Worker Exposure to Secondhand Smoke

Evaluating a prediction model

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OCCUPATIONAL EXPOSURE to secondhand smoke (SHS)—also known as environmental tobacco smoke—still occurs. According to the U.S. Surgeon General, "Approximately 30% of indoor workers in the U.S. are not covered by smoke-free workplace policies" (DHHS, 2006). Occupational safety professionals and agencies have investigated SHS exposures to workers in the hospitality industries (e.g., restaurants, lounges, casinos), as well as in offices or environments where smoking was allowed (Trout, Decker, Mueller, et al., 1998; Repace & Homer, 2005; Repace, Hughes & Benowitz, 2006b).

For example, professionals investigating indoor air quality (IAQ) complaints have long known that one must rule out the possible contribution of smoking to the environmental and health impacts being evaluated (Hodgson, 1989). Given the potential magnitude and concern for SHS in occupational environments (DHHS, 2006; CDC, 2007; Goodwin, 2007; WHO, 2007), SH&E professionals must continue to characterize SHS exposure levels in the workplace.

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[This is particularly true given the fact that legal actions have been initiated by nonsmoking employees against companies that fail to consider SHS exposures (e.g., see primer on legal actions against Casinos found at www.wmitchell.edu/tobaccolaw/documents/casino.pdf). In fact, it is believed that such litigation will only increase (Sweda, 2001)].

It is also conceivable that biomonitoring of employees could mitigate claims of respiratory injuries or cancers against employers if it were determined that the worker's personal smoking habit—off the job, and not the worksite—was a more likely causal factor. The monitoring of tobacco smoke may also be of interest to SH&E professionals when chemicals in SHS are routinely being monitored for in the workplace (e.g., carbon monoxide).

For the SH&E professional, quantitation of worker exposure to SHS is a logical step toward understanding the scope and depth of this issue. One potential tool for exposure assessment that could overcome the potential limitations of area or personal monitoring is biomonitoring. Biological monitoring, when using a validated methodology (Lauwerys & Hoet, 2001; Sexton, Callahan & Bryan, 1995), moves the measurement from the potential of exposure (the opportunity for interaction between the worker and the chemical) to a more direct measure of dose (the specific quantity of the chemical absorbed systemically by the worker). This not only individualizes each worker's exposure, it also eliminates the question of whether area monitoring is sufficient to capture each worker's exposure. For SHS exposures, biomonitoring is performed via serum or urinary nicotine metabolite (cotinine) measurements. (See for example ACGIH's Introduction to the Biological Exposure Indices at www.acgih.org/products/beiintro.htm.)

Furthermore, biomonitoring for specific, exposed employees might well reduce expenditures when compared to wholesale monitoring of an entire site. Thus, the utility of determining SHS exposure through a simple, cost-efficient biomonitoring protocol via urinalysis should be attractive to practitioners.

Short of an enforced smoking ban in all places of business (and all places a worker is expected to be as

a function of his/her job), how can one determine the relative safety of the working population as it relates to SHS? How does an epidemiologist or public health official quantify exposure in a free-ranging population to determine the relative contribution of SHS to health impacts? Not all people work in specific, controlled environments. For example, installers, repair personnel and contractors may visit homes and private businesses where smoking is allowed; thus, they might not be ideal subjects for traditional industrial hygiene evaluation and control methodologies. Mobile employees or those who work outdoors and outside direct management control might themselves smoke, which could skew exposure data.

A benefit to having a noninvasive biological monitoring program that would readily identify exposure patterns to SHS would be the evaluation of ventilation systems in various settings. If nicotine and respirable suspended particles (RSP) concentrations were to be accurately predicted by cotinine in urine, the engineer responsible for ventilation would have excellent data on the efficacy of his/her work without going through the expense of personal and area monitoring. Job safety assessment would be enhanced with such exposure data as well. Worker health programs could be tailored to monitor for those health effects seen in overexposed populations, and ruling out SHS contribution to the total environmental load of a worker's exposure to other contaminants would allow professionals to concentrate on other likely sources of exposure (e.g., PAHs, amines, aldehydes, RSP and other chemicals that come from SHS) (DHHS, 2006). Currently, there is no biological monitoring standard for SHS exposure.

A recent publication by Repace, Al-Delaimy and Bernert (2006) presents a series of simple equations that the authors refer to as the Rosetta Stone calculations (hereafter referred to as *the model* or *the model's equations*). These authors suggest that a reliable mathematical relationship for predicting certain atmospheric markers of SHS from single cotinine biomonitoring measurement now exists. Assuming these equations could be shown as reliably predictive, the equations might be an effective tool for screening or determining the magnitude of worker exposure to SHS, especially the urinary and saliva cotinine as they are noninvasive measurements. Repace, Al-Delaimy, et al. state that using these equations, different markers for SHS exposure can be reasonably estimated if just one surrogate marker is measured, and that these equations then permit "intercomparison of clinical and atmospheric studies of SHS for the first time."

Given this endorsement, SH&E professionals performing assessments of workforce SHS exposure might employ these equations, believing they provide reliable estimates of discrete SHS exposure for specific individuals. However, Repace, Al-Delaimey et al. (2006) concede that these equations tend to better predict group mean or median values and that they are less accurate for individual values as one moves away from the central tendency value of the distribution (Repace, Jinot, Bayard, et al., 1998).

Therefore, the purpose of this article is to perform a simple validation assessment of the model and its reported predictive utility. This was achieved by employing a NIOSH study dataset that contains contemporaneous measurements of most endpoints/outputs of the model's equations. Thus, the NIOSH study provides the kind of data that would be useful for determining how reliably one can extrapolate or predict SHS exposure that resulted in the biomonitoring measurement one has taken.

The NIOSH Data Used for Validation

NIOSH conducted a health hazard evaluation (HHE) of a group of nonsmoking employees of Bally's Park Place Casino Hotel in Atlantic City, NJ (Trout & Decker, 1996; Trout, et al., 1998—hereafter referred to as *the NIOSH casino study*). In this study, samples were collected during a 2-day exposure interval. These included area respirable particulate monitoring, area and personal monitoring of air nicotine, and biological measurements of environmental tobacco smoke (ETS) exposures consisting of both pre- and postshift serum and urine cotinine levels. (The casino workers also answered a questionnaire that provided information on their estimated duration of exposure to ETS while at home and at work on the day that samples were taken, and for the 3 days before samples were collected.)

This NIOSH dataset is the type of SHS exposure scenario an SH&E professional could be faced with in a nonindustrial setting. Repace, Al-Delaimy, et al. (2006) suggest that by using their model one can reliably move between air measurements of SHS exposure and biomonitoring measurements that reflect the nicotine levels associated with that exposure. Physical and pharmacokinetic (PK) models are given that enable intercomparison of studies of SHS exposure using atmospheric markers (CO, RSP and nicotine) and biomarkers (serum saliva, urine cotinine and hair nicotine). According to Repace, Al-Delaimy, et al., the dataset in the NIOSH

Cotinine

Cotinine is a metabolite formed by the body from nicotine, which is a chemical in tobacco smoke and chewing tobacco. Levels of cotinine in blood indicate the amount of exposure a person has had to tobacco smoke. A laboratory test can measure cotinine in blood, urine or saliva.

Cotinine Exposure

Nicotine gets into people's bodies if they:

- Smoke or chew tobacco. All people who smoke have cotinine in their bodies.
- Are exposed to secondhand tobacco smoke (also called environmental tobacco smoke).
- Are involved in tobacco production and handle tobacco.

Abstract: *SH&E professionals may be asked to determine secondhand smoke (SHS) exposures as a part of worker safety or exposure assessments. This article critically examines a recently proposed set of equations for predicting concentrations of SHS markers in air. It concludes that such models should not be employed until they are fully validated and asserts that use of measured, population-specific, SHS concentrations should remain the preferred practice in job safety assessment for this potential workplace hazard.*

Table 1

NIOSH Casino Study, Individual Measurements

Subject[a]	Preshift urine total cotinine (ng/mL)	Postshift urine total cotinine (ng/mL)	Preshift serum cotinine (ng/mL)	Postshift serum cotinine (ng/mL)	Breathing zone nicotine (µg/m³) 8-hour TWA
Thursday evening shift, March 14-15, 1996					
1	159	197	2.74	2.62	7
2	47.6	54	--	--	9
3	16.2	23.6	0.926	1.47	6
4	21.2	45.3	2.72	2.56	9
5	37.7	54.4	1.19	1.45	--
6	16.7	39.1	1.58	2.22	10
7	42.4	58.6	2.78	2.91	12
9	21	28.4	0.885	1.36	6
10	5.76	20.7	1.07	1.21	--
11	14	7.21	1.3	1.57	8
12	23.7	26.7	0.967	1.32	--
Friday evening shift, March 15-16, 1996					
13	51.4	50.5	2.81	2.61	--
14	61.1	59.3	4.24	3.52	--
15	27.3	35.9	1.14	1.95	10
16	28.4	33.9	1.37	1.77	10
17	23.4	25.3	1.39	1.16	11
18	7.63	58	0.23	2.7	15
19	7.98	28.1	1.49	2.03	--
20	16.4	22.6	0.768	1.54	12
21	37	43.2	1.15	1.41	4
22	17.4	32.5	1.05	2.33	12
23	44.9	52.6	2.19	2.57	9
24	2.54	3.87	0.516	0.959	--
25	35.6	51.2	1.35	1.96	14
26	26.8	31.2	2.38	2.56	--
27	19.5	21.7	2.89	3.19	--
28	23	24.1	0.659	0.917	--
29	27.2	33.3	1.16	1.42	--
Arithmetic mean	30.81	41.51	1.59	1.97	9.65
Geometric mean	23.01	33.32	1.34	1.85	9.18
Median	23.55	33.6	1.3	1.95	10
Minimum	2.54	3.87	0.23	0.917	4
Maximum	159	197	4.24	3.52	15

Note. *Data from Bally's Park Place Casino Hotel, Atlantic City, NJ (HETA 95-0375-2590), by D. Trout and J. Decker, 1996, Cincinnati, OH: NIOSH. Workshift length approximately 8 hours for all participants.*
-- not performed. [a]Subject 8 was considered an active smoker and was eliminated from further analyses.

casino study, which collected both SHS exposure measures and biomonitoring samples from a single workplace, should provide a means to evaluate the reliability of the model's equations because all of these measurements were taken contemporaneously and need no qualification. One should be able to calculate the model's equations forwards or backwards to determine their predictive utility using this dataset.

Twenty-nine nonsmoking casino employees participated in the study. They were working one of two 8-hour shifts. Participants provided pre- and postshift urine samples; 28 of 29 also provided pre- and postshift serum samples for cotinine analysis. The urine cotinine concentrations were total cotinine (free cotinine plus cotinine glucuronide). Area air (RSP and nicotine) and personal air (nicotine only) monitoring samples were conducted for approximately 8 hours during each workshift, and the reported air concentration results were expressed as 8-hour time-weighted averages (TWAs). Subject #8 was considered an active smoker (due to high preshift urine and serum cotinine concentrations) and was subsequently eliminated from analyses by the study authors and from the present analysis.

NIOSH staff statistically compared pre- and postshift serum cotinine levels in the remaining 28 participants who reported SHS exposure outside of their work to those who reported no SHS exposure outside of work (Trout, et al., 1998). No statistically significant difference was observed, indicating that the cotinine levels measured in these individuals were not significantly influenced by nonwork SHS exposures. There also were no statistically significant differences in measurements between the two shifts (Trout & Decker, 1996), allowing an analysis to be conducted using combined data from both shifts. Table 1 provides a summary of the NIOSH casino study's individual worker nicotine/cotinine data. Table 2 lists data from area nicotine and RSP air monitoring. Results indicated air nicotine concentrations from personal monitors (4 to 15 $\mu g/m^3$) and area monitors (6 to 16 $\mu g/m^3$) to be comparable across their ranges.

Application of the Model's Equations to the NIOSH Study Data

Repace, Al-Delaimy, et al. (2006) proposed the following equation to model the relationship between urine cotinine and air nicotine:

$$^{a}U = K\varphi\alpha\rho\delta_{r}HN/\delta_{t}\,V_{u}$$ **[Equation 1]**

Where:
U = cotinine in urine, ng/mL
K = conversion factor of 1,000 ng/μg
φ = nicotine to cotinine conversion efficiency by liver enzymes, 0.78 (unitless)
α = nicotine absorption efficiency, 0.71 (unitless)
ρ = typical adult respiration rate for light activity, 1 m^3/hour
δ_r = renal cotinine clearance rate, 5.9 mL/min

δ_t = total cotinine clearance rate, 64 mL/min
V_u = adult daily urine output, 1,300 mL/day
H = hours exposure
N = air nicotine concentration, $\mu g/m^3$

[a]From equation 4, p. 182 and Table 1, p. 184 of Repace, Al-Delaimy, et al. (2006).

Solving for N from measured urine cotinine, the equation is as follows:

$N = U^* \delta_t V_u / K\varphi\alpha\rho\delta_r H$ **[Equation 2]**

Using the default pharmacokinetic parameters and adult respiration rate for light activity, the equation becomes:

$N = U^*25.46/H$ **[Equation 3]**

They then presented equations that encompassed the above-modeled relationship between urine cotinine and air nicotine, as well as the relationship between air nicotine and other markers of SHS in air. The equations that are applicable to adult exposures are shown in Table 3. For some conversion equations (e.g., carbon monoxide, polycyclic aromatic hydrocarbons, salivary cotinine), there is no corresponding measured data in the NIOSH casino study, so these equations could not be evaluated. The remaining applicable set of equations evaluated was: RSP from air nicotine (Equation 4), serum cotinine from urine cotinine (Equation 5), and air nicotine from plasma (serum) cotinine (Equation 6).

Estimating Urine Free Cotinine Concentrations From Urine Total Cotinine Concentrations

It was unclear whether Repace, Al-Delaimy, et al. (2006) used total or free urine cotinine as the input value, and whether cotinine present in preshift samples was to be subtracted from postshift samples. This is noted because an unpublished study of casino workers (Repace, 2006) that initiated this comparative analysis estimated free urinary cotinine levels from the measured total cotinine using a 0.508 conversion factor. Thus, it was surprising that the article describing the model did not mention the need to use free or total cotinine values when estimating air nicotine concentrations from urinary cotinine measurements. Moreover, in two other recent SHS studies by the model's authors (Repace & Homer, 2005; Repace, Hughes, et al., 2006) the equations were applied to estimate SHS exposures in nonsmoking individuals from urine cotinine. However, in all three studies, different, additional procedures for applying the model's equations are revealed that are not presented in the Repace, Al-Delaimy, et al. publication. These additional procedures include:

1) The conversion of urine total cotinine to free cotinine must be made, apparently because the equations were derived based on free cotinine (Repace & Homer, 2005; Repace, 2006). Total cotinine measured in urine is the sum of "free" cotinine plus cotinine that is conjugated with glucuronide. In Repace and Homer, the method for converting urine total cotinine to urine free cotinine is to divide urine cotinine by 1.5 (effectively multiplying total cotinine concentrations by 0.67 to yield the free cotinine levels). As noted, in the unpublished report (Repace), urine total cotinine concentrations were multiplied

Table 2

NIOSH Casino Study, Area Measurements

Location	Air nicotine ($\mu g/m^3$) 8-hour TWA	Respirable dust ($\mu g/m^3$) 8-hour TWA
March 14-15		
2A	7	< 30
2B	6	90
3A	12	80
4A	8	< 30
Poker registration	10	80
March 15-16		
2A	10	< 20
2B	8	< 20
3A	11	--
4A	10	90
Poker registration	16	60
Arithmetic mean	9.8	56[a]
Geometric mean	9	47[a]
Median	10	60[a]
Minimum	6	< 20
Maximum	16	90

Note. *Data from Bally's Park Place Casino Hotel, Atlantic City, NJ (HETA 95-0375-2590), by D. Trout and J. Decker, 1996, Cincinnati, OH: NIOSH; and "Exposure of Casino Employees to Environmental Tobacco Smoke," by D. Trout, J. Decker, C. Mueller, J.T. Bernert and J. Pirkle, March 1998,* Journal of Occupational Environmental Medicine, 40*(3), pp. 270-276. NIOSH measured respirable dust levels includes both RSP from SHS and ambient dusts.*
-- not performed. [a]For nondetects, assumes concentration at the detection limit.

Table 3

Rosetta Stone Conversion Equations for Adult SHS Exposure

SHS marker, unit	Conversion equation
R = RSP, $\mu g/m^3$ **[Equation 4]**	R = 10 N
U = urine cotinine, ng/mL **[Equation 5]**	U = 6.5 P
P = plasma (serum) cotinine, ng/mL **[Equation 6]**	P = 0.006ρHN

Note. *From "Correlating Atmospheric and Biological Markers in Studies of Secondhand Tobacco Smoke Exposure and Dose in Children and Adults (with erratum)," by J.L. Repace, W.K. Al-Delaimy and J.T. Bernert, Feb. 2006),* Journal of Occupational Environmental Medicine, 48*(2), Table 3, p. 191. Units of N in the cotinine equations are* $\mu g/m^3$.

Table 4

Conversion of NIOSH Casino Study Urine Total Cotinine to Urine Free Cotinine, Methods A & B

Subject	Preshift urine total cotinine (ng/mL)	Postshift urine total cotinine (ng/mL)	Method A	Method B
1	159	197	25.3	100.1
2	47.6	54	4.3	27.4
3	16.2	23.6	4.9	12.0
4	21.2	45.3	16.1	23.0
5	37.7	54.4	11.1	27.6
6	16.7	39.1	14.9	19.9
7	42.4	58.6	10.8	29.8
9	21	28.4	4.9	14.4
10	5.76	20.7	10.0	10.5
11	14	7.21	-4.5	3.7
12	23.7	26.7	2.0	13.6
13	51.4	50.5	-0.6	25.7
14	61.1	59.3	-1.2	30.1
15	27.3	35.9	5.7	18.2
16	28.4	33.9	3.7	17.2
17	23.4	25.3	1.3	12.9
18	7.63	58	33.6	29.5
19	7.98	28.1	13.4	14.3
20	16.4	22.6	4.1	11.5
21	37	43.2	4.1	21.9
22	17.4	32.5	10.1	16.5
23	44.9	52.6	5.1	26.7
24	2.54	3.87	0.9	2.0
25	35.6	51.2	10.4	26.0
26	26.8	31.2	2.9	15.8
27	19.5	21.7	1.5	11.0
28	23	24.1	0.7	12.2
29	27.2	33.4	4.1	16.9
Arithmetic mean	30.8	41.5	8.2[a]	21.1
Geometric mean	23.0	33.3	5.4[a]	16.9
Median	23.6	33.6	0.7[a]	17.1
Minimum	2.5	3.9	33.6[a]	2.0
Maximum	159.0	197.0	4.9[a]	100.1

Note. *Method A: Divide pre- and postshift urine cotinine by 1.5 to convert to urine free cotinine and take net difference pre- and postshift. Method B: Postshift urine free cotinine (ng/mL) equals postshift total cotinine x 0.508.*

[a]*Does not include negative values.*

by 0.508 to calculate urine free cotinine levels. This single difference in the application of just one of the model's equations can alter the final RSP/nicotine calculations by 24 to 32%, depending on the correction factor employed.

2) Repace and Homer (2005) took one preshift and two postshift samples (at 2 and 9 hours postexposure). The two postshift samples were averaged, preshift concentrations were subtracted from the postshift averages, and the calculations were applied to the net difference. In contrast, in Repace (2006) only postshift urine samples were taken for cotinine analysis, so the equations were applied to the uncorrected postshift urine cotinine measurement. The timing of the postshift sample collection varied from about 6.5 to 23 hours after the shift end. Thus, the Repace and Homer report shows why a worker's average air nicotine concentration cannot be accurately calculated from a single, postshift urinary cotinine measurement.

3) In Repace and Homer (2005), subjects were instructed to avoid SHS as much as possible for 5 days before their exposure in the bar. In Repace (2006), subjects had worked several days before their examined shift exposure and were, therefore, more similar to the postshift exposure pattern seen in the NIOSH casino study.

4) Repace, Hughes, et al. (2006) was a study similar to that of Repace and Homer (2005), in which urine cotinine was measured in 8 volunteers before a 6-hour visit to an area bar, followed by two postvisit samples at 2 and 12 hours. To obtain the urine cotinine concentration used to estimate exposure to SHS-RSP, background (e.g., preshift) cotinine was subtracted from the postshift concentrations and the two background-corrected postshift samples were then averaged. Repace, Hughes, et al. (2006) did not discuss the issue of free versus total urinary cotinine in that study, and the method the study authors cited describing the urine sample analysis (Bernert, Turner, Pirkle, et al., 1997) appears to be a serum cotinine method.

These disparate methods are referred to as Method A (based on Repace & Homer, 2005) and Method B (based on Repace, 2006). In Method A, urine free cotinine is calculated by dividing total urine cotinine by 1.5, and the equations are run on the difference between pre- and postshift cotinine concentrations. In Method B, urine free cotinine is calculated by multiplying total urine cotinine by 0.508, and applicable equations are applied to the postshift concentrations. These two methodologies were then applied to the NIOSH casino study urine cotinine measurements to estimate the concentration of urine free cotinine to be used in subsequent calculations. The estimates produced by both Method A and Method B are shown in Table 4.

The concentrations derived using Method A and Method B differ considerably. Method A is a determination on the net change of cotinine from pre- and postshift—that is, contribution from preshift exposure is subtracted out. Method B does not include a correction for contributions from preshift exposure, even though this should occur for individuals with known exposures from shifts from previous days. If this correction is not made, the air nicotine and RSP calculated is greater than that from any one shift because not all cotinine derived from metabolism is cleared in 1 day. Thus, postshift serum and urinary concentrations in workers should typically increase for each day of exposure during the week before the measurement is taken.

Three of the NIOSH casino study subjects had preshift urine concentrations that were higher than postshift concentrations. This is likely because of some preshift exposure to SHS that was higher than the exposure during the examined shift. Taking both differences in the methods into consideration, Method B results, on average, in much higher urine cotinine concentrations when multiple exposures have occurred, and so, higher estimated SHS exposure levels than Method A. By dividing total cotinine by 1.5 in Method A, the average estimated free cotinine for a given total cotinine concentration is approximately 1.3 times greater than the free cotinine estimation for Method B (multiplying by 0.508).

Estimating Air Nicotine Concentrations

The model suggests that air nicotine concentration (in units of $\mu g/m^3$) can be estimated from urine free cotinine (ng/mL) using Equations 1, 2 and 3. Equation 3 was applied to the NIOSH study urine free cotinine estimated by both Methods A and B. For Method A, air nicotine estimates were only derived for those subjects with an increase in urine cotinine pre- to postshift; those with a negative change in urine cotinine were excluded from the estimate.

The results are shown in Table 5. The mean estimated air nicotine from Method A urine free cotinine was 26.2 $\mu g/m^3$ (8-hour TWA) and from Method B urine free cotinine was 67 $\mu g/m^3$ (8 hour TWA).

The predictive accuracy of model Equation 3 was tested by comparing estimated nicotine concentrations to personal monitor measurements in the subset consisting of the 17 NIOSH casino study workers for which such monitoring was performed (Table 6, p. 40). Based on the arithmetic averages, the model's equations, when using Method A, overestimated air nicotine concentrations by about 2 to 3-fold. When using Method B, the overestimate was approximately 6 to 7-fold. For subjects with air monitoring data, all air nicotine estimates were exaggerated regardless of the calculation method used.

In addition, as no method for converting "total" cotinine to "free" cotinine is described in Repace, Al-Delaimy, et al. (2006), anyone relying solely upon the model will generate even higher overestimations

Table 5

Estimating NIOSH Casino Study Air Nicotine Concentrations From Urine Free Cotinine Levels

Subject	Method A Δ urine free cotinine levels (ng/mL)	Method A estimation of corresponding nicotine air concentrations (μg/m³)[a]	Method B urine free cotinine levels (ng/mL)	Method B estimation of corresponding nicotine air concentrations (μg/m³)[a]
1	25.3	81	100.1	318.5
2	4.3	14	27.4	87.3
3	4.9	16	12.0	38.2
4	16.1	51	23.0	73.2
5	11.1	35	27.6	87.9
6	14.9	48	19.9	63.2
7	10.8	34	29.8	94.7
9	4.9	16	14.4	45.9
10	10.0	32	10.5	33.5
11	-4.5	neg	3.7	11.7
12	2.0	6	13.6	43.2
13	-0.6	neg	25.7	81.6
14	-1.2	neg	30.1	95.9
15	5.7	18	18.2	58.0
16	3.7	12	17.2	54.8
17	1.3	4	12.9	40.9
18	33.6	107	29.5	93.8
19	13.4	43	14.3	45.4
20	4.1	13	11.5	36.5
21	4.1	13	21.9	69.8
22	10.1	32	16.5	52.5
23	5.1	16	26.7	85.0
24	0.9	3	2.0	6.3
25	10.4	33	26.0	82.8
26	2.9	9	15.8	50.4
27	1.5	5	11.0	35.1
28	0.7	2	12.2	39.0
29	4.1	13	16.9	53.8
Arithmetic mean	8.2[b]	26.2	21.1	67
Geometric mean	5.4[b]	17.1	16.9	54
Median	4.9[b]	15.7	17.1	54
Minimum	0.7	2.3	2.0	6
Maximum	33.6	106.9	100.1	318.5

Note. *[a]Nicotine = 25.46 x (urine free cotinine concentration)/hours in shift, assumed 8 hours. [b]Does not include negative values. neg = Not performed due to negative Δ urine free cotinine.*

Table 6

Personal Monitor Nicotine Concentrations Compared to Estimated Concentrations From Urine Cotinine

Subject	Method A estimated corresponding nicotine air concentrations (µg/m³)[a]	Method B estimated corresponding nicotine air concentrations (µg/m³)[a]	Measured personal monitor air nicotine (µg/m³)[a]
1	81	318	7
2	14	87	9
3	16	38	6
4	51	73	9
5	--	--	--
6	48	63	10
7	34	95	12
9	16	46	6
10	--	--	--
11	neg	12	8
12	--	--	--
13	neg	--	--
14	neg	--	--
15	18	58	10
16	12	55	10
17	4	41	11
18	107	94	15
19	--	--	--
20	13	37	12
21	13	70	4
22	32	53	12
23	16	85	9
24	--	--	--
25	33	83	14
26	--	--	--
27	--	--	--
28	--	--	--
29	--	--	--
Arithmetic mean	31.7	77	9.6
Geometric mean	23.0	62	9.2
Median	17.3	63	10
Minimum	4	12	4
Maximum	106.9	318	15

Note. *-- estimate not performed, because actual measurement not available for individual. neg = estimate not performed because postshift urine cotinine concentrations lower than preshift and Δ urine free cotinine level a negative value.* [a]*As 8-hour TWA.*

should they inadvertently apply these equations to a total cotinine measurement. This comparison indicates that the equations cannot be used to reliably estimate air nicotine exposures from urine cotinine concentrations, either for a group or for a particular individual. Application of this model to urine cotinine measurements tends to result in a significant overestimate of worker SHS exposure.

Estimating Air Nicotine Concentrations From RSP Concentrations

The model provides the following equation for estimating RSP in air from air nicotine:

RSP = 10x (nicotine concentration in air) **[Equation 4]** (Ux25.46/8x10)

RSP concentrations were estimated using:

1) The estimated nicotine concentrations from the NIOSH casino study based on estimated urine free cotinine measurements (Methods A and B);

2) The measured area nicotine concentrations in the NIOSH casino study to derive an estimated RSP concentration.

The results of this comparative analysis are shown in Table 7. The predictive ability of this equation was then examined by comparing estimated RSP concentrations to the area RSP measurements (Table 8, p. 42). This comparison indicates that mean RSP estimated from air nicotine, which was in turn estimated from urine free cotinine levels, was 4.71 times greater using Method A and 12 times greater using Method B than the reported, measured mean for area RSP. The mean estimated RSP derived using measured nicotine concentrations via personal monitors was 1.72 times greater than the measured RSP.

As occurred with the comparisons between estimated and measured air nicotine, using the model's equations to estimate personal or area RSP exposures for SHS from the workers' free urine cotinine measurements (using either Method A or B) results in a significant overestimate of SHS exposure. The more levels of estimation involved (RSP estimation from urine cotinine versus RSP estimation from air nicotine), the greater the degree of SHS overestimation. All group and average measurements, and almost every individual measurement, were exaggerated when the model's equations were used to predict them. For example, the maximum estimated RSP exposure for a NIOSH casino study subject (from Method B urine free cotinine) was 3,185 $\mu g/m^3$, which is 35 times the maximum measured value of area RSP (90 $\mu g/m^3$). The lowest estimated RSP exposure for a NIOSH casino study subject was 63 $\mu g/m^3$, greater than 3 times the lowest measured air RSP concentration reported in the NIOSH casino study (< 20 $\mu g/m^3$).

The range of urine total cotinine measurements in the NIOSH casino study subjects varied about 40 fold (range: 3.87 to 197 ng/mL) from exposures that varied only about 2-fold for nicotine air concentrations and only about 3-fold for air RSP concentrations. Thus, individual worker variations in the inhalation, absorption and metabolism of the respective room air nicotine concentrations, when extrapolated on an individual basis, suggested a greater variation in room air nicotine and RSP concentrations than actually existed.

This variation is important as the implied purpose of the model's equations is to obviate the need to take serum nicotine/cotinine and air nicotine and RSP

measurements by simply taking a worker urine sample and measuring its cotinine level. However, to do so will increase the variation in the estimates of SHS exposure, substantially increase the maximal estimate and, thereby, increase even the average estimate of exposure. In short, there is an obvious potential for the SH&E professional or epidemiologist to overestimate an individual's SHS exposure substantially when one simply applies the model's equations to urine cotinine measurements, for either the individual or the group.

Serum Cotinine Concentrations Estimated From Measured Urine Cotinine Concentrations

The ability of the model to predict or estimate the serum cotinine concentrations from one's urine cotinine concentrations [**Equation 5:** serum cotinine = urine free cotinine/6.5] was examined using the NIOSH casino study data. This equation was applied to preshift and postshift urine free cotinine concentrations as estimated by Method B (urine total cotinine x 0.508 = urine free cotinine). Based on group averages, Equation 5, when applied to urine free cotinine derived by Method B, overestimates measured serum cotinine by about 1.5- to 1.6-fold. A review of individual preshift measurements indicated that serum cotinine was overestimated in 18 of 27 individuals; postshift measurements indicated serum cotinine was overestimated more frequently (24 of 27 individuals), and sometimes by more than 5-fold. This procedure also does not allow one to consider the possibility that the last exposure interval serum cotinine concentrations might have been lower than prior exposure intervals, which in fact occurred in 5 subjects in the NIOSH casino study (subjects 1, 4, 13, 14 and 17).

Estimating Air Nicotine Concentrations From Serum Cotinine

The following equation describes the relationship between serum cotinine and air nicotine concentrations:

(serum cotinine) = 0.006 x (inhalation rate) x (exposure duration) x (air nicotine concentration) **[Equation 6]**

Where:
inhalation rate = assumed 1 m^3/hour;
exposure duration = for this analysis, assumed 8-hour work shift.

Although not stated clearly in Repace, Al-Delaimy, et al. (2006), this equation should be applied to the difference between a pre- and postshift serum concentration for the most accurate results. This equation was, therefore, applied to the NIOSH casino study postshift serum cotinine concentrations, both estimated and measured, to predict air nicotine concentrations. These estimated concentrations were then compared to the measured nicotine concentrations taken from personal air monitoring samples from the NIOSH casino study.

Table 7

Estimation of RSP Concentrations From Estimated Nicotine Concentrations

Subject	Estimated nicotine air levels (µg/m^3) as 8-hour TWA via method A	RSP Estimation (µg/m^3) as 8-hour TWA, method A[a]	Estimated nicotine air concentrations (µg/m^3) as 8-hour TWA via method B	RSP Estimation (µg/m^3) as 8-hour TWA, method B[a]	RSP Estimation (µg/m^3) as 8-hour TWA, via nicotine personal monitor data[a]
1	81	806	318.5	3185	70
2	14	136	87.3	873	90
3	16	157	38.2	382	60
4	51	511	73.2	732	90
5	35	354	87.9	879	--
6	48	475	63.2	632	100
7	34	344	94.7	947	120
9	16	157	45.9	459	60
10	32	317	33.5	335	--
11	neg	neg	11.7	117	80
12	6	64	43.2	432	--
13	neg	neg	81.6	816	--
14	neg	neg	95.9	959	--
15	18	182	58.0	580	100
16	12	117	54.8	548	100
17	4	40	40.9	409	110
18	107	1069	93.8	938	150
19	43	427	45.4	454	--
20	13	132	36.5	365	120
21	13	132	69.8	698	40
22	32	320	52.5	525	120
23	16	163	85.0	850	90
24	3	28	6.3	63	--
25	33	331	82.8	828	140
26	9	93	50.4	504	--
27	5	47	35.1	351	--
28	2	23	39.0	390	--
29	13	129	53.8	538	--
Arithmetic mean	26.2	262	67	671	96
Geometric mean	17.1	171	54	539	92
Median	15.7	157	54	543	100
Minimum	2.3	23	6	63	40
Maximum	106.9	1069	318.5	3185	150

Note. *[a]All RSP concentrations were calculated using Equation 4 (RSP = nicotine x 10) except final column, in which RSP concentrations were estimated from measured air nicotine (RSP = measured air nicotine x 10). -- Estimate not performed because actual measurement not available for individual. neg = Estimate not performed because postshift urine cotinine concentrations lower than preshift and Δ urine free cotinine level a negative value.*

Table 8

Comparing the Average Estimated RSP Concentrations to the Average Measured Area Monitoring Results From the NIOSH Casino Study

	Estimation of RSP (µg/m³) as an 8-hour TWA, method A, air nicotine x 10	Estimation of RSP (µg/m³) as an 8-hour TWA, method B, air nicotine x 10	Estimation of RSP (µg/m³) as an 8-hour TWA, from measured air nicotine, personal monitor air nicotine x 10	Measured respirable dust (µg/m³) as an 8-hour TWA
Arithmetic mean	262	671	96	56[a]
Geometric mean	171	539	92	47[a]
Median	157	543	100	60[a]
Minimum	23	63	40	< 20
Maximum	1069	3185	150	90

Note. *NIOSH measured respirable dust levels includes both RSP from SHS and ambient dusts.*

[a]*For nondetects, assumes concentration at the detection limit.*

The results of these comparisons show that the estimated air nicotine concentrations derived using the model's equations predicted concentrations higher than those actually measured by NIOSH investigators. A comparative analysis (data not shown but available upon request), indicated that measured nicotine concentrations from personal monitoring samples averaged 4.1-fold lower than those estimated via the corresponding model equations. The overestimation was compounded when the model's air nicotine concentration was derived from an estimated serum concentration that in turn was derived from a urinary free cotinine concentration. Air nicotine levels estimated in this manner averaged 7-fold higher than measured values (comparison not shown but available upon request).

Calculating Serum & Urinary Cotinine Concentrations From Measured Air Nicotine Concentrations

As a final examination of the model's predictive utility, the equations were used to reverse-calculate individual serum and urine cotinine concentrations from personal nicotine air measurements taken in the NIOSH casino study. Equation 3 was used to estimate the urinary cotinine concentration from the measured air nicotine concentration, and Equation 6, once rearranged, was used to estimate the serum cotinine concentration from the measured air nicotine concentration. These estimated values were then compared to the measured concentrations (again these results are not shown in the interest of space but can be made available upon request).

Based on group averages, estimating a serum cotinine concentration from an air nicotine measurement resulted in a 4.4-fold underestimate of the serum cotinine. Estimating a urine cotinine concentration from an air nicotine measurement results in an 8-fold underestimate. Just as the model's equations overestimate air concentrations of nicotine and RSP from urine and serum cotinine measurements, the equations conversely underestimate urine and serum cotinine concentrations when using a measured nicotine air concentration.

Conclusion

Whether SHS can be determined to be a health hazard, either by itself or as a contributor to total particulate or chemical exposure, worker exposure to it will be laid at the feet of the professional who makes no effort to characterize these exposures and address them accordingly. Worker exposure to carcinogenic or debilitating agents can generally be effectively monitored through personal or area measurements of the offending agent.

This is the basis for deriving and setting safe workplace exposure values such as threshold limit values as controls for chemical exposures. Some biological monitoring of chemical metabolites has also been accepted as a tool for ensuring that overexposure does not occur (e.g., benzene exposure via phenol in urine and blood lead measurements). Control of exposures deemed excessive by comparison to the recommended exposure guideline can then proceed using traditional safety engineering principles.

In the present analysis, several compounds or metabolites collected while monitoring workers exposed to SHS were evaluated by comparing these measured values to predicted values for each exposure marker generated using a model proposed by Repace, Al-Delaimy, et al. (2006).

The comparative analyses, using contemporaneous data generated by NIOSH of all the model's suggested surrogate marker compounds, revealed that this model (or more precisely, this collection of simple, algebraic equations) cannot be used to accurately estimate one surrogate marker of SHS exposure from the measurement of another surrogate marker of SHS exposure.

In fact, the comparative analysis indicated that the NIOSH casino study data could not be reasonably predicted by the model's equations to any acceptable degree of accuracy—neither for individual measurements nor for the statistical characterizations of group exposures (e.g., mean values). Because of these inaccuracies, which occur if one moves from a biomarker chemical measured in a worker's serum or urine to airborne concentrations of chemicals or vice versa, the authors strongly recommend that this

model or set of equations not be used in either the workplace or in public health studies.

As written, the model's equations tend to underestimate the serum and urinary concentrations of cotinine that an individual generates when s/he metabolizes inhaled nicotine, and correspondingly exaggerate inhaled nicotine and RSP levels when based on an individual's or group's serum/urinary cotinine measurements. The perceived utility of this model's equations is indirect measurement of SHS (i.e., to use the noninvasive urinary cotinine measurement to predict SHS inhalation exposure).

However, use of this model by SH&E personnel in the workplace will only overstate SHS exposure to a substantial degree. Thus, safety assessment is best performed by a direct measurement of accepted SHS markers.

The reason for the inaccuracy of the model's equations rests largely in the fact that there is considerable interindividual variation in the metabolism of nicotine to cotinine. Available data (Benowitz, 1996; Hukkanen, Jacobs & Benowitz, 2005) on the metabolism of nicotine indicates that this variation is too great to be able to convert cotinine to air nicotine levels with a single conversion factor as the model's equations attempt to do.

Thus, the suggestion that a single, linear relationship exists is incorrect and is an oversimplification of the biologic processes involved in the absorption of nicotine, the biotransformation of nicotine to cotinine and the processes for eliminating cotinine from the blood compartment.

As an example of this, comparative analyses using the NIOSH casino study data showed that measured RSP and nicotine exposure levels which varied no more than 3-fold for the group, resulted in a greater than 40-fold variation in the magnitude of group urinary cotinine concentrations. No simple algebraic equation, which always multiplies a single constant

Table 9

Comparing Measured NIOSH Casino Study Serum Cotinine Levels to Serum Cotinine Levels Estimated From Urine Free Cotinine (Method B)

Subject	Column A estimated preshift urine free cotinine (ng/mL), method B	Column B estimated postshift urine free cotinine (ng/mL), method B	Estimated preshift serum cotinine (ng/mL) (column A)	Measured preshift serum cotinine (ng/mL)	Estimated postshift serum cotinine (ng/mL) (column B)	Measured postshift serum cotinine (ng/mL)
1	80.8	100.1	12.43	2.74	15.40	2.62
2	24.2	27.4	--	--	--	--
3	8.2	12.0	1.27	0.926	1.84	1.47
4	10.8	23.0	1.66	2.72	3.54	2.56
5	19.2	27.6	2.95	1.19	4.25	1.45
6	8.5	19.9	1.31	1.58	3.06	2.22
7	21.5	29.8	3.31	2.78	4.58	2.91
9	10.7	14.4	1.64	0.885	2.22	1.36
10	2.9	10.5	0.45	1.07	1.62	1.21
11	7.1	3.7	1.09	1.3	0.56	1.57
12	12.0	13.6	1.85	0.967	2.09	1.32
13	26.1	25.7	4.02	2.81	3.95	2.61
14	31.0	30.1	4.78	4.24	4.63	3.52
15	13.9	18.2	2.13	1.14	2.81	1.95
16	14.4	17.2	2.22	1.37	2.65	1.77
17	11.9	12.9	1.83	1.39	1.98	1.16
18	3.9	29.5	0.60	0.23	4.53	2.7
19	4.1	14.3	0.62	1.49	2.20	2.03
20	8.3	11.5	1.28	0.768	1.77	1.54
21	18.8	21.9	2.89	1.15	3.38	1.41
22	8.8	16.5	1.36	1.05	2.54	2.33
23	22.8	26.7	3.51	2.19	4.11	2.57
24	1.3	2.0	0.20	0.516	0.30	0.959
25	18.1	26.0	2.78	1.35	4.00	1.96
26	13.6	15.8	2.09	2.38	2.44	2.56
27	9.9	11.0	1.52	2.89	1.70	3.19
28	11.7	12.2	1.80	0.659	1.88	0.917
29	13.8	16.9	2.13	1.16	2.60	1.42
Arithmetic mean	15.7	21.1	2.36	1.59	3.21	1.97
Geometric mean	11.7	16.9	1.75	1.34	2.56	1.85
Median	12.0	17.1	1.83	1.3	2.60	1.95
Minimum	1.3	2.0	0.20	0.23	0.30	0.92
Maximum	80.8	100.1	12.43	4.24	15.40	3.52

Note. *Calculation: Serum cotinine (ng/mL) = (urine free cotinine concentration)/6.5.*
-- Not performed due to missing serum measurement.

value by the measured concentration of one surrogate marker of SHS exposure that has been measured, can capture this 40-fold variation. Thus, one cannot use the model's equations to calculate any individual's exposure level or that of a group of individuals. That is, the model lacks the requisite specificity for application on a worker-by-worker basis.

For the equation to accurately predict an individual's RSP/nicotine exposure level, one would have to know the rate of cotinine formation for each individual. For group exposures, one would have to know how nicotine metabolism of each individual group member varied before the correct individual values and corresponding correct group mean values could be calculated. Unfortunately, the model's equations do not and cannot account for the interindividual variations that occur in the metabolism of nicotine to cotinine. This is a key reason as to why these equations lack predictive value.

Additional problems were identified for any SH&E professional using urinary cotinine measurements to predict exposures with these equations. For example, the inhalation exposure estimates derived by these equations are easily skewed if the number of individuals being sampled is not known to be representative of the larger group, especially if one or more large urinary cotinine levels is recorded.

If one randomly selects two subsets of five individuals in the NIOSH casino study, the predicted subgroup mean RSP levels will likely differ. This occurs because a small subset of workers may not capture the full extent of variation in urinary cotinine levels occurring in the cohort (or the general population) from which the subset was selected. Many of the pharmacokinetic or physiologic parameters used in the model's equations will also vary across individuals, compounding the known problem with interindividual variations in the rate of nicotine metabolism. There does not appear to be an easy way to resolve the many identified limitations inherent to this model.

The present attempt to validate the model using the NIOSH casino study data revealed a high error rate. Applying the model's equations overstated the NIOSH-measured RSP levels in at least 27 of 28 individuals (only 1 of 28 individuals yielded a urinary cotinine level that resulted in a calculated RSP level that arguably fell within the range measured by NIOSH investigators).

Thus, for this study, the proposed calculations yield a 96% (or greater) error rate when estimating the RSP levels from the collected urinary cotinine samples. For workplace safety and risk management decisions, such a high error rate in an exposure assessment tool is unacceptable. This high error rate demonstrates, as much as any line of evidence, that the use of this model would tend to grossly overestimate nicotine/RSP levels when calculated from measured urinary cotinine levels.

This analysis stresses the need for SH&E professionals to carefully consider the validity of any model that proposes to substitute exposure/dose predictions for more traditional industrial hygiene air monitoring methods for use in an exposure assessment. The poor predictive ability demonstrated by this model is an example as to how proposing or using models that have not been properly validated can easily lead to inaccurate safety assessments, improper attribution of morbidity or mortality in epidemiological studies, and flawed risk management decisions. ■

References

Benowitz, N.L. (1996). Cotinine as a biomarker of environmental tobacco smoke exposure. *Epidemiologic Reviews, 18*(2), 188-204.

Centers for Disease Control and Prevention (CDC). (2007, May 25). Centers for Disease Control: Exposure to secondhand smoke among students aged 13-15 years—worldwide, 2000-2007. *Morbidity and Mortality Weekly Report, 56*(20), 497-500.

Goodwin, R.D. (2007, May). Environmental tobacco smoke and the epidemic of asthma in children: The role of cigarette use. *Annals of Allergy, Asthma & Immunology, 98*(5), 447-454.

Hodgson, M.J. (1989). Environmental tobacco smoke and the sick building syndrome. *Occupational Medicine: State of the Art Reviews, 4*(4), 835-840.

Hukkanen, J., Jacobs, P. & Benowitz, N.L. (2005). Metabolism and disposition kinetics of nicotine. *Pharmacological Reviews, 57,* 79-115.

Lauwerys, R.R. & Hoet, P. (2001). *Industrial chemical exposure: Guidelines for biological monitoring* (3rd ed.). Boca Raton, FL: Lewis.

Needham, L.L., Pirkle, J.L., Burse, V.W., et al. (1992). Case studies of relationship between external dose and internal dose. *Journal of the Experimental Analysis of Behavior* [Epidemiology Supplement(1)], 209-221.

Repace, J.L. (2006, March 14). Report on the Empress Horsehoe Casino (unpublished). Bowie, MD: Repace Associates Inc.

Repace, J.L., Al-Delaimy, W.K. & Bernert, J.T. (2006). Correlating atmospheric and biological markers in studies of secondhand tobacco smoke exposure and dose in children and adults (with erratum). *Journal of Occupational and Environmental Medicine, 48*(2), 181-194.

Repace, J.L. & Homer, M. (2005). *Laramie, Wyoming bar patron study* (WYSAC Technical Report No. CHES-517). Laramie, WY: Wyoming Survey and Analysis Center, University of Wyoming.

Repace, J.L., Hughes, N. & Benowitz, E. (2006). Exposure to secondhand smoke air pollution assessed from bar patrons' urinary cotinine. *Nicotine & Tobacco Research, 8*(5), 701-711.

Repace, J.L., Jinot, J., Bayard, S., et al. (1998). Air nicotine and saliva cotinine as indicators of workplace passive smoking exposure and risk. *Risk Analysis, 18*(1), 71-83.

Sexton, K., Callahan, M.A. & Bryan, E.F. (1995). Estimating exposure and dose to characterize health risks: The role of human tissue monitoring in exposure assessment. *Environmental Health Perspectives, 103*(Suppl 3), 13–29.

Sweda, E.L. (2001). Litigation on behalf of victims of exposure to environmental tobacco smoke: The experience from the USA. *The European Journal of Public Health, 11*(2), 201-205.

Trout, D. & Decker, J. (1996). *Bally's Park Place Casino Hotel, Atlantic City, NJ* (HETA 95-0375-2590). Cincinnati, OH: NIOSH.

Trout, D., Decker, J., Mueller, C., et al. (1998). Exposure of casino employees to environmental tobacco smoke. *Journal of Occupational and Environmental Medicine, 40*(3), 270-276.

U.S. Department of Health and Human Services (DHHS). (2006). *The health consequences of involuntary exposure to tobacco smoke: A report of the Surgeon General*. Washington, DC: Author, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

World Health Organization (WHO). (2007). Only 100% smoke-free environments adequately protect from dangers of secondhand smoke [Press release]. Geneva, Switzerland: Author. Retrieved July 25, 2008, from http://www.who.int/mediacentre/news/releases/2007/pr26/en/index.html.