

# Partial Vapor Pressures, Activity Coefficients, Henry Volatility, and Infinite Dilution Activity Coefficients of Nicotine from Binary Mixtures with Glycerol and with 1,2-Propanediol at 298.15 K

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Cite This: *ACS Omega* 2023, 8, 7749–7756

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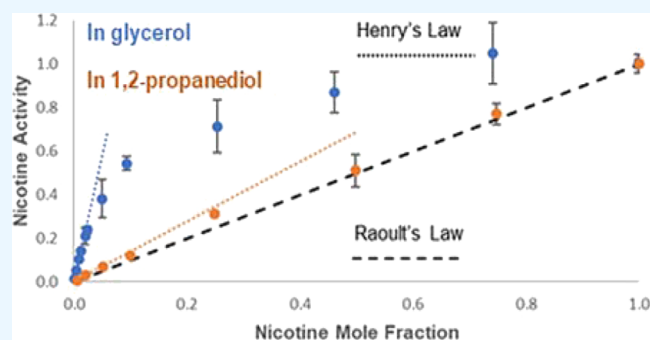
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**ABSTRACT:** The equilibrium headspace concentration of nicotine in nitrogen gas was measured by gas chromatography for binary mixtures of nicotine with glycerol and with 1,2-propanediol at temperatures near 298.15 K. The storage temperature ranged from 296.25 to 298.25 K. The nicotine mole fraction ranged from  $0.0015 \pm 0.00010$  to  $0.998 \pm 0.0016$  for the glycerol mixtures and  $0.00506 \pm 0.000019$  to  $0.999 \pm 0.0038$  for the 1,2-propanediol mixtures ( $k = 2$  expanded uncertainty). The headspace concentration was converted to nicotine partial pressure at 298.15 K using the ideal gas law, followed by the Clausius–Clapeyron equation. Both solvent systems had a positive deviation of nicotine partial pressure from ideal behavior, but the deviation of the glycerol mixtures was much greater than that of the 1,2-propanediol mixtures. For mole fractions of about 0.02 or less, the glycerol mixtures had nicotine activity coefficients of 11, while that for the 1,2-propanediol mixtures was 1.5. The Henry's law volatility constant and infinite dilution activity coefficient  $\pm$  expanded uncertainty for nicotine from glycerol mixtures ( $51.4 \pm 1.8$  Pa and  $12.4 \pm 1.5$ , respectively) were approximately an order of magnitude greater than those from 1,2-propanediol mixtures ( $5.26 \pm 0.52$  Pa and  $1.42 \pm 0.14$ , respectively).



## INTRODUCTION

Electronic nicotine delivery systems (ENDSs), also known as e-cigarettes, vaporize a solution (e-liquid) consisting primarily of the polyols glycerol (1,2,3-propanetriol) and 1,2-propanediol with nicotine (3-[(2S)-1-methylpyrrolidin-2-yl] pyridine) added. The polyols typically make up 90% or more of the e-liquid solution. Nicotine in commercial products ranges from ~0.3 to 5% by weight. Nicotine in polyol solutions can be purchased online in concentrations up to ~10% by weight for use by consumers custom-mixing e-liquids. There have been no published values of nicotine activity in these polyol mixtures, so measurements of the nicotine partial pressure were made from binary mixtures of nicotine in glycerol and in 1,2-propanediol as well as from undiluted nicotine. Nicotine activity is defined as the partial pressure of nicotine divided by the saturated vapor pressure of undiluted nicotine at the same temperature. Including undiluted nicotine headspace measurements simultaneously with the nicotine binary mixture headspace measurements allows nicotine activity to be calculated while canceling systematic sources of experimental variability. Given the wide range of concentrations, and therefore partial pressures, this meant using either an equilibrated headspace technique from flexible bags or a gas-saturation flow technique for the experiments.<sup>1</sup> Since the rate at which nicotine would transfer from the mixtures to gas was

unknown, we decided on headspace sampling from flexible containers. This would allow equilibration times on the order of days and weeks rather than minutes using the gas-saturation flow technique. The use of flexible containers also avoids the need for a vacuum system with fixed volumes and separately heated regions such as described by Chickos.<sup>2</sup>

## EXPERIMENTAL SECTION

The different binary solutions were tested sequentially. The first set of experiments measured the headspace concentration of nicotine from binary mixtures with glycerol. A room with a stable temperature control was used instead of an environmental cabinet to allow ease of access when sampling. Room temperature was measured at each sampling time using a Type K thermocouple and an Omega HH11B Digital thermometer with 0.1 °C resolution. Offset was checked periodically against ice water in a Dewar flask. Room temperature ranged from

Received: November 18, 2022

Accepted: February 6, 2023

Published: February 14, 2023



Table 1. Nicotine (1) Mole Fraction in the Binary Mixtures Used for Headspace Measurement

nicotine-glycerol mixtures			nicotine-1,2-propanediol mixtures		
mole fraction nicotine, $x_1$	standard uncertainty <sup>a</sup> $u(x_1)$	nicotine source	mole fraction nicotine, $x_1$	standard uncertainty <sup>a</sup> $u(x_1)$	nicotine source
0.001497	$4.8 \times 10^{-5}$	Siegfried	0.00506	$9.5 \times 10^{-6}$	Siegfried
0.004993	$4.1 \times 10^{-5}$	Siegfried	0.02015	$3.7 \times 10^{-5}$	Siegfried
0.009267	$3.8 \times 10^{-5}$	Siegfried	0.05044	$9.3 \times 10^{-5}$	Siegfried
0.01213	$1.2 \times 10^{-4}$	TRC <sup>b</sup>	0.09994	$1.7 \times 10^{-4}$	Siegfried
0.02002	$3.7 \times 10^{-5}$	Siegfried	0.2486	$4.6 \times 10^{-4}$	Siegfried
0.0235	$2.1 \times 10^{-4}$	TRC	0.498	$1.0 \times 10^{-3}$	Siegfried
0.05008	$5.1 \times 10^{-5}$	Siegfried	0.747	$1.4 \times 10^{-3}$	Siegfried
0.0932	$8.4 \times 10^{-4}$	TRC	0.999	$1.9 \times 10^{-3}$	Siegfried/TRC <sup>c</sup>
0.2533	$4.4 \times 10^{-4}$	Siegfried			
0.461	$4.6 \times 10^{-3}$	TRC			
0.741	$1.6 \times 10^{-3}$	Siegfried			
0.9975	$8.2 \times 10^{-4}$	Siegfried			

<sup>a</sup>Methodology in S1 Supporting Information on Uncertainty. <sup>b</sup>Toronto Research Chemicals. <sup>c</sup>Three of the 10 samples were TRC nicotine (see S2 Supporting Information Replicate Data).

296.25 to 297.85 K with a mean value of 297.25 K. The second set of experiments measured the headspace concentration of nicotine from binary mixtures with 1,2-propanediol. A walk-in environmental chamber set to 298.15 K/60% relative humidity was used, and headspace was sampled inside the environmental chamber. Room temperature was measured at each sampling time using a Type K thermocouple and ranged from 297.95 to 298.25 K with a mean value of 298.15 K.

**Materials.** Glycerol (1,2,3-propanetriol), CAS# 56-81-5: Sigma  $\geq 99.5\%$  (GC) (Sigma-Aldrich, St. Louis, MO) was used as received. The certificate of analysis stated 99.90% purity with <0.05% water. Glycerol containers were stored in vacuum-sealed Sorbent Systems (Impak Corp., Los Angeles, CA) 5 mil (127  $\mu\text{m}$ ), four-layer foil (type PAKVF4C) bags, which consisted of 16.5  $\mu\text{m}$  poly(ethylene terephthalate) (PET, outer), polyethylene (PE), 8.9  $\mu\text{m}$  aluminum foil, and metallocene PE (inner heat seal). The vacuum-sealed bags were stored in a refrigerator ( $\sim 277$  K) to further prevent water pickup from the environment.

1,2-Propanediol, CAS# 57-55-6: Sigma puriss, p.a., ACS reagent,  $\geq 99.5\%$  (GC) (Sigma-Aldrich, St. Louis, MO) was used as received. The certificate of analysis stated 99.99% purity with 0.002% water. The containers were stored in the same manner as for glycerol.

L-Nicotine, S-(-)-nicotine, (3-[(2S)-1-methylpyrrolidin-2-yl]pyridine), CAS# 54-11-5 (Caution! Pure nicotine is highly poisonous and can be absorbed through the skin. Use care and appropriate personal protection equipment when handling.): Three separate lots of nicotine were used as received. Subsamples of the two Siegfried samples were stored under nitrogen in brown polypropylene bottles kept over Drierite in a freezer. The Toronto Research Chemicals sample was stored in an original amber glass container, which was kept in an evacuated zipper-lock bag in the freezer. The freezer temperature was approximately 253 K.

Binary mixtures with glycerol: Siegfried USP/Ph.Eur. (Interchem Corp., Paramus, NJ). The certificate of analysis stated 99.9% purity (nonaqueous titration), 0.02% water (Karl Fisher), 0.06% myosmine, <0.06% other related substances (HPLC), and <10 ppm cyclohexane residual solvent. Specific rotation was  $-133.8^\circ$  (20  $^\circ\text{C}$ ) and  $-135.6^\circ$  (25  $^\circ\text{C}$ ) in 96% ethanol, and  $-146.9^\circ$  in absolute ethanol (calculated on the anhydrous basis).

Toronto Research Chemicals 98% (North York, ON, Canada): The certificate of elemental analysis indicated 98.42% based on carbon and 98.49% based on nitrogen. Other less specific information states that  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and mass spectrometry conform to the structure and a specific rotation of  $-126.9^\circ$  ( $c = 1.3$ , methanol).

Binary mixtures with 1,2-propanediol: Siegfried USP/Ph.Eur. (Interchem Corp., Paramus, NJ) was used as received. The certificate of analysis stated 99.7% purity (nonaqueous titration), 0.01% water (Karl Fisher), <0.06% sum of related substances (HPLC), and 23 ppm cyclohexane residual solvent. Specific rotation was  $-135.5^\circ$  (25  $^\circ\text{C}$ , 96% ethanol) and  $-148.6^\circ$  in absolute ethanol (calculated on the anhydrous basis).

Extraction solution: Ethyl acetate 99.9% (CAS# 141-78-6) with 5000 ppm triethylamine 99.5% (CAS# 121-44-8), used as received (both from Sigma-Aldrich, St. Louis, MO).

Internal standard (I.S.) for extracted nicotine and nicotine calibration standards: (+/-) Deuterated nicotine (methyl-d3) (Toronto Research Chemicals, Toronto, Canada). Internal standard solutions were made by diluting the d3-nicotine with extraction solution to 10.9  $\mu\text{g}$  d3-nicotine/mL. The extraction solution was subdivided into 4 mL vials, placed into individual zipper-lock bags, and then kept in a jar in the freezer until used. Separate batches of I.S. were made for the analysis of nicotine from the two binary solutions with glycerol and 1,2-propanediol.

Binary mixtures used for headspace analysis: Binary solutions were made with the nicotine mole fractions listed in Table 1. Successive dilutions were made for the Siegfried nicotine mixtures below 0.05 mole fraction. The uncertainty for the mixture being diluted was used along with balance uncertainty to calculate the uncertainty for the diluted sample as described in S1 Supporting Information on Uncertainty.

**Apparatus and Procedure.** The methodology closely follows that described in a previous paper measuring the headspace nicotine from tobacco<sup>3</sup> with slight modifications. The flexible gas bag was constructed as described in ref 3 for the second set of experiments. Briefly, a Sorbent Systems outer bag (described in the Materials Section for glycerol previously) was lined with an aluminum foil inner bag. A 1/8 I.D. stainless steel Swagelok (Monroe, NC) union (SS-200-6) penetrated a gasket, the outer bag, the foil liner, and aluminum tape (to prevent the foil from tearing) through a 6 mm punched hole

and was secured with a bulkhead union nut (SS-202-61) on the inside at the approximate center of the bag face. On the outside of the bag, a poly(tetrafluorethylene) (PTFE) lined septum was placed between a reversed back ferrule and the front ferrule in the union. The needle used for headspace sampling through the septum for the current experiments was changed to a Hamilton 21-gauge, noncoring conical point design for the current experiments. A glass fiber filter pad in an aluminum weighing dish with the edges bent to secure the pad was used to hold the binary mixture being placed in the bag. After folding and taping the foil liner and heat-sealing the outer bag, the bags were filled and emptied with nitrogen gas at least three times prior to filling with nitrogen and sealing the Swagelok union with a septum. The headspace was allowed to equilibrate at least 3 weeks prior to sampling.

As in ref 3, headspace was sampled using 6 mm diameter  $\times$  70 mm long sorbent sampling tubes containing 120 mg of XAD-4 resin (Cat. No. 226-170, SKC Inc. Eighty Four, PA). These sorbent tubes, along with sampling, extraction, and analysis methods have been previously validated for the analysis of nicotine in environmental tobacco smoke.<sup>4–7</sup> The general configuration of the XAD-4 cartridges for sampling is shown in Figure 1. The needle was used to sample through a

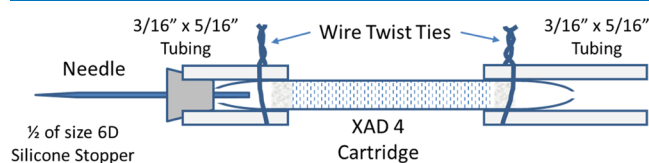


Figure 1. XAD-4 sorbent tube holder.

septum on the gas bags. The other end of the needle was inserted into the sorbent tube. This minimized the dead volume and surface for adsorption of nicotine. This also minimized the potential for the contact of the vapor with rubber or plastic, which has been shown to significantly absorb nicotine.<sup>8–10</sup>

Two changes were made to the sorbent tube holder from that described in ref 3 to minimize the potential for leaks. A film of silicone adhesive was applied to the silicone stopper before inserting it into the tubing. In addition, after inserting the XAD-4 cartridges into the tubing, wire twist ties were added to compress the tubing. Suction was applied to the tubing on the end of the sorbent tube opposite from the needle using either a peristaltic pump or GASTIGHT syringes (10 or 100 mL, Hamilton Co., Reno NV) depending on the volume of headspace sampled. Prior to the 1,2-propanediol mixture experiment, another change was made since the needle tended to push back toward the XAD-4 cartridge when puncturing a septum. A small circle of the diameter of the tubing was cut from an aluminum weighing dish, and a hole was punctured in the center. A bed of silicone adhesive was applied to the stopper and tubing where the needle emerged, and then, the aluminum disk was slid over the needle to the silicone adhesive. After curing, epoxy was applied where the needle emerged from the aluminum disk. This provided a stop to keep the needle from slipping, and the silicone adhesive bed provided additional protection from potential vacuum leaks around the stopper. After sampling, the tubes were capped, placed in capped glass vials, and stored at 253 K until sorbent extraction.

A peristaltic pump was used for collecting headspace samples of 100 mL or greater. The output of the peristaltic pump tubing was connected to flexible nylon tubing with a hose clamp. The nylon tubing was connected using a Swagelok coupling to a 6.35 mm copper tubing coiled inside a 4 L beaker partly filled with water. The tubing output was bubbled into calibrated 200 to 1000 mL volumetric flasks, which had been filled with water and inverted into the beaker. The volumetric flasks (200–1000 mL) were calibrated and marked in 1 mL increments on each side of the rated volume. The calibration procedure used the weight of contained water, along with the density for the measured water temperature, to determine the markings. A Kimax Cassia volumetric flask (Part No. 28066-110) with 0.1 mL etched marks between 100 and 110 mL was also used. As the displaced water level entered the calibrated range on the flasks, the peristaltic pump was turned off; the flask was lifted until the meniscus was just above the water level, and the volume was noted. The distance between markings was estimated to give a fractional mL estimate. The temperature of the water and the air surrounding the gas bag was measured with a type K thermocouple. This assured a known temperature and volume of gas sampled regardless of the storage temperature of the gas bag. The volume was then corrected to the measured temperature of the air in which the gas bag was stored using Charles' (temperature–volume) law.

The XAD-4 resin was extracted by cutting off the ends of the tubes and emptying the glass wool and resin into 4 mL glass vials. The resin was extracted with 3.0 mL of extraction solution along with 60  $\mu$ L of internal standard. The vials were capped and shaken for 25 min on a wrist action shaker. An aliquot of the extract was pipetted from the vials, added to a 1.5 mL screw cap glass vial, and capped with a Teflon-lined septum (Agilent 5182-0715 & 5182-0717, Santa Clara, CA). The extraction solution was ethyl acetate containing 5000 ppm of triethylamine (TEA). The TEA was added to prevent adsorption of nicotine onto glass.<sup>11</sup>

In-syringe sampling was also used for nicotine headspace to check XAD-4 sampling and extraction. It was also used for a single headspace sample of the nominal 0.75 mole fraction nicotine in 1,2-propanediol. For the in-syringe samples, a 10 mL GASTIGHT syringe which had a needle and shutoff valve (Model 1010, Hamilton Co., Reno NV) was used. The needle was a Hamilton Large Hub Removable Needle, 22-gauge, conical point style 5, and custom length 38 mm (part #7732-01). Approximately 2 mL of extraction solution was aspirated into the syringes, then pushed out to a volume of 1.5 mL to remove air, and the syringe valve was closed. The needle was inserted into the septum on a gas bag, the syringe valve was opened, and headspace was slowly aspirated through the extraction solution in the syringe to the desired volume. The needle was removed from the gas bag, a small amount of room air was aspirated, and the syringe valve was closed. The syringe with headspace and solution was then shaken for 5 min before dispensing the solution into the same 1.5 mL GC vials as used for XAD-4 extraction solution. The vials were placed into capped containers and stored at 253 K until analysis. Prior to analysis, 30  $\mu$ L of internal standard solution was added to the vial.

The analysis was performed using gas chromatography/mass spectrometry/MS (GC/MS/MS) on a 7890B/7010B system from Agilent (Santa Clara, CA), in multiple reaction monitoring (MRM) mode. The conditions of analysis are described in Table 2. The column used for the separation was a

DB-Waxetr 30 m  $\times$  0.25 mm i.d. with a film of 0.25  $\mu$ m from Agilent (J&W).

**Table 2. Conditions for the GC/MS/MS Analysis of Nicotine**

parameter	description	parameter	description
initial oven temperature	50 °C	aux. temperature	250 °C
Initial time	1.0 min	solvent delay	3.75 min
oven ramp rate	10 °C/min	gain factor	10
oven temperature 1	240 °C	electron energy	45 V
final time	10 min	MS source temperature	230 °C
total run time	30.0 min	acquisition mode	MRM
inlet temperature	280 °C	d3-nicotine precursor ion	165.1
inlet mode	splitless	d3-nicotine product ion	87.1
purge time	1.0 min	MS1 resolution	unit
purge flow to split vent	15.0 mL/min	dwel time	120 ms
carrier gas	gelium	CE	11 V
injection volume	1.0 $\mu$ L	nicotine precursor ion	162.1
flow mode	constant flow	nicotine product ion	84.1
flow rate	1.0 mL/min	MS1 resolution	Unit
nominal initial pressure	7.65 psi	dwel time	120 ms
GC outlet	MS/MS	CE	11 V

The quantitation for nicotine levels was performed using calibrations of nicotine concentration vs (peak area nicotine/peak area I.S). The peak areas for nicotine and that for I.S. d3-nicotine were generated using MRM mode and the quantitation capability of the instrument (MassHunter workstation software). The calibration ranges were from 3.0 to 2400 ng/mL (glycerol mixtures) and 24.7 to 2473 ng/mL (1,2-propanediol mixtures). The signal-to-noise ratio was 632 for 3.0 ng nicotine/mL (glycerol experiment) and 2391 for 24.7 ng nicotine/mL (1,2-propanediol experiment). These ratios indicate the excellent sensitivity of the procedure. Analytical uncertainty is demonstrated in S1 Supporting Information on Uncertainty.

## RESULTS AND DISCUSSION

**Reliability of the Utilized Sampling Protocol.** As previously described, for most headspace samples, an XAD-4 cartridge was used to capture the nicotine, and the XAD-4 cartridge was subsequently extracted and analyzed. A second method was used primarily for pure nicotine headspace (due to the higher vapor pressure, this did not require XAD-4 cartridges for analytical measurements). This method was based on in-syringe sampling, followed by adding an extraction solution inside the syringe with the headspace bubbled through. The second method was used to check the reliability of the multiple-step XAD-4 cartridge sampling. Pure nicotine headspace was sampled using both methods. A *t*-test assuming unequal variance was used to check the two methods, and for both systems, combined differences were not statistically significant with a *p*-value = 0.44 with the in-syringe method having a mean value 94% of the XAD-4 cartridge value. For the glycerol experiment, the *p*-value was 0.56 with in-syringe results being 92% of those using XAD-4. For the 1,2-propanediol experiment, the *p*-value was 0.062 (close to statistical significance due to the much lower uncertainty of the measurements discussed in S2 Supporting Information Replicate Data), with in-syringe being 97% of the XAD-4. A comparison with published values for pure nicotine gave a secondary check (further discussed).

**Nicotine Partial Pressure, Activity, and Activity Coefficient from the Binary Mixtures.** All replicate data for the nicotine partial pressure are listed in S2 Supporting Information Replicate Data. The small corrections and associated uncertainty in partial pressure from measured temperature to 298.15 K were made using the Clausius–Clapeyron equation as described in S1 Supporting Information on Uncertainty. The standard uncertainty for the partial pressure is the combined uncertainty of this correction with the standard uncertainty of the mean partial pressure. The activity is the nicotine partial pressure of a mixture divided by the vapor pressure of undiluted nicotine. The standard uncertainty of the activity is the combined uncertainty of the partial pressure of the specific nicotine binary mixture and that of pure nicotine. The activity coefficient is the nicotine activity divided by the nicotine mole fraction in the mixture. The uncertainty of the activity coefficient is the combined uncertainty of the activity and mole fraction. The expanded uncertainty of mole fraction is for *k* = 2 times the standard

**Table 3. Mean Nicotine data  $\pm$  Expanded Uncertainty for Nicotine (1) + Glycerol (2) at 298.15 K, Number of Measurements *N*, Mole Fraction  $x_1$ , Partial Pressure  $\bar{p}_1$ , Activity  $\bar{a}_1$ , and Activity Coefficient  $\bar{Y}_1$**

<i>N</i>	$x_1$	$\bar{p}_1$ /Pa	$\bar{a}_1$	$\bar{Y}_1$
3	0.0015 $\pm$ 0.00010 <sup>a</sup>	0.069 $\pm$ 0.019 <sup>b</sup>	0.0168 $\pm$ 0.0062 <sup>b</sup>	11.2 $\pm$ 4.4 <sup>b</sup>
4	0.00499 $\pm$ 0.000081	0.223 $\pm$ 0.039	0.054 $\pm$ 0.013	10.8 $\pm$ 2.7
4	0.00927 $\pm$ 0.000077	0.432 $\pm$ 0.034	0.104 $\pm$ 0.020	11.2 $\pm$ 2.2
5	0.0121 $\pm$ 0.00023	0.584 $\pm$ 0.025	0.141 $\pm$ 0.023	11.6 $\pm$ 1.9
6	0.02002 $\pm$ 0.000073	0.87 $\pm$ 0.15	0.210 $\pm$ 0.048	10.5 $\pm$ 2.4
5	0.0235 $\pm$ 0.00043	0.986 $\pm$ 0.051	0.238 $\pm$ 0.039	10.1 $\pm$ 1.7
6	0.0501 $\pm$ 0.00010	1.58 $\pm$ 0.36	0.38 $\pm$ 0.10	7.6 $\pm$ 2.0
5	0.093 $\pm$ 0.0017	2.253 $\pm$ 0.097	0.544 $\pm$ 0.088	5.83 $\pm$ 0.96
6	0.2533 $\pm$ 0.00089	2.96 $\pm$ 0.49	0.71 $\pm$ 0.16	2.82 $\pm$ 0.62
6	0.461 $\pm$ 0.0091	3.60 $\pm$ 0.36	0.87 $\pm$ 0.15	1.89 $\pm$ 0.33
6	0.741 $\pm$ 0.0032	4.35 $\pm$ 0.56	1.05 $\pm$ 0.20	1.42 $\pm$ 0.27
14	0.998 $\pm$ 0.0016	4.14 $\pm$ 0.50	1.00 $\pm$ 0.17	1.00 $\pm$ 0.17

<sup>a</sup>*k* = 2. <sup>b</sup>95.45% confidence interval for *N*-1 degrees of freedom from Student's *t* distribution.

**Table 4. Mean Nicotine data  $\pm$  Expanded Uncertainty for Nicotine (1) + 1,2-Propanediol (2) at 298.15 K, Number of Measurements  $N$ , Mole Fraction  $x_1$ , Partial Pressure  $\bar{p}$ , Activity  $\bar{a}_1$ , and Activity Coefficient  $\bar{\gamma}_1$** 

$N$	$x_1$	$\bar{p}_1/\text{Pa}$	$\bar{a}_1$	$\bar{\gamma}_1$
4	0.00506 $\pm$ 0.000019 <sup>a</sup>	0.0275 $\pm$ 0.0043 <sup>b</sup>	0.00744 $\pm$ 0.00086 <sup>b</sup>	1.49 $\pm$ 0.18 <sup>b</sup>
5	0.02015 $\pm$ 0.000075	0.1106 $\pm$ 0.0079	0.0298 $\pm$ 0.0030	1.49 $\pm$ 0.15
5	0.0504 $\pm$ 0.00019	0.261 $\pm$ 0.032	0.0704 $\pm$ 0.0074	1.41 $\pm$ 0.15
6	0.0999 $\pm$ 0.00034	0.448 $\pm$ 0.042	0.121 $\pm$ 0.012	1.21 $\pm$ 0.12
6	0.2486 $\pm$ 0.00091	1.164 $\pm$ 0.059	0.314 $\pm$ 0.034	1.25 $\pm$ 0.14
5	0.498 $\pm$ 0.0020	1.91 $\pm$ 0.40	0.51 $\pm$ 0.21	1.03 $\pm$ 0.43
5	0.747 $\pm$ 0.0028	2.87 $\pm$ 0.25	0.77 $\pm$ 0.21	1.03 $\pm$ 0.28
10	0.999 $\pm$ 0.0038	3.714 $\pm$ 0.081	1.00 $\pm$ 0.11	1.00 $\pm$ 0.11

<sup>a</sup> $k = 2$ . <sup>b</sup>95.45% confidence interval for  $N-1$  degrees of freedom from Student's  $t$  distribution.

uncertainty in Table 1. The expanded uncertainties for the partial pressure, activity, and activity coefficient are for 95.45% confidence interval (equivalent to  $k = 2$ ) for  $N-1$  degrees of freedom from Student's  $t$  distribution (Table 2, ref 12).

The mean results vs nicotine mole fraction along with the expanded uncertainty are contained in Table 3 for the nicotine/glycerol binary mixtures and Table 4 for the nicotine/1,2-propanediol binary mixtures.

Both solvent systems had a positive deviation of nicotine partial pressure from ideal (Raoult's law) behavior, but the deviation of the glycerol mixtures was much greater than that of the 1,2-propanediol mixtures as shown by the nicotine activity coefficients. For mole fractions of about 0.02 or less, the glycerol mixtures had nicotine activity coefficients of 11, while that for the 1,2-propanediol mixtures was 1.5. This indicates that glycerol, with hydroxyl units on all three carbons, had a much greater affinity for other glycerol molecules than for nicotine molecules. The behavior of nicotine in glycerol is very similar to that of nicotine in water. Banyasz<sup>13</sup> (Table 3) lists a nicotine activity coefficient of 13 for 0.016 mole fraction nicotine in water. On the other hand, 1,2-propanediol has both polar and nonpolar sites, as does nicotine, and the behavior of the mixture becomes more ideal. The self-affinity of the solvent molecules is also indicated by the vapor pressure of 1,2-propanediol and glycerol at 298.15 K of 17 Pa<sup>14</sup> and 0.022 Pa,<sup>15</sup> respectively. Glycerol vapor pressure, with a slightly higher molecular weight, is 3 orders of magnitude less than 1,2-propanediol.

The nicotine vapor pressure differed between the two studies, with the vapor pressure being higher and the uncertainty being much higher in the glycerol experiment. A two-sample  $t$ -test assuming an unequal variance was used to compare the replicate results from both experiments. The difference was significant at the 95% confidence interval with a  $p$ -value = 0.0791.

The lower uncertainty in the 1,2-propanediol experiment is possibly due to the increase in headspace volume from 8 to 20 mL sampled through the XAD-4 cartridge. At the beginning of the 1,2-propanediol experiment, a 10 mL gas-tight syringe with a polypropylene Luer lock to tubing adapter was used to sample 5 to 8 mL of headspace through the XAD-4 cartridge, and it appeared as if there was an unacceptably large bimodal distribution of results (see S2 Supporting Information Replicate Data). Four of the headspace replicates centered on 2.4 Pa, and three of the replicates centered on 3.2 Pa vapor pressure (uncorrected for temperature). A 100 mL gas-tight syringe was used to sample 20 to 30 mL, and the relative standard deviation in vapor pressure (not temperature corrected) decreased from 0.156 to 0.036. It is also possible

that the 10 mL syringe had problems with the FTFE seals or even the polypropylene Luer lock to tubing adapter. The 100 mL syringe used a removable needle (Hamilton RN) attachment with the needle cut short and permanently inserted through a silicone stopper attached to the tubing shown on the right side of Figure 1. Whether it was the syringe, the increased sampling volume, or both that reduced the variability, the 100 mL gas-tight syringe with 20 to 30 mL headspace sampling was used for the remainder of the 1,2-propanediol experiment. The results using the 10 mL gas-tight syringe with 8 mL headspace sampling were not used but are shown in S2 Supporting Information Replicate Data. Another possible reason for the lower uncertainty for the 1,2-propanediol experiment compared to the glycerol experiment was the temperature control of the environmental chamber with a measured range of 297.95–298.25 K. The relatively stable basement office used for the glycerol experiment had a measured temperature range of 296.25–297.85 K. The within day air temperature variation while sampling headspace was similar for both locations. Only 1 sampling day showed 0.3 K variation with the majority being 0.0 to 0.1 K variation. The temperature correction for the glycerol experimental results accounted for 1/2 of the vapor pressure difference in nicotine vapor pressure from the 1,2-propanediol experimental results.

**Comparison to Values in the Literature: Nicotine-Saturated Vapor Pressure.** Only five published studies were found that have measured nicotine vapor pressures from 293 to 298 K.<sup>3,8,9,16,17</sup> These are listed in Table 5. The authors (ref 3) published nicotine vapor pressure at 296 K when reporting on the nicotine activity in tobacco using very similar methodology to this study. This was adjusted to 298 K using the methodology described in S1 Supporting Information on

**Table 5. Comparison of Measured Nicotine Vapor Pressure at 298.15 K to Values from the Literature, Number of points  $N$ , Mean Vapor Pressure  $\bar{p}$ /Pa, and Standard Uncertainty of Mean  $u(\bar{p})$ /Pa**

$N$	$\bar{p}$ /Pa	$u(\bar{p})$ /Pa	reference
2	2.75	0.064	Harlin and Hixon <sup>8</sup>
10	5.67	0.040	Norton and Bigelow <sup>9</sup>
2	3.86	0.37	Walker et al. <sup>16</sup>
correlation <sup>a</sup>	3.64		Lipkind et al. <sup>17</sup>
21	3.52	0.10	St. Charles and Moldoveanu <sup>3</sup>
14	4.14	0.22	this study <sup>b</sup>
10	3.714	0.029	this study <sup>c</sup>

<sup>a</sup>Cubic equation as  $f(T/K)^{-1}$ . <sup>b</sup>Glycerol experiment. <sup>c</sup>1,2-Propanediol experiment.

Table 6. Calculated Nicotine Vapor Pressures at 298.15 K from the Literature

temperature range	$p/\text{Pa}$	equation used	reference	other data utilized
(293–518) K	15	$\log(p/\text{mm Hg}) = 8.0935 - 2695.5 (T/\text{K})^{-1}$	Young and Nelson <sup>18</sup>	measured <sup>8</sup>
(298–523) K	3.98	Antoine equation	Lencka <sup>19</sup>	18
(300–520) K	5.29	Wagner equation	Basařová <sup>20</sup>	19
(298–523) K	5.38	$\log(p/\text{mm Hg}) = 43.745 - 4929 (T/\text{K})^{-1} - 11.561 \cdot \log T/\text{K}$	Banyasz <sup>13</sup> eq 2	9, 18, 21
(298–323) K	5.43	$\log C/\text{g-cc}^{-1} = 4.47 - 3260 \cdot (T/\text{K})^{-1}$ and ideal gas law	Banyasz <sup>13</sup> eq 3	9, 18, 21
(448–613) K	6	Antoine equation	Siitsman <sup>22</sup>	extrapolation
(288–523) K	2.5	Antoine equation	Ray <sup>23</sup>	measured <sup>8</sup>
(293–519) K	3.4	$\log(p/\text{mm Hg}) = 172.8 - 9492 \cdot (T/\text{K})^{-1} - 60.6 \times \log T/\text{K} + 0.0248 \cdot T/\text{K}$	Boldridge <sup>24</sup>	measured <sup>8,18</sup>

<sup>a</sup>References used were not stated.

Uncertainty. Harlan and Hixon<sup>8</sup> published the first paper on nicotine vapor in 1928 with nicotine air saturation concentrations at 298 K, which allowed nicotine vapor pressure to be calculated. Norton et al.<sup>9</sup> published a paper in 1945 with vapor pressure at 298 K. They were very rigorous in their vacuum distillation purification of five different sources of nicotine as well as with the temperature control stated to be  $\pm 0.02$  K. Walker et al.<sup>16</sup> used nicotine-saturated air diluted with clean air at 293 K as an odor stimulant in an olfactometer. They measured the nicotine concentration for several dilution levels and extrapolated to zero dilution to compare with literature values. This was close enough to 298 K to allow temperature adjustment of vapor pressure using the Clausius–Clapeyron equation as described in S1 Supporting Information on Uncertainty. Lipkind et al.<sup>17</sup> used correlation gas chromatography to develop a cubic equation as a function of  $(T/\text{K})^{-1}$  which covered the range of 298–500 K.

Other authors have combined data from published studies alone or combined with measured data to predict vapor pressure at 298 K. These are shown in Table 6. Young and Nelson<sup>18</sup> measured nicotine vapor pressure over the range of 334–521 K and combined their measurements with those of Harlan and Hixon<sup>8</sup> to extend the range to lower temperatures graphically. Pressure/temperature data were read at 10 K intervals from an enlargement of the graph to develop a predictive equation although the equation tended to overestimate the data by a factor of 5 at the lowest temperatures (303 and 313 K). There was an observed vapor pressure value listed at 303 K, but it was a data point taken from Harlan and Hixon,<sup>8</sup> so it was not relisted in Table 5. Lenka et al.<sup>19</sup> recalculated data and calculated an Antoine equation from the data of Young and Nelson,<sup>18</sup> which was a needed improvement considering the overestimation at lower temperatures of the original equation. Basařová et al.<sup>20</sup> used the data of Lenka<sup>19</sup> to express the temperature dependence of saturated vapor pressure in the form of a Wagner equation. Banyasz<sup>13</sup> used the data of Norton et al.,<sup>9</sup> Young and Nelson,<sup>18</sup> and Gorbachev<sup>21</sup> to develop two equations for the temperature dependence of nicotine vapor pressure. One equation (eq 2) was for the temperature range of 298–523 K, and the other equation (eq 3) was for the temperature range of 298–393 K. Siitsman et al.<sup>22</sup> used the Antoine equation developed from their experimental range of 448–618 K to estimate a vapor pressure of nicotine at 298.15 K. Siitsman et al. also reported extrapolated values at 298 K calculated by Norton et al.<sup>9</sup> using data from Gorbachev<sup>21</sup> and Young and Nelson.<sup>18</sup> Two other documents containing nicotine vapor pressure data were found at the Truth Tobacco Industry Documents database maintained by the University of California, San Francisco. One document by Ray<sup>23</sup> contained a table of measured vapor

pressure data combined with literature data although the table did not differentiate which were measured and which were literature data. An Antoine equation was generated and compared graphically to the measured data. Another document by Boldridge<sup>24</sup> provides measured vapor pressure from 293 to 373 K combined with the data of Harlan and Hixon<sup>8</sup> and Young and Nelson<sup>18</sup> to give an equation, which predicts nicotine vapor pressure over the range of 288–523 K.

**Henry's Law Volatility Constant and Infinite Dilution Activity Coefficient.** Henry's law volatility constant (defined via partial pressure and liquid phase amount fraction),  $H_V^{px}$ , is the partial pressure  $p/\text{Pa}$  of a species divided by the amount fraction  $x$  of that species in the liquid phase under equilibrium conditions at infinite dilution<sup>25</sup>

$$H_V^{px} = \lim_{x \rightarrow 0} \frac{p/\text{Pa}}{x} \quad (1)$$

To determine the Henry volatility constant, the slope ( $dp/dx$ ) at zero mole fraction was determined by fitting the partial pressure,  $p$ , for the lower mole fraction,  $x$ , solutions to a polynomial  $p = bx + cx^2$  with the constant set to zero to assure that the slope was determined at zero. In addition, the constant,  $a$ , for the polynomial was not statistically significant with  $p$ -values  $>0.8$  for the coefficient. The slope  $dp/dx = b + 2cx$ , and at  $x = 0$ ,  $H_V^{px} = b$ . To determine the number of data points to use, the polynomial regressions were calculated with the increasing number of data points until a minimum in the standard error for the coefficient was reached (Table 7). Henry's constant for a solute,  $H_i$ , is equal to the saturated

Table 7. Polynomial Regression Results for Henry's Law Volatility Constant,  $H_V^{px}/\text{Pa}$ , and Infinite Dilution Activity Coefficient,  $\Upsilon_1^{\text{inf}}$ , of Nicotine (1) from the Binary Mixtures, Degrees of Freedom  $\nu$ , Standard uncertainty  $u$ , and Expanded Uncertainty  $U$

experiment	glycerol	1,2-propanediol
Polynomial Regression for $H_V^{px}$		
no. of points	7	6
$\nu$	5	4
R squared	0.9998	0.9994
$H_V^{px}/\text{Pa}$ (coefficient b)	51.38	5.26
$u(H_V^{px})/\text{Pa}$	0.69	0.19
$U(H_V^{px})/\text{Pa}$	1.8	0.52
Infinite Dilution Activity Coefficient, $\Upsilon_1^{\text{inf}}$		
$\Upsilon_1^{\text{inf}}$	12.4	1.42
$\nu$ eff	14.6	4.4
$u(\Upsilon_1^{\text{inf}})$	0.681	0.051
$U(\Upsilon_1^{\text{inf}})$	1.5	0.14

vapor pressure of solute  $p_i^{\text{sat}}$  (Pa)  $\times$  the infinite dilution activity coefficient  $\Upsilon_i^{\text{inf}26}$

$$H_i = \Upsilon_i^{\text{inf}} \times p_i^{\text{sat}} \quad (2)$$

$$\Upsilon_i^{\text{inf}} = H_i / (p_i^{\text{sat}})^{-1} \quad (3)$$

The calculations for the uncertainty and effective degrees of freedom were calculated as described in S1 Supporting Information on Uncertainty. The results emphasize the approximate order of magnitude difference in the volatility of nicotine from dilute mixtures with the two different polyols. Glycerol, with hydroxyl units on all carbons, exhibits much stronger hydrogen bonding with other glycerol molecules than with the less polar nicotine molecules, while 1,2-propanediol with one fully protonated carbon is more compatible with nicotine molecules.

## SUMMARY

The equilibrium headspace concentration of nicotine in nitrogen gas was measured by gas chromatography for binary mixtures of nicotine with glycerol and with 1,2-propanediol at temperatures near 298.15 K. The storage temperature ranged from 296.25 to 298.25 K. The nicotine mole fraction ranged from  $0.0015 \pm 0.00010$  to  $0.998 \pm 0.0016$  for the glycerol mixtures and  $0.00506 \pm 0.000019$  to  $0.999 \pm 0.0038$  for the 1,2-propanediol mixtures ( $k = 2$  expanded uncertainty). The headspace concentration was converted to nicotine partial pressure at 298.15 K using the ideal gas law, followed by the Clausius–Clapeyron equation. The nicotine activity for each mixture was calculated from the diluted nicotine partial pressure divided by the undiluted nicotine partial pressure. The nicotine activity coefficient for each mixture was calculated from the nicotine activity divided by the nicotine mole fraction. The Henry's law volatility constant was calculated from a second-order polynomial regression of the partial pressure as a function of mole fraction for the (6 to 7) smallest mole fraction data points. The infinite dilution activity coefficient was calculated by dividing the Henry's law volatility constant by the saturated nicotine vapor pressure of undiluted nicotine. Both solvent systems had a positive deviation of nicotine partial pressure from ideal behavior, but the deviation of the glycerol mixtures was much greater than that of the 1,2-propanediol mixtures. For mole fractions of about 0.02 or less, the glycerol mixtures had nicotine activity coefficients of 11, while that for the 1,2-propanediol mixtures was 1.5. The Henry's law volatility constant and infinite dilution activity coefficient for nicotine from glycerol mixtures were approximately an order of magnitude greater than those from 1,2-propanediol mixtures.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.2c07421>.

Uncertainty of vapor pressure correction to  $T = 298.15$ /K; uncertainty of molecular mass; balance uncertainty in weighing; example of mole fraction and combined uncertainty calculation for the binary mixtures of nicotine and 1,2-propanediol; nicotine calibration standards concentration uncertainty and analytical uncertainty; treatment of the headspace data; combined

uncertainty for the infinite dilution activity coefficient (PDF)

Replicate nicotine data for the nicotine (1)–glycerol (2) binary mixtures; replicate nicotine data for the nicotine (1)–1,2-propanediol (2) binary mixtures; undiluted nicotine vapor pressure results for omitted 10 mL gas-tight syringe/XAD-4 sampling compared 100 mL gas-tight syringe/XAD-4 and in-syringe sampling (PDF)

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

All present work was performed at the Bowman Gray Technical Center of R.J. Reynolds Tobacco Co.

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