefore, we quantified 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL) in the urine of 144 infants, ages 3 to 12 months, who lived in homes with parents who smoked. Total NNAL is an accepted biomarker of uptake of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Cotinine and its glucuronide (total cotinine) and nicotine and its glucuronide (total nicotine)

were also quantified. Total NNAL was detectable in 67 of 144 infants (46.5%). Mean levels of total NNAL in the 144 infants were  $0.083 \pm 0.200$  pmol/mL, whereas those of total cotinine and total nicotine were  $0.133 \pm 0.190$  and  $0.069 \pm 0.102$  nmol/mL, respectively. The number of cigarettes smoked per week in the home or car by any family member when the infant was present was significantly higher ( $P < 0.0001$ ) when NNAL was detected than when it was not ( $76.0 \pm 88.1$  versus  $27.1 \pm 38.2$ ). The mean level of NNAL detected in the urine of these infants was higher than in most other field studies of ETS exposure. The results of this study show substantial uptake of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in infants exposed to ETS and support the concept that persistent ETS exposure in childhood could be related to cancer later in life. (Cancer Epidemiol Biomarkers Prev 2006;15(5):988–92)

## Introduction

A consistent body of data from over 50 epidemiologic studies shows that environmental tobacco smoke (ETS) is a cause of lung cancer in nonsmokers (1). ETS is classified as a human carcinogen by the IARC, the U.S. Department of Health and Human Services, the Environmental Protection Agency, and other groups (1-5). It is biologically plausible that ETS causes lung cancer because it contains all the same carcinogens and toxicants to which active smokers are exposed.

Most studies of ETS exposure and lung cancer have been concerned with exposure of adults, mainly nonsmoking spouses of smokers and people exposed in the workplace (1). The relationship between exposure to ETS in childhood and the occurrence of lung cancer later in life is less consistent than that for exposure in adulthood (1, 6). Many factors impede the investigation of this relationship, not the least of which is accurate exposure assessment during childhood.

Tobacco carcinogen biomarkers, such as urinary carcinogen metabolites, hemoglobin adducts, and DNA adducts, can be used to assess carcinogen uptake and metabolic activation in nonsmokers exposed to ETS (7). One of the most useful carcinogen biomarkers for ETS studies is total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL, the sum of NNAL and its glucuronides) in urine (7-9). NNAL and its glucuronides are metabolites of the tobacco-specific carcino-

gen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK; ref. 10). NNK causes tumors of the lung, pancreas, nasal cavity, and liver in rodents (10). NNK is believed to play a significant role as a cause of lung cancer in smokers and in nonsmokers exposed to ETS and is classified, along with the related tobacco-specific nitrosamine *N*'-nitrosornicotine, as carcinogenic to humans by IARC (11). The tobacco specificity of NNK, and therefore total NNAL, makes total NNAL a particularly useful biomarker for gauging carcinogen uptake from ETS.

Previous studies have determined levels of total NNAL in the urine of newborns, children, and adults exposed to ETS (7-9, 12-14). However, there are no data in the literature on levels of total NNAL in the urine of infants (children of age  $\leq 12$  months) nor could we identify studies of any other carcinogen biomarker in infants exposed to ETS. Infant exposure to ETS could be higher than exposures during other periods of childhood because infants have relatively limited mobility and independence. Therefore, in this study, we quantified total NNAL, total nicotine, and total cotinine in the urine of 144 infants, ages 3 to 12 months, who lived in homes where at least one parent smoked.

## Materials and Methods

**Subjects.** This study was approved by the University of Minnesota Research Subjects' Protection Programs Institutional Review Board Human Subjects Committee.

**Recruitment and Data Collection Procedure.** Mothers of young children were recruited in the context of a study to assess the effectiveness of an intervention to decrease infant exposure to ETS. The intervention included up to six counseling sessions completed over a period of 6 months to help mothers identify the situations in which their infants were exposed to ETS and then develop strategies to decrease

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**Table 1. Demographic and smoking characteristics of mother-infant dyads**

Characteristic	% (n)	Mean $\pm$ SD
Male infant	50.1 (73)	
Infant age (mo)		6.6 $\pm$ 1.9
Mother age (y)		25.7 $\pm$ 5.7
Ethnicity of mother		
White	71.5 (103)	
Black	13.2 (19)	
Asian	2.1 (3)	
Hispanic	2.1 (3)	
Other	11.1 (16)	
Education of mother		
High school or less	55.2 (79)	
Vocational school	12.6 (18)	
Some college	28.0 (40)	
College degree	4.2 (6)	
Cigarettes/wk (mother)		98.2 $\pm$ 58.9
Other smokers in household		1.1 $\pm$ 1.0

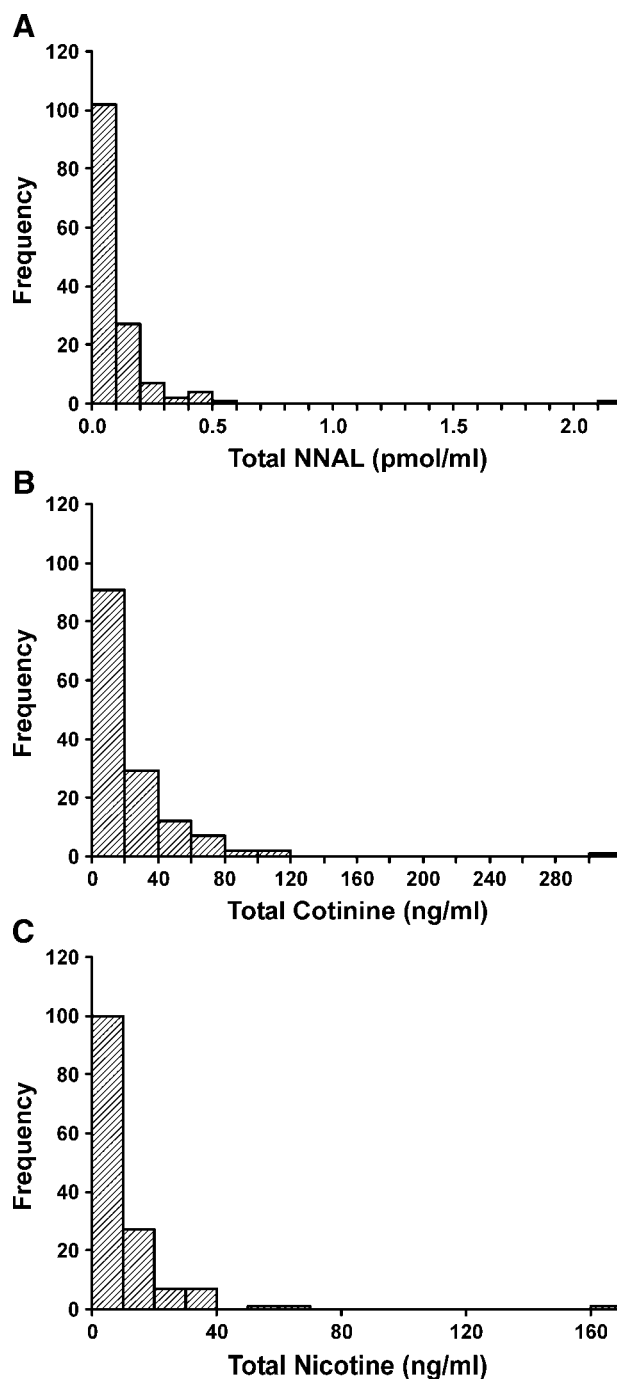
exposure. Subjects were recruited through Women, Infants, and Children clinics (administered by the Food and Nutrition Service of the U.S. Department of Agriculture) and two managed care organizations based in the Minneapolis/St. Paul area. Mothers first completed a screening survey to determine whether they were eligible for the study.

They were eligible if they reported that they were  $\geq 18$  years old, not currently breast feeding, and were daily or occasional smokers, and that someone had smoked tobacco in the previous 7 days either in the home or in the car when the baby was present. Women who met eligibility criteria for the study were asked to complete an interview conducted in their homes; they were given \$25 for participating in the interview.

During the interview, urine was collected from the infants using pediatric urine collection bags. The infant was cleaned as if preparing to change his/her diaper and the bag was attached with its adhesive patches. The bag was left in place for 2 to 4 hours or until a minimum of 2 mL urine had been collected. Urine samples were transported to the laboratory, distributed to one to four vials, depending on the amount of urine provided, and frozen within 24 hours of collection.

**Measures.** Interviewers asked for detailed information about the mother's smoking patterns; tobacco use in the home and car by the mother, other members of the household, and visitors; and the infant's exposure to ETS from all sources in the previous week. These questions were modeled on those used by Hovell et al. (15). The mother's smoking and exposure patterns were determined by first asking the number of cigarettes smoked per day on typical weekdays and weekend days and then, separately for weekdays and weekend days asking how many cigarettes were smoked at work, inside the home, outside the home, in the car, and elsewhere, and then finally asking how many of these cigarettes were smoked when the infant was present. Questions about other smoking in the home and car and the infant's exposure to ETS from cigarettes smoked by persons other than the mother were asked by first enumerating the members of the household and the visitors in the preceding week and then asking, for each category, the number of cigarettes smoked in the home and car and the number smoked in the presence of the infant. Finally, the mother was asked about the number of cigarettes to which the infant was exposed outside the home and car in the previous week. All reports of smoking and ETS were converted to cigarettes per week and several measures of smoking and exposure were derived. These were as follows: direct exposure, the number of cigarettes smoked by anyone in

the presence of the infant (i.e., in the same room or in the car when the baby was present); direct exposure (mother), the number smoked in the presence of the infant by the mother; indirect exposure, the number smoked in the house or car by anyone when the infant was not present; total smoked (mother), the number smoked by the mother, regardless of site and the presence of the infant. More detailed information about the proximity of the infant within the room or car to the source of smoke, or the level of ventilation, was not collected. Mothers were also asked for demographic information, including infant age and sex; the mother's age, ethnicity, and education level; and the number of other smokers living in the household.



**Figure 1.** Distribution of values of total NNAL (A), total cotinine (B), and total nicotine (C) in the urine of 144 infants, ages 3 to 12 months.

**Table 2. Levels of total NNAL, total cotinine, and total nicotine in the urine of 144 infants exposed to ETS**

	% (n)	Mean ± SD	Range
All samples			
Total NNAL (pmol/mL)	100 (144)	0.083 ± 0.200	ND*-2.12
Total cotinine (nmol/mL)	100 (144)	0.133 ± 0.190	ND-1.81
Total nicotine (nmol/mL)	100 (144)	0.069 ± 0.102	ND-1.02
Samples with detectable biomarkers			
Total NNAL (pmol/mL)	46.5 (67)	0.179 ± 0.264	0.029-2.12
Total cotinine (nmol/mL)	93.1 (134)	0.143 ± 0.194	0.006-1.81
Total nicotine (nmol/mL)	97.9 (141)	0.070 ± 0.103	0.006-1.02

Abbreviation: ND, not detected (below the limit of quantitation).

\*Detection limits were calculated for each sample and were as follows: total NNAL (0.09-0.36 pmol/mL), total cotinine (0.5-2 ng/mL), and total nicotine (0.5-2 ng/mL). A value of zero was used for samples which were below the limit of detection. To convert nmol cotinine to ng, multiply by 176; for nicotine, multiply by 162.

## Methods

**Biomarker Analyses.** Total cotinine (cotinine plus cotinine glucuronide), total nicotine (nicotine plus nicotine glucuronides), and creatinine in urine were determined as described previously (16). Total NNAL was measured essentially as described (17), except that the high-performance liquid chromatography purification step was replaced by purification on a solid phase ion exchange cartridge, as previously described (18), and 5-(methylnitrosamino)-1-(3-pyridyl)-1-pentanol was used as internal standard. Coefficients of variation for all assays are <10% and all are highly sensitive and specific for the compounds measured. Limits of quantitation for the analytes were calculated for each sample based on urine volume and recovery. When the analyte level was below the limit of quantitation, a value of zero was used.

**Statistical Analyses.** All statistical analyses were conducted using SAS for Windows, version 9.1. Various exposure levels, measured by the number of cigarettes smoked per week from the groups with and without detectable NNAL, were compared using the two-sided Wilcoxon test.

## Results

A total of 224 mother-infant dyads were included in the intervention trial. Of these, 31 were excluded from the study because the infants were not in the age range 3 to 12 months; 47 were excluded because the infant did not provide sufficient urine for assay of all analytes; and 2 had values for creatinine (>1.0 mg/mL) or total cotinine (>1,000 ng/mL), which indicated that the urine samples were not from infants. Demographic characteristics of the remaining 144 mother-infant dyads are summarized in Table 1. Infants ranged in age from 3.6 to 12.0 months; 50% were male. The sample of mothers ranged in age from 18 to 48 years and was predominately White. Eighty-two percent reported being daily

smokers and 72% lived in households that included other smokers.

The distributions of total NNAL, total cotinine, and total nicotine values are illustrated in Fig. 1. The number of infants with detectable or nondetectable levels of total NNAL, total cotinine, and total nicotine are summarized in Table 2. Sixty-seven infants (46.5%) had detectable NNAL in their urine, whereas the corresponding figures for cotinine and nicotine were 134 (93.1%) and 141 (97.9%), respectively. Twenty-five infants (17.4%) had cotinine values <5 ng/mL and only one of these had detectable total NNAL. Levels of total NNAL, total cotinine, and total nicotine in the urine of the ETS-exposed infants are also summarized in Table 2. Levels of total NNAL for the entire sample were  $0.083 \pm 0.200$  pmol/mL ( $0.431 \pm 1.32$  pmol/mg creatinine), whereas those of total cotinine and total nicotine were  $0.133 \pm 0.190$  nmol/mL ( $0.754 \pm 0.914$  nmol/mg creatinine) and  $0.069 \pm 0.102$  nmol/mL ( $0.445 \pm 0.852$  nmol/mg creatinine), respectively.

The relationship between reported exposure and detectability of NNAL is summarized in Table 3. The mean number of cigarettes smoked per week in the home or car by any family member when the infant was present (termed direct exposure) was significantly higher ( $P < 0.0001$ ) when NNAL was detected than when it was not ( $76.0 \pm 88.1$  versus  $27.1 \pm 38.2$ ). This was also true for direct exposure from the mother but barely missed significance for indirect exposure (number of cigarettes smoked per week in the home or car when the infant was not present). Total cigarettes smoked per week by the mother, including locations other than the home or car, were not significantly related to NNAL detectability. Exposure of infants outside the home and car was infrequent, with a mean of seven cigarettes per week. There were weak but significant correlations between total NNAL and direct exposure in number of cigarettes per week ( $r = 0.22$ ,  $P = 0.01$ ), indirect exposure ( $r = 0.25$ ,  $P = 0.003$ ), and direct exposure only to the mother's cigarettes ( $r = 0.18$ ,  $P = 0.03$ ).

Levels of total NNAL in urine correlated with those of total cotinine ( $r = 0.47$ ,  $P < 0.0001$ ) and total nicotine ( $r = 0.26$ ,  $P = 0.002$ ). Levels of total cotinine correlated with those of total nicotine ( $r = 0.46$ ,  $P < 0.0001$ ).

## Discussion

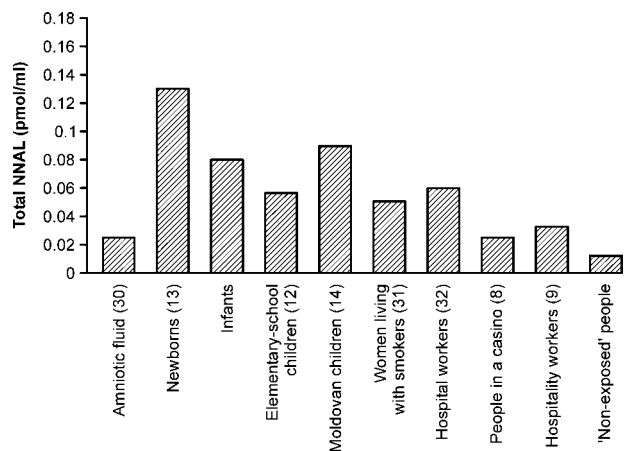
The results of this study show, for the first time, carcinogen uptake by infants exposed to ETS. The presence of NNAL in the urine of these infants can be explained only by their exposure to the tobacco-specific carcinogen NNK. This exposure was most likely through ETS, although uptake of NNK from surfaces, such as rugs or furniture, cannot be excluded. In either case, the NNK originated from tobacco products, which are its only known exogenous source. This is consistent with the data in Table 3 showing significant relationships between direct and indirect exposure to cigarette smoke and NNAL detectability.

**Table 3. Relationship between reported ETS exposure and NNAL detectability in the urine of infants**

Type of exposure to ETS	NNAL not detected		NNAL detected		P
	n	No. cigarettes/wk (mean ± SD)	n	No. cigarettes/wk (mean ± SD)	
Direct*	77	27.1 ± 38.2	67	76.0 ± 88.1	<0.0001
Indirect†	77	47.5 ± 51.7	66	67.5 ± 68.6	0.06
Direct (mother only)	77	13.1 ± 16.1	67	33.0 ± 37.0	<0.003
Total cigarettes/wk (mother only)	77	92.4 ± 63.9	67	105 ± 52.2	0.09

\*Number of cigarettes smoked in home or car by any family member when the infant is present.

†Number of cigarettes smoked in home or car when the infant is not present.



**Figure 2.** Mean levels of total NNAL in the urine of nonsmokers exposed to ETS at various stages of life, from the data in this study and published data. References are given in parentheses next to the type of exposure.

The mean level of total NNAL in the urine of these infants,  $0.083 \pm 0.200$  pmol/mL, was higher than in most other field studies involving NNK uptake from ETS (8, 9, 12, 14). Figure 2 summarizes data from previous studies. All studies in adults gave total NNAL levels ranging from  $\sim 0.02$  to  $0.06$  pmol/mL urine. Two studies in children had mean levels of  $0.056$  and  $0.09$  pmol/mL, the latter value, from a study of Moldovan children, being similar to that reported here. Amounts of total NNAL in amniotic fluid and in the urine of newborns, resulting from transplacental exposure to NNK, were  $0.025$  and  $0.13$  pmol/mL, respectively. The relatively high levels in the present study, which in one infant was  $2.1$  pmol/mL, similar to those observed in some smokers (17), are probably strongly influenced by the proximity of the smoking mother and her child. The contribution of these exposures to cancer risk later in life is of course unknown, but the continual uptake of NNK in the children of parents who smoke must entail some risk, all of which is potentially avoidable.

Anderson et al. (18) evaluated the tumorigenicity of NNK in infant mice. Cr:NIH(S) (NIH Swiss outbred) mice were given  $50$  mg/kg NNK by i.p. injection on postnatal days 1, 4, 7, 10, and 14. At an average age of 13 to 15 months, hepatocellular tumors, including malignant tumors, were observed in 57% of the males and 14% of the females. There were no liver tumors in control mice. A significant increase in primary lung tumors was also observed in NNK-treated males, with an incidence of 57%. The strong effect of NNK on the liver in this experiment, which contrasts to its ability to preferentially induce lung tumors in adult animals, may be due to differences in NNK metabolism in infant versus adult mice. These results indicate that NNK is a moderately potent neonatal carcinogen in mice. This establishes the principle that exposure to NNK in infancy could lead to cancer later in life, although the dose in this mouse experiment was clearly far higher than human exposure levels via ETS.

In a previous study carried out in school children, we found that NNAL was detectable in 50% of samples in which total cotinine levels were  $<5$  ng/mL and in 96% of samples in which total cotinine was  $>5$  ng/mL (12). In the present study, the  $5$  ng/mL value of total cotinine more accurately predicted total NNAL, as only one infant with cotinine  $<5$  ng/mL had detectable NNAL. Overall, NNAL was detected in the urine of 46.5% of the infants, whereas 93.1% had detectable cotinine. The lower frequency of detection of NNAL than cotinine is probably a consequence of analytic sensitivity as the method

used for NNAL is required to detect levels 1,000 times less than those of cotinine.

A significant correlation between urinary total NNAL and total cotinine was observed in this study, similar, although somewhat weaker, than seen in our previous studies of American children ( $r = 0.71$ ) and Moldovan children ( $r = 0.68$ ) exposed to ETS (12, 14). This correlation most likely reflects generally similar patterns of uptake of nicotine and NNK, but is probably weakened by differences in the metabolism of these compounds to cotinine and NNAL, respectively (20, 21). Our results suggest that there may be differences in metabolism of nicotine and NNK between infants and older children, perhaps due to developmental or environmental factors, but no data are available at present.

Many studies have reported levels of cotinine in children exposed to ETS, but relatively few present data for infants in the age range studied here (22). The range of values in the infant studies reported previously is very large and comparisons are difficult because of heterogeneity of ages, exposure conditions, and methods of analysis (23-26). In general, however, our data are within the range reported in studies with children. Fewer studies have measured urinary nicotine. The levels reported here may warrant further attention in view of the addictive properties of nicotine.

In summary, this study clearly shows uptake of the tobacco-specific carcinogen NNK, as well as nicotine, in infants exposed to ETS. Levels of urinary total NNAL in these infants were higher than seen in adults exposed to ETS, probably due to the proximity of the infant and the smoking mother. These exposures could contribute to cancer risk later in life, although further biomarker studies would be necessary to investigate that relationship. A broad range of potentially effective interventions to decrease exposure exists (27). These include efforts to encourage women to quit before or during pregnancy and to avoid postpartum relapse; to encourage smoking cessation among household members; and to establish no-smoking policies for the home and car. Evidence that nicotine is present in dust and surfaces of houses in which smoking takes places indicates that the complete elimination of smoking in homes is preferable to an emphasis on not smoking in the presence of children (28). Regulatory and economic policies (e.g., increasing the excise tax on cigarettes) are important approaches to decreasing the overall prevalence of smoking and therefore decreasing ETS exposure of children. Randomized trials of behavioral interventions with caregivers to decrease children's exposure to ETS have indicated that even low-intensity efforts can be effective, but that more intensive programs, usually involving extended counseling by individuals trained in smoking cessation counseling and provision of educational materials, often with support from a physician, are more likely to significantly decrease exposure (27). Studies have indicated that intensive efforts by pediatricians and their staff to address this issue are rare (29). It is important for pediatricians and other health care providers to recognize this potential hazard and deliver appropriate interventions.

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