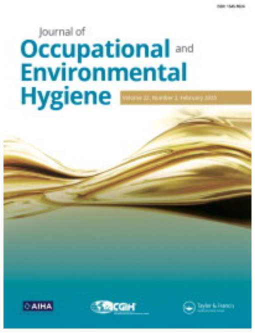

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REPORT

Characterizing dynamic atmosphere generation system performance for analytical method development

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ABSTRACT
A significant portion of the work of developing and validating methods for volatile organic compound (VOC) sampling in workplace atmospheres involves the use of laboratory-generated atmospheres. The sample variability was evaluated from the dynamic atmosphere generation system used for VOC atmosphere generation and sampling. Characterization of the bias and variability of samples was done for a variety of atmospheres containing neat n-heptane and mixtures of VOCs sampled on activated coconut shell charcoal. Estimates of sampling variability ranged from 2% for neat n-heptane to 12% for a component in the 10 VOC mix. Sample variability increased for lower concentration samples and for mixtures of VOCs compared to single component atmospheres. This study can serve as a baseline for future atmosphere sampling experiments evaluating performance at lower concentrations and mixed VOC environments.

KEYWORDS
Air sampling; coconut shell charcoal; sample variability; VOC; volatile organic compound

Introduction

Exposure monitoring methods in occupational environments vary depending on the objective. Sorbent tube sampling has been commonly employed by industrial hygienists and occupational safety scientists to measure volatile organic compound (VOC) concentrations in workplace air (Harper 2000) Sampling occurs when VOCs adsorb to sampling media, such as activated coconut shell charcoal (CSC), from air pumped through sorbent tubes containing sampling media (Ballesta et al. 1992, 1999). CSC has traditionally been the preferred media for measuring many VOCs in workplace air (Harper 2000; NIOSH 2016a, 2016b).

Whenever possible, the use of dynamic atmosphere generation systems (AGSs) is preferred for evaluating the performance of methods and devices designed to measure VOCs in workplace air (BSI 2002; ISO 2004). Factors such as temperature, humidity, and interfering substances can impact the efficiency of VOC collection and recovery using sampling media (Koziel et al. 2004; Allahabady et al. 2022). Dynamic AGSs can maintain and control factors such as temperature, humidity, chemical vapor concentration, and the introduction of interferences. This allows for the evaluation of chemical sampling under conditions that simulate field sampling (Koziel et al. 2004; Allahabady et al. 2022). Static samples, prepared in a bag or bottle, have limitations when evaluating multiple samplers or conditions.

Criteria for the generation of test atmospheres in AGSs include that (1) the system enables simultaneous exposure of multiple samplers to equivalent atmospheres; (2) the system should maintain a continuous referenceable atmosphere for a duration beyond the expected sampling time (usually several hours up to days); and (3) the systems should be capable of producing a range of analyte concentrations, air velocities, temperatures, and humidities (ISO 2003, 2007). Generation of atmospheres that are repeatable, stable,

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and accurate, are characteristics of suitable dynamic AGSs.

The evaluation of bias and variability in the analytical results of generated atmospheres serves as a metric for AGS assessment (Bush and Taylor 1981; Ballesta et al. 1992; Bartley and Irwin 2001). Published evaluations of AGSs and chambers have many designs and purposes, including the use of permeation and diffusion cells (Nano et al. 1987; Worthington and Rey 1991; Ballesta et al. 1999), multi-concentration systems (Dixon et al. 1984), incorporation of automated analyte concentration estimations via mass changes of a diffusion cell (Goelen et al. 1992), and the production of atmospheres of labile chemicals (Wevill and Carpenter 2004; Doepke et al. 2021). Many of the AGSs in published studies focus on the use and evaluation of diffusive samplers (Ballesta et al. 1992; Chung et al. 1999; Bartley and Irwin 2001; Irwin 2001).

Dynamic AGSs operate by continuously introducing analyte into a stream of carrier air (Namieśnik 1984; Woodfin 1984; Naganowska-Nowak et al. 2005). Various techniques have been commonly used for analyte introduction, such as from bottled certified gas mixtures (Gonzalez-Flesca and Frezier 2005), permeation devices, diffusion cells (Miguel and Natusch 1975; Vieira et al. 1991; Martin et al. 2003; Leggett et al. 2007), and vaporization of liquid injections (Ballesta et al. 1992; Cox-Ganser et al. 2011). In this manuscript, the dynamic AGS under evaluation utilized a liquid injection technique. Liquid injection has a significant precedent for method development and is a highly relevant technique for introducing VOCs into dynamic AGSs because it is an easily accessed method for many laboratories. Mixtures of VOCs that are liquid at room temperature are delivered using syringes, and delivery rates via syringe pumps are verifiable via gravimetry. Liquid injection offers advantages in terms of cost, time, and complexity when aiming to achieve satisfactory performance from a dynamic AGS.

The objective of this study was to quantify the variability in the concentration of VOCs sampled from the current AGS for single as well as mixtures of compounds as a function of operating configurations of the AGS. Quantification of uncertainties associated with sampling variability for such AGS systems is important for establishing overall analytical figures of merit of analytical methods during their development and evaluation. The experiments were not aimed at validating the sampling device (sorbent tube samplers in this case) but rather focused on evaluating the sample variability with changes to conditions of sample generation in the dynamic AGS. Furthermore, the variability was compared with historical data on sampling methods to provide contextual information to the observed results.

Materials and methods

A block diagram depicting the dynamic atmosphere generation system that was used is shown in Figure 1. An airflow, temperature, and humidity controller (Miller-Nelson HCS-501, Assay Technologies, Livermore, CA, USA) was used to condition the carrier air for the AGS. The carrier air was routed through a series of tubes inside the environmental chamber (model KB030-AA-DA, Darwin Chambers Co., Saint Louis, MO, USA). The environmental chamber was used to control the temperature of the experiment. The carrier air temperature and humidity were measured with a sensor (S-THB-M002, Onset Computer Corporation, Bourne, MA, USA) inside the environmental chamber. Additionally, temperature, pressure, and flow rate were measured with a flow meter (model 4043, TSI Incorporated, Shoreview, MN, USA) to confirm the readings of the Miller-Nelson controller and environmental chamber. Atmosphere conditions were 50% relative humidity (RH), 20 °C, with a linear air velocity of 0.3 m/s across the samplers as it flowed through the sampling column.

All VOCs and solvents were analytical laboratory grade. Chemicals were placed in gas-tight syringes (Hamilton Company, Reno, NV, USA). A syringe pump (Cole-Parmer, Vernon Hills, IL, USA) was used to control the flow from the syringe. The syringe was connected to polyether ether ketone (PEEK) capillary tubing that was routed to a glass column where the VOCs evaporated in a stream of carrier air. The glass column was connected to a 2-liter glass mixing chamber (DWK Life Sciences LLC, Millville, NJ, USA), then through a three-way valve that directed the atmosphere to a sampling column (Ace Glass, Vineland, NJ, USA) or exhaust. The sampling column was a 2.54 cm (1-inch) diameter by 61 cm (24-inch) length glass tube with 12 sampling ports spaced at 5 cm intervals along the length of the column. The option to direct the air VOC mixture to the exhaust allowed the sampling ports to be opened to load samplers without exposing the samplers or laboratory workers to VOCs. The carrier air containing the VOC vapors exited the sampling column and was directed to a fume hood. The evaporation and sampling components of the systems were contained inside a temperature-controlled environmental chamber. During the generation, a

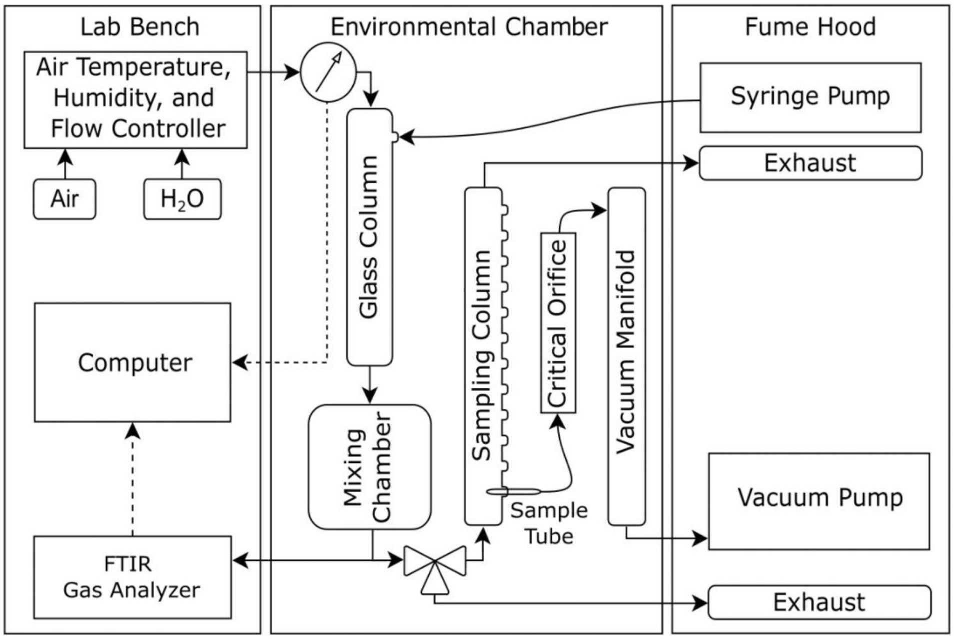

Figure 1. Block diagram of the dynamic atmosphere generation system, where air was conditioned for humidity, temperature, and flow rate. Tubing inside a temperature-controlled environmental chamber where the airflow was combined with liquid analyte from a syringe pump. The analyte-containing air flowed through a sampling column where a portion of it was drawn through a sample tube with the flow controlled by a critical orifice.

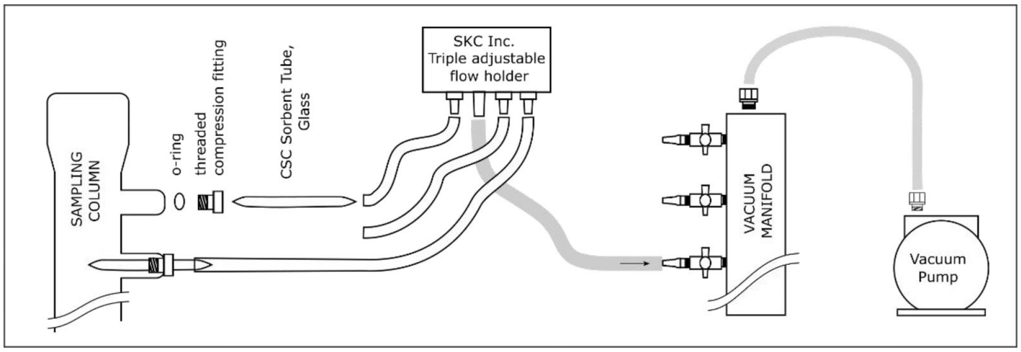

Figure 2. An illustration of the connections between the sampling column, sampling tube (CSC Sorbent), the critical orifices (SKC Inc. Triple), and the vacuum manifold.

Fourier-transform infrared (FTIR) gas analyzer (DX4105, Gasmet Technologies OY, Vantaa, Finland) was used to monitor for stability of VOC concentrations in the generated atmospheres.

Samples of VOC atmospheres were collected on CSC sorbent media (Anasorb CSC, Part # 226-01, Lot #2000, SKC Inc., Eighty Four, PA, USA) in 6 × 70 mm glass tubes with 100 mg/50 mg charcoal. Samples were collected simultaneously in sets of 4 four sorbent tube samplers per run (except where noted). The CSC sampling tube locations were selected from the twelve ports on the sampling column to cover a range of sampling proximities and locations along the sampling column. Sorbent tube samplers were placed in the ports of the sampling column so that the sampler opening was positioned in the center of the sampling column as in Figure 2. A threaded insert was used to compress an O-ring, which created a seal between the sorbent tube and the sampling column. The glass CSC sampler tubes were connected via flexible tubing to critical orifices, and then to a vacuum manifold (M20-250-4-SS, Pneumadyne, Plymouth, MN, USA). The sampling flow rate was controlled by the critical orifices (Triple Adjustable Low Flow Tube Holder, SKC Inc., Eighty Four, PA, USA) connected with a vacuum pump (MZ 2 NT, Vacuubrand Inc., Essex, CT, USA). Flow rates of air through the critical orifices with representative CSC sample tubes inline were measured using a flowmeter (Defender 510 DryCal, Mesa Labs, Lakewood, CO, USA).

The atmospheres of *n*-heptane at 40, 400, and 800 ppmv were approximately 0.5 times the NIOSH recommended exposure limit (REL) of 85 ppmv, the OSHA permissible exposure limit (PEL) of 500 ppmv, and the Immediately Dangerous to Life or Health (IDLH) of 750 ppmv, respectively (NIOSH 2019; OSHA 2021). In a study of *n*-heptane concentrations of 40, 400, and 800 ppmv, the 40 ppmv and 400 ppmv samples were generated and then collected at a rate of 40 mL/min for 120 min, while the 800 ppmv samples were collected at 40 mL/min for 60 min. Six CSC samplers were used to simultaneously sample the atmospheres at each of the generated concentrations.

For the remainder of the experiments, VOC atmospheres were generated and sampled in sets of 16 runs, where 4 CSC samplers were used in each run. Atmospheres containing 40 ppmv n-heptane were generated, then sampled at a rate of 50 mL/min for 30 min on CSC samplers for a 1.5-liter sample volume with replicates of 16 runs of 4 samplers each.

A mixture of benzene, toluene, ethylbenzene, and o-xylene (BTEX) in an equimolar solution was used to generate atmospheres at a target concentration of 0.1 ppmv for each compound, which was sampled at a rate of 100 mL/min for a duration of 1 h. BTEX samples generated at 0.1 ppmv were chosen because of the 0.1 ppmv REL for benzene.

Ten VOCs (mesitylene, benzene, chloroform, ethylbenzene, n-heptane, o-xylene, tetrachloroethylene, p-xylene, toluene, and trichloroethylene) in an equimolar solution were used to generate atmospheres at a target concentration of 0.1 ppmv each. Atmospheres containing the 10 VOC mixture were generated and then sampled at a rate of 50 mL/min for 1 hr, equating to a total of 3-liter sample volumes collected on the CSC sorbent tube.n-Heptane was a compound that was well-behaved in terms of its characteristics during generation and analysis and was featured in the evaluation of samples from our AGS. BTEX was included because it is ubiquitous in many industries and occupational hygiene exposure assessments. In the 10 VOC mixture, the chlorinated compounds were included due to the significant health risk they pose, and recent interest in lowering the exposure limits for those compounds. The inclusion of BTEX and heptane in the 10 VOC set was because it enabled comparison of performance to the previous BTEX and n-heptane generation sets. Mesitylene was included in the 10 VOC set as another data point for alkyl benzene, and it is also relatively common to see it with BTEX when performing exposure assessment where petrochemical exposure is evaluated.

Identical dynamic AGS systems were constructed at two laboratories, designated Laboratory A and Laboratory B. The n-heptane concentration study and the BTEX set were generated and sampled at Laboratory B. The n-heptane 16-run set and the 10 VOC set were generated and sampled at Laboratory A, with each 16-run set done by separate researchers. Analysis of all samples was done at Laboratory B.

The CSC sampling tube media were desorbed in CS_2 and analyzed by gas chromatography-flame ionization detection (GC-FID) with a Phenomenex ZB-1 column (60 m × 0.32 mm ID 1-µm film thickness) following procedures listed in NIOSH 1500 which included a 1 µL injection volume at an initial column temperature of 35 °C which was ramped at 7.5 °C/min (NIOSH 2003b). As part of the quality control done during the analysis of samples, two laboratory control spikes (LCS), and two blind spikes (BS) were spiked on charcoal media and desorbed with 1 mL of CS_2. The LCS, BS, and two sample replicates (SR) from each run were analyzed as duplicate injections. For each of the 16-run sets, target concentration and recovery information for the LCS, BS, and sample replicate injections are provided in the Supplementary information in Table S1. The desorption efficiency as mean bias from the recovery of the two LCSs was used to correct the results of the analysis.

Results and discussion

The data sets were produced using multiple AGSs at different locations, operated by different researchers. The 16-run sets were generated across multiple days, analyte mixtures, and concentrations. Factors that could be related to the results including day and run, and AGS components such as sampling port location and critical orifice, were examined versus sample recovery using multiple-linear-regression analysis. The regression analysis indicated that within a data set, these factors were not uniquely influential upon the recovery or sample variability.

Variability of n-heptane recovery in neat and mixed VOC atmospheres

The recovery of n-heptane as a percent of the target concentration of the generated atmosphere was evaluated for intra-run variability at 40 ppmv, 400 ppmv, and 800 ppmv. The LCS samples had a mean recovery of 99.0% which was used to apply a correction to the sample recovery of all samples in the concentration study. For a target of 40 ppmv ($n = 6$), mean recovery was 103% with a relative standard deviation (RSD) of 6%, for 400 ppmv recovery was 111% with an RSD of 4%, and 800 ppmv recovery was 109% with an RSD of 3%. The RSD of the mean intra-run recovery versus concentration is plotted in Figure 3. The trend demonstrates that lower concentrations resulted in a higher RSD. Data was plotted with the concentration axis in log scale in Figure 3 to illustrate that the relationship between sample concentration and variability is more appropriately portrayed when the x-axis is plotted logarithmically so that it does not imply the extension of the trend line to the y-intercept (Horwitz 1982; Sáez and Rittmann 1992; Zorn et al. 1997).

The RSD of intra-run percent recoveries of 40 ppmv n-heptane from a data set of 16 runs of four samples per run are plotted in Figure 4 where they ranged from 0.24% to 3.95%. The mean of the intra-run RSD was 2.19 ± 1.02% for the 16 runs. There was a high degree of consistency of variability across the sample sets for the 16 runs. The mean intra-run RSD of 2.19% ($n = 64$) was less than the RSD of 6.19% ($n = 6$) at 40 ppmv from the concentration study, and closer to the RSD of 2.47% ($n = 6$) for the 800 ppmv samples in Figure 3.

The experiments for the n-heptane 40 ppmv samples in the concentration study and the 16-run study were done at separate laboratories by separate researchers. The larger RSD of the recovery could have been due to the researcher's experience and technique. There was also a larger sample loading and sampling time (4.8 liters during 120 min) in the concentration study experiments than (1.5 liters during 30 min) in the 16 runs of the 40 ppmv dataset.

In a mixture of 10 VOCs, the intra-run RSD of the percentage of *n*-heptane recovery from 16 runs (Figure 5) ranged from 2.6% to 13.1% with a mean of 8.33 ± 3.4% for the 16 runs. This result was consistent with expectations that a lower concentration would result in larger variability (Taylor et al. 1977). The RSD of the recovery is comprised of several factors including atmosphere variability, analytical variability, and variability in desorption efficiency. The variability of the analytical spikes was relatively consistent for heptane between the 40 ppmv dataset and the 10 VOC mixture dataset (plotted in Figures S1 and S2 in the supplementary information), which indicated that the variability in the atmosphere and desorption efficiency were the larger influences on the differences in variability between the two datasets. Influences contributing to the greater variability of n-heptane recovery from the 0.1 ppmv VOC mixture versus the 40 ppmv n-heptane samples could include irreversible chemisorption on CSC which contains surface metal oxides and organic functional groups which becomes more of a factor at lower concentrations (Guenier and Muller 1984; Ballesta et al. 1999; Harper 2000). Variability in adsorption efficiency or the coefficient of desorption can both be affected by matrix effects in the presence of more than one compound (Ballesta et al. 1992).

The bias of intra-run recovery from dynamically generated atmospheres containing VOCs

The bias of the recovery was evaluated from three different VOC profiles from datasets of sixteen replicate runs, with 4 samplers in each run. For each run, the mean concentration of the intra-run result of analysis versus the target concentration of the generated atmosphere was calculated as a percent recovery. A Grubb's test for rejection of an observation was applied to each of the datasets. Histograms showing the distribution of the percent recovery for each of the chemicals are included in the supplementary information in Figures S3 through S5. Most compounds had some variation of a bell-shaped distribution around a central maximum, however, there were outlying recovery bins, somewhat skewed distributions, and what appeared to be bi-modal distributions. In the case of toluene, the outlier which was identified from the Grubbs test was easily identifiable via a visual inspection of the histograms. In the case of

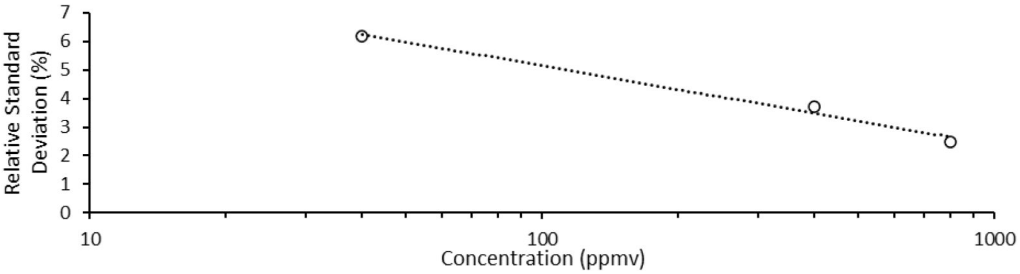

Figure 3. Relative standard deviation of the intra-run mean ($n = 6$ samplers) percentage recovery of n-heptane in the generated atmosphere versus target concentration plotted with the concentration axis in log scale.

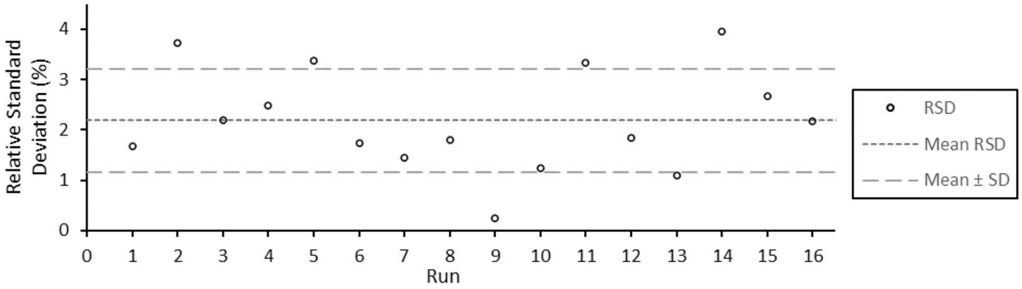

Figure 4. Intra-run RSD of percentage recovery of n-heptane from samplers ($n = 4$) collected from 16 runs of 40 ppmv n-heptane.

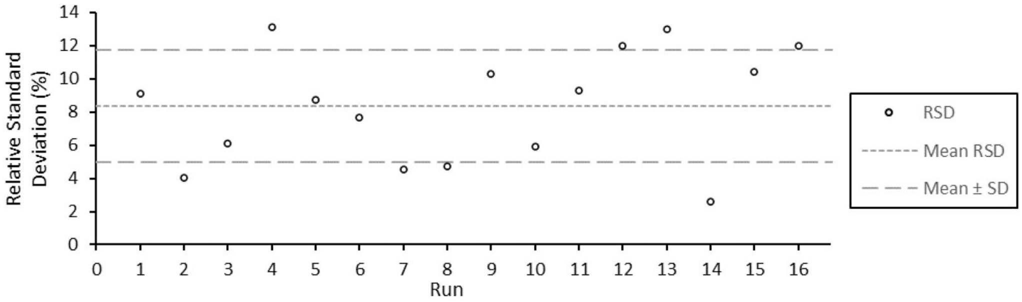

Figure 5. The plot of intra-run RSD of the percent recovery of n-heptane from solid sorbent samplers ($n = 4$) collected from 16 runs of generated atmospheres of 0.1 ppmv 10 VOC mixture. The mean (short dashes) plus/minus the standard deviation (long dashes) of the intra-run RSDs are shown.

Table 1. The recovery and standard deviation as a percent of the 40 ppmv n-heptane target atmosphere concentration from 16 runs of 4 samplers ($n = 4$) in each run (except run 9 where $n = 3$).

Run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
% recovery	104 ± 2	107 ± 4	107 ± 2	99 ± 2	104 ± 4	106 ± 2	104 ± 2	106 ± 2	103 ± 0	103 ± 1	102 ± 3	106 ± 2	106 ± 1	102 ± 4	103 ± 3	96 ± 2

Table 2. The bias as mean intra-run percent recovery and standard deviation of measurements ($n = 4$) in each of 16 replicate runs sampled from a 0.1 ppmv BTEX atmosphere.

% Recovery/run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Benzene	101 ± 3	104 ± 4	101 ± 9	95 ± 5	95 ± 5	101 ± 3	103 ± 6	103 ± 4	100 ± 2	94 ± 2	97 ± 3	100 ± 5	99 ± 4	97 ± 4	98 ± 4	97 ± 4
Toluene	102 ± 4	106 ± 4	103 ± 9	95 ± 5	94 ± 7	101 ± 5	104 ± 5	103 ± 5	100 ± 3	95 ± 2	98 ± 4	101 ± 6	100 ± 4	98 ± 4	100 ± 2	97 ± 4
Ethylbenzene	101 ± 5	106 ± 4	104 ± 9	98 ± 5	95 ± 6	102 ± 4	104 ± 6	103 ± 4	99 ± 3	94 ± 2	97 ± 4	100 ± 5	101 ± 4	99 ± 4	101 ± 2	99 ± 4
O-xylene	100 ± 4	104 ± 4	100 ± 8	96 ± 4	92 ± 7	98 ± 3	100 ± 6	99 ± 4	96 ± 3	92 ± 2	94 ± 4	97 ± 6	97 ± 4	96 ± 4	97 ± 1	95 ± 4

toluene, the outlier which was identified from the Grubbs test was easily identifiable via a visual inspection of the histograms.

The recovery of n-heptane with a target concentration of 40 ppmv as an intra-run mean and standard deviation for each of the 16 replicate runs is shown in Table 1. The mean recovery of the 63 samples was 104 ± 3%. None of the intra-run mean recoveries were rejected via Grubb's test. One sample tube from run 9 broke before it could be analyzed. Recovery was corrected for a desorption efficiency of 105% from the LCS recoveries. Analytical spike and LCS data have been included in the supplementary information in Table S1.

The intra-run mean recovery and the standard deviation of the mean recovery are shown in Table 2 from dynamically generated atmospheres containing BTEX at a target of 0.1 ppmv for each component. The mean recovery of benzene was 99 ± 5%. Toluene and ethylbenzene, both had a mean recovery of 100 ± 5%, and o-xylene, 97 ± 5%. The LCS mean desorption efficiencies of 95.3%, 95.2%, 97.6%, and 92.9% for the BTEX components, respectively, were used for the correction of the recoveries. No results in this set were rejected via Grubb's test.

In a dynamically generated atmosphere of a 10 VOC mixture targeted at 0.1 ppmv of each component, the percent recovery of the intra-run mean ($n = 4$ samples per run) and standard deviation of each of the chemical components are shown in Table 3. Although chloroform was below the LOQ but above the LOD, the results have been included as contextual information. Grubb's test rejected one sample result of toluene from run 15, which was identifiable in the histogram of recovery in the supplementary information Figure S3I.

Table 3. The mean percent recovery and standard deviation of the percent recovery of measurements ($n = 4$) from 16 runs of generating and sampling atmospheres of mixtures of 10 VOCs at 0.1 ppmv each.

Chemical/run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Mesitylene	105 ± 7	104 ± 7	109 ± 2	106 ± 15	106 ± 11	99 ± 10	100 ± 3	96 ± 11	95 ± 7	96 ± 7	103 ± 7	108 ± 9	107 ± 10	100 ± 7	105 ± 3	101 ± 7
Benzene	98 ± 10	100 ± 15	102 ± 2	96 ± 12	88 ± 8	86 ± 13	89 ± 4	93 ± 5	93 ± 5	99 ± 11	96 ± 5	100 ± 11	99 ± 6	97 ± 12	99 ± 10	97 ± 11
Chloroform*	121 ± 4	119 ± 10	106 ± 7	127 ± 8	108 ± 17	102 ± 9	111 ± 10	116 ± 8	109 ± 7	122 ± 3	117 ± 10	111 ± 15	113 ± 2	108 ± 9	110 ± 10	111 ± 4
Ethylbenzene	93 ± 11	92 ± 4	94 ± 7	94 ± 20	90 ± 6	78 ± 9	80 ± 5	84 ± 9	85 ± 5	86 ± 7	89 ± 7	94 ± 3	92 ± 14	92 ± 2	92 ± 11	87 ± 6
N-heptane	92 ± 8	96 ± 4	99 ± 6	92 ± 12	86 ± 7	75 ± 6	89 ± 4	86 ± 4	83 ± 9	91 ± 5	88 ± 8	92 ± 11	93 ± 12	90 ± 2	87 ± 9	91 ± 11
O-xylene	96 ± 11	92 ± 4	101 ± 5	93 ± 13	89 ± 6	81 ± 9	90 ± 4	85 ± 8	87 ± 6	89 ± 10	87 ± 3	93 ± 1	94 ± 8	88 ± 4	89 ± 10	91 ± 9
Tetrachloroethylene	97 ± 8	104 ± 4	101 ± 7	106 ± 11	99 ± 3	97 ± 5	97 ± 3	98 ± 13	96 ± 6	100 ± 3	98 ± 7	105 ± 8	97 ± 8	104 ± 7	100 ± 5	106 ± 7
P-xylene	92 ± 10	94 ± 3	97 ± 9	90 ± 17	85 ± 7	79 ± 6	86 ± 4	84 ± 9	81 ± 8	81 ± 10	85 ± 8	93 ± 5	93 ± 11	85 ± 4	87 ± 5	86 ± 6
Toluene	98 ± 10	103 ± 5	104 ± 5	103 ± 16	96 ± 15	88 ± 8	98 ± 11	94 ± 14	99 ± 8	93 ± 5	102 ± 16	97 ± 8	101 ± 19	90 ± 9	113 ± 14	96 ± 8
Trichloroethylene	92 ± 9	101 ± 8	96 ± 8	110 ± 9	96 ± 9	95 ± 5	96 ± 8	94 ± 10	96 ± 11	97 ± 5	107 ± 5	93 ± 5	95 ± 3	99 ± 4	104 ± 9	95 ± 2

*The chloroform concentration was below the method LOQ.

Toluene had the highest percent recovery among the VOCs (excluding chloroform) with a 113% percent recovery in run 15. The identification of toluene as an outlier while the remainder of the VOCs were not identified as outliers suggests that the difference may be due to variability associated with the analysis of toluene, not the generation of the VOC atmosphere. However, toluene is also present in many lab environments and contamination cannot be ruled out as affecting this result. The lowest mean intra-run recovery was observed for n-heptane at 75% in run six, however, this was not excluded via the Grubbs test, though the lower recoveries of other VOCs in that run would suggest that there was a difference in performance in run six. The QC spikes, done during the analysis, produced a maximum desorption efficiency of 106% for heptane, and a minimum of 100% for o-xylene (analytical spike desorption efficiencies for all 10 VOCs shown in the supplementary information Table S2). The laboratory control spike recovery values were used to correct sample recovery results. Seven out of the ten analytes had their lowest recovery in run six, however, the variability for that run was not flagged as an outlier in the evaluations using Grubb's test, or Bartlett's test for homogeneity of variance.

There was an expectation of a relatively low bias from the sampling and analysis methods from previous evaluations of alkanes on CSC sampling media (NIOSH 2003a, 2003b). NIOSH Method 1500 lists biases between 1% and 10% for a range of comparable alkanes, which was within the range of the biases measured except for chloroform, which was below the LOQ (NIOSH 2003b). Recoveries from the 0.1 ppmv 10 VOC mixture had a larger bias on average than the other data sets, 40 ppm *n*-heptane, and BTEX.

Bartlett's test for homogeneity of recovery variance from n-heptane, BTEX, and 10 VOC mixture atmospheres

A Bartlett's test for homogeneity of variance was used to determine if all the samples in the 16-run set could be combined to calculate a pooled RSD. The Bartlett's test was computed using the R language and environment for statistical computing using the Bartlett test function (R Core Team 2018). Bartlett's test null hypothesis, $p > 0.05$, indicated that the intra-run RSD values could be pooled as shown in Table 4. The pooled RSD ($s_{r,p}$) was determined using the formula in Equation 1 from (Olofsson et al. 1981; NIOSH 1995):

$$s_{r,p} = \left[\sum\left(\frac{s_i^2}{\bar{x}_i^2}\right)(n_i - 1)/\sum(n_i - 1)\right]^{1/2} \tag{1}$$

where s is the standard deviation, $\bar{x}$ is the mean, and n is the number of samples. The pooled RSD can be thought of as an improved estimate of the imprecision of the process (Olofsson et al. 1981). There are several contributing sources of uncertainty including inter-day and inter-run variabilities in the pooled RSD, which are not present in the intra-run imprecision. Thus, the pooled RSD should be considered a computation of the total imprecision or variability of the system.

For 16 runs there were 15 degrees of freedom (DoF) or categories (runs) that were independent of each other. The closer that $\chi 2$ (the statistical result of the chi-squared test) divided by the DoF comes to unity is indicative of higher confidence in the data fitting. The maximum $\chi 2$ values for 15 DoF at the 5% significance level is 24.996. All values of $\chi 2$ indicated confidence in the fitting of the data, though the fitting of ethylbenzene and o-xylene in the 10-VOC mixture was approaching the limits of fitting and confidence in homogeneity.

The pooled RSD of the recovery showed an increase with a greater number of compounds in the generated atmosphere. Among the different atmospheres tested, the single component 40 ppmv n-heptane atmosphere exhibited the lowest pooled RSD as shown in Table 4. This was followed by the 0.1 ppmv BTEX atmosphere samples, while the 10 VOC mixture had the highest pooled RSD for both

Table 4. Figures of merit for measurement of variability from analysis of VOCs sampled from generated atmospheres.

VOC Name	Degrees of freedom	Chi-squared χ^2	p	Mean Recovery (%)	Pooled RSD
N-heptane	15	17.3	0.30	103.6	0.0243
Benzene	15	14.3	0.50	99.0	0.0450
Toluene	15	9.8	0.83	100	0.0479
Ethylbenzene	15	10.6	0.78	100	0.0462
O-xylene	15	11.3	0.73	97.0	0.0474
Mesitylene	15	15.6	0.41	101	0.0824
Benzene	15	16.1	0.38	93.2	0.1021
Chloroform*	15	19.5	0.19	110	0.0833
Ethylbenzene	15	23.5	0.07	87.7	0.1009
N-heptane	15	14.7	0.47	84.7	0.0944
O-xylene	15	22.6	0.09	90.2	0.0844
Tetrachloroethylene	15	15.3	0.43	97.3	0.0741
P-xylene	15	17.3	0.30	85.2	0.0982
Toluene	15	13.4	0.57	93.6	0.1194
Trichloroethylene	15	16.1	0.38	96.6	0.0753

*Sample concentration below method LOQ.

Sixteen runs of four samples each were tested for homogeneity of intra-run variability using Bartlett's test to produce a chi-squared and *p*-value. The mean recovery and pooled RSD of the percent sample recovery versus theoretical concentration in the generated atmosphere are shown.

Table 5. The pooled RSD of the analytical spikes ($\bar{S}_{r1}$) and the generated samples ($\bar{S}_{r2}$), were used to calculate the sampling variability ($\bar{S}_{rS}$) for n-heptane, BTEX, and 10 VOC sample sets.

Compound	$\bar{S}_{r1}$	$\bar{S}_{r2}$	$\bar{S}_{rS}$	$\bar{S}_{rA+\overline{DE}}$	$\hat{S}_{rT}$
N-heptane	0.0128	0.0243	0.0206	0.0134	0.0557
Benzene	0.0126	0.0450	0.0432	0.0132	0.0674
Toluene	0.0187	0.0479	0.0441	0.0194	0.0695
Ethylbenzene	0.0163	0.0462	0.0432	0.0170	0.0682
O-xylene	0.0155	0.0474	0.0448	0.0161	0.0690
Mesitylene	0.0186	0.0824	0.0802	0.0193	0.0965
Benzene	0.0193	0.102	0.100	0.0200	0.114
Chloroform	0.0222	0.0833	0.0803	0.0230	0.0974
Ethylbenzene	0.0100	0.101	0.100	0.0104	0.113
N-heptane	0.0144	0.0944	0.0933	0.0149	0.107
O-xylene	0.0189	0.0844	0.0822	0.0195	0.0982
Tetrachloroethylene	0.0150	0.0741	0.0726	0.0155	0.0895
P-xylene	0.0206	0.0982	0.0961	0.0213	0.110
Toluene	0.0142	0.1194	0.1185	0.0147	0.129
Trichloroethylene	0.0353	0.0753	0.0665	0.0365	0.0909

The additional figure of merit $\bar{S}_{rA+\overline{DE}}$, derived from $\bar{S}_{r1}$, along with the estimated personal sampling pump error S_{rP}, were used to calculate the $\hat{S}_{rT}$, which is the estimated total variability of the method.

sample recovery and bias (mean recovery % − 100%). This was consistent with samples of test atmospheres containing a single VOC having been previously shown to have lower variability than samples of atmospheres containing mixtures of VOCs (Ballesta et al. 1992).

Contributions of variability from analysis and generation

For air-sampling method development, NIOSH has defined total variability in Equation 2, which includes variability from aspects of sampling in Equation 3, and analysis in Equation 4 (NIOSH 1995). The estimate of the variability of the total procedure ($\hat{S}_{rT}$) or method variability is the square root of the sum of the squares of variability in sampling ($\bar{S}_{rS}$), analysis and desorption efficiency ($\bar{S}_{rA+\overline{DE}}$), and a pump error ($S_{rP}$) as in Equation 2 and shown in Table 5 for each of the VOC sets.

$$\hat{S}_{rT}=\sqrt{\left(\bar{S}_{rS}\right)^2+\left(\bar{S}_{rA+\overline{DE}}\right)^2+\left(S_{rP}\right)^2} \tag{2}$$

The S_{rP}, used to approximate variability due to personal sampling pumps used during field sampling, is typically estimated as 5%, which is added as a component of the total uncertainty of the method.

The variability of sampling and generation ($\bar{S}_{rS}$), shown in Equation 3, is the square root of the difference of squares of the pooled variability of generated samples ($\bar{S}_{r2}$) and the pooled variability obtained from the analysis of spiked samples ($\bar{S}_{r1}$). The $\bar{S}_{rS}$ as an estimate of the precision attributed to sampling in the AGS is shown in Table 4 for each compound. In cases where $\bar{S}_{r1}$ was larger than $\bar{S}_{r2}$, $\bar{S}_{rS}$ is set as zero, and alternative calculations are used to calculate the variability of the method (Taylor et al. 1977).

$$\bar{S}_{rS}=\sqrt{\left(\bar{S}_{r2}\right)^2-\left(\bar{S}_{r1}\right)^2} \tag{3}$$

The $\bar{S}_{rS}$ may have contributions from components of the AGS such as analyte and carrier air delivery systems, variability of the CSC sampling tubes such as charcoal packing, and the critical orifices used to control the sample flow rate. It is important to recognize that compounds applied as liquid spikes to generate analytical samples have the potential to desorb differently than compounds that were adsorbed via vapor pulled through the sorbent tube. There are a couple of factors that differentiate spiked samples from air samples. The amount of water present in the air samples has the potential to affect desorption efficiency, particularly for compounds that have some solubility in water (OSHA 2024). Second, spiked samples are injected into a small region of the sampling media rather than being distributed more evenly through the sorbent material as an air sample drawn through the media.

The analytical and desorption efficiency variability $\overline{S}_{rA+\overline{DE}}$ is a derived correction to $\overline{S}_{r1}$ based upon sample size (n is the number of samples) as shown in Equation 4:

$$\overline{S}_{rA+\overline{DE}} = \overline{S}_{r1}\sqrt{\frac{(n+1)}{n}} \tag{4}$$

The pooled variability from the analysis procedure ($\overline{S}_{r1}$) has contributions from both the sorbent desorption procedure and the instrumental analysis and was quantified using the quality control (QC) spike data. The experimental designs in this study included replicates of analytical spikes, which were used as variability of the analysis procedure. The pooled variability of the QC spikes done during analysis was calculated as $\overline{S}_{r1}$ from the RSD of the laboratory control spike replicates ($\overline{S}_{rLCS}$), the blind spike replicates ($\overline{S}_{rBS}$) and sample replicates ($\overline{S}_{rSR}$). Analytical spike targets and recoveries were included in the supplementary information Table S1, along with $\overline{S}_{r1}$, the pooled RSD of the analytical spikes in Table S3.

For all analytes, there was low analytical variability $\overline{S}_{r1}$ and additional variability from contributions due to generation and sampling in $\overline{S}_{r2}$. The analytical variability $\overline{S}_{r1}$ was similar to and in some cases lower than the historical data in Table 6. One exception was benzene, which was larger in the NIOSH source data in Table 6. Compared to the other compounds, there was a relatively large contribution of the analytical variability of trichloroethylene in our study as shown in Table 5 which was also present in Table 6.

$\overline{S}_{rS}$ calculated from the total variability of the generated samples $\overline{S}_{r2}$ and the analytical variability $\overline{S}_{r1}$ has contributions from two distinct sources, the generation process, and the sampling. The variability from generation and variability from the sampling method cannot be easily separated using the data available in the experiments that have been presented. However, a low $\overline{S}_{r2}$ indicates that both the variability attributable to the generation system and the variability attributable to the sampling method are low. The low $\overline{S}_{r2}$ of 0.0243 for n-heptane in the 16-run set was consistent with historical data in Table 6 and was an indication that the AGS had low variability on par with previous AGSs used to produce the data in Table 6. At lower concentrations of n-heptane in the 0.1 ppmv 10 VOC mixture, the generated sample variability, $\overline{S}_{r2}$, was 0.0944 and was consistent with expectations of increased variability at lower concentrations.

The $\hat{S}_{rT}$ denotes an estimated total precision of the method and was largely influenced by the inclusion of S_{rP}, compared to the contributions of $\overline{S}_{rS}$ in Table 6. $\overline{S}_{rS}$ in Table 6 was calculated using Equation 3 from $\overline{S}_{r1}$ and $\overline{S}_{r2}$ data provided by Taylor et al. (1977). Generally, lower concentrations and mixed VOC samples had a larger total variability $\hat{S}_{rT}$ in Table 5 than the historical data from Table 6. The $\hat{S}_{rT}$ in Table 6 does not consider concentration dependence though it was derived from single-compound evaluations at three relatively high concentrations related to exposure limits. Also, the effects of multiple VOCs were not present in the Table 6 data. The $\hat{S}_{rT}$ of the historical data at 5% for toluene was not far from the 7% at the lower concentration BTEX data set. Additionally, it was found that the variability of tetrachloroethylene at 0.1 ppmv was 9%, whereas the historical data at a much larger concentration was 5%. The similarity of $\hat{S}_{rT}$ for trichloroethylene in our data at 9% and the 8% from the historical data was particularly remarkable given the significant difference in the concentration of the samples. The larger $\hat{S}_{rT}$ from our BTEX and the 10 VOC mixture studies were consistent with the variability of sampling of multi-analyte mixtures at low concentrations versus single analytes at the higher concentration ranges in the data from NIOSH methods. The mesitylene data from OSHA 1012 was

Table 6. Bias and precision data from selected comparable methods for VOC sampling.

Method	Compound	Bias (%)	Method Range (ppmv)	$\overline{S}_{r1}$	$\overline{S}_{r2}$	$\overline{S}_{rS}$	($\hat{S}_{rT}$)	Ref.
NIOSH 1500	N-heptane	−6.5	244–976	0.0161	0.0233	0.0168	0.0556	(Taylor et al. 1977; NIOSH 2003b)
NIOSH 1501	Ethylbenzene	−7.6	51–204	0.0010	0.0627	0.0627	0.089	(Taylor et al. 1977; NIOSH 2003a)
NIOSH 1501	Benzene	−0.4	13–52	0.036	0.028	Sr1> Sr2	0.059	(Taylor et al. 1977; NIOSH 2003a)
NIOSH 1501	Toluene	1.6	145–581	0.011	0.015	0.010	0.052	(Taylor et al. 1977; NIOSH 2003a)
NIOSH 1501	Xylene(o-,m-,p-)	−1.2	50–200	0.010	0.033	0.031	0.060	(Taylor et al. 1977; NIOSH 2003a)
NIOSH 1003	Chloroform	1.3	20–85	0.0469	0.0444	Sr1 > Sr2	0.057	(Taylor et al. 1977; NIOSH 2003c)
NIOSH 1003	Tetrachloroethylene	−7.2	97–405	0.0115	0.0126	0.00515	0.052	(Taylor et al. 1977; NIOSH 2003c)
NIOSH 1022	Trichloroethylene	−7.19	89–377	0.0384	0.0636	0.0507	0.082	(Taylor et al. 1977; NIOSH 2003d)
		Recovery (%)					Precision (±%)	
OSHA 1020	Mesitylene	−2.59	0.072 – 25	n/a	n/a	n/a	10.5	(OSHA 2016)

N/a—not available.

generated using sampling concentrations closer to the concentration of the 10 VOC mix and had an overall precision of 10.5%, which is similar to the 9.65% from our observations of mesitylene in the 10 VOC mixture. Differences in method development procedures did not enable direct comparison for several components of the mesitylene evaluation and, thus were not applicable (n/a).

Limitations

For some aspects of the sample generation, collection, and analysis there was no way to isolate individual components for an independent measure of variability. This limited the ability to assign sources of variabilities. The data upon which this paper is based were assembled from independent studies and some of the differences in these studies limit the ability to draw conclusions that otherwise might have been determinable from a different experimental design. The set of VOCs studied was representative of a small number of compound types. There may be VOC-dependent variabilities that were not observed in the limited VOC set. The conclusions drawn have made the best use of the experimental design and available data to understand the observed variabilities.

Conclusions

The sampling variability ($\bar{S}_{rS}$) from a dynamic AGS was between 2% and 12% for all tested compounds, even at low concentrations in relatively complex mixtures of VOCs. The calculated $\bar{S}_{rT}$ was between 5% and 13% percent for all compounds tested. The analysis of the 40 ppmv n-heptane atmosphere resulted in lower intra-run and pooled variability compared to the analysis of n-heptane in the 0.1 ppmv mixture of 10 VOCs. Analysis of higher concentrations tended to have a lower variability, and as concentrations decreased, the variability increased, which is consistent with previous evaluations of sampling methods. (Taylor et al. 1977) Though not experimentally investigated here, it is known that several factors contribute to greater variability at lower concentrations: (1) the noise associated with the analytical instruments; (2) increased measurement uncertainty when measuring closer to the limit of quantification of the method; and (3) problems of adsorption on surfaces (Horwitz 1982).

When using an AGS to assess the overall uncertainty of the method, it is crucial that the contribution of the AGS to the overall variability of the generated samples ($\bar{S}_{r2}$) remains relatively small. However, if the actual variability attributed to the method is minimal, then the AGS's contribution to the observed variability of the generated samples could become significant. Based on the low variability observed in the high-level n-heptane samples, it can be inferred that the AGS will only make a substantial contribution to the total variability in cases where method variability is low. Consequently, it can concluded that the AGS performs adequately for method evaluation. This was demonstrated by the AGS consistently generating samples with variability comparable to that observed in historical data for similar concentrations of n-heptane. The authors acknowledge that it was difficult to attribute variability to any single factor or component of the AGS when evaluating the variability of generated samples.

The bias of samples obtained from the dynamic AGS was found to be consistent with the ranges observed in previous evaluations conducted by NIOSH and the evaluation of mesitylene by OSHA. Mixtures of analytes and lower analyte concentrations lead to greater variability compared to single component samples and have a large influence on the variability observed in generated samples. The increased variability with increasing sample complexity and decreasing concentrations suggests that for multi-analyte methods it was approaching the limits of acceptable variability and bias. However, this appeared to be a property inherent to sampling at low concentrations and in mixtures rather than a property of the AGS. The dynamic AGS design presented in this study has proven capable of producing test atmospheres with varying concentrations and analytes while maintaining low sample variability over multiple days of generation and sampling. These results provide valuable insights into how mixture complexity and concentration can affect sample variability when using techniques described in this study.

Recommendations

When generating dynamic atmospheres for method development it is important to design experiments that enable analysis of the variability of the sample results, which be used to distinguish between multiple sources of variability. If possible, determining the variability and/or bias inherent to the AGS, and subtracting that from the overall observed variability and bias during method evaluation can give a more accurate measure of the sampling and analytical method variability and bias. Historically, much of the work related to the variability of samples from dynamically generated atmospheres and environmental air monitoring has focused on concentration ranges around exposure limits. The studies in this manuscript show that variability for lower concentrations of analytes can increase compared to variability at moderate concentrations near the exposure limits. With current trends for existing exposure limits to be revised to lower concentrations and increased interest in low-level chronic exposures, it is important to characterize generation system variability at low levels as part of method development.

Disclaimers

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. This activity was reviewed by the CDC and was conducted consistent with applicable federal law and CDC policy. §See e.g., 45 C.F.R. part 46; 21 C.F.R. part 56; 42 U.S.C. §241(d), 5 U.S.C. §552a, 44 U.S.C. §3501 et seq.

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Data availability statement

Datasets are available online at the NOISH Data and Statistics Gateway at https://www.cdc.gov/niosh/data/default.html.

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