

This article was downloaded by: [Centers for Disease Control and Prevention]

On: 28 January 2011

Access details: Access Details: [subscription number 919555898]

Publisher Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Occupational and Environmental Hygiene

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713657996>

Correcting Diacetyl Concentrations from Air Samples Collected with NIOSH Method 2557

Jean Cox-Ganser^a; Gary Ganser^b; Rena Saito^a; Gerald Hobbs^c; Randy Boylstein^a; Warren Hendricks^d; Michael Simmons^d; Mary Eide^d; Greg Kullman^a; Chris Piacitelli^a

^a Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, West Virginia ^b Department of Mathematics, West Virginia University, Morgantown, West Virginia ^c Department of Statistics, West Virginia University, Morgantown, West Virginia ^d Salt Lake Technical Center, Occupational Safety and Health Administration, Sandy, Utah

First published on: 10 January 2011

To cite this Article Cox-Ganser, Jean , Ganser, Gary , Saito, Rena , Hobbs, Gerald , Boylstein, Randy , Hendricks, Warren , Simmons, Michael , Eide, Mary , Kullman, Greg and Piacitelli, Chris(2011) 'Correcting Diacetyl Concentrations from Air Samples Collected with NIOSH Method 2557', Journal of Occupational and Environmental Hygiene, 8: 2, 59 – 70, First published on: 10 January 2011 (iFirst)

To link to this Article: DOI: 10.1080/15459624.2011.540168

URL: <http://dx.doi.org/10.1080/15459624.2011.540168>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Correcting Diacetyl Concentrations from Air Samples Collected with NIOSH Method 2557

Jean Cox-Ganser,¹ Gary Ganser,² Rena Saito,¹ Gerald Hobbs,³
Randy Boylstein,¹ Warren Hendricks,⁴ Michael Simmons,⁴ Mary Eide,⁴
Greg Kullman,¹ and Chris Piacitelli¹

¹Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Morgantown, West Virginia

²Department of Mathematics, West Virginia University, Morgantown, West Virginia

³Department of Statistics, West Virginia University, Morgantown, West Virginia

⁴Salt Lake Technical Center, Occupational Safety and Health Administration, Sandy, Utah

Diacetyl (2,3-butanedione), a diketone chemical used to impart a buttery taste in many flavoring mixtures, has been associated with bronchiolitis obliterans in several industrial settings. For workplace evaluations in 2000–2006, National Institute for Occupational Safety and Health (NIOSH) investigators used NIOSH Method 2557, a sampling and analytical method for airborne diacetyl utilizing carbon molecular sieve sorbent tubes. The method was subsequently suspected to progressively underestimate diacetyl concentrations with increasing sampling site humidity. Since underestimation of worker exposure may lead to overestimation of respiratory health risk in quantitative exposure-effect analyses, correction of the diacetyl concentrations previously reported with Method 2557 is essential. We studied the effects of humidity and sample storage duration on recovery of diacetyl from experimental air samples taken from a dynamically generated controlled test atmosphere that allowed control of diacetyl concentration, temperature, relative humidity, sampling duration, and sampling flow rate. Samples were analyzed with Method 2557, and results were compared with theoretical test atmosphere diacetyl concentration. After fitting nonlinear models to the experimental data, we found that absolute humidity, diacetyl concentration, and days of sample storage prior to extraction affected diacetyl recovery as did sampling flow rate to a much smaller extent. We derived a mathematical correction procedure to more accurately estimate historical workplace diacetyl concentration based on laboratory-reported concentrations of diacetyl using Method 2557, and sample site temperature and relative humidity (to calculate absolute humidity), as well as days of sample storage prior to extraction in the laboratory. With this correction procedure, quantitative risk assessment for diacetyl can proceed using corrected exposure levels for air samples previously collected and analyzed using NIOSH Method 2557 for airborne diacetyl.

Keywords correction equation, diacetyl, humidity effect, sample storage effect

Correspondence to: Jean Cox-Ganser, Field Studies Branch, Division of Respiratory Disease Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 1095 Willowdale Road, MS 2800, Morgantown, WV 26505–2888; e-mail: jjc8@cdc.gov.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health or Occupational Safety and Health Administration.

INTRODUCTION

Diacetyl (2,3-butanedione, CAS no. 431–03–8), a diketone chemical used to impart a buttery taste in many flavoring mixtures, has been associated with severe respiratory disease in several different occupational settings, including microwave popcorn manufacturing, flavoring production, and diacetyl manufacturing.^(1–3) Laboratory animal studies have documented that diacetyl alone has toxic properties that are similar to the effects of exposure to diacetyl-containing artificial butter flavoring mixtures.^(4,5) The Occupational Safety and Health Administration (OSHA) is in the process of rulemaking on occupational exposure to diacetyl.

National Institute for Occupational Safety and Health (NIOSH) researchers developed and published an analytical method, NIOSH Method 2557, to measure airborne diacetyl in the workplace.^(6,7) This method specifies air sample collection through carbon molecular sieve (CMS) sorbent tubes, followed by extraction with acetone/methanol (99:1) and analysis by gas chromatography with flame ionization detection (GC/FID) within 7 days of sampling. Subsequent to the use of this sampling method in several workplace investigations, NIOSH researchers found that the method appeared to progressively

underestimate diacetyl concentrations with increasing sampling site humidity as compared with OSHA Method PV2118.⁽⁸⁾ Silica gel is used as the collection medium in the OSHA method.⁽⁹⁾ NIOSH Method 2557 should not be used to measure airborne diacetyl in future studies.

We studied the effect of humidity on measured diacetyl air concentrations using NIOSH Method 2557 with the aim of developing a means for mathematically correcting previously obtained measurements of airborne diacetyl. In addition, we investigated sample storage stability over time because we were aware that some previously obtained field samples had been analyzed beyond the method's specified 7-day maximum storage duration.

METHODS

Protocol

The initial objective of our experiments was to determine if sampling site humidity affects diacetyl recovery in air samples and, if so, to develop a mathematical procedure to correct existing diacetyl air sampling data from previous workplace studies for those effects. NIOSH and OSHA investigators conducted a total of 6 weeks of tests during five visits by NIOSH investigators to the OSHA Salt Lake Technical Center (SLTC) laboratory. During the first week of tests, we started to investigate the effect of humidity and sampling flow rate, as well as the homogeneity of diacetyl mixing in the dynamically generated controlled test atmosphere. During the second and third weeks, we investigated effects of temperature, sampling duration, sampling flow rate, and test atmosphere diacetyl concentration on diacetyl recovery.

Based on results of the first 3 weeks of tests, during the following 2-week test period, we ran tests to further evaluate the effect of test atmosphere diacetyl concentration. In addition, during that 2-week test period we studied sample storage stability using a single test atmosphere diacetyl concentration. Based on the sample storage stability results, we further evaluated the test atmosphere diacetyl concentration effect during a final week of tests. Since we found an effect of sample storage duration on diacetyl recovery, which was dependent on both humidity and test atmosphere diacetyl concentration, the primary objective was extended to include this effect in the mathematical correction procedure.

During each of the five visits, we also collected a number of samples using OSHA Method PV2118 (OSHA 1013⁽¹⁰⁾ was used once it became available) to compare with test atmosphere diacetyl concentration.

Test Atmosphere Generation

Test atmospheres of diacetyl were generated at the OSHA SLTC laboratory by pumping an aqueous diacetyl solution (approximately 1 to 100% diacetyl depending on target concentration), using a syringe pump (Series D; Teledyne Isco Inc., Lincoln, Neb.), through a short length of 0.53 mm diameter uncoated fused silica capillary tubing into a vapor generator where it was heated and evaporated into a dilution

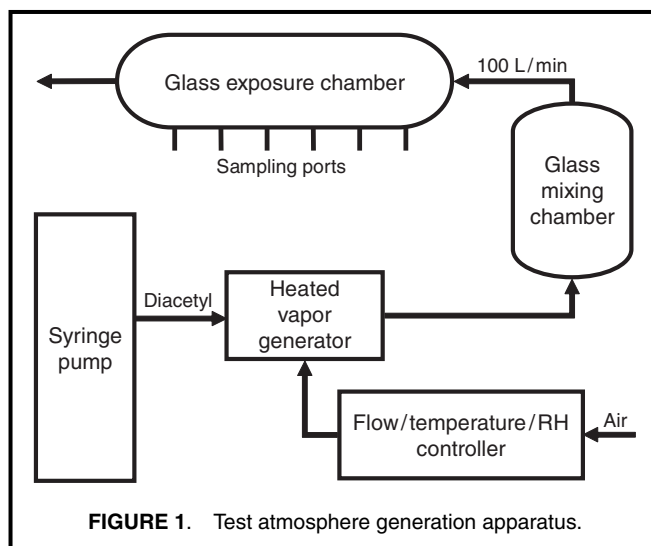


FIGURE 1. Test atmosphere generation apparatus.

airstream (Figure 1). The vapor generator, a 20 cm length of 3 cm diameter glass tubing with a side port for introduction of the capillary tubing, was wrapped with heating tape to evaporate the solution. Humidity, temperature, and volume of the dilution stream of air were regulated by use of a flow-temperature-humidity control system (Model HCS-401; Miller-Nelson Instruments Inc., Pleasanton, Calif.).

The diacetyl-laden air passed from the vapor generator into a glass mixing chamber (76 cm length \times 15 cm diameter) and then into a glass exposure chamber (76 cm length \times 8 cm diameter). Eighteen evenly spaced glass tube sampling ports extended from the exposure chamber: nine from the bottom and nine from a side. The temperature and relative humidity were measured at the exit of the exposure chamber with a digital thermo-hygrometer (Model RH-411; Omega Engineering, Inc., Stamford, Conn.). The test atmosphere generation apparatus was located in a walk-in hood. Theoretical test atmosphere concentrations of diacetyl were derived using mass flow calculations. These calculations used syringe pump flow rate, chamber airflow rate, and diacetyl concentration in the aqueous solution.

Sampling Procedure

CMS sorbent tubes (Anasorb CMS 226-121; SKC, Eighty Four, Pa.) and pairs (in series) of SKC Model 226-183 silica gel sorbent tubes were attached to the sampling ports, and the test atmosphere was pulled via vacuum through the sorbent tubes with sampling flow rate controlled by adjustable orifices. For each test, flow through each sorbent tube was pre- and post-calibrated with a flowmeter (Model 4100; TSI, Inc., Shoreview, Minn.). After sampling, the sorbent tubes were immediately capped, wrapped in foil, and placed on ice packs in a cooler along with blank sorbent tubes. The coolers were shipped nightly via express mail to a NIOSH-contracted analytical laboratory, where the sorbent tubes were extracted on arrival on Day 1 after sampling (or later, as directed for a few sets of CMS tubes used for storage stability experiments) and analyzed by GC/FID.

TABLE I. Test Atmosphere Conditions and Sample Numbers

Target Diacetyl Concentration (ppm)	Actual Diacetyl Concentration		Actual AH Range (mg H ₂ O/L air)	Actual RH Range (%)	Actual Temperature Range (°C)	Sampling Duration (hr)	Target Sampling Flow Rate (cc/min)	Number of Samples ^A
	Mean (ppm)	Range (ppm)						
Humidity Test Samples								
0.2	0.23	0.23–0.24	4.69–19.12	21–81	23.9–26.2	4, 8	50, 150	87
0.5	0.58	0.56–0.60	3.51–19.26	17–91	22.6–26.3	2, 4, 8	50, 150	107
1.0	1.1	1.1	6.99–14.92	29–62	25.8–26.0	2	50, 150	41
5.0	5.5	5.0–5.9	3.65–22.50	17–92	22.8–27.0, 31.9–33.8	2, 4, 8	50, 150	373
25	24.8	24.5–25.7	3.57–19.06	16–92	22.4–26.1	2	50, 150	109
Stability Test Samples ^B								
0.5	0.57	0.57–0.58	3.51–18.17	17–91	22.6–23.3	4, 8	50	54
5.0	5.6	5.6–5.7	3.65–18.67	17–92	22.8–25.7	2	50	107
25	25.0	24.9–25.1	3.57–18.66	18–92	22.4–22.8	2	50	53

^ANumber of samples used in equation development analyses.

^BNine each of the 0.5 and 25 ppm samples and 18 of the 5.0 ppm samples were used in both humidity and storage stability analyses.

Sampling Test Conditions

Samples were collected between January 2008 and December 2009 during four 1-week periods and one 2-week period of tests. We collected a total of 964 CMS tube samples during 80 tests, with relative humidity (RH) levels ranging from 16 to 92% and temperatures of 22.4 to 33.8°C giving absolute humidity (AH) levels ranging from 3.5 to 22.5 mg H₂O/L air and with diacetyl concentrations ranging from 0.23 to 25.7 ppm. Samples were collected over 2, 4, or 8 hr to test for differences in diacetyl recovery due to sampling duration or because of limit of detection (LOD) concerns during tests at low diacetyl concentrations. Samples were collected using sampling flow rates of 50 or 150 cc/min to investigate any effect on diacetyl recovery associated with differences in sampling flow rate. The test atmosphere conditions and sample numbers are summarized in Table I.

Over the five visits, we collected 134 silica gel samples at a flow rate of 50 cc/min during 43 of the 2-hr tests. These samples were collected with an AH range of 3.57 to 22.50 mg H₂O/L air and diacetyl concentrations from 0.56 to 25.7 ppm.

Sample Storage Stability Tests

In total, storage stability of diacetyl both in the sampling tubes (in-tube) and after extraction from the tubes was investigated using 214 samples (Table I). In the first set of experimental conditions, six sets of triplicate samples were collected at 50 cc/min from a 5.7 ppm diacetyl test atmosphere at each of three AH levels: 3.97, 8.59, and 18.67 mg H₂O/L air (RH = 17, 36, and 78%, respectively, at 25.7°C). Samples were sent overnight on ice to the analytical laboratory, where they were extracted and analyzed according to NIOSH Method

2557 for diacetyl 1, 4, 7, 10, 13, and 16 days post-sampling. All samples were stored in a refrigerator until the scheduled day of extraction.

After analysis of the first set of samples on Day 1 post-sampling, the remaining liquid portion (without sorbent material) of each sample was split into two new vials and one stored at room temperature and the other refrigerated. These samples underwent further stability testing via re-analysis 1, 2, 5, and 11 days post-extraction. New septum caps were placed on each vial after each analysis, and freshly prepared standards were used for each re-analysis. To investigate diacetyl concentration effect on storage stability, during the final week of tests, six sets of triplicate samples each were collected from 0.57, 5.6, and 25.0 ppm diacetyl test atmospheres at each of three mean AH levels: 3.6, 8.5, and 18.5 mg H₂O/L air. The samples were extracted and analyzed 1, 4, 7, 10, 16, and 35 days post-sampling. When splitting the samples for the extract storage stability tests, equal portions of the sorbent material were placed into the two vials with the liquid to better simulate treatment of field samples as directed in Method 2557. Re-analysis of these samples was completed on Days 2, 5, 13, and 34 post-extraction.

Data Analyses

Statistical analysis was carried out using JMP V.8 software (SAS Institute, Cary, N.C.). We used the nonlinear modeling platform to calculate the parameter coefficients for the correction model. Details of models used in the JMP nonlinear platform are discussed in the Results section. We used analysis of variance modeling to investigate effects of sampling port position, sampling duration, and sampling flow rate on percent diacetyl recovered.

RESULTS

Of 964 CMS samples collected, 717 were used in humidity effect analyses (extraction Day 1 after sampling), 214 were used in sample storage stability analyses (36 of these were used in both analyses), 42 samples from 1 day of tests were excluded due to excessive analytical laboratory variability (the mean coefficient of variation for that day's tests was 73% as compared with a range of 3% to 23% for other days), 13 were excluded due to greater than 5% changes in sampling flow rate during the tests, 3 were excluded due to errors during sampling, 1 had missing data from the analytical laboratory, 1 outlier (greater than 300% recovery) was excluded, and 9

samples collected at low concentration and high humidity were excluded because of nondetectable diacetyl.

Of the 134 silica gel samples, 121 that had matching CMS sample groups during 39 tests were used in the comparison analyses.

Effects of Sampling Port Position, Sampling Duration, and Sampling Flow Rate

During the first week of tests, homogeneous mixing of diacetyl in the exposure chamber was investigated, and analysis of variance indicated no significant effects of sampling port position on diacetyl recovery. An analysis of variance model using data from the first three laboratory visits ($n = 448$) with

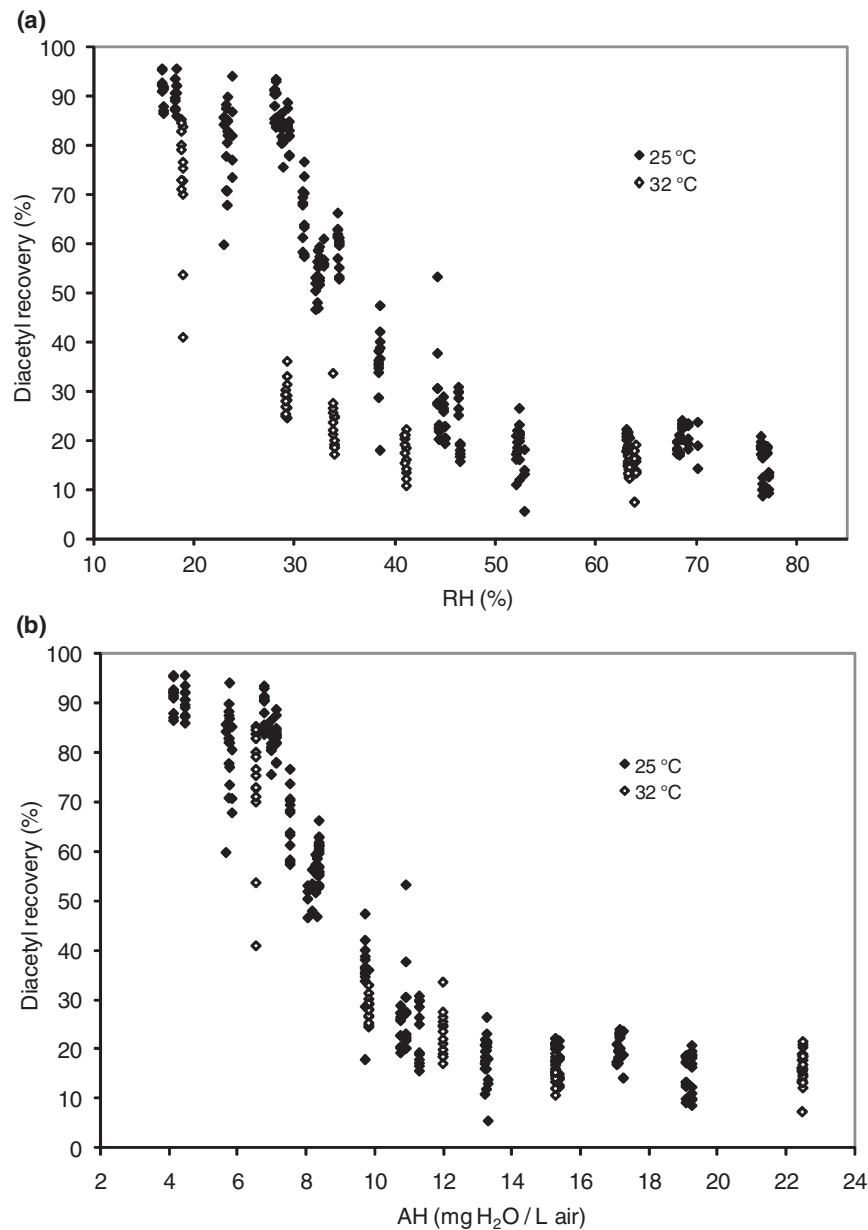


FIGURE 2. Plots for 5.0 ppm target diacetyl concentration data from 25°C and 32°C showing diacetyl recovery in terms of (a) RH and (b) AH.

percent diacetyl recovery as the outcome variable and AH, test atmosphere diacetyl concentration, target sampling flow rate, and sampling duration as the predictor variables indicated a significant ($p = 0.0042$) effect of sampling flow rate, with percent diacetyl recovery being higher for the 150 cc/min sampling flow rate than for 50 cc/min. The magnitude of the effect was not large; the adjusted means (least squares means) for 150 cc/min and 50 cc/min were 44.9 and 40.3% diacetyl recovery, respectively. In this model there was no significant effect for sampling duration ($p = 0.89$), with adjusted means of 42.3, 41.8, and 43.7% diacetyl recovery for sampling durations of 2, 4, and 8 hr, respectively.

Absolute Humidity Effect—Model for Data from Samples Extracted on Day 1 After Sampling

We investigated the effect of temperature on diacetyl recovery by plotting percent diacetyl recovered against either RH (Figure 2a) in % or AH (Figure 2b) in mg H₂O/L air using data from samples collected from a target diacetyl concentration of 5 ppm at target temperatures of 25°C and 32°C. We calculated AH from RH and temperature (T_c) using Eq. 1, which we derived from a National Weather Service approximation for humidity calculations in surface observations.⁽¹¹⁾

$$AH = \frac{13.25 RH \exp\left(\frac{17.67 T_c}{T_c + 243.50}\right)}{T_c + 273.15} \quad (1)$$

As seen in Figure 2, the substantial difference in diacetyl recovery for the two temperatures was removed when humidity was expressed as AH. Thereafter, we modeled the percent recovered diacetyl in terms of AH.

Using the JMP model library of nonlinear functions, we visually determined that the 4-parameter logistic function was suitable to describe the sigmoidal relationship of percent recovered diacetyl with humidity, for samples extracted on Day 1 after sampling. The 4-parameter logistic model has parameters θ_1 , θ_2 , θ_3 , and θ_4 , each of which has graphical meaning. The parameter θ_1 represents the horizontal asymptote on the right-hand side of the graph where humidity is at the highest level; θ_2 represents the horizontal asymptote on the left-hand side of the graph where humidity is at the lowest level; θ_3 is the “slope” or the shape parameter; and θ_4 is the humidity at which 50% of the maximal response is observed. The general equation in terms of the 4-parameter logistic model is:

$$Y = \theta_1 + \frac{\theta_2 - \theta_1}{1 + \exp[\theta_3(X - \theta_4)]} \quad (2)$$

In our models, percent recovered diacetyl was the Y variable, and humidity was the X variable.

We fitted separate 4-parameter logistic models to the data for each of the target test atmosphere diacetyl concentrations (0.2, 0.5, 5.0, and 20 ppm). We had too few levels of AH for the 1.0 ppm test atmosphere diacetyl concentration to adequately fit the 4-parameter logistic model. Figure 3 shows the separate 4-parameter logistic models for percent recovered diacetyl vs. AH as fitted through the overall test data (for both sampling flow rates combined).

Using information from these models, we created one nonlinear model for the data overall; this model took into account differences in the 4-parameter values for the individual logistic models. We found that θ_1 was well approximated ($R^2 = 0.99$) by a linear function of target concentration C_0

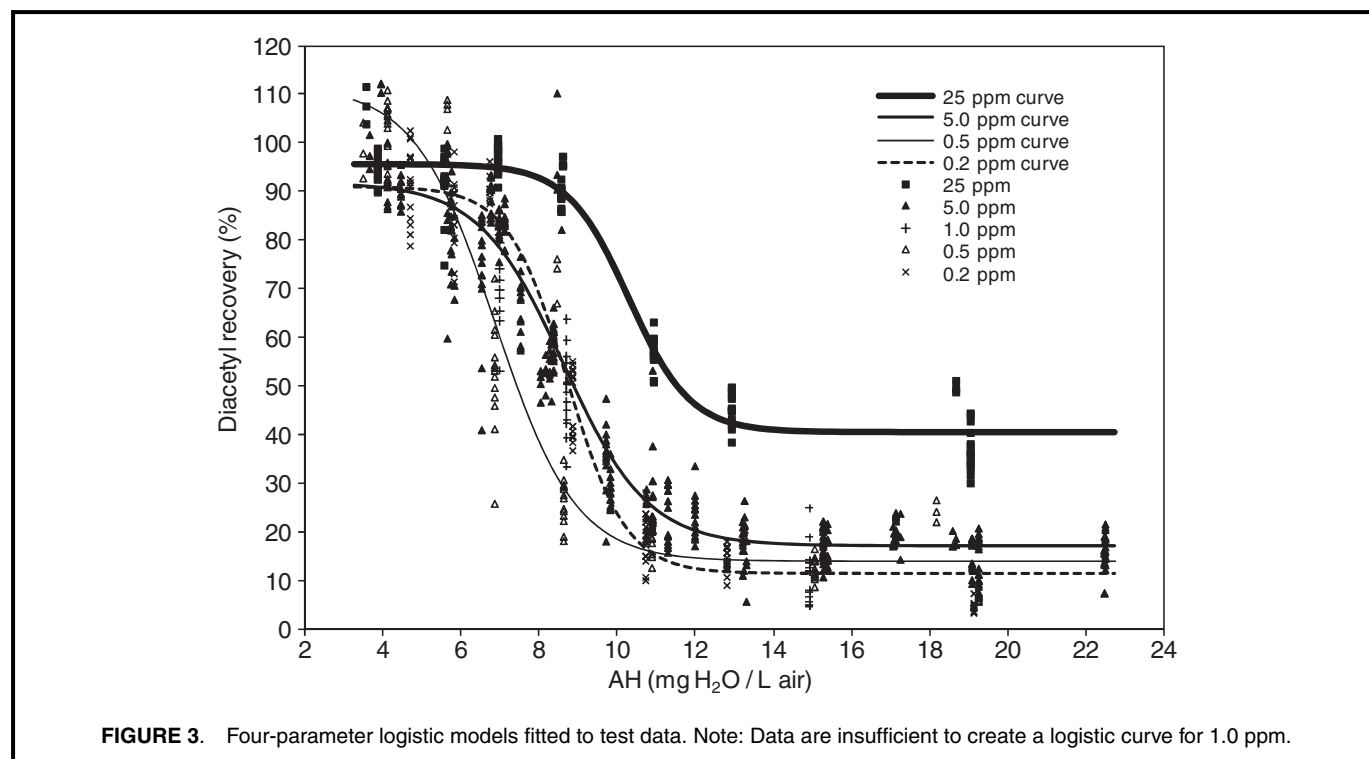


FIGURE 3. Four-parameter logistic models fitted to test data. Note: Data are insufficient to create a logistic curve for 1.0 ppm.

TABLE II. Parameter Coefficients for the Overall Diacetyl Correction Equation and for Two Sampling Flow Rates

Parameter	Overall	Sampling Flow Rate	
		50 cc/min	150 cc/min
b_0	6.91166	5.85971	8.32618
m_1	1.69272	1.70372	1.68917
θ_2	101.31390	101.06329	101.81000
θ_3	0.72068	0.70943	0.73539
θ_4	8.22607	8.18808	8.26746
q	0.05362	0.05362	0.05362
r	0.41384	0.41384	0.41384
s	-0.00589	-0.00589	-0.00589
u	-0.01719	-0.01719	-0.01719
v	0.30359	0.30359	0.30359
w	0.00558	0.00558	0.00558
x	0.00153	0.00153	0.00153
y	0.26802	0.26802	0.26802
z	-0.00002	-0.00002	-0.00002

(i.e., $\theta_1 = b_0 + m_1 C_0$, where b_0 is the intercept and m_1 is the slope) and so substituted this linear function into the 4-parameter logistic function using the values for b_0 and m_1 as starting values for the overall model. Since the other parameters showed variability but no trend with levels of C_0 , we used the arithmetic means of the separate model θ_2 , θ_3 , and θ_4 parameters for the four target test atmosphere diacetyl

concentrations as the overall model starting values for these three parameters. We expressed percent recovered diacetyl ($100c/C_0$, where c is the recovered concentration reported by the laboratory) by rewriting Eq. 2 as follows:

$$\text{Percent recovered diacetyl} = \frac{100c}{C_0} = h(C_0, AH) = b_0 + m_1 C_0 + \frac{\theta_2 - b_0 - m_1 C_0}{1 + \exp[\theta_3(AH - \theta_4)]} \quad (3)$$

We entered this form of the equation (Eq. 3) into the nonlinear fitting platform for a fit through all the data (including the data for a test atmosphere diacetyl concentration of 1.0 ppm). We repeated the fit through the data stratified by sampling flow rate. The final values for the parameters (b_0 , m_1 , θ_2 , θ_3 , and θ_4) both overall and for the two sampling flow rates are given in Table II (the table also contains parameter values for the effect of in-tube storage as described below). The R^2 (amount of total variability in the data accounted for by the model) for the overall model was 0.91. The R^2 for the 150 cc/min model was 0.93, and the R^2 for the 50 cc/min model was 0.90. Figure 4 shows how Eq. 3 describes the pattern of diacetyl recoveries for a range of concentrations both overall and for the two sampling flow rates and illustrates that the effect of sampling flow rate was not large.

Equation 3 predicts that at a concentration of approximately 56 ppm, the diacetyl recovery would be approximately 100% at all AH values (this was similar for the overall model and the 50 and 150 cc/min models). At diacetyl concentrations above these values, the model predicts diacetyl recoveries of higher than 100% across the range of AH values, which does not represent a real-life solution. Predicted diacetyl recoveries

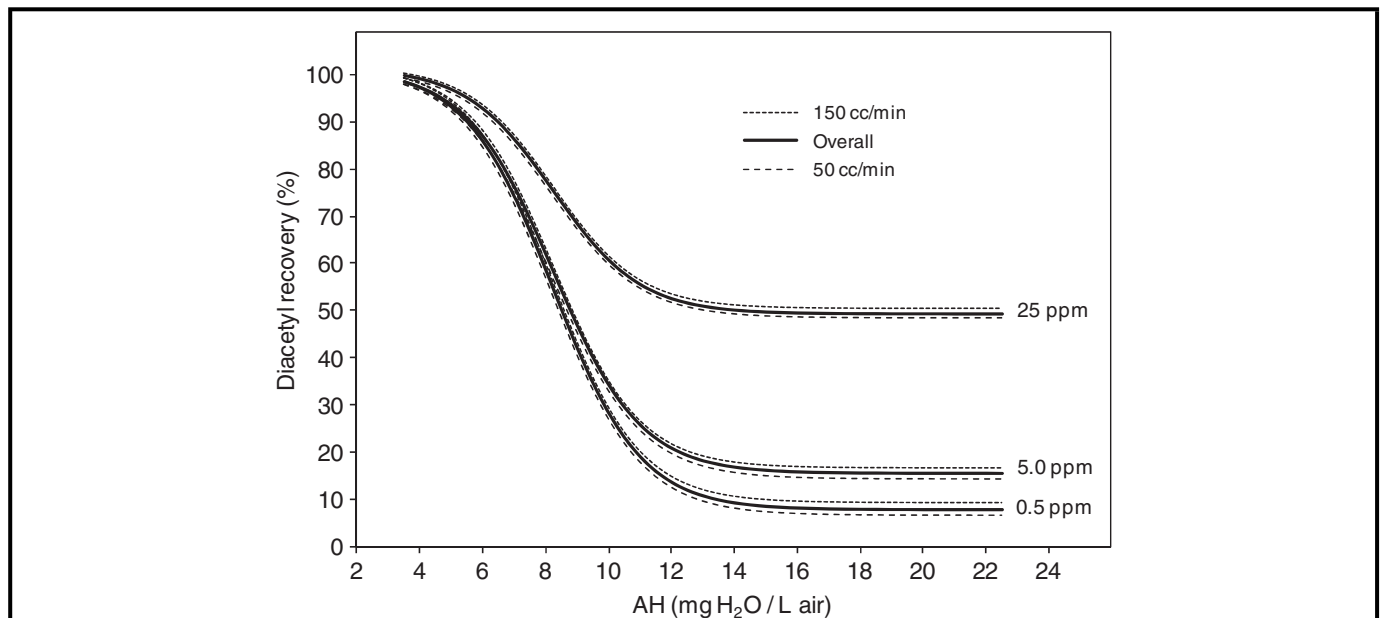
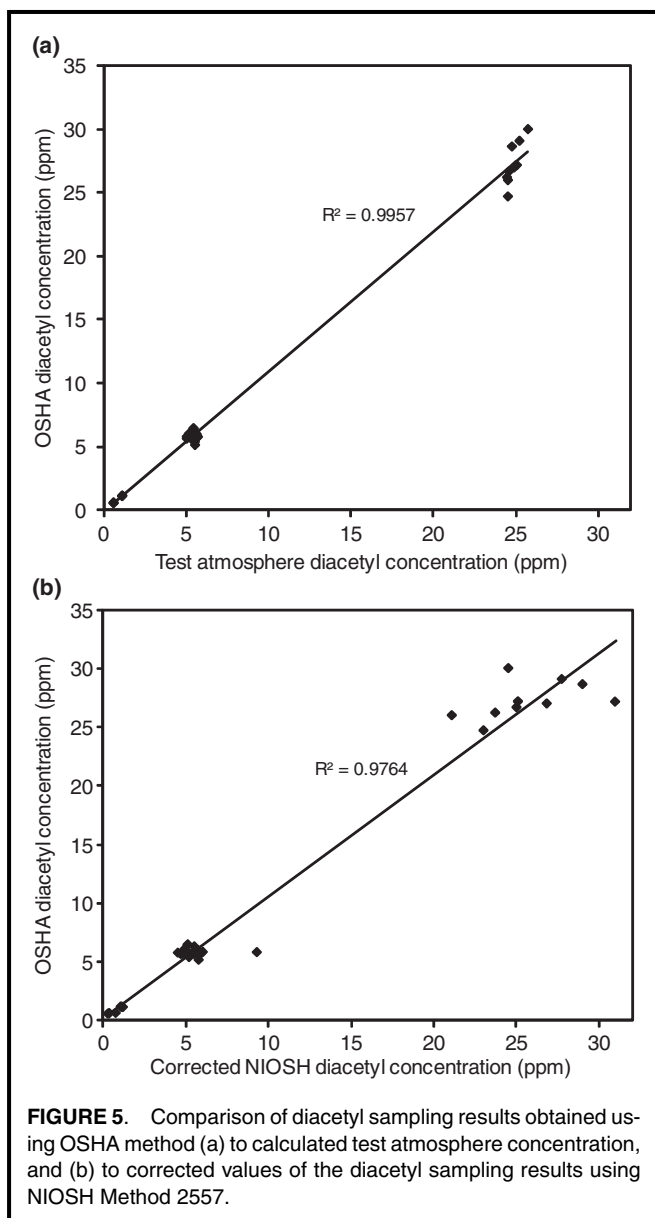


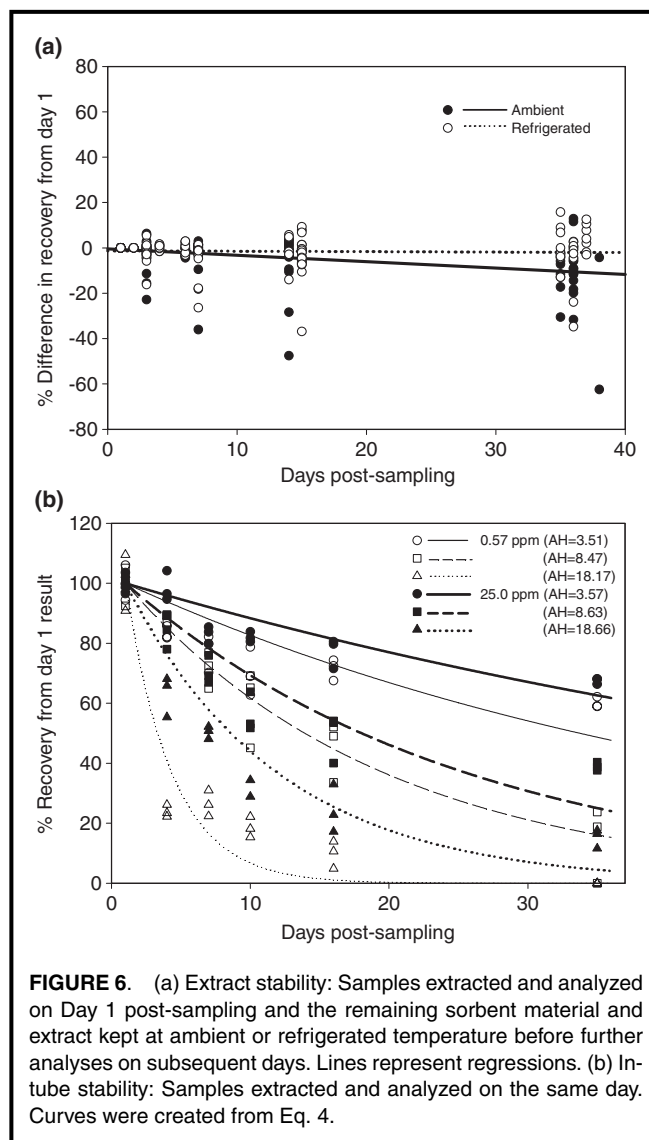
FIGURE 4. Model for data from samples extracted on Day 1 after sampling (Eq. 3) applied at three diacetyl concentrations using parameter coefficients (b_0 , m_1 , θ_2 , θ_3 , θ_4) for the whole data set (overall) and the two sampling flow rates used in the experiment.



from Eq. 3 for very low diacetyl concentrations do not have the same problem since, mathematically, in the limit as the diacetyl concentration goes to zero, the recoveries range from approximately 100% to approximately 7% as AH goes from low to high.

OSHA Silica Gel Sample Results

Diacetyl concentrations from the 121 silica gel samples taken at a number of AH conditions were quite similar to the calculated test atmosphere concentrations (Figure 5a) and were not affected by AH. Using the model (Eq. 3) we calculated the corrected diacetyl concentrations from the matched NIOSH Method 2557 CMS samples, and as shown in Figure 5b, we found a strong linear relationship with the silica gel results.



Model for Effect of In-Tube Storage

Plots of extract storage and in-tube storage stabilities are shown in Figure 6. Samples stored as extracts, either with or without sorbent material, under refrigerated conditions were stable, having less than 2% loss at each of the three AH levels over nearly 40 days of storage (1.4% at 7 days and 1.7% at 38 days). Under ambient conditions, the loss was 2.9% at 7 days and 11.0% at 38 days. In contrast, plots of diacetyl recovered by number of days of in-tube storage (i.e., days from sampling to extraction) indicated decreased recovery over time, with the changes over time showing dependence on both AH and diacetyl concentration. For a given diacetyl concentration, diacetyl losses over time were greater with increasing AH. For a given AH, diacetyl losses over time were greater with decreasing concentration.

To model in-tube storage effects, we used first-order decay functions to estimate decay constants for the 12 combinations of diacetyl concentrations and AH. We normalized the diacetyl recovery data by dividing the diacetyl recovery data by the

mean for recovery on Day 1 after sampling and included (t-1) in the first-order decay functions (see below). The first-order decay model is given by: $Y = (\text{starting amount}) \exp[-k(t-1)]$, where starting amount = 1 for normalized data, t = days from sampling to extraction, and k is the decay constant.

We substituted functions of AH and diacetyl concentration for the decay constants (k). This was accomplished in two steps. In Step 1, we fitted quadratic functions to the k values for the three target diacetyl concentration (0.5 ppm, 5 ppm, and 25 ppm) curves of k vs. AH. In Step 2, we substituted three-parameter first-order decay functions for the coefficients for the intercept, the AH term and the AH² term of the quadratic function based on the diacetyl concentrations. This gave estimates for the nine coefficients (q, r, s, u, v, w, x, y, and z) in the model (as shown below). In a final step, the values of the nine parameters were used as starting values to get a fit of this nonlinear model through the full set of in-tube storage data. The R² for this model was 0.90. The coefficients are given in Table II. The form of the nonlinear model for the effect of in-tube storage was:

$$\text{Normalized recovery} = g(C_0, \text{AH}, t) = \exp[-(f_1(C_0) + f_2(C_0)\text{AH} + f_3(C_0)\text{AH}^2)(t - 1)] \quad (4)$$

where

$$\begin{aligned} f_1(C_0) &= q \exp(-rC_0) + s \\ f_2(C_0) &= u \exp(-vC_0) + w \\ f_3(C_0) &= x \exp(-yC_0) + z \end{aligned}$$

Full Model

The full model can be conceptualized in two steps. First, the AH, the recovered diacetyl concentration (c), and the number of days from sampling to extraction (t) are used to predict the recovered diacetyl concentration on Day 1 of extraction after sampling. Second, this predicted diacetyl value and AH is used to predict the corrected concentration. The full model for the percent of diacetyl recovered is:

$$\text{Percent recovered diacetyl} = \frac{100c}{C_0} = h(C_0, \text{AH})g(C_0, \text{AH}, t) \quad (5)$$

where h is given by Eq. 3 and g is given by Eq. 4.

Since, in practice, the values of c, AH, and t are known, and the value of C₀ is the predicted corrected diacetyl concentration, we solved Eq. 5 for C₀. Using Eqs. 3 and 4, Eq. 5 can be rewritten as:

$$aC_0^2 + bC_0 - \left(\frac{c}{g(C_0, \text{AH}, t)} \right) = 0 \quad (6)$$

where

$$\begin{aligned} a &= m_1/100 + \frac{-m_1/100}{1 + \exp[\theta_3(\text{AH} - \theta_4)]} \\ b &= b_0/100 + \frac{(\theta_2 - b_0)/100}{1 + \exp[\theta_3(\text{AH} - \theta_4)]} \end{aligned}$$

Since this is a nonlinear equation for C₀, it is necessary to use an iterative procedure to find C₀. Initially, Eq. 6 is solved for C₀ using the quadratic formula with the dependence of g on C₀ ignored:

$$C_0 = \frac{-b + \sqrt{b^2 + 4a \left(\frac{c}{g(C_0, \text{AH}, t)} \right)}}{2a} \quad (7)$$

(Note: The other solution for Eq. 6 using the quadratic formula yields a nonphysical negative value for C₀ since a > 0 and b > 0.)

In Eqs. 6 and 7 the value of $\left(\frac{c}{g(C_0, \text{AH}, t)} \right)$ is the estimate for the diacetyl concentration corrected for days to extraction after sampling.

To solve Eq. 7, an iterative procedure is used with the i value C₀⁽ⁱ⁾ used to calculate the (i+1) value C₀⁽ⁱ⁺¹⁾

$$C_0^{(i+1)} = \frac{-b + \sqrt{b^2 + 4a \left(\frac{c}{g(C_0^{(i)}, \text{AH}, t)} \right)}}{2a} \quad (8)$$

It is necessary to start the procedure with an initial C₀ (i.e., C₀⁽¹⁾). We found the procedure robust to the choice of starting value and suggest the use of c (the recovered concentration reported by the laboratory).

The sequence of solutions is then calculated until two consecutive values for C₀ are identical to a chosen number of decimal places (convergence). We tested the model for regions of convergence using theoretical recovered concentrations (c) from 0.001 to 70 ppm, AH from 2 to 25 mg H₂O/L air, and days to extraction from 1 to 36. We found that convergence occurred for all concentrations above 1.0 ppm. For lower concentrations, convergence occurred whenever AH was less than 14.5 mg H₂O/L air and days to extraction were fewer than 9. The region of convergence improved from a concentration of 0.001 to 1.0 ppm. At 1.0 ppm, convergence occurred whenever AH was less than 21 mg H₂O/L air and days to extraction were fewer than 17.

As discussed above, for values of C₀ > 56 ppm, the Day 1 model does not yield real-life solutions. For these values, only the model for effect of days to extraction should be applied and we predict the concentration of diacetyl for Day 1 of extraction after sampling. If the converged value as calculated above is > 56 ppm, use it as the starting value C₀⁽¹⁾ in an iterative procedure using the equation:

$$C_0^{(i+1)} = \frac{c}{g(C_0^{(i)}, \text{AH}, t)} \quad (9)$$

The sequence of solutions is then calculated until two consecutive values for C₀ are identical to a chosen number of decimal places. Figure 7 is a flow diagram of the correction procedure as described above. When corrected diacetyl concentrations fall between 0.23 and 25.7 ppm, which were the lowest and highest diacetyl test atmosphere concentrations

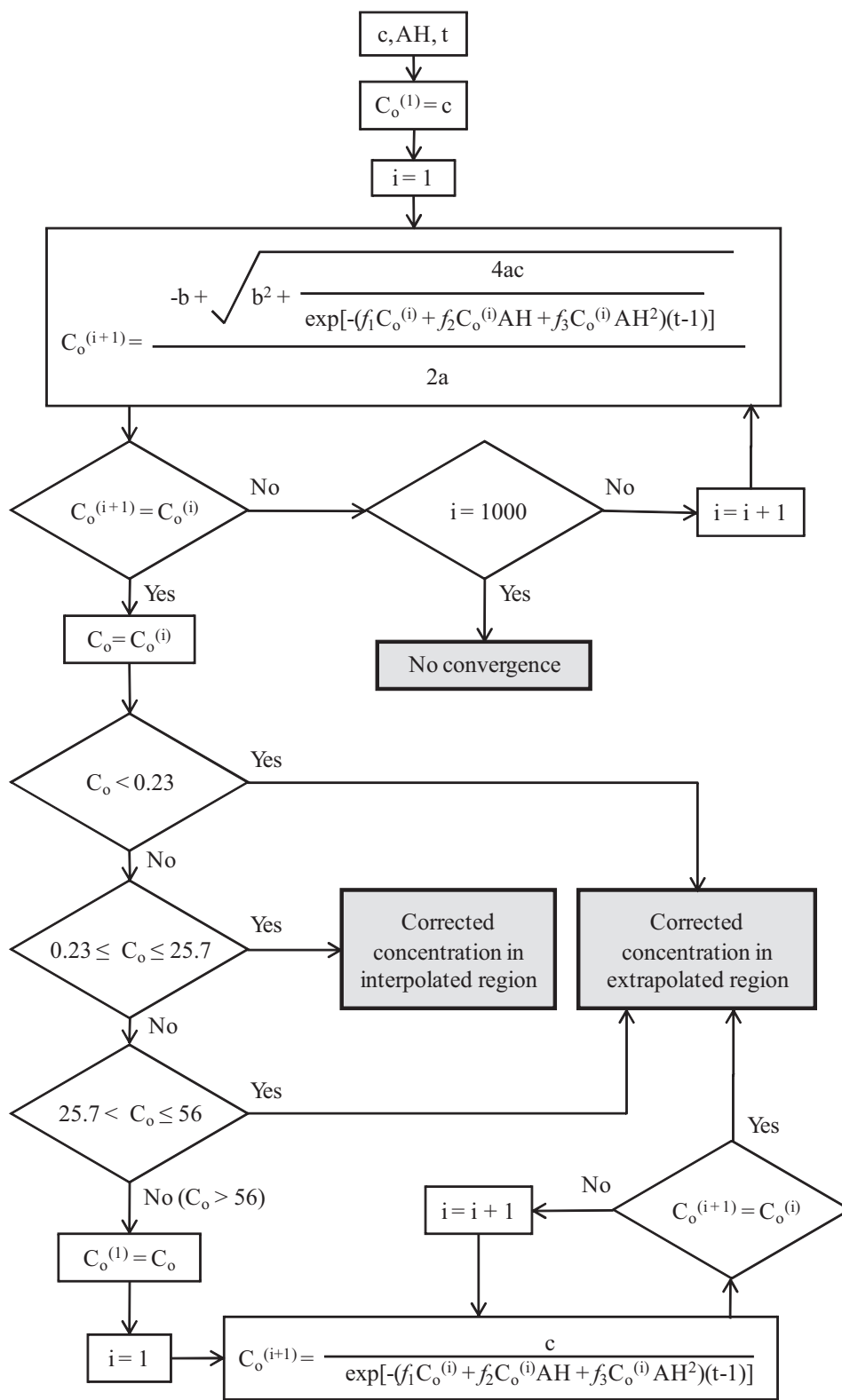


FIGURE 7. Flow diagram of the correction procedure that begins with known values of recovered diacetyl concentration (c), absolute humidity (AH) during sampling, and the number of days from sampling to extraction (t), and ends with the corrected diacetyl concentration in either the interpolated or extrapolated region. As explained in the text, there are some conditions of no convergence.

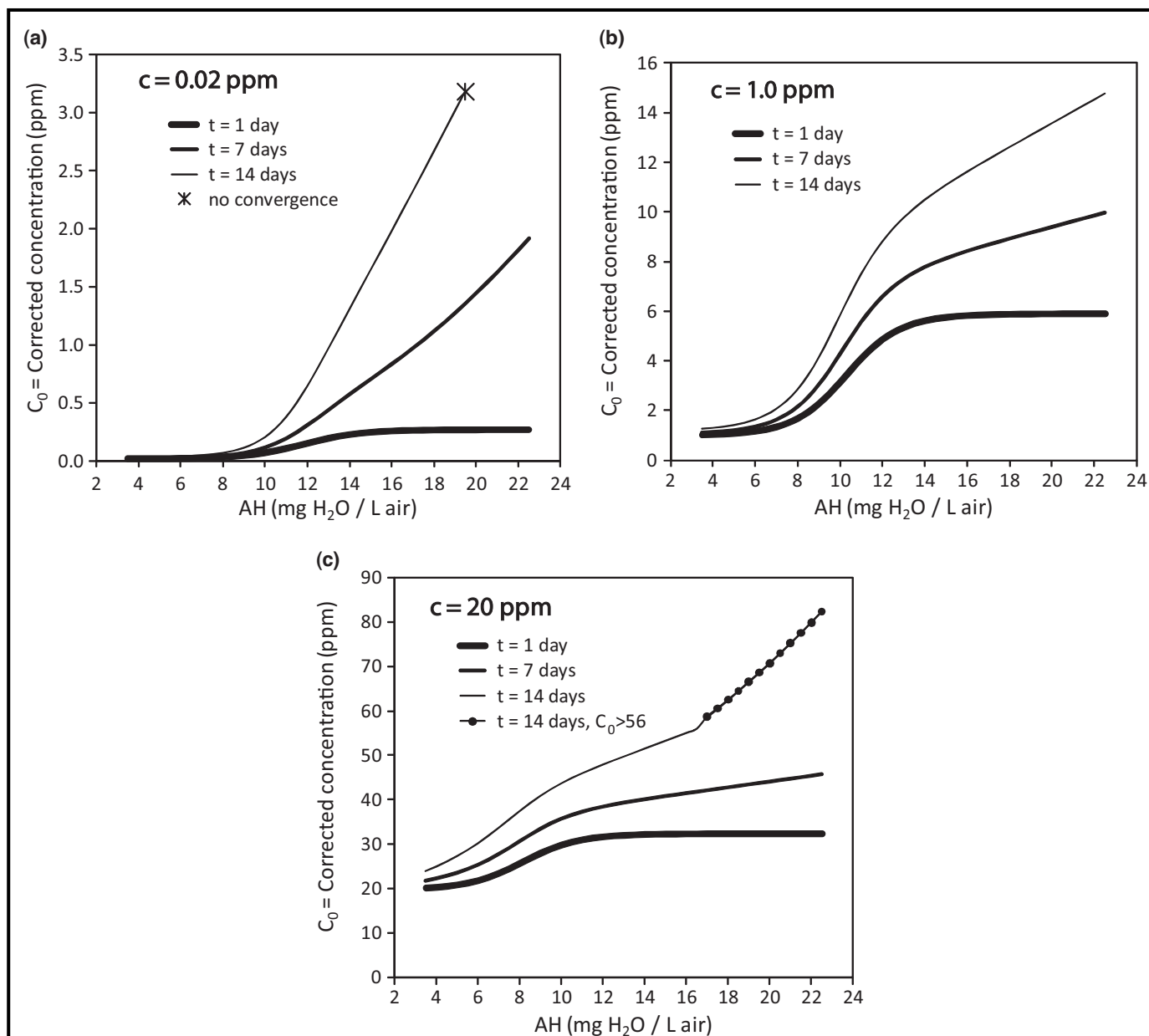


FIGURE 8. Predicted diacetyl concentrations using the model at selected laboratory-reported (recovered) concentrations of (a) 0.02 ppm, (b) 1.0 ppm, and (c) 20 ppm.

used in our experiments, we consider the corrections to be within the interpolated range and have the most confidence in these values. Figure 8 shows diacetyl concentrations predicted by our models for a number of different conditions. We chose three laboratory-reported diacetyl concentrations (c) of 0.02, 1.0, and 20 ppm over a wide range of AH and days from sampling to extraction (t) that should represent possible field conditions. We see that both changes in AH and t substantially affect the value of the corrected concentration. In Figure 8a, we indicate a point where nonconvergence begins for $c = 0.02$ ppm and $AH = 19$ on the 14 days from sampling to extraction curve. In Figure 8c, we indicate a region where $C_0 > 56$, which is only corrected for days from sampling to extraction.

DISCUSSION

From experimental test atmosphere work, we have created a procedure that allows historical diacetyl concentration data from analysis of samples using NIOSH Method 2557 to be corrected to more accurately estimate historical workplace airborne diacetyl concentrations. This correction procedure provides a means for applying these diacetyl concentration estimates in planned quantitative risk assessment relating health effects observed among workers to their diacetyl exposure. In addition, it will allow for a better understanding of historical workplace concentrations of diacetyl that will give insight for exposure control strategies. Use of this correction procedure

requires laboratory-reported concentrations of diacetyl in ppm (samples collected and analyzed using NIOSH Method 2557), temperature and RH (to calculate AH) conditions at the time of sampling, and the number of days from sample collection to sample extraction for analysis. We give overall parameter values for the full model, as well as for sampling flow rates of 50 and 150 cc/min (Table II). Since the effect of sampling flow rate was not large, investigators have the option of using the overall parameter values, especially if their historical data were collected at sampling flow rates other than 50 and 150 cc/min.

A strength of this work was the use of a controlled test atmosphere to simulate historical field survey conditions where airborne diacetyl was sampled together with humid air. By using two target temperatures with similar ranges of RH, we were able to show that both temperature and RH had an effect on diacetyl recovery and that using AH (mg H₂O/L air) was the key variable to connect the correlation between temperature and concentration. This finding extends the work of McKernan and colleagues,⁽⁸⁾ who were unable to separate the effect of temperature and RH in their field-based work. By running tests with several different test atmosphere diacetyl concentrations over a wide range from 0.23 to 25.7 ppm, we were able to observe differences in diacetyl recovery related to theoretical diacetyl concentration. We found a large difference in diacetyl recovery between the test atmosphere diacetyl concentration of about 25 ppm and all the lower concentrations, especially at the higher AH values. The final correction equation predicts that humidity would no longer have an effect on diacetyl recovery at approximately 56 ppm, but we have no empirical data to test this prediction. Corrected diacetyl concentrations that lie outside our test atmosphere range represent extrapolations of the models, and we have less confidence in these concentrations.

We do not suggest the use of the correction procedure with historical concentration data below the limit of detection (LOD), for which concentration may have been estimated (e.g., using LOD/2 or LOD/ $\sqrt{2}$). It is not possible to know if the workplace diacetyl concentration was indeed below the LOD or if the losses due to humidity and days from sampling to extraction in the laboratory caused the sample value to be below the LOD. We did find some regions of AH and days from sampling to extraction for recovered concentrations of 1.0 ppm or less where the full model does not converge; however, such conditions should not occur often in the field.

Our storage stability test findings were contrary to the NIOSH Method 2557 specification of good stability for 7 days from sampling to analysis.⁽⁷⁾ This may have been due to the fact that storage stability tests completed during method development used spiked sampling tubes without using humid air rather than our actively sampled tubes using a test atmosphere. As our results showed, early extraction minimized further sample loss, especially when the samples were refrigerated in accordance with the method, which means that delays in analysis after extraction should not cause ap-

preciable loss. A limitation of our work is that we did not collect in-tube storage data for all the tests to determine the effect of AH on sample recovery, but we did collect data for three target test atmosphere diacetyl concentrations and three target AH values. Thus, we estimated the effect of AH and the effect of in-tube storage on different data sets and combined the two models mathematically to create the final model.

Our correction equations accounted for about 90% of the variability in the experimental data by taking into account the effects of AH, test atmosphere diacetyl concentration, sampling flow rate, and days of in-tube storage. The variability seen in the data at any combination of AH and diacetyl concentration values has a number of sources, including variability in keeping test atmosphere conditions constant, variability in sampling flow rates during the tests, sampling duration differences (although not found significant), and analytical laboratory variability.

Our test atmosphere experiments used no flavoring chemicals besides diacetyl. In field situations, diacetyl may occur together with other chemicals in the air. Any effect of these mixtures on the diacetyl recovery using NIOSH Method 2557 might not be accounted for with our correction procedure.

Comparison between corrected diacetyl concentrations and the results from side-by-side samples taken with OSHA methods indicated a high correlation, which increases our confidence in the applicability of the correction method. Despite the limitations, the correction procedure enables more accurate quantitative risk assessment now under way for regulatory guidance on occupational exposure to diacetyl. Representative exposures in the flavoring manufacturing industry are difficult to assess because of short-duration batch production methods in which hour-to-hour and day-to-day variations in diacetyl exposures is expected in workplaces where scores of different kinds of flavorings are manufactured. Hence, relative stability of diacetyl exposures in microwave popcorn production facilities offers the advantage of less potential for exposure misclassification.

However, without appropriate correction, the systematic underestimation of true diacetyl exposures in the 2000–2006 historical data would lead to overestimation of health risk associated with diacetyl exposure. Accordingly, use of our correction procedure to recalculate the historical exposure estimates from microwave popcorn production facilities previously studied by NIOSH and others will contribute to ongoing efforts to understand the health risk associated with occupational exposure to diacetyl. Our experimental work may also motivate further research exploring the mechanism by which analyte recovery from CMS sorbent may be affected by sampling site humidity for a variety of analytes.

CONCLUSIONS

We have developed a mathematical procedure that allows measurements from historical diacetyl samples collected and analyzed using NIOSH Method 2557, which

may be biased low, to be adjusted for a more accurate exposure assessment. In addition to the historical laboratory-reported diacetyl concentrations, this correction procedure requires data on AH (determined from temperature and RH measurements) during sampling and on the number of days between sample collection and laboratory extraction of the sampling tubes. NIOSH Method 2557 should not be used to measure airborne diacetyl in future studies.

REFERENCES

1. **Kreiss, K., A. Goma, G. Kullman, et al.:** Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N. Engl. J. Med.* 347:330–338 (2002).
2. **Kanwal, R.:** Bronchiolitis obliterans in workers exposed to flavoring chemicals. *Curr. Opin. Pulm. Med.* 14:141–146 (2008).
3. **Van Rooy, F.G., J.M. Rooyackers, M. Prokop, et al.:** Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am. J. Respir. Crit. Care Med.* 176(5):498–504 (2007).
4. **Hubbs, A., L. Battelli, R. Mercer, et al.:** Inhalation toxicity of the flavoring agent, diacetyl (2,3-butanedione), in the upper respiratory tract of rats. *Toxicol. Sci.* 78(Suppl 1): 438–439 (2004).
5. **Hubbs, A.F., W.T. Goldsmith, M.L. Kashon, et al.:** Respiratory toxicologic pathology of inhaled diacetyl in Sprague-Dawley rats. *Toxicol. Pathol.* 36:330–344 (2008).
6. **Pendergrass, S.M.:** Method development for the determination of diacetyl and acetoin at a microwave popcorn plant. *Environ. Sci. Technol.* 38(3):858–861 (2004).
7. “Diacetyl: Method 2557. NIOSH Manual of Analytical Methods (NMAM).” [Online] Available at <http://www.cdc.gov/niosh/nmam/pdfs/2557.pdf> (Accessed May 21, 2010).
8. **McKernan, L.T., E. Burroughs, J. Deddens, et al.:** Analytical performance criteria: Field evaluation of diacetyl sampling and analytical methods. *J. Occup. Environ. Hyg.* 5:D111–D116 (2008).
9. “Diacetyl: Method PV2118. OSHA Sampling and Analytical Methods.” [Online] Available at <http://www.osha.gov/dts/sltc/methods/partial/t-pv2118/t-pv2118.html> (Accessed May 21, 2010).
10. “Diacetyl: Method 1013. OSHA Sampling and Analytical Methods.” [Online] Available at <http://www.osha.gov/dts/sltc/methods/validated/1013/1013.html> (Accessed May 21, 2010).
11. **Bolton, D.:** The computation of equivalent potential temperature. *Mon. Wea. Rev.* 108:1046–1053 (1980).