Uptake of the Tobacco-Specific Lung Carcinogen 4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone by Moldovan Children

Irina Stepanov,[1] Stephen S. Hecht,[1] Gheorghe Duca,[2] and Igor Mardari[3]

[1]The Cancer Center, University of Minnesota, Minneapolis, Minnesota; [2]Academy of Sciences of Moldova; and [3]Department of Industrial and Ecological Chemistry, Moldova State University, Chisinau, Moldova

Abstract

The evidence of an association between childhood exposure to environmental tobacco smoke (ETS) and an increased risk of lung cancer is inconsistent. However, taking into account the existing association between lung cancer and adulthood ETS exposure, it is plausible that children exposed to ETS also would be at risk of developing lung cancer later in life. In this study, we investigated the uptake by Moldovan children of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) by measuring total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), the sum of the NNK metabolites, NNAL, and its O-glucuronide and N-glucuronide (NNAL-Glucs) in urine. We also measured urinary cotinine and its glucuronide (total cotinine). Total NNAL was detected in 69 of 80 samples, including those that were low in cotinine (<5 ng/mL). The mean $\pm$ SD level of total NNAL (0.09 $\pm$ 0.077 pmol/mL) was comparable with those observed in previous studies of children and adults exposed to ETS. Total NNAL correlated with total cotinine ($r = 0.8$, $P < 0.0001$). The mean $\pm$ SD levels of total NNAL and total cotinine were higher in children who were exposed to ETS (0.1 $\pm$ 0.08 and 109 $\pm$ 126 pmol/mL, respectively) than in those who were classified as unexposed to ETS based on questionnaire data (0.049 $\pm$ 0.016 pmol/mL and 0.043 $\pm$ 0.040 nmol/mL). The results of this study for the first time show widespread and considerable uptake of nicotine and the tobacco-specific lung carcinogen NNK in Moldovan children. These results should be useful in heightening the awareness of the dangers of smoking and ETS exposure in this eastern European country. (Cancer Epidemiol Biomarkers Prev 2006;15(1):7–11)

Introduction

Recently, the IARC reviewed >50 studies aimed at evaluating the association between exposure to environmental tobacco smoke (ETS) and the risk of lung cancer (1). A number of cohort studies of nonsmokers reported an increased risk of lung cancer associated with exposure to ETS from the spouse/partner (2-5). Studies based on general exposure to ETS produced similar results (6, 7). Similarly, a large number of case-control studies conducted in several countries provided evidence of an increased risk for lung cancer associated with ETS exposure from the spouse, indicating an exposure-response relationship (8-12). The evidence for an association between lung cancer and childhood exposure to ETS is less consistent than that for exposure in adulthood. The results of case-control studies on exposure to ETS during childhood and lung cancer risk are not consistent, only few of them reporting a significant increase related to exposure from a parent (13-16). However, taking into account the existing association between lung cancer and adulthood ETS exposure, it is plausible that children exposed to ETS also would be at risk of developing lung cancer later in life.

Data on the exposure of children to ETS are limited. In a study conducted in 1988 to 1994 in seven European countries, exposure to secondhand smoke in childhood was reported by 66% of respondents (17). A U.S. national survey indicated that 43% of children ages 2 months to 11 years live in homes with at least one active smoker (18). Parent-reported exposure to ETS among children varied widely in different countries (19). Considerable variations in exposure according to socioeconomic status have been observed. In a comprehensive cross-sectional study that examined exposure to ETS in 17,448 children in the United States, 41% of children of lower socioeconomic status and only 21% of children of higher socioeconomic status were exposed daily to ETS in their home (20). Exposure did not vary by race, family size, gender, or season (20). The lack of common standards for estimating ETS exposure in children and the possibility of inaccurate parental reports represent an additional challenge when comparing data between countries or social groups. An alternative measure of ETS exposure is analysis of uptake of tobacco smoke constituents by exposed children.

Our goal in this study was to investigate the uptake by Moldovan children of a tobacco-specific lung carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). NNK is a lung carcinogen in rodents and occurs in cured tobacco as well as in mainstream and sidestream smoke of cigarettes and in ETS. NNK has been suggested as a causative agent for adenocarcinoma of the lung in smokers and is implicated as a potential cause of lung cancer in nonsmokers as well (21-23). NNK uptake can be measured by analysis of the sum of the metabolites, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its O-glucuronide and N-glucuronide (NNAL-Glucs), referred to as total NNAL, in urine (24, 25).

The Republic of Moldova is a small eastern European country. Its economy was drastically affected by the disintegration of the former Soviet Union in 1991. Currently, poverty in Moldova constitutes a critical problem that crosses all social strata. Smoking has an alarming profile in Moldova, especially in rural areas, where 61% of men and 17% of women ages 15 to 50 years were smokers in 1997 (26). National regulations prohibit smoking in educational and health care
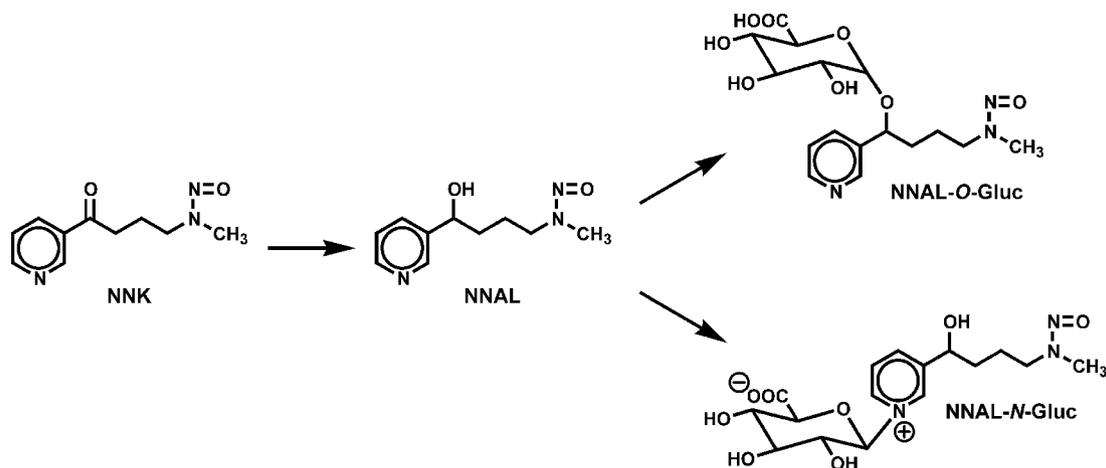
Figure 1. Structures of NNK, NNAL, NNAL-*O*-Gluc, and NNAL-*N*-Gluc.

facilities, public transport, governmental buildings, and workplaces. However, these regulations are not always respected, and bans on smoking in homes, cars, bars, and restaurants are uncommon. Therefore, Moldovan children practically cannot avoid being exposed to ETS at home, on playgrounds, at school (from schoolmates or teachers who smoke), and in vehicles. Evaluation of the association between total NNAL levels in the urine of these children with ETS exposure reported by parents perhaps could result in heightened awareness of the need for improved tobacco control in this eastern European country.

Materials and Methods

Subjects and Data Collection. This study was approved by the Moldovan Ministry of Health. Principals of randomly selected schools and kindergartens received an initial contact letter describing the study and asking permission to conduct the study at their school. If the principal agreed to collaborate, children and their families were contacted through the class teacher, who provided them with a letter describing the study, inviting them to volunteer, and explaining that a recruiter would contact them. Recruiters met with children and their parents at teacher-student conferences to explain the study and answer any questions. Parents/guardians of 80 children ages 5 to 10 years agreed to participate. Among those were children attending nursery and elementary schools in rural and urban areas of Moldova. A written consent from each child's parent or guardian was obtained, and answers were provided to a questionnaire regarding ETS exposure (27). Urine samples (15-100 mL) were collected, under the supervision of a school nurse, in 100-mL polypropylene containers and frozen at −15 °C until transportation to the Cancer Center for analysis.

Laboratory Analyses

Caution. NNAL (Fig. 1) is carcinogenic and mutagenic and should be handled with extreme care, using appropriate protective clothing and ventilation at all times.

Chemicals and Enzymes. NNAL and C_5-NNAL were purchased from Toronto Research Chemicals, Inc. (Toronto, Ontario, Canada). [CD_3]Cotinine and β-glucuronidase (type IX-A from *Escherichia coli*) were purchased from Sigma Chemical Co. (St. Louis, MO).

Total Cotinine (Cotinine plus Cotinine Glucuronide). Total cotinine was analyzed by a method similar to that described previously (28). Urine (0.4 mL) was mixed with 0.1 mL of 1 N NaOH, and the mixture was incubated at 80 °C for 30 minutes. [CD_3]Cotinine (5 ng) (Sigma Chemical) was added to a 5-mL glass centrifuge tube (Kimble, Vineland, NJ) containing 0.3 mL

H_2O and 0.4 mL of 25% aqueous K_2CO_3. The base-treated urine (0.2 mL) was added to the tube, and the mixture was extracted once with 1 mL CH_2Cl_2. The CH_2Cl_2 layer was transferred into 4-mL silane-treated vials (Chrom Tech., Inc., Apple Valley, MN) and mixed with 200 μL methanol. This solution was concentrated under a gentle stream of nitrogen to a total volume of 100 to 200 μL methanol. The samples were transferred to gas chromatography-microinsert vials and analyzed by gas chromatography-mass spectrometry−selected ion monitoring as described previously (28).

Total NNAL (NNAL plus NNAL-Glucs). Total NNAL was analyzed by a modification of a method described previously (27, 28). C_5-NNAL (1 ng) was used as internal standard. Other modifications will be described separately. Detection was by gas chromatography with nitrosamine-selective detection (27, 28).

Statistical Analyses. Analyses were done on square root transformed data to correct for skewness in the distributions. The questionnaire included several categories, and there were multiple variables in each category. To identify predicting variables that were significantly associated with the response variables (total NNAL and total cotinine), total NNAL and total cotinine were regressed on each potential predicting variable separately. The predicting variable was used for later modeling, if the resulting P was <0.2. The stepwise model selection method was used to formulate the final model.
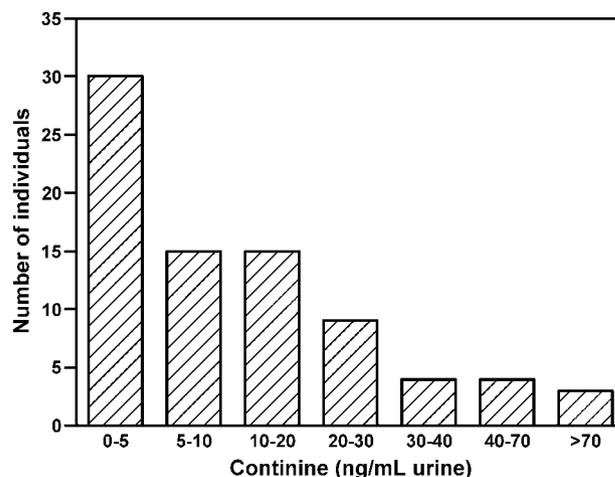

Figure 2. Distribution of total cotinine levels in the urine of 80 Moldovan children.
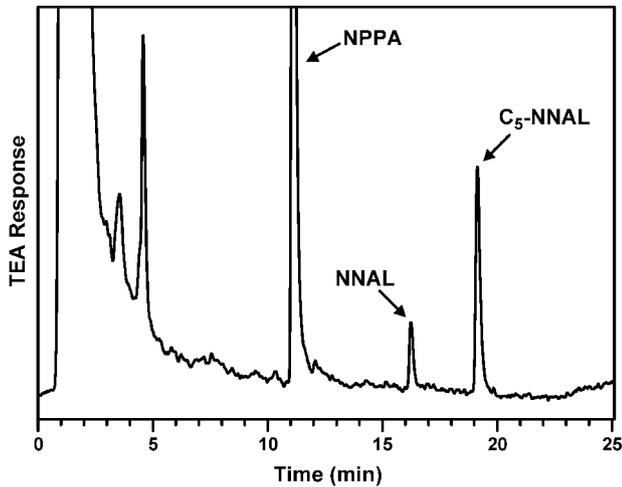
Figure 3. A typical gas chromatogram obtained upon analysis, using nitrosamine-selective detection, of total NNAL in the urine of a Moldovan child.

Results

The total number of urine samples was 80, collected from 80 children. Forty-nine percent of these children were female. The mean ± SD age was 7.75 ± 1.3 years. Nineteen samples (23.8%) were collected from children attending elementary schools in rural areas. Another 61 samples were collected from children attending two different kindergartens (41 children ages 5-7 years) and an elementary school (20 children ages 9-10 years) in Chisinau city, the capital of Moldova.

Cotinine was detected in the urine of 77 children (96.3%). Fifty children (62.5%) had total cotinine levels of ≥5 ng/mL urine. The distribution of total cotinine levels is presented in Fig. 2.

Total NNAL was analyzed in all samples, including those in which no cotinine was detected. A typical gas chromatographic trace of a urine sample is illustrated in Fig. 3. The method produced very clean chromatograms, with clear NNAL and C_5-NNAL peaks and good recovery of the internal standard. Total NNAL was detected in 49 of 50 samples, in which total cotinine was ≥5 ng/mL, and in 20 of 30 samples, in which total cotinine was <5 ng/mL, including one in which no cotinine was detected. Total NNAL and total cotinine levels are summarized in Fig. 4. Mean levels ± SD of total NNAL and total cotinine were 0.090 ± 0.077 pmol/mL and 16 ± 20 ng/mL (or 0.092 ± 0.11 nmol/mL), respectively. These levels were generally higher in urine from children living in the urban area; the difference was statistically significant for total cotinine ($P = 0.007$) but not total NNAL ($P = 0.15$). There was a strong correlation between total NNAL and total cotinine ($r = 0.8$, $P < 0.0001$, $N = 80$; Fig. 5).

The distribution of total NNAL and total cotinine levels for different reported exposure levels is summarized in Table 1. Both total NNAL and total cotinine were detected when no exposure was reported: 0.049 ± 0.016 pmol/mL and 7.5 ± 7.0 ng/mL (or 0.043 ± 0.040 nmol/mL), respectively. The levels of analytes were generally higher when exposure was reported than when it was not. Total NNAL and total cotinine levels were significantly higher when the child was exposed to ETS at home from the primary caregiver who smoked ($P = 0.0032$ and $P = 0.0012$, respectively) then when there was no such exposure. These values were also higher when the parent or guardian was aware of ETS exposure outside the child's home than when they were not ($P = 0.0027$ and $P = 0.0009$). The highest mean levels of total NNAL and total cotinine (0.13 pmol/mL and 27 ng/mL, respectively) were observed in children who were exposed to ETS both at home and at other indoor enclosed locations, or outdoors. Total NNAL was higher in boys (0.097 ± 0.089 pmol/mL, $n = 41$) than girls (0.081 ± 0.058 pmol/mL, $n = 39$) ($P = 0.0015$) and in younger children than in older ones ($P = 0.0081$). Total cotinine was higher when children spent most of their after school time indoors rather than outdoors ($P = 0.015$).

Discussion

We analyzed urinary metabolites of nicotine and NNK (total cotinine and total NNAL) in Moldovan children. The children attended kindergartens and elementary schools in urban and rural areas of Moldova. The results show substantial uptake of nicotine and NNK by Moldovan children. Total NNAL correlated with total cotinine and was detected even in samples that were low in cotinine (<5 ng/mL). Both total NNAL and total cotinine were found in the urine of children who were classified as unexposed to ETS based on questionnaire data. The amounts of the analytes were higher in children who were exposed to ETS (as reported by their parent/guardian) than in those who were not.

Forty-nine of 50 children with urinary total cotinine ≥5 ng/mL had detectable levels of NNAL, whereas only 20 of 30 children with urinary total cotinine levels <5 ng/mL were positive for NNAL. Thus, in agreement with previously published data (27), detection of total NNAL in children's urine was more likely when total cotinine was ≥5 ng/mL than when it was <5 ng/mL. However, the cutoff of 5 ng/mL

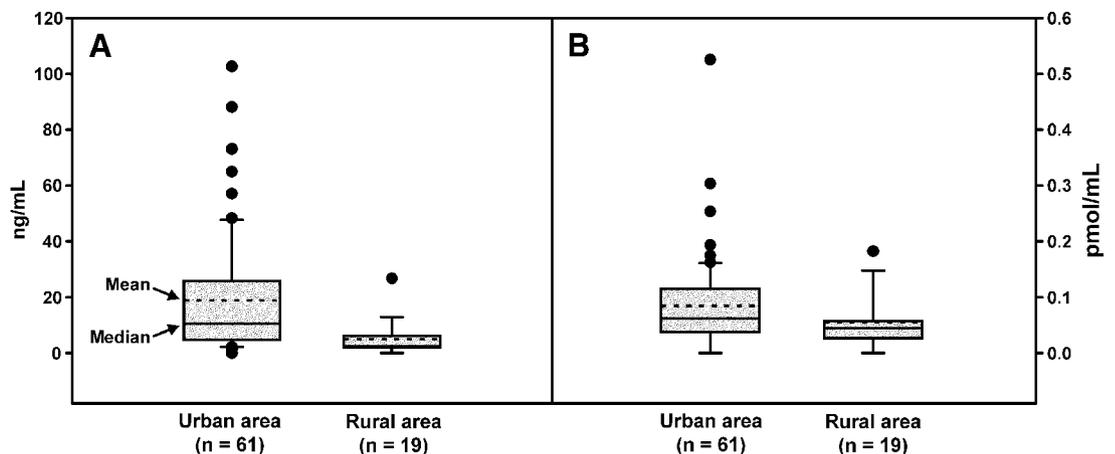
Figure 4. Metabolites of tobacco smoke constituents in the urine of Moldovan children: (*A*) total cotinine and (*B*) total NNAL. *Boxes,* 25th and 75th percentiles; *lines outside boxes,* 10th and 90th percentiles; *dots,* outliers.
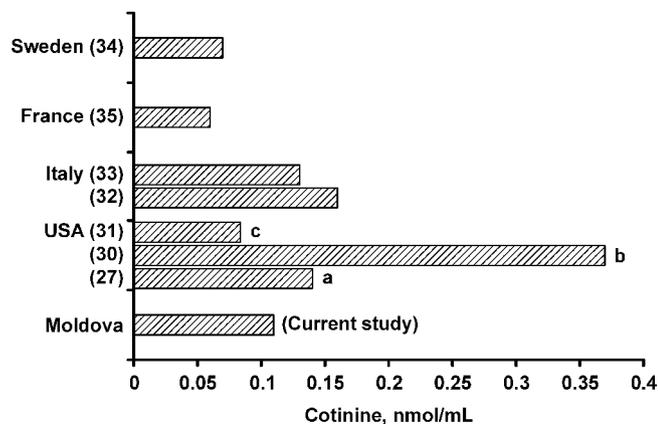
Figure 5. Total cotinine levels in the urine of children whose parents reported exposure to environmental tobacco smoke. Reference numbers are given in parentheses: *a*, low-income 6-year-olds; *b*, inner-city children; *c*, elementary school-aged children.

total cotinine, which is frequently used to indicate potential ETS exposure in adults, may be too high with respect to estimating presence of NNAL in the urine of children. In our study, the mean ± SD level of cotinine in samples negative for NNAL was 2.6 ± 1.3 ng/mL urine (n = 11). NNAL detection in a urine sample that was negative for total cotinine supports the idea that the probability of detecting total NNAL after a given exposure to ETS may be greater than that of detecting cotinine. This is consistent with the longer half-life of NNAL than cotinine in smokers and smokeless tobacco users.

Children living in the urban area had generally higher total NNAL and total cotinine levels than those living in rural areas (Fig. 4). This is consistent with the reported higher smoking prevalence in Moldovan cities compared with rural areas (26). Furthermore, population density is higher in the urban area, with housing being represented mainly by apartment buildings. These conditions create a higher probability of ETS exposure in Moldovan children living in urban areas than in those living in villages.

Younger children had higher levels of NNAL in their urine than older ones, probably because they spend substantial amount of time around older family members (parents, grandparents, and/or older siblings) who may smoke, have smoking friends, or visit public places where the risk of being exposed to ETS is high. Thus, younger children have more chances to be exposed to ETS than older ones who are more independent and spend most of their after-school time doing homework or playing on the playgrounds. In a previous study, urinary cotinine was shown to inversely correlate with age (29).

Substantial amounts of total NNAL and cotinine were detected even in the urine of children classified as unexposed based on questionnaire data. The presence of cotinine in the urine of children whose parents reported no ETS exposure has been repeatedly demonstrated (27, 29-34). This may be explained partially by inadequate reporting and partially by parental unawareness with regard to possible ETS exposure outside the child's home. This confirms the importance of total cotinine and total NNAL as biomarkers to reflect actual exposure to ETS. The levels of total NNAL found in Moldovan children with no exposure reported (0.049 pmol/mL) were similar to those found in nominally unexposed children from the United States (0.039 pmol/mL; ref. 27) and can also be compared with those in the urine of women who live with smokers (0.050 pmol/mL; ref. 25). The levels of cotinine in nominally unexposed Moldovan children (0.043 nmol/mL) were slightly higher than those found in reportedly unexposed children from the United States and Sweden (27, 31, 34) but lower than those reported for unexposed children from Italy (32, 33). However, because of the small number of children involved in the current study, the difference in total NNAL and cotinine levels between nominally unexposed children from Moldova and other countries is open to question and needs to be studied in a larger sample.

Levels of total NNAL and cotinine were higher in the urine of children with reported exposure to ETS compared with children with no exposure reported. These levels were somewhat similar in children who lived with a smoker but were classified as unexposed to ETS outside their homes and in children who were not exposed at home but were reported to be exposed to ETS in other enclosed facilities, outdoors, or indoors other than their homes. Total NNAL and total cotinine increased 2- to 3-fold when both kinds of exposure were reported (Table 1). This result is in agreement with those obtained by Preston et al. (29) who showed that exposure to more than one source of tobacco smoke results in nearly two to three times the level of urinary cotinine of children exposed to one source. This shows that uptake of tobacco smoke constituents by children could be substantially reduced by establishing bans on smoking in homes or other indoor or enclosed facilities where a child is present. The mean total NNAL level in the urine of children whose parents reported any kind of exposure (0.1 ± 0.083 pmol/mL) was similar to that found in American children reported as exposed to ETS (0.095 ± 0.088 pmol/mL; ref. 27). The range of total cotinine levels in the urine of children whose parents were aware of any kind of exposure was comparable with those reported for children from the United States and other countries (27-35). The mean total cotinine level (0.11 ± 0.13 pmol/mL), however, was slightly higher than in French (35) and Swedish (34) children and lower than in American inner-city children (30) and Italian children (32, 33) exposed to ETS (Fig. 5).

Limitations of this study include the small number of subjects and the measurement of total NNAL and cotinine on a single occasion. Cotinine levels may vary considerably in individual children (36). The small numbers of children in

Table 1. Total cotinine and total NNAL in the urine of Moldovan children with different reported exposures

Group	No. children			Mean ± SD	
	In the group	Cotinine detected	NNAL detected	Cotinine, ng/mL*	NNAL, pmol/mL
All	80	77	69	16 ± 20	0.09 ± 0.077
No exposure reported	22	20	15	7.5 ± 7.0	0.049 ± 0.016
Exposure reported	58	57	54	19 ± 22	0.1 ± 0.083
At home	7	6	6	4.6 ± 5.8	0.061 ± 0.036
Other†	20	20	20	11 ± 7.9	0.073 ± 0.031
Both	31	31	28	27 ± 28	0.13 ± 0.1

*To convert ng to nmol, divide by 176.
†Exposure in enclosed facilities, outdoors, or indoors other than the child's home.
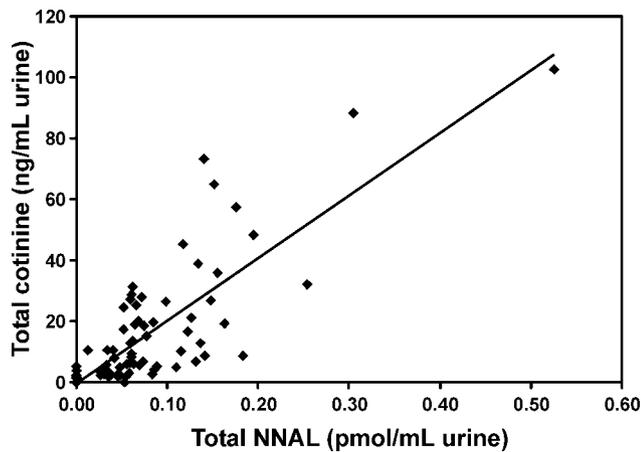
Figure 6. Relationship between levels of total cotinine and total NNAL in the urine of 80 Moldovan children.

groups with different reported exposures are likely to have reduced the reliability of the mean urinary total NNAL and cotinine in these groups.

The correlation of total NNAL with total cotinine observed in this study (Fig. 6) was similar to those reported earlier for 74 American children ($r = 0.71$; ref. 27) and 223 smokers ($r = 0.68$; ref. 22).

In summary, the results of this study for the first time show widespread and considerable uptake of nicotine and the tobacco-specific lung carcinogen NNK by some Moldovan children. Although the small number of samples analyzed in this study limits its generalizability to all Moldovan children, our findings clearly show that there is a considerable uptake of tobacco smoke constituents even in those children whose parents were unaware of possible ETS exposure outside of the child's home. Although there is no clear evidence for an association between childhood exposure to ETS and development of lung cancer later in life, NNK uptake by some children involved in this study is comparable with that of nonsmoking adults for whom this association has already been established. The results of this study should be useful in heightening the awareness of the dangers of smoking and ETS exposure in Moldova and can be envisioned as an important step toward the control of tobacco-related cancer in this country.

Acknowledgments

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