Nicotine, the addictive substance in cigarettes that maintains smoking behaviors, is metabolized by the cytochrome P450 (CYP)2A6 enzyme to cotinine, which is pharmacologically inactive. In adults, cotinine has a mean half-life of 16–18 h and is used as a quantitative biomarker for cigarette smoke consumption in smoking studies and as a biomarker for secondhand smoke (SHS) exposure in nonsmokers, including infants and children.

Several pediatric studies have measured cotinine levels in plasma, saliva, urine, hair, and occasionally meconium to document SHS exposure. Some of these studies have found substantially higher cotinine levels in infants and children relative to those found in adults exposed to SHS; some studies have found cotinine levels in children at levels comparable to those of active adult smokers.

There are several possible explanations for high levels of cotinine in children. One is inconsistent measurements of cotinine by different methods. Immunoassay methods, used in several pediatric studies, may cross-react with substances other than cotinine and result in higher reported cotinine SHS levels as compared with chromatography or chromatography–mass spectrometry methods, which generally have higher specificity.

CYP2A6 Genotype but not Age Determines Cotinine Half-Life in Infants and Children

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The formation of cotinine, the main proximate metabolite and a biomarker of nicotine exposure, is mediated primarily by cytochrome P450 (CYP)2A6. Our aim was to determine whether higher cotinine levels in young children exposed to secondhand smoke (SHS) are a result of age-related differences in pharmacokinetics. Forty-nine participants, aged 2–84 months, received oral deuterium-labeled cotinine, with daily urine samples for up to 10 days for cotinine half-life measurement. DNA from saliva was used for CYP2A6 genotyping. The estimate of half-life using a mixed-effect model was 17.9 h (95% confidence interval: 16.5, 19.3), similar to that reported in adults. There was no statistically significant effect of sex, age, race, or weight. Children with normal-activity CYP2A6*1/*1 genotypes had a shorter half-life than those with one or two reduced-activity variant alleles. Our data suggest that higher cotinine levels in SHS-exposed young children as compared with adults are due to greater SHS exposure rather than to different cotinine pharmacokinetics.
Dempsey et al.\textsuperscript{13} collected daily blood samples for 3 days and urine samples for up to 7 days from newborns of smokers and analyzed the samples for nicotine and cotinine by gas chromatography–mass spectrometry. Although nicotine had a longer half-life than that in adults, the cotinine half-life was similar, with a mean of 16.3 h (95% confidence interval (CI): 12.4–23.9) based on blood data and 22.8 h (95% CI: 19.5–25.8) based on urine data.\textsuperscript{13}

The two cotinine half-life studies in children kept SHS-exposed children in a smoke-free hospital environment and collected one or two daily urine samples. Leong et al.\textsuperscript{14} studied SHS-exposed children who were admitted to the hospital as patients (nonresearch) and ranged in age from 0 months to 14.5 years, although 57% were younger than 2 years of age. Their urine was collected at admission and at 12, 24, and 48 h. Among those younger than 2 years, the median half-life was 28.3 h, with a range of 6.3–285 h.\textsuperscript{14} Collier et al.\textsuperscript{9} admitted 44 SHS-exposed children younger than 3 years of age to a research ward for up to 6 days and collected urine several times daily. They found no difference in half-life between the sexes or between whites and African Americans. For those younger than 1 year, the mean half-life was 108 h (standard deviation (SD) ± 152); for those 12–23 months old, it was 86 h (±74); and for those 24–36 months old, it was 40.5 h (±10).

All four studies analyzed the urine for cotinine derived from the nicotine acquired from SHS. However, these types of studies can be compromised by inadvertent ongoing exposure to nicotine by off-gassing from clothing and hair or by surreptitious smoking by a visitor. This study used oral doses of deuterium-labeled cotinine in SHS-exposed infants and children. Deuterium is a harmless, naturally occurring, nonradioactive isotope of hydrogen. Deuterium-labeled cotinine, which has been widely studied, has the same pharmacokinetics as natural cotinine.\textsuperscript{15,16} Labeling the cotinine allows the half-life to be studied independent of ongoing SHS exposure because it can be assayed using liquid chromatography–tandem mass spectrometry without interference from SHS-derived cotinine.

More than 70% of nicotine is metabolized to cotinine by the liver enzyme CYP2A6, and cotinine is further metabolized exclusively by CYP2A6 to trans 3′-hydroxy cotinine. CYP2A6 is genetically polymorphic, and the clearance of cotinine is altered by genotype differences.\textsuperscript{1,16} There is racial/ethnic variation in the frequency of CYP2A6 variant alleles among racial/ethnic groups.\textsuperscript{17} Therefore, when comparing cotinine half-life among children of different racial/ethnic groups, it is important to consider the impact of genetic variation in CYP2A6.

The overall aim of our study was to determine the half-life of cotinine in the infants and young children to allow better interpretation of cotinine levels in babies and young children exposed to SHS, specifically those between 2 and 84 months of age, an understudied population. Measurement of disposition kinetics across this age range would also allow for the identification of developmental changes in CYP2A6 activity from infancy to early childhood. No data are available on the effect of CYP2A6 genotype on cotinine half-life in children. One pediatric study has found significant differences in cotinine levels associated with SHS exposure between young African American and Hispanic children,\textsuperscript{3} and this difference is well documented in adults.\textsuperscript{18} Therefore, another aim of the study was to determine the effects of CYP2A6 genotype and of race on cotinine half-life in children. Using a mixed-effects model (population) analysis of the pooled data, we were able to handle imbalance in the data (e.g., unequal number of samples among individuals) and test for covariate effects.

**RESULTS**

Forty-nine subjects completed the study. Their age ranged from 1–1.9 years, with a median of 1.5 years (SD ± 2.5) and a mean of 1.510 years (95% CI: 0.7–1.3). Their weight ranged from 2.5 to 82.4 months, with a median of 34.2 months and a mean of 34.6 months (SD ± 21.9 months). Their weight ranged from 4.9 to 31.5 kg, with a median and a mean of 15 kg (SD ± 6.0 kg). Among the 44 subjects with successful genotyping, 23 (46.9%) had the CYP2A6*1/*1 genotype, which corresponds to normal metabolic activity; 7 (14.3%) had the CYP2A6*1/*9 genotype and comprised the group of those with intermediate activity; and the remaining 28.6% had slow activity, with 10 of these subjects having the CYP2A6*1/*17 genotype and 1 subject each having the remaining four genotypes (CYP2A6*1/*2, CYP2A6*1/*20, CYP2A6*9/*9, and CYP2A6*17/*17). By race/ethnicity, all white or Latino children (n = 9) had the CYP2A6*1/*1 genotype; among African-American children (n = 27), 13 had the CYP2A6*1/*1, 7 had the CYP2A6*1/*17, 4 had the CYP2A6*1/*9, and 1 each had the CYP2A6*1/*2, CYP2A6*1/*20, or CYP2A6*9/*9 genotype; among mixed race/ethnicity children (n = 8), 3 each had the CYP2A6*1/*9 or CYP2A6*1/*1 genotype, and 1 each had the CYP2A6*1/*1 or CYP2A6*1/*17 genotype (Table 1). A higher percentage of younger as compared with older children had *1/*1 genotypes (Table 2).

Urine cotinine levels, with and without correction for creatinine, over time for individual subjects are displayed in Figures 1

| Table 1 | Prevalence of CYP2A6 genotype by race/ethnicity |
|---------|---------------------------------------------|
| Genotypes | White | Black | Mixed | Total |
| *1/*1   | 9     | 13    | 1     | 23    |
| *1/*2   | 0     | 1     | 0     | 1     |
| *1/*9   | 0     | 4     | 3     | 7     |
| *9/*9   | 0     | 1     | 0     | 1     |
| *1/*17  | 0     | 7     | 3     | 10    |
| *17/*17 | 0     | 0     | 1     | 1     |
| *1/*20  | 0     | 1     | 0     | 1     |
| Unknown | 3     | 2     | 0     | 5     |
| Total   | 12    | 29    | 8     | 49    |

| Table 2 | Distribution of CYP2A6 genotype by age |
|---------|----------------------------------------|
| Age groups (years) | n | % *1/*1 (Wild type) |
| <1    | 11 | 64 |
| 1–1.9 | 7  | 71 |
| 2–2.9 | 8  | 37.5 |
| 3–3.9 | 8  | 25 |
| 4–4.9 | 7  | 43 |
| 5–6   | 8  | 37.5 |
and 2. Table 3 displays the cotinine half-life estimates (95% CIs), shown by sex, race, and age, based on analysis of urine levels with and without creatinine correction. Coincidentally, the overall half-life estimates and 95% CI (after rounding) are identical for creatinine-corrected and uncorrected data.

Figures 1 and 2 show smoothed population mean curves for cotinine in genetically normal and intermediate/slow metabolizers. Table 4 displays the estimates of half-life by genotype activity. Normal metabolizers had a significantly shorter creatinine-corrected urine cotinine half-life as compared with intermediate and slow metabolizers.

For creatinine-corrected urine cotinine, there was no statistically significant effect (defined as $P < 0.01$) of sex, race, or weight (all $P > 0.2$). Age was marginally significant ($P = 0.056$) when treated as a categorical variable (<1 year old vs. >1 year old) in the absence of genotype in the model but not when genotype was included ($P = 0.19$).

For creatinine-uncorrected cotinine, genotype effect was marginally significant ($P = 0.036$) when the intermediate and slow variant groups were combined but not when each group was

### Table 3 Half-life estimates by sex, race, and age

|                      | Half-life point estimate (95% CI) |
|----------------------|-----------------------------------|
|                      | Creatinine-corrected | Creatinine-uncorrected |
| All subjects         | 49                   | 17.9 (16.5, 19.3)       | 17.9 (16.5, 19.3)       |
| Sex                  |                      |                      |
| Male                 | 25                   | 18.4 (17.1, 19.7)       | 18.5 (17.1, 19.9)       |
| Female               | 24                   | 17.4 (15.2, 19.6)       | 17.4 (14.8, 19.6)       |
| Race                 |                      |                      |
| White                | 12                   | 17.5 (15.5, 19.5)       | 17.7 (15.3, 20.1)       |
| Black                | 29                   | 18.1 (16.4, 19.8)       | 17.7 (15.9, 19.5)       |
| Mixed                | 8                    | 18.2 (15.4, 21.0)       | 18.8 (14.1, 23.5)       |
| Age groups (years)   |                      |                      |
| <1                   | 11                   | 15.7 (13.6, 17.8)       | 13.7 (12.0, 15.4)       |
| 1–1.9                | 7                    | 18.5 (15.9, 21.1)       | 18.4 (16.3, 20.5)       |
| 2–2.9                | 8                    | 18.5 (15.6, 21.4)       | 10.5 (7.0, 14.0)        |
| 3–3.9                | 8                    | 17.2 (13.6, 20.8)       | 16.8 (13.6, 20.6)       |
| 4–4.9                | 7                    | 18.6 (15.7, 21.5)       | 20.0 (16.0, 24.0)       |
| 5–6                  | 8                    | 19.3 (16.8, 21.8)       | 19.6 (16.4, 22.8)       |

CI, confidence interval.

### Table 4 Half-life estimates by genotype activity

| CYP2A6 genotype activity          | Point estimate (95% CI) |
|-----------------------------------|-------------------------|
|                                   | Creatinine-corrected    | Creatinine-uncorrected |
| Normal (*1/*1)                    | 23                      | 16.4 (14.7, 18.1)       | 16.2 (14.5, 17.9)       |
| Intermediate (*1/*9)              | 7                       | 19.6 (16.7, 22.5)       | 20.0 (15.6, 24.4)       |
| Slow (*1/*17, *1/*2, *1/*20, *9/*9, *17/*17) | 14                      | 19.4 (16.6, 22.1)       | 18.8 (15.9, 21.7)       |
| Intermediate/slow                  | 21                      | 19.5 (17.4, 21.6)       | 19.2 (16.8, 21.6)       |
| Unknown                           | 5                       | 19.7 (16.7, 22.7)       | 20.9 (16.4, 25.4)       |
| Normal vs. intermediate vs. slow  | 0.022                   | 0.096                   |
| vs. unknown                       |                         |                         |
| Normal vs. intermediate/slow vs.  | 0.006                   | 0.036                   |
| unknown                           |                         |                         |

CI, confidence interval.

### Notes

1. One 18-month-old black male (CYP2A6*1/*17) was excluded from the creatinine-corrected urine half-life calculation because of missing creatinine levels, for a total of 48 subjects with creatinine-corrected results.
2. Included Hispanic Whites.
treated separately or when either age or weight was in the model. There was a statistically significant effect of age and weight; however, the model fit did not improve when both were present in the model, relative to the fit with either one alone, presumably because in growing infants and children age and weight are correlated. The effects of age and weight were marginally significant \((P = 0.015 \text{ for age and } P = 0.021 \text{ for weight})\) after correcting for genotype activity. Neither sex nor race had a significant effect (both \(P > 0.3\)).

**DISCUSSION**

We present novel data on the half-life of cotinine using stable-isotope methodology in infants and young children. The use of labeled cotinine enabled us to study cotinine pharmacokinetics without potential confounding by ongoing environmental exposure to nicotine (and resulting generation of cotinine) and allows high sensitivity of measurement so as to permit the measurement of cotinine levels for several days after exposure. We provide novel data on the effects of age, sex, race/ethnicity, and \(CYP2A6\) genotype on cotinine elimination rate in the very young.

The estimate of the typical value of the half-life of cotinine, \(17.9\,\text{h}\), is similar to that observed in adult smokers and similar to what we measured previously in neonates who had been exposed to tobacco smoke in utero.\(^{13}\) For creatinine-corrected half-life, we found no effect of age on cotinine half-life. However, we did see significant (when tested singularly) or marginally significant (when tested with genotype in the model) effects of age with creatinine-uncorrected measurements. There is a lower average cotinine half-life in children younger than 1 year of age, but this is probably due to chance distribution from \(CYP2A6\) genotype, such that a higher percentage of younger children had \(^*1/*1\) genotypes, which are associated with shorter half-lives (Table 2).

Overall, our data suggest little or no developmental change in \(CYP2A6\) activity after controlling for \(CYP2A6\) genotype after 2 months of age. Our data are consistent with studies of \(CYP2A6\) metabolic activity in livers from people of different ages. For example, Al Koudsi et al. found no relationship between age and either \(CYP2A6\) protein levels or nicotine C-oxidation activity in a liver bank that included a number of livers from people younger than 10 years.\(^{19}\) Others have reported similar findings, including no difference between fetal and adult livers.\(^{20–22}\)

We observed no significant effect of race but did find a strong effect of \(CYP2A6\) genotype on cotinine half-life. Children with one or more reduced-function variants (i.e., \(^*2, ^*9, ^*17,\) or \(^*20\)) have a significantly longer estimate of typical half-life (19.5 h) as compared with those without such variants (16.4 h). Similar genotype effects have been observed on cotinine clearance and half-life in adults.\(^{18}\) We expected to see an effect of race on half-life on the basis of the higher prevalence of reduced-function \(CYP2A6\) alleles in African Americans as compared with whites. We did not find the expected half-life difference by race, even in univariate analysis, presumably because of relatively small sample size and inadequate power. Of note, as expected, a higher frequency of African-American and mixed-ethnicity children had genotypes containing variants alleles relative to those of white children (48, 89, and 0%, respectively).

A limitation of using cotinine half-life as an indicator of developmental changes of \(CYP2A6\) activity is that total cotinine clearance is determined not just by \(CYP2A6\) activity but also by enzymes involved in glucuronidation and N-oxidation, as well as by some renal clearance of unchanged cotinine.\(^{23}\) However, the similarity between the half-life observed in this study and that previously measured in adults, as well as the similar degree of impact of \(CYP2A6\) genotype on cotinine half-life in adults and children, suggests a minimal effect of age on \(CYP2A6\) activity. Because half-life is inversely proportional to clearance and directly proportional to volume of distribution of the central compartment, we cannot rule out a commensurate change with age in these two parameters resulting in no effect of age on half-life, but this situation seems unlikely.

Our findings have implications for understanding tobacco smoke exposure in young children. First, our findings that the half-life of cotinine in young children is similar to that seen in adults are inconsistent with some other studies in children.\(^{3,9,14}\) We suspect that those studies suffer from methodological problems of nonspecific cotinine assays and/or persistent exposure to nicotine in the environment, with ongoing generation of cotinine. It is also possible that deep tissue stores of nicotine could result in prolonged production of cotinine and a longer half-life, although we did not observe that in our prior study in which we measured cotinine in neonates for several days following birth.\(^{13}\)

Second, we and others have found that cotinine levels in African-American children are much higher than those observed in children of other races/ethnicities.\(^{3,24}\) This could be due either to greater SHS exposure or to slower cotinine metabolism. The presence of reduced-function \(CYP2A6\) variants results in higher cotinine levels for any given level of nicotine intake.\(^{25}\) African Americans are known to have a higher frequency of reduced-function \(CYP2A6\) variants than Caucasians or Hispanics.\(^{17,26}\) However, the present study suggests that the effects of race or of reduced-function \(CYP2A6\) variants on half-life is relatively small. Assuming that half-life measured in urine reflects clearance of cotinine, the much higher levels of cotinine previously observed in African-American children as compared with white children cannot be accounted for solely by differences in cotinine metabolism. Greater SHS exposure is likely to account for more of the racial difference in cotinine levels.

In summary, we present novel data on the half-life of cotinine in infants and young children. The half-life of cotinine was similar to that observed in adults and was influenced by \(CYP2A6\) genotype but not independently influenced by age, sex, or race/ethnicity. Our data will help in the interpretation of cotinine levels measured in SHS-exposed children.

**METHODS**

**Overview.** This was a study of the half-life of deuterium-labeled cotinine (COT-d4), which was dosed orally in infants and children; the half-life was based on urine COT-d4 levels.

**Subjects.** Participants were infants and children, between 2 and 83 months of age, who by parental report were currently exposed to SHS in their homes. A total of 173 parents and their infant or child were screened for eligibility, and 67.6% were not enrolled. Of those who were...
not enrolled, 47.7% declined to participate and 52.3% were excluded for the following reasons: no SHS exposure, 11%; parental time conflict, 10.3%; failed screening (nonmedical), 9.4%; medical (e.g., asthma), 9.4%; race/ethnicity/sex enrollment cell full, 5.1%; age older than 6 years, 2.6%; and reason not recorded, 5.1%.

Fifty-six participants were enrolled, and 49 had sufficient urine data to be included in this analysis. All participants were healthy by history and physical examination, had documented up-to-date immunizations and well-baby/child visits, and had their medical records reviewed before enrollment. Exclusion factors were as follows: currently on any medication or dietary supplements, asthma and other chronic illnesses, parental substance or alcohol abuse, and foster-care placement. Fifty-one percent were male, and the racial/ethnic distribution was 59% African American, 25% white or Latino, and 16% other or mixed race/ethnicity. Participants were aged 2.5–83.4 months, with the following age distribution: <12 months (22.4%); 12–23 months (14.3%); 24–35 months (16.3%); 36–47 months (16.3%); 48–59 months (14.3%); and 60–83 months (16.3%).

Recruitment and screening. Subjects were recruited via letters with flyers to pediatric offices/clinic and to churches, postings on Craigslist, through participants in our adult smoking studies and by word of mouth from parents of study participants. Parents contacted us via our telephone recruitment line, and a telephone screening was conducted to describe the study and determine that the participant fulfilled study criteria and had made no exclusion factors. Those who fulfilled study criteria were scheduled for a screening visit, at which time the study was explained in detail and consent obtained. Other forms were filled out (for demographic information; parental use of tobacco, alcohol, and drugs; and SHS exposure history), and a home visit by the study coordinator was scheduled. At the home visit, consent from the other parent was obtained by the study coordinator. Saliva and urine samples were obtained from the participant to verify that the participant would cooperate with sample collection. After the participant’s medical records were obtained and health and immunization status and regularity of well-baby/child visits were verified, the participant was enrolled in the study. The study was approved by the Committee on Human Research at the University of California, San Francisco, and parents were compensated for their time ($290 for one 10-h stay on the research ward and seven 1- to 2-h home visits to collect urine and saliva samples).

Study procedures. Parents and participants arrived at the Clinical Research Center at San Francisco General Hospital by 9:00 AM. There was no restriction on eating or drinking relative to cotinine dosing, and age-appropriate food was available for the participants and parents. Parents remained with the participants throughout their time at the Clinical Research Center. After a baseline urine sample and a saliva sample for genotyping were collected, subjects were orally dosed with 0.05 mg/kg of COT-d4 solution. Deuterium labeling made it possible to distinguish the degradation of deuterium-labeled cotinine in infants and children was approved by our research group.27 An investigational new drug application for the use of deuterium-labeled cotinine in infants and children was approved by the US Food and Drug Administration. The dose selected was the lowest dose that would give detectable COT-d4 levels over 4 days, assuming that the pharmacokinetics were similar to weight-corrected adult values. On the basis of anticipated weight distribution, >80% of subjects would receive a dose that was less than one-tenth the oral adult dose (10 mg) that we have used in previous studies.28 A liquid solution of COT-d4 was added to 1–2 ounces of participants’ preferred beverage. Participants and parents were discharged from the Clinical Research Center 8 h after dosing.

Research assistants made five or six visits spread over 10 days after dosing. A research assistant went to a participant’s home to collect a 20-ml spot urine sample on day 1, ~24 h after dosing, and on days 2 and 3 after dosing. The first 13 subjects had two additional postdosing home visits; subjects 14–49 had three additional home visits for sample collection. The change was made to ensure that the three samples would be collected after the third day after dosing to be able to characterize a prolonged terminal half-life that might exist (e.g., days 4 or 5, days 7 or 8, and days 9 or 10). Toilet-trained participants urinated into a plastic hool placed in the toilet to capture urine. For non-toilet-trained children, the study coordinator placed a cotton ball into a clean diaper. After urination, the urine was squeezed out of the cotton balls into a 20-ml plastic bottle with a tight lid. The minimum volume recovered by the cotton ball method was 5 ml, more than that required for the cotinine assay.

Genotyping. Saliva was collected using the Oragene-DNA saliva sponge kit (OG-250, CS1; http://www.dnagenotek.com). Three to five sponges on sticks were placed in the cheek pouches and allowed to absorb saliva (60 s). The sponges were then placed in the Oragene-DNA kit and covered with the liquid provided, which preserves the DNA collected by the sponges; samples were frozen until shipped to the University of Toronto for genotyping.

DNA was extracted according the manufacturer’s instructions (Oragen). Briefly, 500 µl of Oragene solution containing saliva was mixed with 20 µl of PT-L2P (proprietary) solution, incubated on ice for 10 min, and centrifuged for 5 min at room temperature at 13,000 rpm. Ethanol was added to the supernatant to precipitate DNA. DNA of sufficient yield and quality was obtained for all but five subjects.

The DNA samples were genotyped for alleles that were relatively abundant in the Caucasians and African Americans and have established impact on CYP2A6 activity, including CYP2A6*1B, *2, *4, *9, *12, *17, *20, *23, *24, *25, *26, *27, *28, *31, and *35, using a two-step gene-specific PCR amplification technique.17,26,28,30

Analytical methods. Urine concentrations of deuterium-labeled cotinine were measured using liquid chromatography–tandem mass spectrometry using a published procedure, modified for the determination of COT-d4, using the corresponding ion transition m/z 181 >84.31 The limit of quantitation for cotinine was 0.5 ng/ml.

Data analysis. The measure of interest was the half-life of deuterium-labeled cotinine, estimated using urine cotinine concentrations. Analyses were performed with and without correction for urine creatinine. A mixed-effects model analysis was carried out using the program NONMEM, version 7.2.0 (Icon Development Solutions, Ellicott City, MD) with first-order conditional estimation and interaction.31 Plots were done using the program R, version 2.12.1 (http://www.rproject.org/). The structural model used was a monoexponential decay with instantaneous input because the first sample was taken after most, if not all, of absorption had occurred.

The residual error was an exponential model (i.e., the error was additive to ln-transformed values). The covariates tested in the pharmacokinetic data set were age, total body weight, race/ethnicity, and CYP2A6 genotype. Goodness-of-fit plots (individual and population predictions vs. observation; population prediction and time vs. conditional weighted residual) were used to check interim and final models.

Hypothesis testing for model development was based on the likelihood-ratio test, which compares full vs. reduced models with degrees of freedom equal to the difference in the number of parameters. Formal covariate testing was performed in the following order: (i) singular addition, (ii) stepwise addition of significant covariates (starting with covariate/parameter addition having greatest significance from step i), (iii) singular deletion from a full model containing significant covariates based on step ii, and (iv) stepwise deletion (starting with the covariate/parameter with least significance from step iii). A P value of 0.01 (Δ objective function value: −6.63 with 1 degree of freedom) was considered statistically significant; for steps (i–iii) of covariate tests, a less stringent critical P value of 0.05 (Δ objective function value: −3.84 with 1 degree of freedom) was applied. A nonlinear (power) model was used for models of continuous covariates, and a multiplicative model was used for categorical covariates. Standard errors reported are those obtained.
from the covariance step of the NONMEM program. Estimates of all parameters are given as their typical values and 95% CIs.

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AUTHOR CONTRIBUTIONS

D.A.D., N.C.S., P.J., E.H., R.F.T., E.F.-A., and N.L.B. wrote the manuscript; D.A.D., R.F.T., E.F.-A., and N.L.B. designed the research; D.A.D., P.J., E.H., R.F.T., and N.L.B. performed the research; and D.A.D. and N.C.S. analyzed the data.

CONFLICT OF INTEREST

R.F.T. has been involved in one-day workshops for Novartis and McNeil. She has been involved in the review or decision process for this article. N.L.B. has been a Clinical Pharmacology & Therapeutics Associate Editor. R.F.T. has been involved in one-day workshops for Novartis and McNeil. She has been involved in the review or decision process for this article. D.A.D., P.J., E.H., R.F.T., and N.L.B. have received research grants from the US National Institutes of Health, the Centre for Addiction and Mental Health, and the Canada Foundation for Innovation (grant 20289 and 16014). D.A.D. was supported by the US National Institutes of Health/National Center for Research Resources University of California, San Francisco Clinical and Translational Science Institute. N.L.B. has received research grants from the US National Institutes of Health/National Center for Research Resources University of California, San Francisco Clinical and Translational Science Institute.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Levels of cotinine, a metabolite and biomarker of nicotine exposure, are higher in young children exposed to SHS than in older children and adults. It is unknown whether this difference reflects different SHS exposure or age-related changes in pharmacokinetics. Cotinine is metabolized primarily by CYP2A6.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ This study examined the influence of age, sex, race, and CYP2A6 genotype on cotinine half-life in infants and young children.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ The cotinine half-life in infants and young children is similar to that of adults and is influenced by CYP2A6 genotype but not independently by age, sex, or race.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ Our data will help the interpretation of cotinine levels in SHS-exposed children. We provide novel information on developmental aspects of CYP2A6 activity in people.
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