

# Conversion of Nicotine in Tobacco Smoke to Its Volatile and Available Free-Base Form through the Action of Gaseous Ammonia

JAMES F. PANKOW,\* BRIAN T. MADER, LORNE M. ISABELLE, WENTAI LUO, ANDREA PAVLICK, AND CIKUI LIANG

Department of Environmental Science and Engineering, Oregon Graduate Institute, P.O. Box 91000, Portland, Oregon 97291-1000

Ammonia-forming compounds are routinely added to cigarette tobacco. The U.S. Food and Drug Administration (FDA) has argued that this is done to promote the formation of the volatile free-base form of nicotine in mainstream smoke (MSS) particles, thus increasing its availability to the smoker. The presence of ammonia in tobacco smoke may also be expected to promote the volatilization of nicotine from environmental tobacco smoke (ETS) particles in indoor air. The gas/particle partitioning of nicotine can be parameterized in terms of the gas/particle partitioning constant  $K_p = c_p/c_g$ , where  $c_p$  (ng/ $\mu$ g) is the concentration in the particle phase and  $c_g$  (ng/m<sup>3</sup>) is the concentration in the gas phase. The ability of ammonia to increase the amount of nicotine in the gas phase, as compared to the particle phase, was measured and confirmed. A gas-phase ammonia pressure of  $p_{\text{NH}_3}$  of  $\sim 100 \times 10^{-6}$  atm (100 ppmV) was found to reduce the  $K_p$  value for the partitioning of nicotine to tobacco smoke particulate matter by more than 100-fold. The agreement between ETS and MSS at  $p_{\text{NH}_3} \approx 100$  ppmV was excellent, suggesting that the overall physical properties (e.g., polarity and number-average molecular weight) of ETS and MSS particulate material are very similar. Because gas-phase nicotine deposits more readily in the respiratory tract than does particle-phase nicotine and because free-base nicotine is more lipid soluble than is protonated nicotine, such a reduction in  $K_p$  will increase the availability of nicotine from MSS as well as from freshly formed ETS particles. At 20 °C and a relative humidity of 60%, the partitioning constant for the free-base form of nicotine is estimated to be  $K_{p,\text{fb}} = c_{p,\text{fb}}/c_g = 10^{-4.94}$ . Correction to a body temperature of 37 °C yields  $K_{p,\text{fb}} = 10^{-5.97}$ . Calculations using this  $K_{p,\text{fb}}$  value indicate that about 25% of the nicotine will be in the gas phase at a temperature of 37 °C for inhaled MSS under the full ammonia effect at a total suspended smoke particulate matter level of  $3 \times 10^6$   $\mu$ g/m<sup>3</sup>.

## Introduction

The base ammonia, as well as ammonia-forming compounds such as diammonium phosphate (DAP) and urea, is routinely added to the tobacco used in domestic cigarettes (1-4). Though denied by the major domestic tobacco companies,

the U.S. Food and Drug Administration (FDA) has argued that an intent of this use of ammonia is to increase as well as to control the delivery of the alkaloid nicotine to the respiratory tract of the smoker (4). The presumed mechanism underlying this proposed ammonia effect involves the formation, in the liquid tobacco smoke particles, of the volatile, free-base form of nicotine. In arguing their case that cigarettes are being manufactured as nicotine delivery devices, the FDA (4) has presented the following quote from one tobacco company's "leaf blender's manual":

"Ammonia, when added to a tobacco blend, reacts with the indigenous nicotine salts and liberates free [base] nicotine. As a result of such change, the ratio of extractable nicotine to bound nicotine in the smoke may be altered in favor of... [free-base] nicotine. As we know, extractable (i.e., free-base) nicotine contributes to impact in cigarette smoke, and this is how ammonia can act as an impact booster".

We also note that the conferees at a 1983 BATCO (British American Tobacco Co.) research conference in Rio de Janeiro agreed that in order to achieve the goal of "develop[ing] products that give improved smoker satisfaction", that it was important to know as much as possible about nicotine, including (4) "factors that affect the transfer of nicotine from leaf to smoke aerosol" as well as "factors that influence the rate of transfer of nicotine from particulate matter to the vapour phase".

Nicotine can exist in a diprotonated +2 form (Figure 1a), a monoprotonated +1 form (Figure 1b), and in the free-base form (Figure 1c). When protonated, the nitrogen on the pyridine (six-membered) ring ( $pK_1 = 3.12$  at 20 °C) is considerably more acidic than the nitrogen on the pyrrolidine (five-membered) ring ( $pK_2 = 8.02$  at 20 °C). From standard acid-base theory, the fraction of the nicotine that is in the free-base form ( $\alpha_{\text{fb}}$ ) is given by

$$\alpha_{\text{fb}} = \frac{1}{1 + 10^{-\text{pH}}/10^{-\text{p}K_2} + 10^{-2\text{pH}}/10^{-(\text{p}K_1 + \text{p}K_2)}} \quad (1)$$

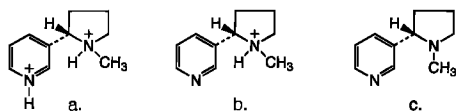
Since pH values as low as  $\sim 3$  are not expected in tobacco smoke particles, only the +1 and free-base forms are expected to be important in tobacco smoke. Under these conditions, eq 1 simplifies to

$$\alpha_{\text{fb}} = \frac{1}{1 + 10^{-\text{pH}}/10^{-\text{p}K_2}} \quad (2)$$

When  $\text{pH} < \text{p}K_2$ , the nicotine speciation is dominated by species other than the free-base form, and  $\alpha_{\text{fb}} < 1.0$ . On the other hand, raising the pH toward 8 (as for example through the action of a base such as ammonia) will drive  $\alpha_{\text{fb}}$  toward 1.0 (5). An unverified assumption that underlies both eqs 1 and 2 is that no smoke-phase activity corrections are required for any of the nicotine species.

In both mainstream tobacco smoke (MSS) and in environmental tobacco smoke (ETS = sidestream + exhaled mainstream smoke), the nonvolatile, protonated forms of nicotine can reside essentially only in the particle phase. (Nicotine salts possess very low volatilities.) However, the volatile free-base form can reside in the particle phase and can also partition into the gas phase. Increasing the proportion of the particle-phase nicotine that is in the free-base form will therefore tend to drive more nicotine into the gas phase. Fundamental principles of gas and particle deposition (6) predict that the conversion of nicotine to the volatile free-base form through the action of ammonia should thereby enhance the delivery of nicotine from inhaled smoke because (1) gas-phase nicotine diffuses more rapidly in air than does

\* To whom all correspondence should be addressed. Fax: 503-690-1556. E-mail: pankow@ese.ogi.edu.



**FIGURE 1. Forms of nicotine: (a) diprotonated, (b) monoprotonated, and (c) free-base.**

particle-phase nicotine and will therefore deposit more efficiently in the respiratory tract than will particle-phase nicotine and (2) nicotine that deposits from the gas phase will be depositing to lung tissue in molecular form and so will be able to begin diffusing into the body immediately. Furthermore, increasing the proportion of the particle-phase nicotine that is in the free-base form will increase the availability of the nicotine in those particles that deposit in the respiratory tract: free-base nicotine is much more lipid soluble than is protonated nicotine and will diffuse out of deposited particles and into adjacent tissue much more rapidly than will protonated nicotine.

The effect of pH on the absorption of nicotine from inhaled aerosols of saline solution amended with nicotine was investigated by Burch *et al.* (7). Those investigators found that increasing pH was associated with enhanced absorption of nicotine in the respiratory tract as measured by increased plasma concentrations of nicotine. That increasing pH and in particular the action of ammonia can increase the availability of nicotine from tobacco smoke has not, up to now, been demonstrated by any study conducted in the public domain. It is, however, consistent with the reported properties of tobacco smoke and nicotine. Particles of cigarette smoke have been found to be naturally acidic due to the presence among the pyrolysis products of many carboxylic and inorganic acids (8). Direct measurements of the pH of tobacco smoke particles made some years ago at unknown ammonia concentrations yielded values in the range 5.0–6.5 (9–11). pH is a relevant parameter in tobacco smoke particles because of the presence of a significant amount of water in these particles. Ambient ETS particles collected in a heavily contaminated indoor environment have been found to contain ~15% by weight water at a relative humidity (RH) value of 52% (5). In mainstream smoke and within the respiratory tract, RH values approaching 100% can be expected, causing yet higher levels of water in the particle phase.

The above view of the role of ammonia in tobacco smoke is analogous to what occurs when the alkaloid cocaine is “free-based”, or used in “crack” form. Free-based cocaine and crack are typically prepared by reacting “street” cocaine (usually the HCl salt of cocaine) with aqueous ammonia and sodium bicarbonate, respectively (12). In both cases, the result is the more lipid-soluble, free-base form of cocaine, which is then smoked. Smoking volatilizes and aerosolizes the free-base cocaine which is rapidly absorbed into the body, leading to an immediate and intense high that is said to be comparable to that obtained with the intravenous injection of cocaine (12). In this paper, we demonstrate the ability of gaseous ammonia to increase the availability of nicotine from both mainstream and ETS particles. This was done by measuring the ability of particle-phase nicotine to leave that phase and enter the gas phase.

### Gas/Particle Partitioning of Nicotine

A temperature- and humidity-dependent equilibrium partitioning constant  $K_{p,fb}$  ( $m^3/\mu g$ ) can be defined for the distribution of free-base nicotine between the gas and particle phases (5):

$$K_{p,fb} = c_{p,fb}/c_g \quad (3)$$

where  $c_{p,fb}$  ( $ng/\mu g$ ) is the concentration of the free-base nicotine in the particle phase and  $c_g$  ( $ng/m^3$ ) is the concen-

tration of nicotine in the gas phase (assuming only the free-base form is volatile). If  $c_p$  ( $ng/\mu g$ ) is the total (protonated + free-base) concentration of nicotine in the particle phase, then

$$K_{p,fb} = \alpha_{fb}c_p/c_g \quad (4)$$

At a given temperature and RH, the value of  $K_{p,fb}$  should be fairly independent of the specific type of tobacco that has been burned: a mixture of pyrolysis products (including some water) with more or less constant physical properties (except pH) can be expected. In the absence of direct information on the value of  $\alpha_{fb}$ , the overall partitioning constant  $K_p$  can be measured where (5)

$$K_p = c_p/c_g = K_{p,fb}/\alpha_{fb} \quad (5)$$

When the tobacco smoke particles are at acidic pH values so that  $\alpha_{fb} \ll 1.0$ , the protonation of nicotine reduces its tendency to volatilize to the gas phase, and  $K_p$  becomes large. Adding a base like ammonia to tobacco smoke will drive  $\alpha_{fb}$  upward toward 1.0, thereby reducing  $K_p$  asymptotically toward  $K_{p,fb}$ , and increasing the volatilization and availability of the nicotine from the smoke particles. Thus, while  $K_{p,fb}$  might be roughly constant at a given temperature and RH for different samples of tobacco smoke particles,  $K_p$  will be highly dependent on the distribution and acidities of the pyrolysis products found in the particles and on the amounts of bases like ammonia as well as nicotine itself that are available for reaction with those acids.

A  $K_p$  value for nicotine of  $10^{-2.83} m^3/\mu g$  at 20 °C and 60% RH has been measured using ETS particles collected in a large hall very heavily contaminated with cigarette smoke (5). Given the relatively high pure compound vapor pressure exhibited by free-base nicotine [ $10^{-1.48}$  Torr at 20 °C (13)], this measured  $K_p$  value is much higher than what would be expected for  $K_{p,fb}$  for nicotine sorbing to such particles (5). This result was taken to suggest that (1) the value  $K_p = 10^{-2.83} m^3/\mu g$  was affected strongly by pH according to eq 5, (2) the addition of gas-phase ammonia to ETS would cause the measured  $K_p$  value to decrease markedly toward some  $K_{p,fb}$  value as the gas-phase partial pressure  $p_{NH_3}$  is increased, and (3) the presence of significant ammonia in mainstream smoke will depress nicotine’s mainstream  $K_p$  toward that  $K_{p,fb}$  value.

### Experimental Section

**ETS Measurements.** ETS particles were collected on a precleaned 18.5 cm × 23.7 cm Teflon membrane filter (TMF) (2 μm pore size, Gelman Sciences) using a standard “hi vol” air sampler. Air sampling took place in a large public hall that was heavily contaminated with tobacco smoke. This was the same site used previously (5). The average air temperature and RH during the sampling for this study were 16.2 °C and 62.8%, respectively. The flow rate was 1.35 m<sup>3</sup>/min. The sampling time was 3 h, 35 min, for a total sample volume of 290 m<sup>3</sup>. The filter was weighed, wrapped in aluminum foil, then placed in a -70 °C freezer, all within 1 h of sampling. The total suspended particulate (TSP) level for the sampling event was 420 μg/m<sup>3</sup>, with the filter weighed at 48% RH. This is comparable to the TSP levels found by Benner *et al.* (14) in the Baltimore Harbor Tunnel, a major roadway tunnel (geometric mean TSP = 456 μg/m<sup>3</sup>). We note here that the term RSP (respirable suspended particulate material) is more common in the tobacco smoke literature than is TSP. TSP ≈ RSP for the tobacco smoke particle size range.

The ETS particle load on the filter was 287 μg/cm<sup>2</sup>; at the time of the analysis, the nicotine concentration  $c_p$  in the particles was 16 ng/μg and was determined as follows. A 47 mm diameter punch from the main filter was first spiked with 8000 ng of the surrogate standard nicotine-*d*<sub>3</sub>, wetted

with 0.5 mL of ethanol, then extracted 4 times for 2 min each time using 10 mL aliquots of water that had been acidified to pH = 0 with sulfuric acid. The extracts were combined, adjusted to pH >12 with concentrated NaOH, then back extracted 4 times with 10 mL aliquots of methylene chloride. After concentration to 0.5 mL and the addition of naphthalene-*d*<sub>8</sub> as an internal standard, the sample was analyzed by capillary column gas chromatography/mass spectrometry (GC/MS) using a DB-5 column.

All of the ETS nicotine desorption experiments were carried out within about 1 month of sampling. In each experiment,  $K_p$  was measured by determining the initial rate at which free-base nicotine was volatilized from the filter when clean, 20 °C, RH = 60% nitrogen gas at varying  $p_{NH_3}$  levels was passed at ~1.5 L/min through the filter. The apparatus and experimental approach employed was similar to that used previously (5), except that valved flow (15–30 mL/min) from a bubbler in an NH<sub>4</sub>OH solution (0–1.5 mol/L) was added as a variable source of NH<sub>3</sub> for the gas flowing over the ETS-loaded filter. For each run, two separate 47 mm diameter filter punches were taken from the 18.5 cm × 23.7 cm TMF. One was used to determine the total nicotine on the filter; the second was mounted in a 47 mm stainless steel filter holder, then exposed to the  $p_{NH_3}$  level selected for that run. Adsorption losses of nicotine to the stainless surface in this system were checked, and found to be insignificant (<1%).

Three to four sequential measurements of the gas-phase nicotine concentration  $c_g$  in the flow leaving the filter were made over the course of each run, using sampling periods that ranged from 20 to 90 min. The total desorption flow through the filters ranged from 40 to 100 L. The approach used to analyze the data was the same as employed previously (5). For each run, the  $p_{NH_3}$  level in the flow just upstream of the filter was measured using a 6 mm i.d. × 150 cm borosilicate glass “denuder” tube coated with oxalic acid. Approximately 25% of the total gas flow was passed through the denuder. After sampling, each denuder was extracted with 15–100 mL of NH<sub>3</sub>-free water. Dissolved NH<sub>3</sub> was determined by the phenate method (15). The use of backup denuders revealed no significant breakthrough during sampling.

Gaseous nicotine was collected separately using the same type of oxalic acid-coated denuder tube employed for NH<sub>3</sub> collection. After sampling, each nicotine denuder was spiked with 4000 ng of nicotine-*d*<sub>3</sub>, then extracted with 40 mL of water. Subsequent treatment and analysis of the 40 mL water extract proceeded as described above for the filter extracts. As in the ammonia determinations, the use of backup denuders revealed no significant breakthrough during sampling.

**MSS Measurements.** Several packs of two major brands of commercial cigarettes were purchased in Portland, Oregon. Each cigarette was individually numbered, weighed, and placed in a chamber with RH = 70% for at least 24 h before smoking. The two different brands were placed in separate chambers. Mainstream smoke was collected at room temperature (20–24 °C) on 35.5 mm diameter, 2 μm pore size TMFs (Gelman Sciences, Ann Arbor, MI), using 2 s puffs of ~30 mL each and a puff rate of once every 30 s. Each cigarette was smoked until the combustion zone was ~0.5 cm from the cigarette filter. Under these conditions, 14–15 puffs were taken from each cigarette over 6.5–7.0 min. Each filter was weighed immediately after smoking, then stored at –70 °C for less than 12 h. One cigarette was smoked per filter, yielding a particle load on the filter of ~10 mg, or ~0.1 mg/cm<sup>2</sup> (including water). The corresponding values for nicotine were ~0.55 mg and ~0.055 mg/cm<sup>2</sup>. After removal from cold storage, each filter was allowed to return to room temperature, reweighed, then immediately loaded into the filter holder in the desorption apparatus described above. During desorption at 20 °C, the nitrogen flow rate through the filter was ~1.5

**TABLE 1. Measured Values of Log  $K_p$  for Environmental Tobacco Smoke (ETS) Particles and Mainstream Smoke (MSS) Particles from Two Brands of Commercial Cigarettes (A and B) as a Function of  $p_{NH_3}$  at 20 °C and two RH Values**

$p_{NH_3} \times 10^6$ (atm)	RH (%)	log $K_p$ (m <sup>3</sup> /μg)
<b>ETS</b>		
0	60	–2.83 <sup>a</sup>
0.01	60	–3.00
1.7	60	–3.72
3.0	60	–3.77
21	60	–4.38
127	60	–4.93 <sup>b</sup>
<b>MSS-A</b>		
0.0	60	–4.43
1.04	60	–4.43
18.6	60	–4.73
80.4	60	–4.88 <sup>b</sup>
185	60	–4.95 <sup>b</sup>
196	60	–4.90 <sup>b</sup>
427	90	–4.99 <sup>b</sup>
<b>MSS-B</b>		
140	60	–5.02 <sup>b</sup>
296	90	–4.94 <sup>b</sup>
average of high $p_{NH_3}$ values = log $K_{p,fb}$		–4.94

<sup>a</sup> This data point from Liang and Pankow (5) for ETS was obtained at the same ETS sampling site used in this study. <sup>b</sup> Log  $K_p$  values included in the estimate of log  $K_{p,fb}$ .

L/min. The total desorption flow through the filters for the different runs ranged from 40 to 100 L.

After desorption, each filter was reweighed, then spiked with 10 000 ng of nicotine-*d*<sub>3</sub>. To determine the remaining nicotine, each filter was then extracted in the same manner as with the ETS-loaded filters. This remaining amount was added to the cumulatively desorbed nicotine to calculate the initial mass of nicotine on each filter. All filter and denuder extracts were analyzed by GC/MS as described above.

**QA/QC.** Nicotine standards with concentrations of 2, 20, 40, and 100 ng/μL were run at the beginning of each series of nicotine analyses. Sample extracts were in every case within the range 4–20 ng/μL. Standards were also run during or at the end of each series of nicotine analyses. For each set of nicotine analyses, the standard deviation of the nicotine response factors for the different standard runs was always less than 10% and in most cases was in the range 4–7%. As noted above, nicotine-*d*<sub>3</sub> was used as a surrogate standard compound for nicotine. The absolute nicotine-*d*<sub>3</sub> recovery was checked for each nicotine analysis and found to be in the range 35–60%. The accuracy of the ammonia method was checked and found to be 20% relative to known standards. The precision for ammonia replicates was 6%.

## Results and Discussion

**Determination of  $K_{p,fb}$ .** The log  $K_p$  vs  $p_{NH_3}$  data for 20 °C, RH = 60%, and RH = 90% are given in Table 1, and plotted in Figure 2. The ETS results for RH = 60% were found to be reproducible in a separate series of experiments using quartz fiber filters (QFFs). The log  $K_p$  values for both ETS and MSS undergo a dramatic drop as ammonia is added to the gas phase. As  $p_{NH_3}$  rises to ~80 × 10<sup>–6</sup> atm [80 parts per million by volume (ppmV)], log  $K_p$  begins to approach an asymptotic limit which we estimate as log  $K_{p,fb}$  = –4.94 at 20 °C. The measurements carried out at RH = 60% and 90% for MSS suggest that  $K_{p,fb}$  does not depend strongly on RH.

The agreement between the ETS and MSS data at  $p_{NH_3}$  > 80 ppmV is excellent. The fact that the MSS data lie below the ETS data for  $p_{NH_3}$  < 50 ppmV may have been due to the presence of some residual ammonia in the MSS samples. Those MSS samples may therefore have been more in equilibrium with the lower  $p_{NH_3}$  values (as so at a higher pH)

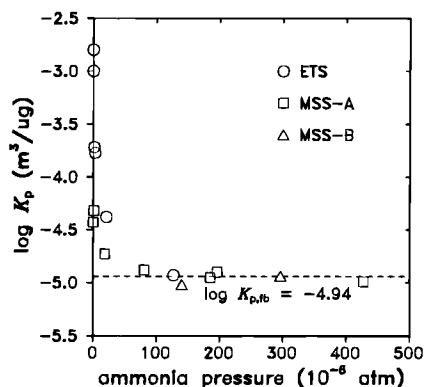


FIGURE 2.  $\log K_p$  ( $\text{m}^3/\mu\text{g}$ ) vs ammonia pressure  $p_{\text{NH}_3}$  for environmental tobacco smoke (ETS) and mainstream tobacco smoke from two different brands of commercial cigarettes (MSS-A and MSS-B). At high  $p_{\text{NH}_3}$  values,  $\log K_p$  asymptotically approaches  $\log K_{p,\text{fb}}$ .

than the ETS samples. At “high”  $p_{\text{NH}_3}$  levels, any residual ammonia would have been unimportant compared to the applied  $p_{\text{NH}_3}$ , leading to a convergence of the MSS data with the ETS data as observed here.

As discussed above, in the absence of added ammonia, a sample of ETS particles yielded  $K_p = 10^{-2.83}$  (5). Since  $10^{-4.94}/10^{-2.83} = 10^{-2.11}$ , eq 5 implies that  $\alpha_{\text{fb}} = 10^{-2.11}$  when  $\log K_p = -2.83$ . By eq 2, this occurs when  $\text{pH} = 5.91$ , which would be consistent with the common view that cigarette smoke is naturally acidic. As  $p_{\text{NH}_3}$  increases, the  $\text{pH}$  in the tobacco smoke particle phase will rise, driving  $\alpha_{\text{fb}} \rightarrow 1$ . For  $\alpha_{\text{fb}}$  to reach 0.90, so that  $\log K_p \approx \log K_{p,\text{fb}}$ , at 20–25 °C we require that  $\text{pH} \approx 8.9$ .

Gaseous ammonia levels in mainstream tobacco smoke for contemporary commercial cigarettes have not been measured. However, according to the FDA (4), ammonia-containing additives like diammonium phosphate can comprise as much as 10% by weight of “reconstituted tobacco sheet” (RTS). Tobacco blends in cigarettes typically contain 20–30% RTS. These data indicate that ammonia-containing compounds can comprise as much as 2–3% of contemporary cigarette tobacco. Nicotine, of course, is also itself a base, and as such particle-phase nicotine will affect the particle-phase  $\text{pH}$ . The relative magnitudes of the relative roles of ammonia and nicotine in driving  $K_p$  toward  $K_{p,\text{fb}}$  in contemporary commercial cigarettes are not presently known, though it seems likely that ammonia is very important.

**$K_p$  for Tobacco Smoke as a Function of Dilution.** Liang and Pankow (5) reported a  $K_p$  value of  $10^{-2.83}$  for ETS that was collected in a smoky indoor air environment ( $\text{TSP} = 455 \mu\text{g}/\text{m}^3$ ) and returned to the laboratory for determination of  $K_p$  values by desorption. This ETS was probably exposed to the room air (including lab air after sampling) long enough to lose a significant amount of its original ammonia (and nicotine) by volatilization. Such a loss seems the likely explanation for why this value is so large compared to our estimate of  $10^{-4.94}$  for  $K_{p,\text{fb}}$ . As noted above, this type of loss may also explain why for  $p_{\text{NH}_3} < 50 \text{ ppm V}$  the ETS data in Figure 2 plot above the MSS data. It is therefore of interest to examine  $K_p$  values which might be calculated for tobacco smoke from commercial cigarettes using actual gas- and particulate-phase nicotine values found in the literature, seeking evidence of loss of the  $\text{pH}$ -affecting compounds ammonia and nicotine as a function of smoke age and/or dilution.

Two studies with useful data are available, namely Caka *et al.* (16), who examined simulated ETS, and Lewis *et al.* (17), who examined MSS. Both of these studies used contemporary commercial cigarettes. For the Caka *et al.* (16) study, their “best” gas- and particle-phase concentrations were combined with their measured TSP values. For the Lewis *et al.* (17)

TABLE 2. Values of  $\log K_p$  for Tobacco Smoke Particles at Room Temperature as a Function of TSP<sup>a</sup>

TSP ( $\mu\text{g}/\text{m}^3$ )	$\log K_p$ ( $\text{m}^3/\mu\text{g}$ )
ETS, Caka <i>et al.</i> (16)	
184	-3.76
190	-3.73
196	-3.79
930	-4.44
930	-4.46
990	-4.76
MSS, Lewis <i>et al.</i> (17)	
$1.7 \times 10^7$	-5.08

<sup>a</sup> Values calculated based on reported values of  $c_p$ ,  $c_g$ , and TSP.

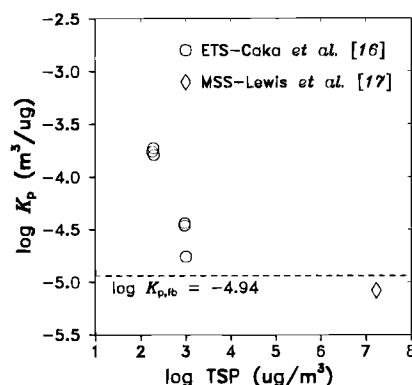


FIGURE 3.  $\log K_p$  ( $\text{m}^3/\mu\text{g}$ ) vs  $\log \text{TSP}$  ( $\mu\text{g}/\text{m}^3$ ) for environmental tobacco smoke (ETS) and mainstream tobacco smoke (MSS).

study, their reported gas- and particle-phase fractions of 0.7 and 99.3% were combined with their reported TSP value of  $1.7 \times 10^7 \mu\text{g}/\text{m}^3$ . The resulting  $K_p$  values are presented in Table 2. As tobacco smoke becomes diluted and TSP falls, the value of  $p_{\text{NH}_3}$  will decrease, causing  $K_p$  to rise. Figure 3 illustrates how this data would be consistent with this expected effect, and the resemblance to Figure 2 is striking. These results suggest that the  $c_p/c_g$  ratio for nicotine can be expected to change as concentrated tobacco smoke becomes diluted in indoor air.

**Percent Nicotine in the Gas Phase.** The product  $c_p \text{TSP}$  gives the amount of particle-phase nicotine (protonated + free-base) in the smoke in units of nanograms per cubic meter. The percent  $P_g$  of the nicotine that is in the gas phase is then given by

$$P_g (\%) = \frac{c_g}{c_g + c_p \text{TSP}} 100\% \quad (6)$$

When there is particle/gas equilibrium so that  $c_p/c_g = K_p$ , then

$$P_{g,\text{eq}} (\%) = \frac{1}{1 + K_p \text{TSP}} 100\% \quad (7)$$

It is interesting to make some order of magnitude calculations with eq 7: TSP level in MSS is variable and depends on the presence or absence of a filter, the ventilation allowed by the wrapping and filter “tipping” papers, and other parameters (18). For filter cigarettes, a TSP level of  $\sim 4 \times 10^7 \mu\text{g}/\text{m}^3$  might be considered typical. This is based on data indicating that filter cigarettes yield  $\sim 12 \text{ mg}$  of particulate matter (18), and assuming 8.35 mL puffs per cigarette. In the past, the study of inhaled tobacco smoke has involved a 35 mL puff followed by dilution into a single lung “tidal volume” of 500 mL (19). This yields a dilution factor of 14 and a TSP of  $2.86 \times 10^6 \mu\text{g}/\text{m}^3$ . Additional diffusive mixing at the front

**TABLE 3. Calculated Values of the Fraction  $P_{g,eq}$  of Nicotine in the Gas Phase for Equilibrium Particle/Gas Equilibrium for Three Values of TSP (MSS, MSS/14, and MSS/28) and Two Values of Log  $K_p$  (Small Ammonia Effect and Full Ammonia Effect for Which  $K_p = K_{p,fb}$ )**

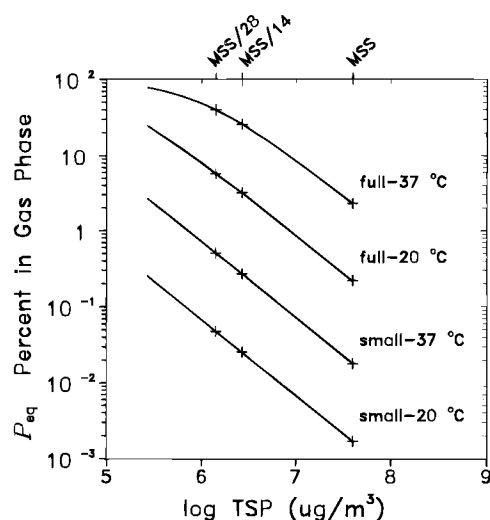
smoke type	TSP ( $\mu\text{g}/\text{m}^3$ )	ammonia effect	log $K_p$ ( $\text{m}^3/\mu\text{g}$ )	percent in gas phase ( $P_{g,eq}\%$ )
<b>20 °C</b>				
MSS	$4.00 \times 10^7$	small	-2.83	0.0017
MSS/14	$2.86 \times 10^6$	small	-2.83	0.024
MSS/28	$1.43 \times 10^6$	small	-2.83	0.047
MSS	$4.00 \times 10^7$	full	-4.94	0.22
MSS/14	$2.86 \times 10^6$	full	-4.94	3.0
MSS/28	$1.43 \times 10^6$	full	-4.94	5.7
<b>37 °C</b>				
MSS	$4.00 \times 10^7$	small	-3.86	0.018
MSS/14	$2.86 \times 10^6$	small	-3.86	0.25
MSS/28	$1.43 \times 10^6$	small	-3.86	0.51
MSS	$4.00 \times 10^7$	full	-5.97	2.3
MSS/14	$2.86 \times 10^6$	full	-5.97	25
MSS/28	$1.43 \times 10^6$	full	-5.97	40

of the inhaled tobacco smoke can yield additional dilution (e.g., say an additional factor of two for an overall dilution factor of 28). Table 3 gives the  $P_{g,eq}$  values for a MSS value of  $4 \times 10^7 \mu\text{g}/\text{m}^3$ , this MSS value diluted by a factor of 14 (i.e., MSS/14), and this MSS value diluted by a factor of 28 (i.e., MSS/28). These TSP levels are combined with the 20 °C values of log  $K_p = -2.83$  (small ammonia effect) and log  $K_p = -4.94$  (full ammonia effect). The term small ammonia effect rather than no ammonia effect is used to refer to the log  $K_p = -2.83$  value because even though no ammonia was added to the gas stream during that measurement, some residual ammonia from the original cigarette smoke may have remained in the smoke particle phase, thereby depressing the measured log  $K_p$  value below what would have been obtained for a truly zero ammonia system for that smoke material.

The calculations in Table 3 for equilibrium at 20 °C indicate that with the full ammonia effect acting on an MSS value for TSP of  $4 \times 10^7 \mu\text{g}/\text{m}^3$ , only ~0.2% of the mainstream nicotine will be in the gas phase. Measurements made on burning cigarettes indicate that MSS is in fact often close to ambient temperatures (20). As noted above, the ambient-temperature, commercial filter cigarette MSS measurements of Lewis *et al.* (17) at TSP =  $1.7 \times 10^7 \mu\text{g}/\text{m}^3$  yielded a gas phase percentage of ~0.7% for nicotine. This is in very reasonable agreement with the ~0.5% that would be calculated for that TSP level and 20 °C and assuming the full ammonia effect.

The temperature of the human body is 37 °C. For partitioning to organic aerosols, it is known that  $K_p$  values are inversely proportional to vapor pressure (21). Since the vapor pressure of nicotine increases by a factor of ~10.8 between 20 and 37 °C (22), correction of the  $K_p$  values at 20–37 °C involves division by ~10.8. The nicotine fractions that are in the gas phase at equilibrium in MSS at 37 °C are calculated to be 0.018% and 2.3%, without and with the full ammonia effect, respectively. The potential for the absorption of gaseous nicotine from MSS in the oral cavity therefore seems small.

In order to obtain upper bounds for the amounts of nicotine that can be in the gas phase, we will assume here that the nicotine starts to equilibrate before significant ammonia is lost (i.e., in contrast to what is depicted in Figure 2, we will assume for the following calculations that  $K_p$  under the full ammonia effect does not decrease with TSP, at least not immediately). Under this assumption, the dilution of the MSS that accompanies a first-breath dilution factor of 14 increases the calculated equilibrium gas-phase fractions at 37 °C to 25% with the full ammonia effect and 0.25% without. For the former, the gas-phase fraction is now very significant,



**FIGURE 4. Percent in gas phase at equilibrium ( $P_{eq}$ ) vs log TSP ( $\mu\text{g}/\text{m}^3$ ), i.e., as a function of dilution.  $K_p$  values are assumed to hold constant with dilution. Key: MSS, TSP =  $4 \times 10^7 \mu\text{g}/\text{m}^3$ ; MSS/14, TSP =  $2.86 \times 10^6 \mu\text{g}/\text{m}^3$ ; MSS/28, TSP =  $1.43 \times 10^6 \mu\text{g}/\text{m}^3$ .**

with the ammonia causing a boost to the gas-phase of 100-fold. Of course, nicotine at equilibrium in MSS will not reach its new equilibrium position for diluted, inhaled smoke instantaneously. However, the work of Lewis *et al.* (18) indicates that significant volatilization of nicotine can take place from MSS particles within time frames of a few seconds. These time frames are consistent with recent studies of the “off-gassing” of fluorene and phenanthrene from diesel soot particles observed by Kamens and Coe (23). Figure 4 provides plots for a range of TSP values.

We note for the various TSP/temperature/ammonia combinations in Table 3 and Figure 4 that the values of  $P_{g,eq}$  given there might, at least under some circumstances, be underestimates of the fractions of the nicotine that could be delivered by gas deposition from smoke initially at particle/gas equilibrium. Indeed, deposition of gas-phase nicotine to the surfaces of the respiratory tract will lower the local nicotine gas-phase concentration. This disturbance of the particle/gas partitioning will draw more nicotine into the gas phase, and that nicotine will in turn be available for deposition from the gas phase. The process will continue until the remaining particles are exhaled. As noted above, experimental results obtained with MSS indicate that this volatilization can occur in seconds, with three times more nicotine capable of being drawn into the gas phase within 10 s than was initially present in that phase (17).

**Implications of These Findings.** The addition of ammonia to tobacco smoke particles has been found to greatly increase the volatility of nicotine from those particles. We interpret this result as being due to the conversion of nicotine from its protonated form to its free-base form. In particular, such an increase in the fraction of the particle-phase nicotine that is in the free-base form will increase the amount of nicotine that is in the highly available gas phase, and would also permit a more rapid absorption of free-base nicotine from particles that deposit in the respiratory tract.

#### Acknowledgments

The authors express their deep appreciation to the Oregon Graduate Institute for its support of this research. In addition, J.F.P. would like to express his gratitude to Dawn M. Larson for encouraging and supporting this work. The able assistance of Joelle M. Roche with a portion of the experimental work is also gratefully acknowledged.

## Literature Cited

- (1) *Wall Street J.* October 18, 1995, p 1.
- (2) Glantz, S. A.; Slade, J.; Bero, L. A.; Hanauer, P.; Barnes, D. E. *The Cigarette Papers*; University of California Press: Berkley, 1996; p 211.
- (3) Kluger, R. *Ashes to Ashes*; Alfred A. Knopf: New York, 1996; pp 744–745.
- (4) Food and Drug Administration, *Federal Register*; 21 CFR Parts 801, 803, 804, and 897, August 11, 1995. *Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco Products to Protect Children and Adolescents: Proposed Rule, and Analysis Regarding FDA's Jurisdiction Over Nicotine-Containing Cigarettes and Smokeless Tobacco Products; Notice.*
- (5) Liang, C.; Pankow, J. F. *Environ. Sci. Technol.* **1996**, *30*, 2800–2805.
- (6) Boubel, R. W.; Fox, D. L.; Tanner, D. B.; Stern, A. C. *Fundamentals of Air Pollution*; Academic Press: San Diego, 1994; pp 104–106.
- (7) Burch, S. G.; Gann, L. P.; Olsen, K. M.; Anderson, P. J.; Hiller, F. C.; Erbland, M. L. *J. Aerosol Sci.* **1993**, *6*, 45–52.
- (8) Eatough, D. J.; Benner, C. L.; Bayona, J. M.; Richards, G.; Lamb, J. D.; Lee, M. L.; Lewis, E. A.; Hansen, L. D. *Environ. Sci. Technol.* **1989**, *23*, 679–687.
- (9) Sensabaugh, A. J., Jr.; Cundiff, R. H. *Tob. Sci.* **1967**, *11*, 25–30.
- (10) Brunnemann, K. D.; Hoffmann, D. *Food Cosmet. Toxicol.* **1974**, *12*, 115–124.
- (11) Armitage, A. K.; Turner, D. M. *Nature* **1970**, *226*, 1231–1232.
- (12) Inciardi, J. A. Crack Cocaine in Miami. In *The Epidemiology of Cocaine Use and Abuse, Research Monograph 110*; Schober, S., Schade, C., Eds.; U.S. Department of Health and Human Services: Washington, DC, 1991; p 265.
- (13) Timmermans, J. *Physico-chemical Constants of Pure Organic Compounds*; Elsevier Scientific Publishing Co.: New York, 1950.
- (14) Benner, B. A.; Gordon, G. E.; Wise, S. A. *Environ. Sci. Technol.* **1989**, *23*, 1269–1278.
- (15) *Standard Methods for the Examination of Water and Wastewater*; American Public Health Association: Washington, DC, 1985.
- (16) Caka, F. M.; Eatough, D. J.; Lewis, E. A.; Tang, H.; Hammond, S. K.; Leaderer, B. P.; Koutrakis, P.; Spengler, J. D.; Fasano, A.; McCarthy, J.; Ogden, M. W.; Lewtas, J. *Environ. Sci. Technol.* **1990**, *24*, 1196–1203.
- (17) Lewis, D. A.; Colbeck, I.; Mariner, D. C. *J. Aerosol Sci.* **1995**, *26*, 841–846.
- (18) Guerin, M. R.; Jenkins, R. A.; Tomkins, B. A. *The Chemistry of Environmental Tobacco Smoke: Composition and Measurement*; Lewis Publishers: Boca Raton, FL, 1992; pp 50–58.
- (19) Phalen, R. F.; Cannon, W. C.; Esparaza, D. In *Fine Particles*; Lin, B. Y. H., Ed.; Academic Press: New York, 1976; 731–737.
- (20) Baker, R. R. *Recent Adv. Tob. Sci.* **1980**, *6*, 184–188.
- (21) Pankow, J. F. *Atmos. Environ.* **1994**, *28*, 189–193.
- (22) Weast, R. C. *Handbook of Chemistry and Physics*, 51st ed.; CRC Press: Boca Raton, FL, 1970; p D-160.
- (23) Kamens, R. M.; Coe, D. L. *Environ. Sci. Technol.* **1997**, *31*, 1830–1833.

Received for review May 7, 1997. Revised manuscript received June 13, 1997. Accepted June 19, 1997.<sup>Ⓢ</sup>

ES970402F