Correlating Atmospheric and Biological Markers in Studies of Secondhand Tobacco Smoke Exposure and Dose in Children and Adults

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Objective: *We sought to directly compare secondhand smoke (SHS) atmospheric markers to each other and to SHS dosimetric biomarkers, permitting intercomparison of clinical and atmospheric studies.* ***Methods:*** *We used atmospheric and pharmacokinetic (PK) models for the quantitative estimation of SHS exposure and dose for infants, children, and adults, based on building smoker density and air exchange rate, and from exposure duration, default PK parameters, and respiration rates.* ***Results:*** *We estimate the SHS serum cotinine doses for the typical and most-exposed individuals in the U.S. population; predictions compare well to measurements on a national probability sample. Using default respiration rates, we estimate serum cotinine dose from SHS nicotine exposure for 40 adults exposed to SHS in an environmental chamber; predictions agreed with observations. We correlate urine cotinine and hair nicotine levels for 127 infants exposed to parental smoking, and estimate corresponding atmospheric nicotine exposure via PK modeling.* ***Conclusions:*** *Our "Rosetta Stone" Equations allow the SHS atmospheric markers, respirable particles, nicotine, and carbon monoxide, to be related to the SHS biomarkers, cotinine in blood, urine, and saliva and nicotine in hair, permitting intercomparison of clinical and atmospheric studies of SHS for the first time.* (J Occup Environ Med. *2006;48: 181–194*)

Secondhand smoke (SHS) causes a number of disabling conditions and fatal diseases in both adults and children.[1] These include mortality from ischemic heart disease, lung, bladder and other cancers, and respiratory symptoms among adults and sudden infant death syndrome (ie, SIDS), low birth weight, asthma initiation and aggravation, lower respiratory illness, and middle ear infections among children.[1] Many of these studies estimate the probability of SHS exposure through questionnaires, whereas some actually quantify exposure using SHS atmospheric or biomarkers. The use of markers for SHS exposure improves the study of SHS disease. For example, Whincup et al[2] observed that prospective studies of passive smoking and coronary heart disease in adults based solely on reports of smoking in a partner appear to underestimate the risks relative to studies using biomarkers. Mannino et al[3] observed that, in studies of asthma in children, the use of biomarkers can reduce exposure misclassification and allow comparisons of high-exposure to low-exposure groups.

Disease usually is well documented through medical records and other means, but quantification of SHS exposure has relied most often on using questionnaires that document the subject's spousal or parental smoking habits or, less often, workplace smoking policies and social exposures. However, as the

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NHANES III probability sample of the U.S. non-tobacco-using population ≥4 years in 1988–1991 showed, the fraction of this population reporting exposures at home or at work differs by more than 2 orders of magnitude in levels of serum cotinine, a prime biomarker of SHS exposure.[4] Moreover, although 88% of these nontobacco users manifested detectable serum cotinine, half denied receiving any SHS exposure at either home or at work. Furthermore, many of those reporting "no SHS exposure" actually had higher cotinine concentrations than those who did report exposure. Thus, questionnaires alone may lead to substantial exposure misclassification and therefore underestimate the actual risk of SHS.

A sampling of recent literature exemplifies the diversity of biomarkers and atmospheric markers being used in secondhand smoke studies (examples in Appendix A), including urine cotinine, serum cotinine, saliva cotinine, and hair nicotine, respirable particles (RSP), particle-bound polycyclic aromatic hydrocarbons (PPAH), air nicotine, and carbon monoxide (CO). However, the plethora of diverse biomarkers and atmospheric markers of SHS makes it difficult for researchers to quantitatively compare exposure in clinical and epidemiologic studies with the same disease endpoint.

In this work, we review time-averaged physical models for estimating SHS air nicotine and RSP concentrations from the ratio of the smoker density to the air exchange rate in a home, and compare those predictions to a set of observations that define typical and extreme domestic exposures. Second, we review a time-averaged pharmacokinetic (PK) model for serum cotinine and relate its predictions for population SHS exposure to a national probability sample, and related saliva and urine cotinine analogs are reviewed. Third, we present a peak-dose model for the analysis of serum and urine cotinine concentrations from short-term exposures, and apply the models to the analysis of controlled studies of serum and urine cotinine in adults and children. Fourth, we correlate measurements of hair nicotine to measured urine cotinine among infants, and use the PK model to estimate antecedent air nicotine exposures from hair nicotine. Finally, we present the "Rosetta Stone" equations for correlating the various SHS atmospheric markers and biomarkers to each other, and apply these equations to clinical and epidemiologic studies using specific atmospheric- and bio-markers to show how those markers can be extrapolated to the remainder of the spectrum of SHS markers, allowing inter-comparison of disparate studies for the first time.

Materials and Methods

Part I: Time-Averaged Models for Predicting SHS RSP and Nicotine Concentrations in the Home

We use a simplified time-averaged mass-balance equation called the Habitual Smoker Model (HSM), which was developed for the prediction of RSP 3.5 μm or less ($PM_{3.5}$) from SHS (SHS-RSP), in units of micrograms per cubic meter ($\mu g/m^3$).[5–7] A closely related fraction, $PM_{2.5}$, is airborne particulate matter 2.5 μm or less in mass-median aerodynamic diameter and is a federally regulated outdoor air pollutant. Repace[7] found, in both field studies and in a controlled experiment, a SHS-RSP to SHS-PPAH ratio of ≈2000:1.

$$SHS_{RSP} = 217 \frac{D_{hs}}{C_v} (\mu g/m^3) \quad (1)$$

Repace and Lowrey[8] extended this model to the prediction of nicotine, also in units of $\mu g/m^3$:

$$SHS_{NIC} = 21.7 \frac{D_{hs}}{C_v} (\mu g/m^3) \quad (2)$$

where D_{hs} is the habitual smoker density (in units of habitual smokers per hundred cubic meters of indoor space volume) and C_v is the air exchange rate of the exposure space (in units of air changes per hour, h^{-1}). $D_{hs} = 3D_s$ where D_s is the time-averaged number of burning cigarettes. Habitual smokers are assumed to emit 14 mg of SHS-RSP from cigarettes smoked at the average rate of two cigarettes per hour. An updated derivation and use of HSM for the prediction of SHS-RSP ($PM_{3.5}$ or $PM_{2.5}$), and SHS nicotine in the evaluation of field studies are given in previous studies.[5–10] The HSM is independent of the smoking patterns and generally is valid, provided the initial and final exposure conditions are the same. In the event that they are not, a mass-balance model correction factor may be applied: $\Delta X/C_vT$, where ΔX is the difference between the initial and final concentrations, C_v is the air exchange rate, and T is the averaging time.[11] For many cases of interest, $\Delta X \ll C_vT$, and the correction can be ignored. Extensive discussion of more complex models and of the mathematics of time-averaged and dynamic mass balance models are given in the comprehensive works of Ott et al.[11,12]

Part II: Pharmacokinetic Models for SHS Cotinine Concentrations

An extensive discussion of the utility of cotinine as a biomarker for SHS is given by Benowitz.[13] A person's exposure to SHS nicotine will manifest as its metabolite, cotinine, in blood, urine, and saliva. Repace and Lowrey[8] derived the following time-averaged dose models for blood serum P and urinary cotinine U, in units of nanograms of cotinine per milliliter of body fluid (ng/mL). For serum (plasma) cotinine:

$$P = \frac{\phi\alpha\rho HN}{\delta_t T_d} (ng/ml) \quad (3)$$

and for urine cotinine U:

$$U = \frac{\phi\alpha\delta_r\rho HN}{\delta_t V_u} (ng/ml) \quad (4)$$

where ϕ is the nicotine-to-cotinine conversion efficiency (#), α is the lung absorption efficiency for inhaled nicotine (#), ρ is the subject's

respiration rate (m^3/hr), H is the daily exposure duration (hours), N is the atmospheric nicotine exposure concentration ($\mu g/m^3$), δ_t is the nonsmokers' total cotinine clearance rate (mL/min), or rate at which cotinine is removed from the blood, and is the ratio of the volume of distribution to the cotinine residence time. T_d is the averaging time = 1440 minutes for a daily average, which is usually desired. δ_r is the nonsmokers' renal cotinine clearance (ml/min), and V_u is the daily urinary excretion (mL). $P_o = \phi\alpha\rho N/\delta_t$ is the equilibrium concentration of serum cotinine in units of ng/mL. $D = \phi\alpha\rho NH$ is the total cotinine dose delivered. The mass-balance correction factor can usually be ignored for daily averages.

Saliva cotinine (*S*) is estimated from serum cotinine (*P*), by $S = \gamma P$, where $\gamma = 1.16$.[9] Repace et al[9] developed point-estimate and Monte Carlo models for the prediction of airborne nicotine in offices and saliva cotinine in office workers, and found a reasonable overall fit to observational data for both 12 open-plan offices and for 89 office workers in 2 separate studies (16% difference for air nicotine and 2% difference for saliva cotinine between predicted and observed medians).

Equations 3 and 4 show that cotinine depends upon individual physiological (respiration, absorption, metabolism, and excretion), temporal (exposure duration), and physical (exposure concentration) parameters. Although the physiological parameters ρ, α, ϕ, and the δ values may vary from individual to individual, in large numbers of subjects they will tend toward group means.[13] The utility of these models in predicting the results of clinical epidemiological studies is discussed in Repace et al[8,9] and is further illustrated as follows. Using Equations 3 and 4, assuming that the population was exposed at work or at home only, Repace and Lowrey[8] estimated that the typical and most-exposed persons in the population in the late 1980s respectively had serum cotinine levels of 0.95 ng/mL and 9.5 ng/mL. These predictions assumed an outdated value for $\phi = 0.86$. Adjusting these predictions for the updated value of $\phi = 0.78$, the ratio of (0.78/0.86; Benowitz N, personal communication),[9] yields a correction factor of 0.91, and the adjusted values: P_{typ} (0.91)(0.95) = 0.86 ng/mL, and $P_{max} = (0.91)(9.5) = 8.6$ ng/mL, respectively.

Figure 1 plots these values against the NHANES III national U.S. population serum cotinine distribution for nonsmokers reporting exposure to SHS at home or work only, conducted by the U.S. CDC from 1988 to 1991. The predicted typical value coincides with the mode of the log-normal distribution, whereas the most-exposed scenario is underpredicted because the general cutoff from light active smoking to heavy passive smoking is generally taken at approximately 10–15 ng/mL. Pirkle et al[4] reported, for U.S. adult nontobacco users with both home and work exposure, a geometric mean of $P = 0.926$ ng/mL; for home exposure only, $P = 0.651$ ng/mL; and for work exposure only, $P = 0.318$ ng/mL.

With respect to urinary cotinine, the model of Repace and Lowrey[8] predicted a level of 6.2 ng/mL for the average person and 62 ng/mL for the most-exposed; when updated for $\phi = 0.78$, these values become 5.6 ng/mL and 56 ng/mL, respectively. The weighted mean for seven studies of urine cotinine in adults totaling nearly 4000 persons at that time was 5.6 ng/mL.[8] The upper bound for urine cotinine generally is taken to be in the range of 50 to 90 ng/mL. A U.S. national statistical sample was not and is not available for urine. For adults and children, the elimination kinetics of cotinine are similar,[14–16] although the respiration rates and urine volumes will both be smaller in infants and children than for adults.

Table 1 summarizes default values for the various parameters. We calculate estimated urine, saliva, and serum cotinine values for adults (Equations 5–9), where the parameters and their units are given in Table 1. Note that respiration rates and urine outputs both increase with age.

Substituting the default pharmacokinetic parameter values from Table 1 into Equations 3 and 4 yields the following reduced equations for serum and urine cotinine in units of nanograms per milliliter (ng/mL) as a function of duration of daily hours (h) of exposure H and nicotine concentration N in units of micrograms per cubic meter ($\mu g/m^3$). In applications, default respiration rates are obtained from Table 1 (the conversion factor of 1000 has units of nanograms per microgram):

$$P = \phi\alpha\rho HN/\delta_t T = (1000)(0.78)(0.71)\,\rho HN/\{(64)(1440)\} = 0.006\,\rho HN, \quad (5)$$

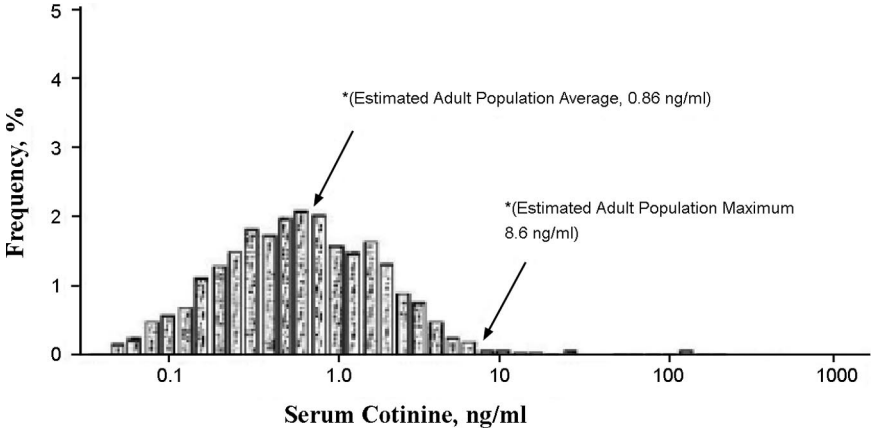

Fig. 1. NHANES III Distribution of Serum Cotinine in U.S. Nonsmoking population ≥4 years of age (1988–1991), exposed at home or at work[4] versus PK model predictions for typical and most-exposed persons in U.S. population using Equation 3.[8]

TABLE 1
Serum, Urine, and Saliva Cotinine Pharmacokinetic Parameters for Adults, Children, and Infants

Parameter	Adults (19–65+ Years)	Children 6–8 Years	Infants 0–2 Years
α, nicotine lung absorption*	0.71	0.71	0.71
δ_r, renal cotinine clearance*	5.9 mL/min	5.9 mL/min	5.9 mL/min
δ_t, total cotinine clearance*	64 mL/min	64 mL/min	64 mL/min
ϕ, nicotine-cotinine conversion efficiency†	0.78	0.78	0.78
ρ, respiration rate (sedentary)‡	0.5 m^3/hr	0.4 m^3/hr	0.28 m^3/hr
ρ, respiration rate (light activity)‡	1.0	1.0	0.38 m^3/hr
ρ, respiration rate (long-term exposures)‡	females 11.3 m^3/d males 15.2 m^3/d	10 m^3/d	4.5–6.8 m^3/d
V_u, daily urine volume§	1300 mL	800 mL	544 mL
Saliva/Serum conversion efficiency*	1.16	1.16	1.16

*Repace et al.[9]
†N. Benowitz, personal communication.
‡U.S. EPA.[30]
§Bakerman.[60]

$$S = \gamma\phi\alpha\rho HN/\delta_t T = (1.16)(1000)(0.78)(0.71)\,\rho HN/\{(64)(1440)\} = 0.007\,\rho HN, \quad (6)$$

$$U = \phi\alpha\rho\delta_r HN/\delta_t V_u = (1000)(0.78)(0.71)(5.9)\,\rho HN/\{(64)(V_u)\} = 50.7\,\rho HN/V_u, \quad (7a)$$

$$U_{Adult} = \phi\alpha\rho\delta_r HN/\delta_t V_u = (1000)(0.78)(0.71)(5.9)\,\rho HN/\{(64)(1300)\} = 0.039\,\rho HN. \quad (7b)$$

To apply Equations 5, 6, and 7a to adults, children, and infants, use the age-appropriate inhalation rates, and for Equation 7a, the age-appropriate urine outputs from Table 1. Equation 7b gives the adult urine cotinine equation.

Results

Application of the Models to SHS Exposure Analysis

Atmospheric Models. The physical models are applied to the analysis of measured SHS-RSP and nicotine as follows. In the NYSERDA study, Leaderer et al[17,18] measured RSP ($PM_{2.5}$) and nicotine using area monitors in 96 homes in two New York State counties with detectable nicotine concentrations in study in the winter of 1986. A major goal of that study was to determine the effect of cigarette smoking on the concentration of combustion products. These homes had a global mean air exchange rate $C_v = 0.54$ hours^{-1}, and a global mean volume $V = 353$ m^3. This is close to the mean of 340 m^3 for a typical single-family home built in 1980.[19] A mean daily cigarette usage of 14.2 cigarettes was reported per home, and measured 7-day averages for SHS-RSP and SHS-Nicotine were 29 $\mu g/m^3$ (SD 25.9) and 2.2 $\mu g/m^3$ (SD 2.43), respectively.

As an illustration, we apply the HSM model to the NYSERDA study as follows: per smoker, we predict for RSP during smoking: SHS-RSP = 217 D_{hs}/C_v = (217)(1/3.53)/(0.54) = 114 $\mu g/m^3$. At 2 cigarettes per smoker-hour, 14.2 cigarettes smoked daily yields an estimated (14.2 cig/d)/(2 cig/hour) = 7.1 hour of daily smoking; thus the global 24-hour-average estimated RSP level for these homes is (7.1/24)(114) = 33.7 $\mu g/m^3$, and the estimated SHS-Nicotine = 3.4 $\mu g/m^3$, which are also taken as weekly averages. The HSM predicts the average measured level of ETS-RSP to within 14%, and the nicotine level to within 50%, well within the standard deviations in the measurements for these single-family homes of typical global volume and air exchange rate. A review of 5 such residential studies prior to 1992[20] suggested that the average nicotine concentration in residences with smoking occupancy ranged from ~2 to 10 $\mu g/m^3$. Jenkins et al[21] report an average of 7.2 $\mu g/m^3$ (SD 5.5 $\mu g/m^3$) nicotine for 22 international studies encompassing more than 300 homes.

SHS and nicotine are estimated for the upper extreme case for domestic exposure as follows: Wilson et al[22] reported measurements of California residential air exchange rates and residence volumes for >800 homes; 500 were studied during 1984–1985, and a statewide probability sample of 300 was performed during 1991–1992. Seasonal, geographical, and heating and cooking appliance relationships to air exchange rates were also collected. Air exchange rates were found to approximately follow a lognormal distribution. The bottom 10% of the homes with gas-forced-air heat had volumes between 4500 and 8000 cubic feet and air exchange rates C_v between 0.1 and 0.2 air changes per hour. How high would the 24-hour SHS-RSP and nicotine levels rise in a home with one smoker at an air exchange rate of 0.1 ach and a volume of 4500 ft^3 (127 m^3) assuming 7 hours of daily smoking? The smoker density is D_{hs} = (100)(1/127) = 0.78 hs/100 m^3 Equation 1 yields an estimated 24-hour ave. SHS-RSP level of SHS_{RSP} = 217(D_{hs}/C_v)(7/24) = (217)(0.78)/(0.1)(0.29) = 494 $\mu g/m^3$, and an estimated nicotine level of SHS_{NIC} = 49 $\mu g/m^3$, per smoker.

Thus the estimated range from typical to extreme 24-hour average exposure concentrations in U.S. homes per smoker smoking at the rate of 2 cigarettes per hour for 7 hours daily is of the order of 3 $\mu g/m^3$ to 49 $\mu g/m^3$ for SHS-nicotine, and 30 $\mu g/m^3$ to 494 $\mu g/m^3$ for SHS-RSP. To place the estimated SHS-

RSP levels in perspective, the National Ambient Air Quality Standard (NAAQS) for P.M.$_{2.5}$ is 15 μg/m^3, annual average concentration.

Pharmacokinetic Model Applications: Serum, Saliva, and Urine Cotinine

For the evaluation of short term experiments a variant of Equation 3 is used. Cotinine (and the nicotine from which it is derived) follow first order kinetics of the form $P(t) = P_o(1 - e^{-\lambda t})$, where P_o is the equilibrium dose of cotinine, and the rate constant $\lambda = 1/\tau_c$ (where τ is mean life (min), and is 1.44 times the half-life) is the time for one full volume of blood to be cleansed of cotinine. When t = H is short compared to the mean life (for cotinine the half life is ~17 hours and the mean life τ_c is ~24.5 hours, and $\lambda = 0.0408$ hours^{-1}), the maximum concentration is given by $P_{max}(H) \sim P_oH/\tau_c$ [note that T_d should not be confused with τ_c, although they are numerically almost identical (T_d = 24 hours, and τ_c = 24.5 hours)]:

$$P_{max}(t = H) = \phi\alpha\rho HN/\delta_t\tau_c \quad (8)$$

Serum and Saliva Cotinine in Adults. In a study that will be reported in detail elsewhere, Bernert et al[23] measured serum and saliva cotinine in 40 seated adult subjects before and after H = 4 hours individual exposure to steady-state sidestream smoke nicotine from either Marlboro King Filter HP or Newport 100 Filter menthol HP cigarettes in a 17.3 m^3 exposure chamber ventilated at 0.73 ± 0.09 air changes per hour. Respiration rates were not measured. The mean chamber SHS-CO level was 8.6 ppm, and the mean SHS-nicotine concentration was 147 μg/m^3. Of these 40 subjects, 21 were women, 19 were men, 18 were black, and 22 were white. All subjects had similar cotinine response rates and elimination kinetics to these exposures, irrespective of cigarette type, gender, or race. Salivary cotinine *S*, which was measured every 30 minutes, increased linearly during the exposure. At $t = 4$ hours, observed saliva cotinines increased to $S(4) = 2.95$ ng/mL above baseline; by two hours post-exposure, *S* had increased to $S(6) = 3.15$ ng/mL (SD 0.21) over baseline ($n = 40$), whereas serum cotinine $P(6)$ increased by 2.66 ng/mL (Bernert et al. 2004). The conversion efficiency, γ, estimated from ratio of the means, $S/P = \gamma = 1.19$, and by linear regression analysis ($n = 40$), $\gamma = 1.17$ ($R^2 = 0.95$), in good agreement with the value in Table 1. Thus, $S = \gamma P = 1.18\ P$, confirming earlier data.[9,24,25]

The respiration rate was not measured in the experiments of Bernert et al[23]; however, it can be estimated by comparing the model to the data. A problem arises because the simplified models of Equations 3, 4, 10, and their derivative equations assume that nicotine is completely converted to cotinine, and thus represents the peak level at termination of exposure. Benowitz and Jacob[26] found that plasma cotinine, derived from infused nicotine in a 30 minute dosage experiment on 6 adult nonsmokers, peaked about 3.5 hours after infusion terminated, and appeared to plateau for ~8 hours. The results of Willers et al[16] in an experimental study discussed below, were quite similar for urine cotinine derived from SHS nicotine: they found that when SHS exposure ceased, urine cotinine continued to increase for ~3 hours and then plateaued for ~8 hours. This time-lag is likely attributable to the incomplete conversion of nicotine, which has a 2-hour half life, to cotinine. Thus, when comparing the model predictions to controlled experimental data results, this lag to peak concentration needs to be taken into account. Strictly speaking, this could be done through a 2-compartment model,[12] taking into account the different volumes of distribution of nicotine and cotinine. However, the data available to calibrate such a model do not exist. The simplest way to approximate the lag is to scale the measured cotinine concentration 2 hours backwards using its full kinetics. This is done by extrapolating the observed concentration at the 6-hour mark, $P_{Obs}(6) = 2.66$ ng/mL, back to $P_{Obs}(4)$ by the ratio:

$$P_{Obs}(4) = P_{Obs}(6)[1 - e^{-(0.0408)(4)}]/[1 - e^{-(0.0408)(6)}] = (2.66)(0.694) = 1.85 \text{ ng/mL}.$$

We apply Equation 8 to the results of the Bernert et al[23] study: The exposure duration is H = 4 hours, and for all 40 adults, $N = 146.6$ μg/m^3 is the average nicotine exposure concentration. $P_{max}(t = H) = \phi\alpha\rho HN/\delta_t\tau_c = (0.78)(0.71)(\rho)(4)(146.6)/(64)(1470) = 3.45\ \rho$ ng/mL. This is equated to $P_{Obs}(4) = 1.85$ ng/mL, and we solve for the estimated global respiration rate for these 40 adults: $\rho = (1.85)/(3.45) = 0.54$ m^3/hour. This is in good agreement with the value for sedentary persons in Table 1. At $P(6) = (3.45)(0.54)/0.694 = 2.68$ ng/mL, in good agreement with observations (2.66 ng/mL). The ratio of P to N is then: P/N = 2.68/(146.6) = 0.0183.

Table 2 summarizes the predictions and observation for all 40 subjects at 6 (H = 4,+2) hours, and for the four subgroups within, broken down by gender and race by applying Equation 8 with the appropriate value of N. Figure 2 shows a regression of measured serum cotinine versus measured nicotine concentration (data from all 40 subjects). $P_{observed} = 0.018$ N, $R^2 = 0.2$, validating $P_{Predicted}$. Figure 3 plots $P_{observed}$ against $N_{observed}$, with the regressions on the mean and median data when grouped by nicotine level ($n = 8$) also, respectively yielding $P_{observed} = 0.018$ N, ($R^2 = 0.67$) and $P_{observed} = 0.019$ N, ($R^2 = 0.59$). R^2 values improve from 0.2 to 0.7 for the means, with little difference between the means and medians for the grouped data. Benowitz[13] has observed that the coefficient of variation for the nicotine conversion to cotinine

TABLE 2
Predicted Versus Measured Serum Cotinine 2 Hours After Exposure as a Function of Measured SHS Nicotine for 40 Adults by Gender and Race, With an Estimated Respiration Rate of $\rho = 0.54$ m^3/h, Using Equation 8

Group, *n*	Nicotine, *N*, μg/m^3	$P_{predicted}$, ng/mL	$P_{observed}$, ng/mL	Pred/Obs (%)
All subjects, 40	146.6	2.68	2.66	101
Female, 21	154.9	2.83	2.91	97
Male, 19	137.4	2.51	2.41	104
Black, 18	132.2	2.42	2.40	101
White, 22	158.8	2.90	2.90	100

Measured values from Bernert et al.[23]

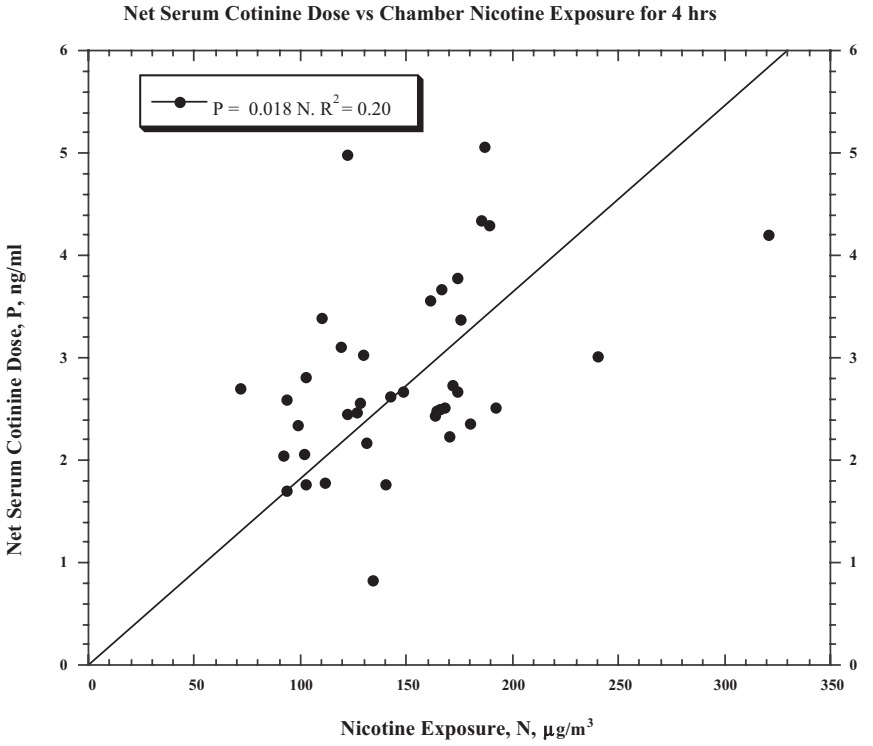

Fig. 2. Measured adult serum cotinine versus measured nicotine exposure ($n = 40$). Regression slope for observed data forced through zero.

is approximately 22%, not great compared with the variability in the clearance of most other drugs, and much less than the variability typically observed for human pharmacokinetic parameters, leading to the conclusion that even with this inevitable degree of imprecision, cotinine in large groups would be expected to accurately reflect group exposure to nicotine from SHS.

It should be noted that there is an apparent conflict between our model of the postexposure response in serum and saliva cotinine measurements made during this same study, which suggested a more modest increase in saliva cotinine concentrations during the postexposure period than was reported in the studies of Benowitz and Jacob[26] and Willers et al.[16] This in turn would predict a lower postexposure increase in serum cotinine and, thus, a greater value for ρ than what was calculated by our model. This result clearly is an indication that additional data are needed to confirm the response of cotinine levels during the postexposure interval in multiple matrices, and under different conditions of exposure.

Urine Cotinine in Adults and Children. Willers et al[16] performed a semi-experimental exposure study on 21 nonsmokers—7 adults (ages, 37–42 years; mean, 40 years) and 14 children (ages, 4–11 year; mean, 8.1 years)—exposed to a mean level of 110 μg/m^3 (TWA) of well-mixed SHS-nicotine from Red Prince cigarettes (1.1 mg nicotine, Swedish Tobacco Company) on a tour bus for $H = 2$ hours in Sweden. Respiration rates were not measured. The children were reported to be more active than the adults, with some of them changing seats. Density-corrected urine cotinine in units of ng/mL was reported. Urine cotinine, as discussed earlier, rose until 3 hours post-exposure, plateaued for 12 hours in children and 8 hours in adults (range, 1–22 hours), then declined log linearly to the end of the collection period of 144 hours. These increases likely represent conversion of the remaining serum nicotine to cotinine. The lengthy plateaus were followed by a log-linear decrease in concentration with a half-life of 19 hours, 95% CI = 17–20 hours, similar to the half-life of cotinine in blood serum. This prolonged plateau may represent nonserum compartments emptying into the blood circulation, and indicate that urine measurements are stable for some time post exposure. Mean peak urine cotinine levels in adults were U_{Adults} $(H + 3) = 12.6$ ng/mL (SD 3.87; median, 11 ng/mL) and in the children, $U_{Children} = 22.2$ ng/mL (SD 7.37; median 23 ng/mL), corrected for urine density and for preexposure background.

Willers et al[16] found no significant difference in cotinine elimination kinetics between the adults and children, and speculated that the adult–child cotinine difference was attributable to higher breathing rate or to metabolic differences. If the ratio of respiration rates for short-term exposure for children and adults while seated is nearly the same (Table 1), and if

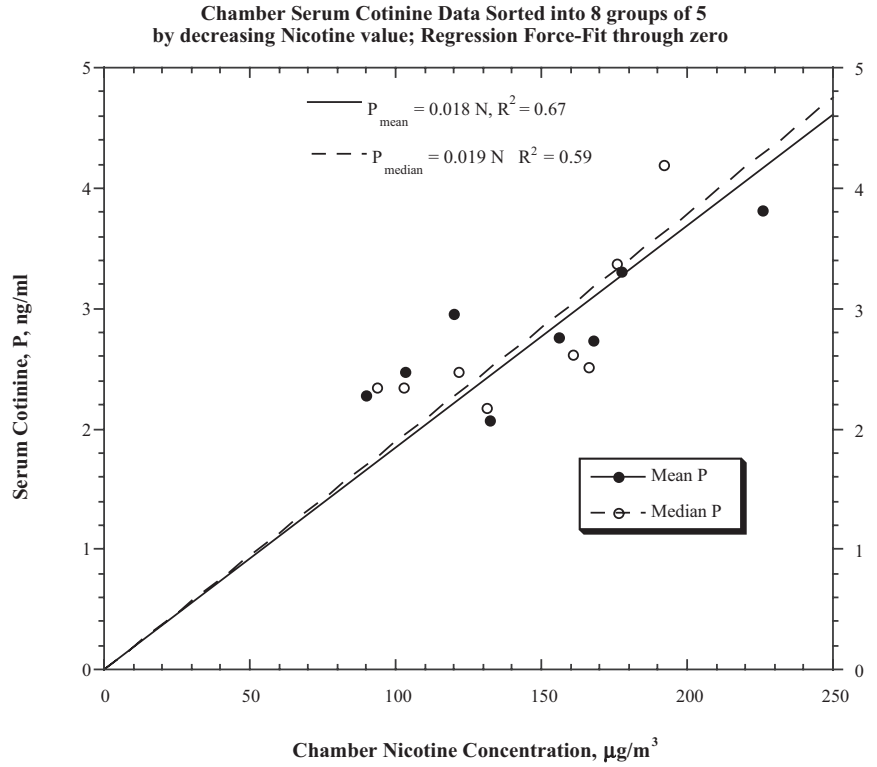

Fig. 3. Measured mean and median serum cotinine versus measured chamber nicotine when sorted into eight groups of five by decreasing nicotine value.

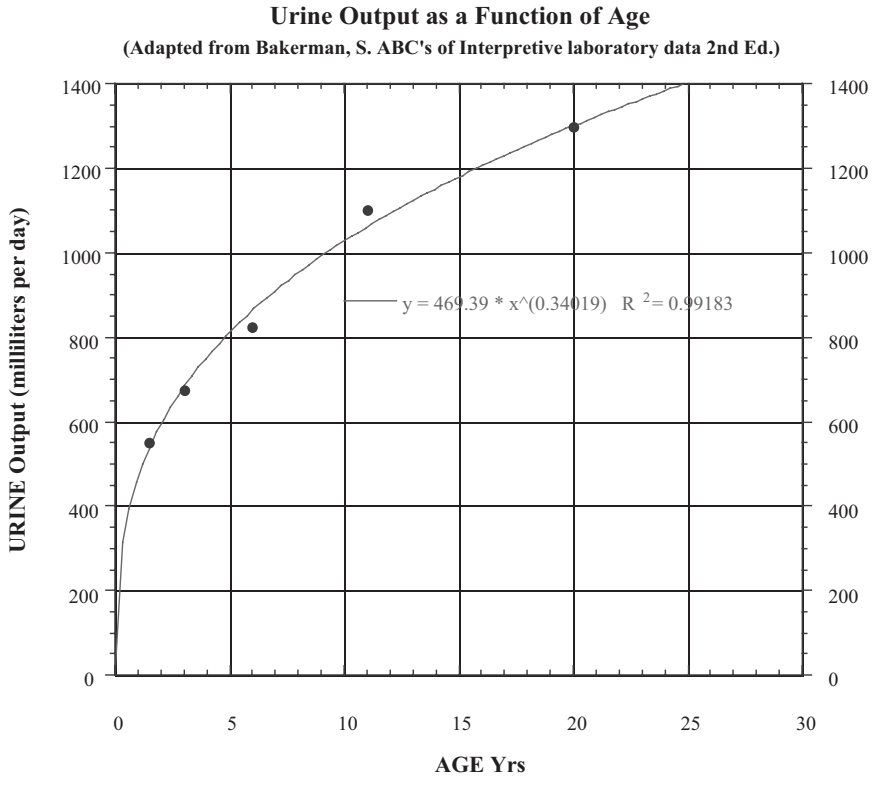

Fig. 4. Urine output as a function of age from infant to adult. A curve-fit is made to the midpoint of ranges as a function of age. (Adapted from Bakerman.[57])

children have the same elimination kinetics but a higher urine cotinine, Fig. 4 suggests that the higher urinary cotinine levels measured in the children might be attributable to lower urine volume.

If the regression equation of Fig. 4 is used with the data for the 14 Swedish children studied by Willers et al,[16] the cotinine values can be age-adjusted for estimated urine output. The adults are assumed to all have 1300 mL/d output, while the childrens' urine output is adjusted for each child according to his or her age. For example, for one 4-year old, the measured urine cotinine is U_4 = 33 ng/mL. Figure 4 gives an estimated urine output of 752 mL. Adjusting U_4 by the ratio (752/1300) yields 19 ng/mL. Similar adjustments are made for each child, aged 4 to 11. The adjusted and un-adjusted data are compared in Fig. 5:

Analysis of the results of Fig. 5 shows that before the adjustment, the urine cotinines of adults and children were respectively 12.6 ng/mL (SD 3.87) and 22.2 ng/mL (SD 7.37); after the adjustment the adults remained the same, and the children's cotinines averaged 15.8 ng/mL (SD 4.46) (median 16.8 ng/mL). Thus, simply adjusting for estimated urine output reduces the difference between the adult and child mean cotinine levels by two thirds, from 76% to 25%.

We now model the peak exposures at H = 2 hours. As with the analysis of the serum cotinine experiment, these predicted peaks do not take into account the post-exposure increase in cotinine. Therefore we scale observations backward 3 hours to compare with predictions using the measured global half life of urine cotinine in this experiment: $T_{1/2}$ = 19 hours. The mean life is then (1.44)(19) = 27.4 hours, and the time constant is λ_u = 1/27.4 = 0.365 hours^{-1}. Thus, $U_{Obs}(2) = U_{Obs}(5)[1 - e^{-(0.365)(2)}]/[1 - e^{-(0.365)(5)}] = 0.422\ U_{Obs}(5)$. Applying this to the observed peak urine cotinine levels 3 hours post exposure yields the esti-

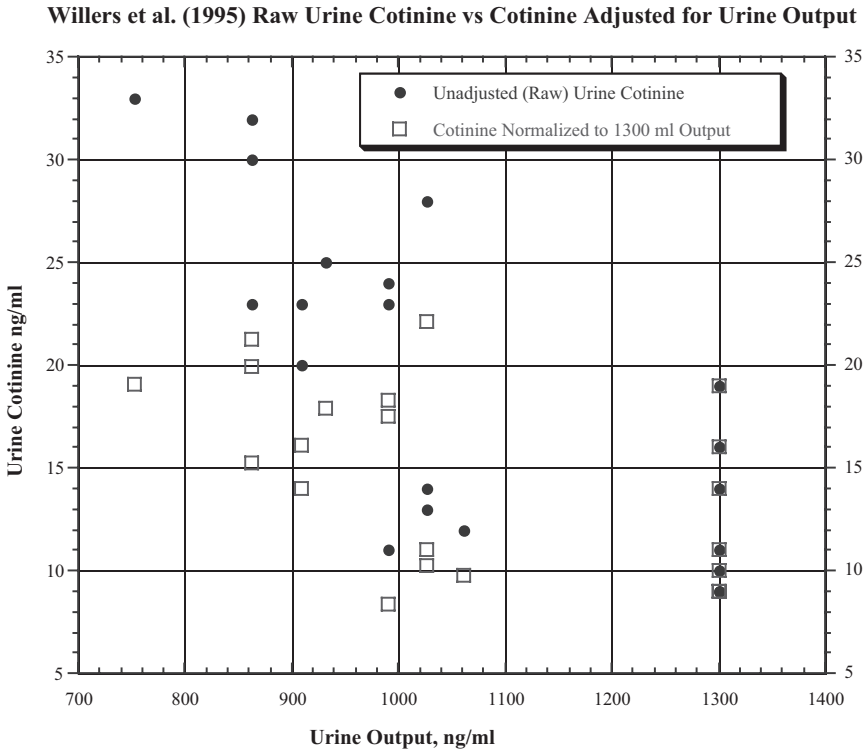

Fig. 5. Density-adjusted urine cotinine data for 14 children and 7 adults, as reported by Willers et al[16] (solid circles) and as age-adjusted for children according to age of each and urine output (open squares) estimated from the regression equation of Fig. 4, by the ratio of their estimated urinary output to that of adults (1300 mL/d). The adult cotinines were unadjusted.

mated observed levels 3 hours earlier at H = 2: $U_{Adults\ Obs}(2) = 0.422\ U_{Obs}(5) = (0.442)(12.6) = 5.31$ ng/mL. $U_{Child\ Obs}(2) = 0.422\ U_{Obs}(5) = (0.442)(22.2) = 9.37$ ng/mL. The predicted value of $U_{Child\ Pred}$ for children at H = 2 is, using Equation 7a with a default urinary output $V_u = 800$ mL/d from Table 1 is $U_{Child\ Pred} = 50.7\ \rho HN/V_u = 50.7\ \rho HN/800 = (0.063)(\rho HN)$:

$$U_{Adults\ Pred}(2) = 0.039\ \rho HN = (0.039)(\rho)(2)(110) = 8.58\ \rho; \quad (9)$$

$$U_{Child\ Pred}(2) = 0.063\ \rho HN = (0.063)(\rho)(2)(110) = 13.9\ \rho \quad (10)$$

Equating $U_{Adults\ Pred}(2) = 8.58\ \rho = U_{Adults\ Obs}(2)\ \rho$, and solving for ρ yields: $\rho_{Adult} = (5.31)/(8.58) = 0.62$ m^3/hr. Similarly, equating $U_{Child\ Pred}(2) = 13.9\ \rho = U_{Child\ Obs}(2)$, and solving for ρ yields: $\rho_{Child} = (9.37)/(13.9) = 0.67$ m^3/hr. These values are less than halfway between sedentary and light work (Table 1) and close to the default respiration rate of ρ = 0.6 m^3/hr recommended for seated persons.[9,28] Thus, our urine cotinine model is consistent with this semi-experimental study.

Hair Nicotine in Infants. In a study involving 133 infants in New Zealand, Al-Delaimy et al[29] compared two biomarkers of exposure to SHS: hair nicotine and urine cotinine, using questionnaires to inquire as to SHS exposure status in infants. The infants were aged 3–27 months of age from August 1997 to October 1998. Urine samples were collected within 24 hours of admission. SHS exposure over the previous 6 months was recorded by questionnaire in terms of the number of cigarettes smoked by parents, and whether smoking was permitted in the homes and vehicles of the parents. A length of 1–2 cm of hair was cut from each subject's scalp, and thus reflects the previous 1 to 2 months' average SHS exposure since hair grows at the rate of 1 cm/month. 10–50 mg of hair was collected, and nicotine in hair ranged from 0.19 ng/mg of hair to 47.82 ng/mg of hair. Mean hair nicotine levels were 5.10 ng/mg (SD 6.81 ng/mg), median, 2.37 ng/mg. The respective creatinine-adjusted urine cotinine levels were 7.42 ng/mL (SD 12.5 ng/mL; median, 3.04 ng/mL).

We now apply the PK model to the analysis of urine cotinine and hair nicotine in infants. Figure 6 shows a plot of creatinine-normalized urine cotinine U' in units of ng/mL versus hair nicotine Ω for 125 infants whose hair nicotine, urine cotinine, age, and respiration rate were recorded, unadjusted ($R^2 = 0.33$), and adjusted for both respiration rate and age and respiration rate only ($R^2 = 0.39$). The latter two adjustments yield the same result, likely because respiration rate increases with infants' age. The adjusted ratio of $U'/\Omega = 1.41$ results from the regression. Thus, $\Omega = 0.71\ U'$. Assuming that $U' \approx U$, and using Equation 7 adapted for infants for a default urinary output of 544 mL/d [(1300/544)(0.039) = 0.094], or $U_{Infants} = 0.094\ \rho HN$, and for a default of respiration rate of 0.28 m^3/hr, $U_{Infants} = (0.094)(0.28)\ \rho HN = 0.026$ HN, and if H is taken as 24 hours, $U_{Infants\text{-}24\ hours} = (0.026)(24)\ N = 0.624\ N$. Thus, for this set of infants, the hair nicotine Ω may be estimated by the equation: $\Omega_{Infants}$ [ng/mg] $= 0.71\ U = (0.71)(0.624\ N) = 0.44\ N$ [μg/m^3]. Solving the U and Ω equations for N yields:

$$N\ [\mu g/m^3] \approx 1.60\ U_{Infants}\ [ng/mL] \approx 2.27\ \Omega_{Infants}\ [ng/mg] \quad (11)$$

where N in Equation 11 represents an average of daily nicotine exposures over the previous 1 to 2 months, whereas U represents a daily average for the previous 1–2 days. Finally, Figs. 7, and 8 give plots of measured

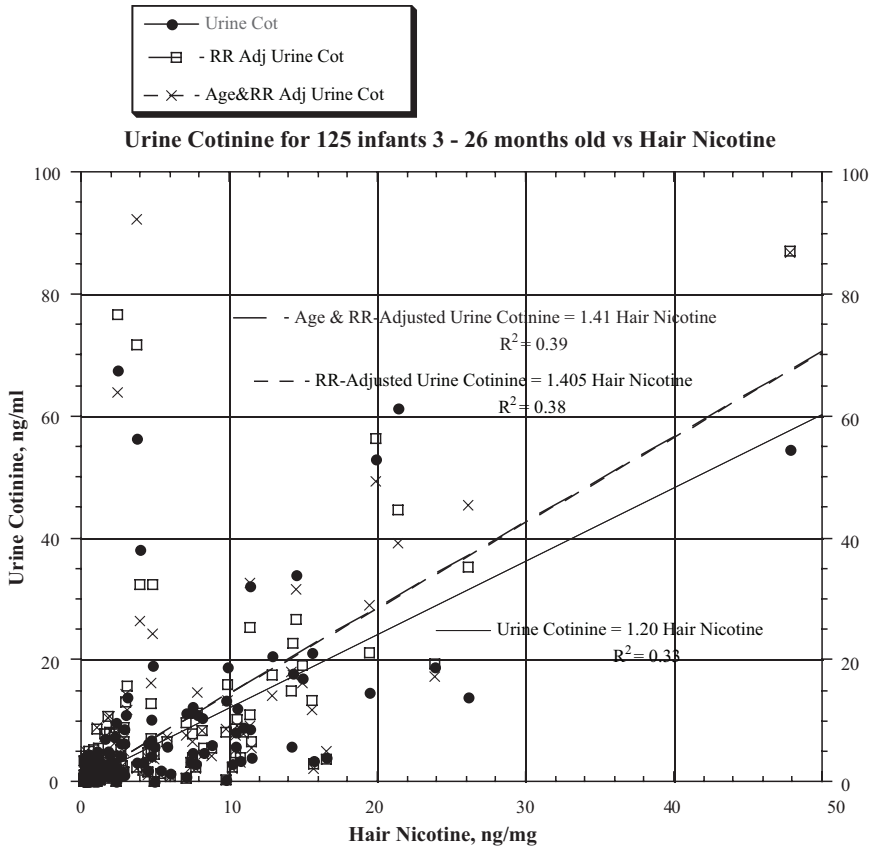

Fig. 6. Urine cotinine U, adjusted for creatinine, versus hair nicotine Ω, in ng/mg, unadjusted for age or respiration rate (RR) (solid regression line) and adjusted for age as well as for both age and respiration rate (overlapping dashed lines). Data from Al-Delaimy et al.[29]

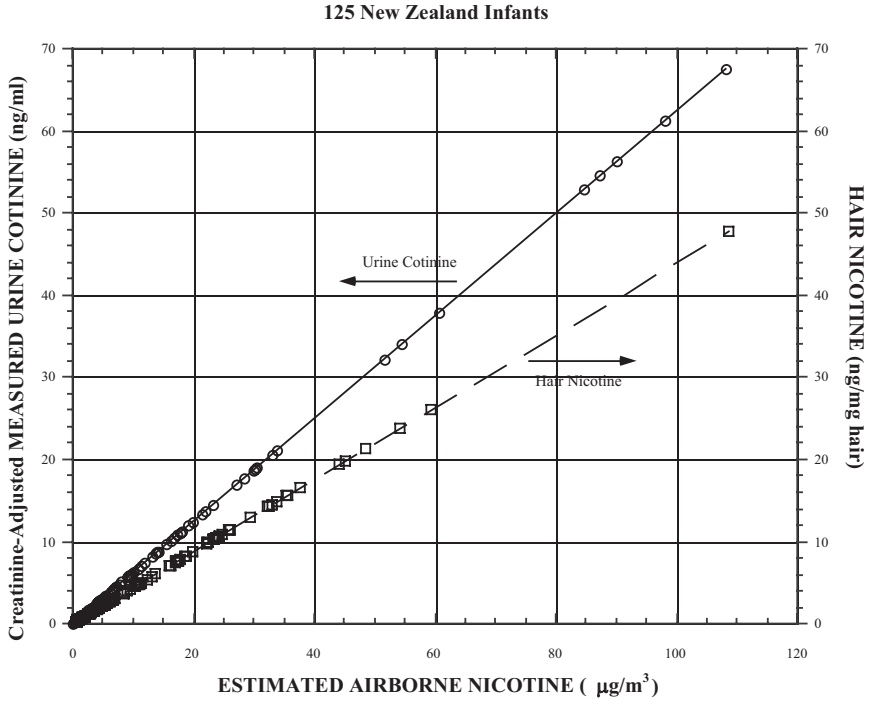

Fig. 7. Measured urine cotinine and hair nicotine versus estimated airborne nicotine using Equation 12. Airborne nicotine represents a 1- to 2-day daily average based on urine and a 1- to 2-month average based on hair.

U and Ω versus estimated daily average SHS-RSP and nicotine exposure concentrations for these infants as a reality check. The predicted range in N (5% to 95%) is about 0.5 to 50 μg/m^3, with an estimated median value of about 5 μg/m^3, and the range for SHS-RSP is from 0.1 to 300 μg/m^3, with an estimated median of 50 μg/m^3. By comparison, the U.S. EPA[20] reported, at a time when U.S. smoking prevalence was approximately 30%, that in homes with smoking occupancy, average daily or weekly nicotine values typically ranged from <1 to 10 μg/m^3, whereas average daily or weekly SHS-RSP ranged from 18 μg/m^3 to 95 μg/m^3 depending on the number of smokers and smoking rates, which is somewhat lower than the range in Fig. 8. However, in New Zealand, the smoking prevalence among the indigenous Maori people is very high, at 51.2% in 2001.

Discussion

Applications of the "Rosetta Stone" Equations to Environmental Epidemiology. We now turn to examples of the utility of the physical–PK models shown previously, coupled with dose–response relationships.

Reading Scores. Yolton et al[20] studied the effect of SHS on reading scores in 4399 children aged 6–16 years who were tested for reading ability by a standardized test (WRAT-R) and whose serum cotinine levels were measured in the Third National Health and Nutrition Examination Study (NHANES III) conducted from 1988–1994. Yolton et al[31] found the following equation for reading scores RS as a function of serum cotinine P, (P. Auinger, personal communication, 2005):

$$RS = 90.69 - 2.487 \log_{10} P. \quad (12)$$

If we want to assess the expected decrement in reading scores for a child but only urine cotinine were available, Equation 12 is easily converted into an expression involving urinary cotinine for this age group using the ratio of Equations 5 and 7a

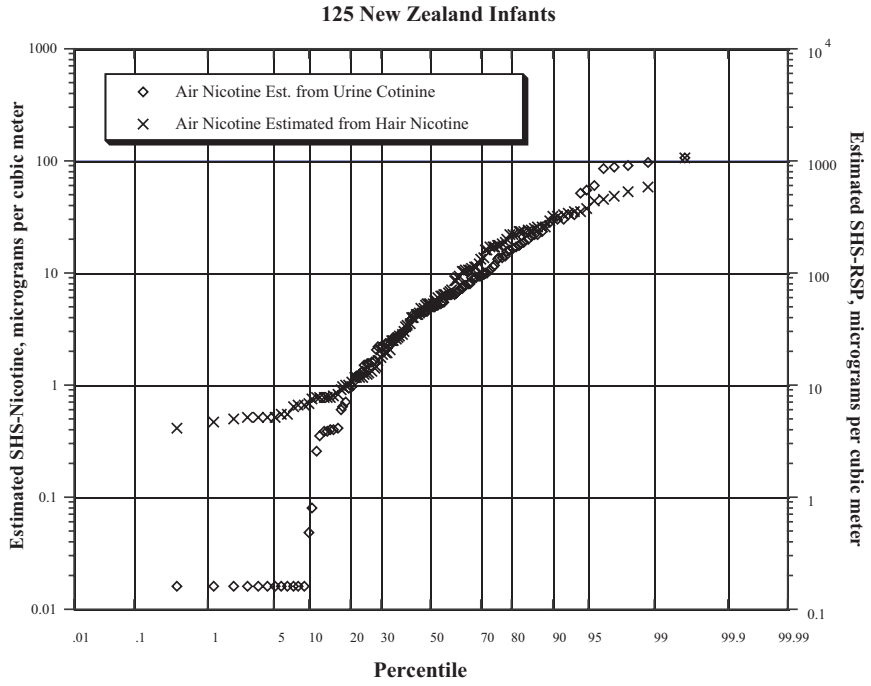

Fig. 8. Log-probability plots of estimated SHS-nicotine and SHS-RSP derived from infants' urine cotinine (daily average) and hair nicotine (monthly average). A total of 95% of the estimated nicotine levels are less than 50 $\mu g/m^3$ and 95% of the RSP levels are less than 500 $\mu g/m^3$.

(with V_u = 800 mL), P/U = 0.095. Replacing P by 0.095 U in Equation 12 yields the expression:

$$RS = 93.23 - 2.487 \log_{10}(U). \quad (13)$$

Estimation of SHS-RSP and Nicotine From Cotinine

Adults. What are the serum, urine, and saliva cotinine for adults exposed to a uniformly diluted SHS-Nicotine daily average exposure of 3.4 $\mu g/m^3$ as measured in the NYSERDA study? For adult females, with a long-term respiration rate (ie, averaged over a 24-hour period) of 11.3 m^3/d or 0.47 m^3/hr, the estimated serum cotinine level would be $P_{Females\ SF}$ = 0.006 ρHN = (0.006)(0.47)(24)(3.4) = 0.23 ng/mL in a single-family home, and for exposure in a house trailer at 49 $\mu g/m^3$, $P_{Females\ HT}$ = (49/3.4) (0.23) = 3.3 ng/mL. The corresponding saliva cotinine concentrations would be about 16% higher, whereas the estimated urine cotinine levels would be U_{SF} = 6.5 P = (6.5)(0.23) = 1.5 ng/mL for the single family home, and U_{HT} = (6.5)(3.3) = 21 ng/mL for the house trailer, assuming uniform mixing. Proximity effects may increase actual exposures.

Infants. What are the serum, urine, and saliva cotinine and hair nicotine equivalents to a uniformly diluted SHS-Nicotine daily average exposure of 3.4 $\mu g/m^3$ for infants as measured in the NYSERDA study? We repeat the same calculation for infants, assuming 16 hours/d exposure: $P_{Infants\ SF}$ = 0.0017 ρHN = (0.0017)(0.30)(24)(3.4)(16/7) = 0.1 ng/mL in a single-family home, and for exposure in a house trailer at 49 $\mu g/m^3$, $P_{Infants\ HT}$ = (49/3.4) (0.1) = 1.4 ng/mL. The corresponding saliva cotinine concentrations would be about 16% higher, whereas the estimated urine cotinine levels would be $U_{Infants\ SF}$ = 15.3 P = (15.3)(0.1) = 1.5 ng/mL for the single-family home, and $U_{Infants\ HT}$ = (15.3) (1.4) = 21 ng/mL for the house trailer. Actual doses might be higher due to proximity effects. For long-term exposure, hair nicotine values are estimated for the single-family home for infants to be $\Omega_{Infants\ SF}$ [ng/mg] = 0.71 U = (0.71)(1.5) = 1.1 ng/mg (about the 30th percentile based on the assumed nicotine level of 3.4 $\mu g/m^3$ using Fig. 4, and for the house trailer, $\Omega_{Infants\ SF}$ [ng/mg] = 0.71 U = (0.71)(21) = 14.9 ng/mg, or about the 90th percentile using Fig. 4, based on the assumed nicotine level of 49 $\mu g/m^3$; these results appear reasonable.

Asthma. On the basis of the level of exposure for the small-volume poorly ventilated trailer-park home described above with a nicotine concentration of N = 49 $\mu g/m^3$ per smoker, with 2 smokers, for N = 98 $\mu g/m^3$, the equivalent estimated serum cotinine level is from Equation 7, P = 0.006 ρHN = (0.006)(0.28)(12)(98) = 2 ng/mL. What is the increased risk of asthma for such a child? Mannino et al. (2001) found that 4-year old children in the highest tertile of serum cotinine, in the range 0.5–20 ng/mL, had a 5-fold increased risk of current asthma, and a nearly doubled risk of missing 6 or more days of school per year, relative to children with serum cotinines below 0.1 ng/mL.

The Rosetta Stone Equations. Table 3 summarizes the equations correlating SHS exposure (nicotine, RSP and CO) and dose (serum, saliva, and urine) for adults and for hair nicotine and urine cotinine in children. With respect to the latter relationship, it is important to note that hair nicotine and urine cotinine have significantly different averaging times. Using the Equations in Table 3 enables comparison of studies performed with different atmospheric or biological markers with one another and with microenvironmental parameters of space volume, air exchange rate and smoker density. Recommended default breathing rates as a function of age, gender and activity level may be found in the EPA Exposure Factors Handbook, chapter 5, Table 5–23[30] or in the ICRP handbook on Reference Man.[32]

As an example of an application of the Rosetta Stone Equations of Table 3, we compare the U.S. and German national cotinine studies, which were

TABLE 3
Rosetta Stone Conversion Equations for SHS Atmospheric Biomarker Estimation for Adults (as a Function of Respiration Rate ρ, Daily Hours of Exposure, *H*) and Between Hair Nicotine and Urine Cotinine in Infants

SHS Marker, Units	Conversion Equation
R = RSP, $\mu g/m^3$	R = 10 N
N = Nicotine, $\mu g/m^3$	N = 21.7 D_{hs}/C_v
CO = Carbon monoxide, ppm_{mass}	CO = 0.004 R
PPAH = Particulate polycyclic aromatic hydrocarbons, $\mu g/m^3$	PPAH = R/2000
P = Plasma (Serum) cotinine, ng/mL	$P = 0.006\ \rho HN$
S = Saliva cotinine, ng/mL	S = 1.16 P
U = Urine cotinine, ng/mL	U = 6.5 P
$\Omega_{infants}$ = Hair nicotine, ng/mg	$\Omega_{infants} \approx 0.7\ U_{infants}$

Note that the units of N in the cotinine equations are $\mu g/m^3$.

D_{hs} indicates smoker density (no. of habitual smokers smoking 14 mg SHS-RSP/cigarette at the rate of 2 cigarettes/hr in the micro environment per 100 m^3 of space volume); C_v, air exchange rate of space volume in air changes per hour (hr^{-1}).

based respectively on serum and urine cotinine. We transform the actual serum cotinine NHANES III values for the typical and most-exposed U.S. nonsmoking adults during the period 1988–1991, from the distribution plotted in Fig. 6, into urine cotinine from U = 6.5 P, as: $U_{typ} = 6.5\ P_{typ} = (6.5)(0.86) = 5.6$ ng/mL (estimated geometric mean), and $U_{max} = 6.5\ P_{max} = (6.5)(15) = 98$ ng/mL.

The adult German Environmental Survey, measured urine cotinine in adults (18–69 y) in 1998, at a time when the German adults smoking prevalence was 34% (Heinrich et al., 2004). Heinrich et al. report, for adults exposed to SHS at home, a geometric mean urine cotinine of 5.25 (95% CI = 3.49–7.90) ng/mL.[33] Converting this into serum cotinine to compare to NHANES[4] yields an estimated: $P_{typ} = U_{typ}/6.5 = (5.25/6.5) = 0.8$ ng/mL, and if this is further adjusted by the ratio of smoking prevalence as (27.5%/34%) (0.8) = 0.65 ng/mL. By comparison, NHANES III reported for adults ≥17 y and exposed to SHS at home only, a geometric mean serum cotinine level of 0.70 ng/mL (0.586–0.835) (the U.S. adult smoking prevalence in 1988 declined from about 29% to 26% in 1991).

As a second example, Otsuka et al[33] reported that exposure to 6 ppm of carbon monoxide from SHS (SHS-CO) for 30 minutes induces endothelial dysfunction in nonsmokers. Lam et al[34] observed that this work would have more widespread application if SHS-CO had been related to SHS-RSP or nicotine. Using methods similar to those embodied in Table 3, Repace[35] calculated that workplace exposure to 6 ppm of SHS-CO was comparable to ~1500 $\mu g/m^3$ of SHS RSP (150 $\mu g/m^3$ nicotine), and a salivary cotinine level of ~7 ng/mL, a level somewhat less than that measured in London bartenders.[24]

PK Model Results. For the specific controlled experiments involving short-term serum and urine cotinine exposures, our results are as follows. Using the PK model of Equation 3, with reasonable assumptions for default respiration rates and global PK parameters from the literature, serum cotinine levels as a result of short-term exposures in the CDC chamber study of Bernert et al[23] were predicted very accurately. Using the PK model of Equation 4, applied to the measured urine cotinine values for adults and children to estimated respiration rates yielded results very close to expected default respiration rates in Table 1 indicating that if we had simply used the default respiration rates to estimate the cotinine values, we would have come close to actual observations. Using the model of Equation 3, population average median and peak cross-sectional serum cotinine levels for the U.S. population exposed at home or at work during 1988–1991 are predicted quite well. For the small number of clinical samples available for saliva cotinine, measures of central tendency were predicted quite well. For the much larger number of samples available for urine cotinine, measures of central tendency were also predicted quite well, while the upper bound predicted was at the lower end of the upper bound. However the urine comparisons, unlike for serum cotinine, are limited by the lack of availability of a national statistical sample for the United States.

In predicting or comparing adult biomarker levels with those of children and infants, differences in respiration rate should be taken into account for serum and saliva cotinine, whereas for urinary cotinine, both differences in respiration rate and urinary output should be accounted for. Activity levels are important predictors of respiration rates and need to be specified in making predictions. Steady-state serum cotinine levels are independent of volume of distribution and thus body size differences (although dynamic levels are not) (N. Benowitz, personal communication, Feb. 2005), so adults and children would be expected to have similar serum cotinine levels for the same inhaled dose of SHS nicotine. However, infants have lower respiration rates than older children and adults, and therefore should have lower serum and saliva cotinine for the same SHS exposure. Reported higher levels of serum cotinine in infants may be a function of proximity to maternal smoking, and very high cotinine levels in infants may the result of the intake of nicotine and cotinine in breast milk. By contrast, these equations suggest that infants' and childrens' urine cotinine concentrations should be about 90% of adult values at the same respiration rate when their lower urinary output is accounted for.

It is of interest to compare Equation 3 with the model of Benowitz

and Jacob,[26] who gave an equation for estimating the daily average intake of nicotine D_{sm} (μg/d) in smokers from their steady state cotinine levels P_{ss} (ng/mL): $D_{sm} = KP_{ss} = 80\ P_{ss}$. From our aforementioned work, for nonsmokers, $P_{ss} = (1000\ ng/\mu g)\phi\alpha\rho HN/\delta_t T_d$ ng/mL and $D_{ns} = \alpha\rho HN/T_d$ (μg/d) Then $K_{ns} = D_{ns}/P_{ss} = (\alpha\rho HN/T_d)/(1000)(\phi\alpha\rho HN/\delta_t T_d) = \delta_t/1000\phi$ ml/d = (64 mL/min)(1440 minutes/d)/(780) = 118. However, Benowitz and Jacob report $\phi = 0.72$ and $\delta_t = 40.6$ mL/min for smokers; with these values $K_s = \delta_t/1000\phi$ ml/d = (40.6 mL/min)(1440 min/d)/(720) = 81. Thus, Equation 3 is consistent with the results of Benowitz and Jacob.[26]

Hair Nicotine Versus Urine Cotinine. Urine cotinine, with a half-life of approximately 17 hours, reflects SHS exposure within the previous 1–2 days: a given cotinine level will decline to 6% of its value in 2 days. Hair nicotine reflects SHS exposure at the rate of 1 month per centimeter of hair analyzed. Al-Delaimy et al[29] concluded that, relative to urine cotinine, hair nicotine levels were better able to discriminate the groups of infants according to household smoking habits, that hair nicotine was more strongly correlated with the number of smokers in the home, the number of cigarettes smoked by household smokers, and to the questionnaire variables of smoking. However, unlike urinary cotinine, it has not been previously possible to correlate hair nicotine levels with average airborne nicotine exposure from SHS. The conversion equation given here makes it possible for the first time to roughly compare hair nicotine to cotinine in body fluids and atmospheric SHS markers. Hair nicotine reflecting 1-month SHS exposure and urine cotinine reflecting 1–2 day SHS exposure in 127 New Zealand infants ≤2 years are correlated, on the assumption that the SHS exposure of infants is reasonably stable from day-to-day. Using this model, hair nicotine and urine cotinine appear to translate into similar estimated values of air nicotine exposure from the 20th to the 95th percentiles of the nicotine distribution.

Future Research Needs. Additional controlled studies that measure respiration rates would improve the reliability of the calibration of the PK model; studies that measure the relative serum, saliva, and urine cotinine concentrations of adults, children, and infants under experimental conditions; as well as hair nicotine studies which involve daily cotinine measurements during the period represented by the hair samples (however, there is at least one study of this type that was conducted using beard hair and nicotine gum—not smoke exposure). In addition, further study of the response of cotinine levels during the post-SHS-exposure interval is needed in serum, saliva, and urine. Finally, pharmacodynamic models that permit prediction of cotinine levels over a period of several days' intermittent exposure would be very useful for the interpretation of levels of SHS exposure.

Conclusions

Physical and PK models are given that enable intercomparison of studies of SHS exposure using atmospheric markers (CO, RSP, and nicotine) and biomarkers (serum, saliva, and urine cotinine, and hair nicotine). The pharmacokinetic models applied to analyze or predict biomarkers for adults, children, and infants should reflect differences in respiration rate and urinary output. Elimination kinetics appear to be the same irrespective of age and gender. Previously published comparisons of predictions of the serum cotinine models for the typical and most-exposed individuals in the population based on Equation 3 are found to agree well with a national probability sample.

The serum PK model was used to predict serum cotinine from environmental nicotine for 40 nonsmoking adults to steady-state SHS nicotine in a chamber for 4 hours to American SHS; model predictions compared very well with observations, yielding an estimated default respiration rate in the expected range. The urine PK model was used to predict urinary cotinine in 7 adults and 14 children exposed to Swedish SHS on a tour bus for 2 hours to SHS-nicotine; model predictions when compared with observations, yielded estimated default respiration rates close to those expected.

Hair nicotine is mapped into urine cotinine and air nicotine using a pharmacokinetic model for the first time. Applications of these models allows generalizing dose-response and exposure–response relationships published in the literature eg, for reading scores and asthma in children, to biomarkers other than those given in the original studies, as well as cross-cultural comparisons between national studies of urine cotinine in Germany and serum cotinine in the United States.

The physical and PK models we develop and demonstrate in simplified form as the "Rosetta Stone Equations" permit a much broader intercomparison of clinical epidemiological studies using atmospheric and biomarkers for SHS than previously possible.

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Appendix 1. A Sampling of Studies Using Diverse Markers for SHS

Clinical epidemiologic studies have used diverse biomarkers, such as hair nicotine,[29,36] urine cotinine,[37–45] saliva cotinine,[24,46–50] and serum cotinine.[2,4,51–55] Other studies have sought to measure SHS exposures using various atmospheric markers, such as respirable particles,[5,7,11,12,17,56] PPAHs,[7,57,58] atmospheric nicotine,[18,43,59] and carbon monoxide concentrations[11,32,58] in microenvironments such as homes, offices, restaurants, and bars, as well as vehicles and exposure chambers.