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RESEARCH ARTICLE

Automated crude oil vapor inhalation exposure system

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ABSTRACT

Objective: Inhalation exposure systems are tools for delivering compounds (particles, vapors, and gases) under well-controlled conditions for toxicological testing. The objective of this project was to develop an automated computer-controlled system to expose small laboratory animals to precise concentrations of crude oil vapor (COV).

Materials and Methods: Vapor from heated Deepwater Horizon surrogate oil was atomized into a fine mist then diluted with filtered air, then the air/droplet mixture was routed into an evaporation column with an high efficiency particulate air (HEPA) filter on its exit port. The HEPA filter was used to remove oil particles, thus ensuring only vapor would pass. The vapor was then introduced into a custom-built exposure chamber housing rats. A calibrated flame ionization detector was used to read the total volatile organic compounds (TVOC) in real time, and custom software was developed to automatically adjust the amount of oil entering the atomizer with a syringe pump. The software also controlled relative humidity and pressure inside the exposure chamber. Other exposure chamber environmental parameters, e.g. temperature and CO_2 levels, were monitored. Four specific components within the COV were monitored during each exposure: benzene, toluene, ethylbenzene, and xylenes.

Results: The TVOC vapor concentration control algorithm maintained median concentrations to within ±2 ppm of the target concentration (300 ppm) of TVOC during exposures lasting 6 h. The system could reach 90% of the desired target in less than 15 min, and repeat exposures were consistent and reproducible.

Conclusion: This exposure system provided a highly automated tool for conducting COV inhalation toxicology studies.

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Crude oil vapor; deepwater horizon; inhalation exposure; exposure chamber; VOC inhalation

Introduction

Crude oil vapor inhalation

In August 2020 there were over 186,000 employees in the oil and gas extraction industry in the United States (United States Department of Labor. Bureau of Labor Statistics 2020a,b,c). Many workers in the upstream oil extraction industry have a potential risk of crude oil vapor (COV) inhalation. There are many current knowledge gaps regarding the health effects from inhalation of complex mixtures found in COVs. To aid research in filling these gaps, an automated system that could carefully deliver and control the COV concentration within an animal inhalation exposure chamber was developed. This article focuses on the design and testing of that system. Studies reporting on the health effects of COV exposures, using this system, in the pulmonary, cardiovascular, immune system, kidneys, and brain have been published (Fedan et al. 2022; Investigative Team 2022; Krajnak et al. 2022; Sager et al. 2022; Sriram et al. 2022; Weatherly et al. 2022). A detailed overview of the purpose of these investigations is reported in Fedan (2022).

Generation of gas mixtures

Namies (1984) describes several common methods of generating gas mixtures, and divides them into two main categories: static and dynamic. Static methods are based on mixing known amounts of test compounds and dilution components then storing them, often in a flexible container. Generation of the mixture is stopped when the flexible container is filled. Samples are then taken from the flexible container. Dynamic systems use continuous generation of the test compounds and the dilution components at known rates. Dynamic methods are preferred with inhalation exposures because they provide animals with a continuous air supply. There are several dynamic generation methods including the evaporation method and the injection method. The evaporation method is one in which dilution gas passes through or over a component to be vaporized. The evaporation method is not well suited for COV generation because of its complex mixture of volatile and semi-volatile components. If this method was used the most volatile components of the mixture would off-gas early during an exposure run, leaving less volatile components behind in the evaporation jar. This would result in changing compound levels during a 6-hour long exposure run. The injection method is one in which a volatile liquid is continuously introduced into a flowing dilution gas stream. Most injection methods use a syringe pump. Syringe pumps used for putting liquids into an air stream have been extensively used since 1950s for

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generation of standard gases in many applications, including inhalation toxicity studies (Sidney et al. 1994; Goldsmith et al. 2011).

The crude oil inhalation exposure system described in this paper used a syringe pump to inject the crude oil into an air steam (dynamic injection gas generation method); however its design was optimized from the typical T-shaped injection fitting. The liquid from the syringe pump was fed into an atomizer. The atomizer created a fine mist increasing the surface area of the liquid, thus enhancing evaporation of the constituents. A catch tank was added below the injection point for the less volatile components to drain *via* gravity and to remove them from direct contact with the input air stream. This design was an efficient and reliable method for generating COV.

Advantages of computer-controlled inhalation systems

It has been shown that in addition to monitoring and logging data during an exposure, computers can effectively be used to automatically control the exposure environment (O'Shaughnessy and Hemenway 1994; Johnson et al. 1995; Decker et al. 2001; Wong 2003; McKinney and Frazer 2008). These authors highlight several advantages to using automation to control inhalation exposure systems over manual user control: (1) the target concentration is reached quickly with minimal overshoot during the start of an exposure, (2) less concentration fluctuation over the duration of an exposure run, (3) more consistency during repeat exposures, (4) exposure duration is precisely controlled, (5) automated systems require less operator intervention, thus allowing for more experiments to be run during the same day, (5) the system can automatically shut down when exposure parameters fall outside of the accepted ranges.

Crude oil vapor exposure system requirements

The COV exposure system was required to meet the following design specifications set by in-house (NIOSH-Morgantown) project managers, and the institutional animal care and use committee: (1) the exposure chamber total volatile organic compound (TVOC) concentration had to be maintained at a selected value ranging between 50 and 400 ppm (300 ppm for the animal exposure studies), and this concentration had to be automatically controlled with minimal fluctuations during a 6-h exposure period, (2) the exposure concentration response time had to quickly reach equilibrium after the animals had been placed into the exposure chamber, (3) the overshoot in exposure concentration at the beginning of an exposure period had to be minimal, (4) the exposure chamber had to house up to 24 rats within individual cage partitions, (5) the exposure chamber pressure had to be automatically maintained at zero pressure differential with respect to the laboratory housing the unit, (6) the exposure chamber relative humidity had to be automatically controlled with a target of 40%, (7) the exposure chamber temperature and CO_2 levels had to remain within acceptable ranges, 71 – 75 °F and below 4,000 ppm, respectively (set by the NIOSH-Morgantown animal care and use committee), and 8) the system had to be computer-controlled and require little, if any, operator intervention over an exposure period lasting 6 h. The system described in this report satisfied all these criteria.

Methods

COV inhalation exposure system design

The custom inhalation exposure system devised for COV inhalation exposure experiments is shown in Figure 1. COV was generated using a computer-controlled syringe pump (Teledyne ISCO 500 D; Lincoln, NE), which injected a flow of heated (85 °F) oil into a collision atomizer (3076; TSI Inc.; Shoreview, MN). This stainless-steel atomizer used a constant 4 liter per minute (l/min) of high-efficiency particulate air (HEPA)-filtered dry air to create a fine mist of oil droplets. The air and oil droplet mixture exited the atomizer and was combined with 40 l/min of additional heated (85 °F) clean air. This additional dilution air was humidified to achieve a constant 40% relative humidity inside the exposure chamber. The humidity was maintained constant during all exposures by custom software that made continuous adjustments to the amount of air that passed through a heated water bath and the amount that bypassed it (see Figure 1). All air flows were metered by using mass flow controllers (Alicat Scientific; Tucson, AZ). The atomizer's exhaust and dilution air combined then entered a 3-foot-long PTFE tube with 1 inch outside diameter. This tube acted as an evaporation and mixing column. This allowed time for droplets to produce vapors and for larger droplets to settle and drain through the atomizer into an air-tight catch tank. A two-stage HEPA filter was mounted on top of this column to remove all oil droplets, thus allowing only the vapors to pass. The HEPA filters were not heated and allowed for the air/vapor to cool to lab temperature (approximately 72 °F) before entering the exposure chamber. The HEPA filter was changed daily during inhalation exposure studies. The total air flow entering the exposure chamber was 44 l/min resulting in 9 air changes per hour. This was sufficient ventilation to maintain CO_2 levels below the max value of 4,000 ppm.

The TVOC concentration was measured inside the exposure chamber with continuous samples by a flame ionizing detector (Model 10 FID; VIG Industries Inc.; Anaheim, CA), and adjustments were made automatically to the oil injection flow entering the atomizer *via* custom control software in order to maintain a constant TVOC level. The TVOC monitor was calibrated using benzene, toluene, ethylbenzene and xylenes (BTEX) gas as a standard. Calibration BTEX gas tanks (Butler Gas Co.; Pittsburgh, PA) were obtained at TVOC levels of 30, 120, 240 and 480 ppm. The BTEX mixtures had equal concentrations of each compound at 5, 20, and 80 ppm (note there are 3 types of xylenes in BTEX, thus the mixture had 6 compounds total). The calibration data is shown in Figure 2. The solid line in Figure 2 is the linear fit to the calibration data for

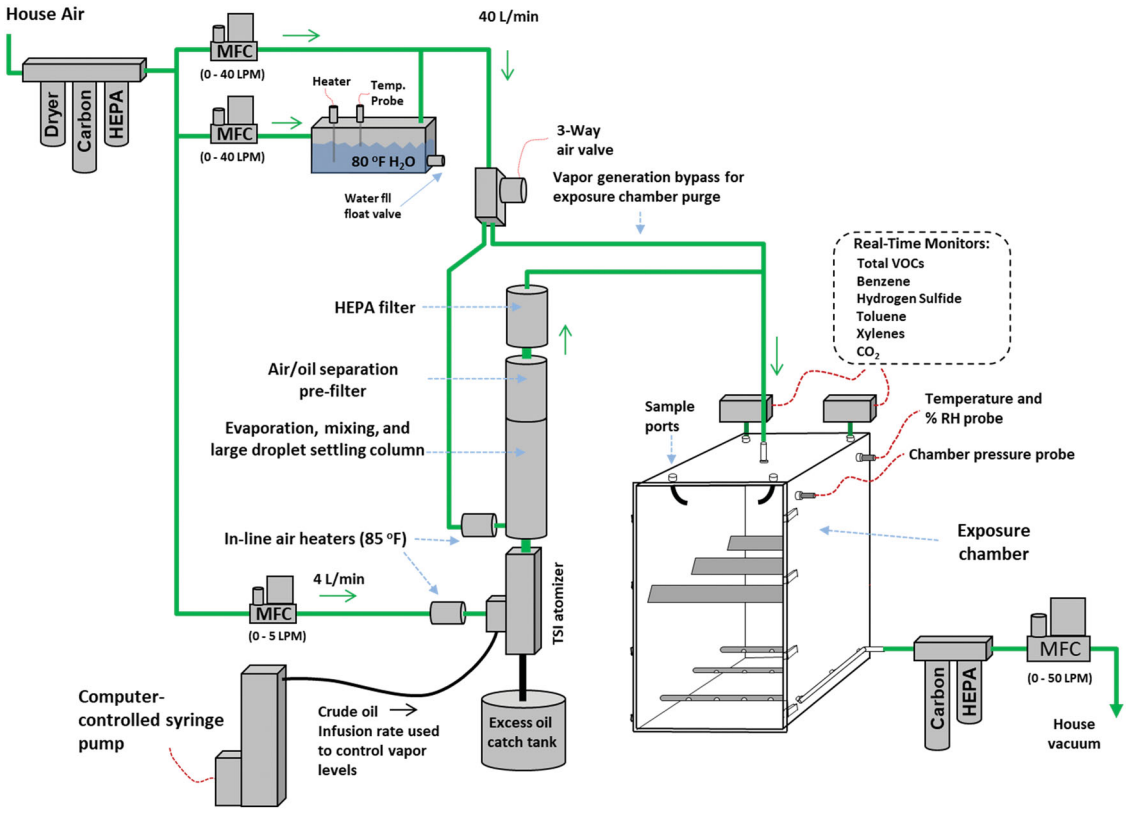

Figure 1. Crude oil inhalation exposure system diagram.

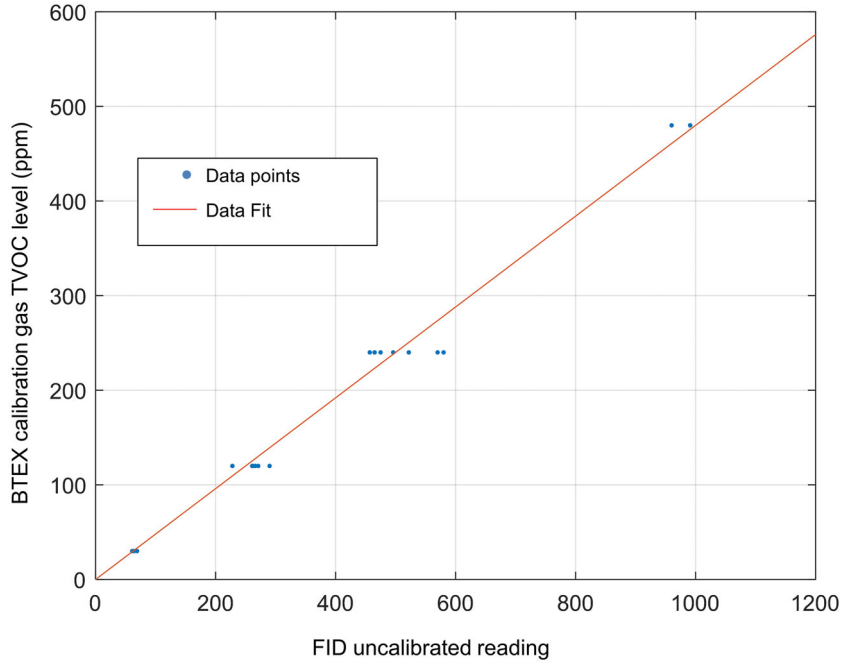

Figure 2. FID calibration data plot.

the instrument. The equation for this calibration was TVOC = (instrument reading) × 0.48. This fit resulted in a R^2 value of 0.997. In addition to TVOC, BTEX and other unidentified VOC were monitored during inhalation exposures (Model 8610 C GC-FID; SRI Instruments; Torrance, CA). This was done to track changes in vapor composition over time. The methods used to analyze the samples collected by the GC-FID are described in section *2.5* below.

Exhaust air exited the exposure chamber through rails with several small holes located below the animal cages. More information about the custom exposure chamber is given in section *2.2*. The exhaust air was then routed through HEPA and charcoal filters. A mass flow controller, with its downstream port connected to lab vacuum, controlled the amount of air leaving the exposure chamber based on the exposure chamber's pressure differential *vs.*

ambient pressure within the laboratory. This pressure was measured with a pressure transducer (Model 264 ± 7.5″ H_2O; Setra Systems; Boxborough, MA). The custom exposure system software was set to maintain exposure chamber pressure at 0” H_2O at all times. A CO_2 probe (model GMP252; Vaisala; Helsinki, Finland) was used to monitor the CO_2 levels in the exhaust air, and a temperature and humidity probe (model HMP60; Vaisala) was mounted inside the exposure chamber.

Exposure chamber

A custom-built, air-tight exposure chamber was designed and fabricated for use with the COV inhalation exposure system. An overview of the exposure chamber design is shown in Figure 3. The chamber was 22 × 22 × 37 inches (W × D × H) in size. 16-Gauge stainless steel was used for all exposure chamber walls, with a clear polycarbonate 1/4-inch thick front door. The transparent door allowed for visual monitoring of animals during exposures. A rubber gasket and several latches around the perimeter of the door were used to provide an air-tight seal. The COV entered the top center of the exposure chamber from a 1/2 inch OD stainless steel tube. This tube had a custom-built dispersion nozzle mounted to its outlet inside the exposure chamber located approximately 2 inches from the top wall. This nozzle assisted in uniform gas mixing within the chamber. The nozzle had eight 1/8-inch diameter holes equally spaced pointed downward at 45° angles. Air exited the exposure chamber through 1/8-inch diameter holes drilled into the bottom of exhaust rails near the bottom of the exposure chamber (see Figure 3). These three exhaust rails were made from 3/8-inch OD stainless steel tubes.

The exposure chamber was designed to hold two removable animal cage racks. The stainless-steel racks had twelve individual partitions measuring 5 × 7 × 5 inches each, arranged in a 4 × 3 matrix. The cage wire bottom floor surface was of sufficient diameter to allow the animal to comfortably rest without bedding present. The lower cage rack would rest on the exhaust rails and the upper cage rack would rest on stainless steel angle bars. The angle bars were oriented to direct animal excretions into the upper excretion pan (see Figure 3). This pan had large open spaces, 2.5 × 22 inches, directly under the angle bars so fumes could readily flow from the upper portion of the exposure chamber to the lower section. A second, identical exposure chamber was built and used to expose control animals to HEPA-filtered air under the same conditions.

The COV exposure chamber was a modified version of a previously described chamber, the Cube 150, by Goldsmith et al. (2011). The COV exposure chamber was taller so that it could accommodate an additional cage rack. The Cube 150 was previously tested for concentration homogeneity within the cage partitions using aerosol droplets and was reported to have less than 5% variation between all animal locations in the chamber. The COV exposure chamber used the same dispersion nozzle, the same exhaust rails, and the same width and length in its design, thus providing thorough internal mixing. The fact that vapors tend to mix more uniformly than aerosols assisted with the mixing of COV. When animals were exposed using the COV exposure system they were rotated daily from the top and bottom cage racks, so that potential variations in concentration would average out. The real-time VOC analyzer sampled from the middle of the exposure chamber using PTFE tubing.

COV inhalation exposure system software

The computer software controlling the exposure system was implemented in the LabVIEW (National Instruments; Austin, TX) programming environment. A screenshot of the main control screen of the custom exposure system software is shown in Figure 4. The software allowed a user to select the system inputs in Table 1.

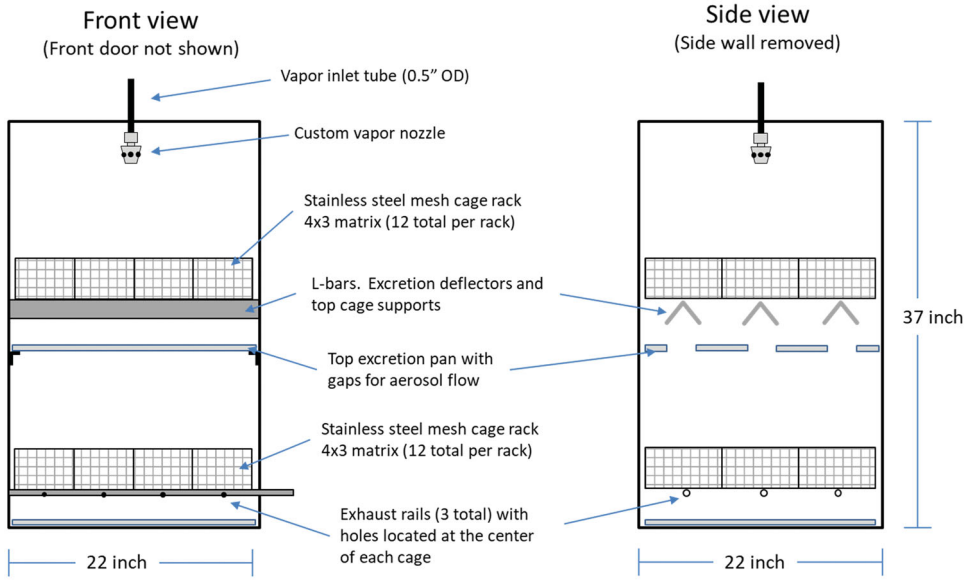

Figure 3. Exposure chamber diagram (24 rat capacity).

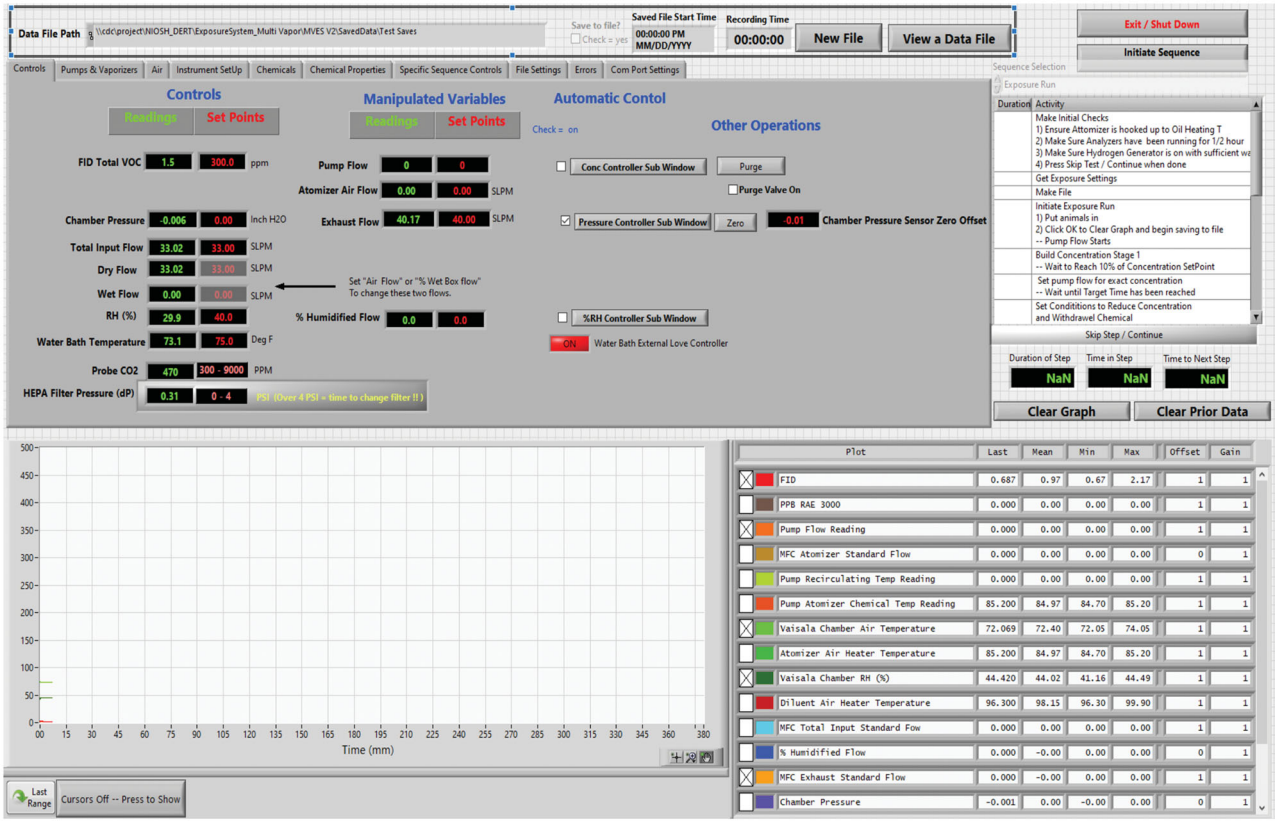

Figure 4. Custom software's main screen.

Table 1. Custom software inputs.

User selectable system parameter	Typical value during exposures
TVOC target concentration	300 ppm
Crude oil pump flow	Software controlled to maintain target concentration
Crude oil temperature	85 °F
Atomizer supply air flow	4 l/min
Atomizer supply air temperature	85 °F
Total dilution air flow	40 l/min
Dilution air temperature	85 °F
Exposure chamber relative humidity	40%
Dilution wet flow	Software controlled to maintain target humidity
Dilution dry flow	Software controlled to maintain target humidity
Water bath temperature for wet flow	75 °F
Exposure chamber differential pressure	0 inch-H_2O
Exposure chamber exhaust flow	Software controlled to maintain target chamber pressure
Automatic TVOC concentration control	On
Automatic humidity control	On
Automatic chamber pressure control	On
Save data to data-file	On
Purge mode	Off
Exposure duration	6 h

When data logging enabled all settings in Table 1 and their readings were saved to the computer every 2 sec, in addition to exposure chamber air temperature and CO_2 level. These settings and readings are in the upper left pane of the software's main screen (see Figure 4). The purge mode button would set atomizer flow to zero, crude oil pump flow to zero, dilution flow to 50 l/min, automatic concentration control to off, and activated the generator bypass valve. While in purge mode clean air was provided directly to the exposure chamber.

The lower half of the user screen is occupied by a large interactive graph display. All exposure system readings are displayed *vs.* time in this graph. The graph allows a user to turn on or off any of these plots given their visual preference. Each of these plots can be scaled or offset on the display by setting a "gain" and "offset." The gain and offset values are used in the graph display only and do not affect the saved data.

The "initiate sequence" button located in the upper right section of the screen was used by laboratory technicians to start an automated exposure run. When this button is pressed the system enters full automatic control mode. While in automatic control mode the software will: (1) prompt the user for target exposure concentration and

exposure duration, (2) check the amount of crude oil remaining in the syringe pump, then ask the user to add more if needed, (3) activate all heaters, (4) prompt the user to load the animals into the exposure chamber and shut the chamber door, (5) start saving all exposure readings and setting to a data file, (6) activate automatic control of exposure concentration, pressure, and humidity, (7) go into purge mode when desired exposure duration has been completed, and (8) prompt the attendant to remove animals from the chamber after concentration is reduced to 5 ppm or below.

Exposure system feedback control loops

The COV exposure system employed three different automated feedback loops which, when enabled, continuously controlled: (1) the animal exposure chamber TVOC concentration, (2) the animal exposure chamber pressure, and (3) the exposure chamber humidity. The exposure concentration was maintained at a constant value by adjusting the oil flow rate into the atomizer based on real-time TVOC measurements. The pressure in the animal exposure chamber was regulated by making corrections once every 2 sec to the exhaust flow based on readings from a pressure transducer. The exposure chamber relative humidity was controlled by making adjustments to the amount of dilution air entering a heated water bath and the amount of air bypassing it.

A form of proportional-integral-derivative (PID) control algorithm (Nise 1995) was implemented for each of the feedback control loops employed by the inhalation exposure system. The constants P_{gain}, I_{gain}, and D_{gain} used by each PID control loop were determined using manual tuning methods. In brief, (1) the adjustment period was set to 1.75-times the system delay and I_{gain} and D_{gain} were set to zero, (2) step responses were conducted at various values of P_{gain} until 25% overshoot and non-increasing oscillations were observed, (3) additional step responses were conducted while adjusting D_{gain} until overshoot was reduced to under 5% and steady-state oscillations were eliminated, and (4) I_{gain} was then adjusted to eliminate steady-state error.

Crude oil analysis

The crude oil used was provided by BP Exploration and Production, Inc. The sample is reference material associated with the 2010 Deepwater Horizon spill from the Macondo Well in Mississippi Canyon Block 252 (MC 252), i.e. "surrogate oil," a sample of a Gulf of Mexico Sweet Louisiana Crude Oil that is physically and chemically similar to the Macondo Well crude oil from Mississippi Canyon Block 252. The oil was sent to Stratum Laboratories (Shenandoah, TX) for analysis, the results of which are provided in the Supplementary Material. It had an °API gravity (60 °F) of 34.2. Upon receipt the oil was distributed in aliquots in air-tight lined metal containers and stored at 68 °F until used.

During each 6-h exposure run two samples were taken from inside the exposure chamber by a gas chromatograph flame ionizing detector (GC-FID) instrument (Model 8610 C GC-FID; SRI Instruments, Torrance, CA). These two samples were taken at the 2 and 4 h time points. The GC-FID was set up with the temperature ramp given in Table 2. The temperature ramp lasted 36 min total and provided good separation of peaks in the instrument's spectrum for COV.

Table 2. GC-FID temperature ramp.

Initial temperature (°C)	Initial temperature hold (min)	Ramp rate (°C/min)	Final temperature (°C)
37	10.25	30	75
75	5	30	85
85	7	30	150
150	5	60	195
195	3	N/A	N/A

An example of one of the chromatogram3 produced by the GC-FID during an exposure is shown in Figure 5. The data is presented as a graph with detector response on the ordinate-axis and retention time on the abscissa-axis. Retention time windows, shown as red bars in Figure 5, were used to identify analyte. The instrument's software was used to calculate the area of each peak and was recorded for every sample. This was done to track changes in vapor composition over time.

Four of these peaks were identified as BTEX and calibrated to ppm levels using BTEX gas mixtures (Butler Gas Co.; Pittsburgh, PA) of known concentrations (5, 20, and 80 ppm). A linear fit was used to find the relationship between the area of detected BTEX peaks and concentration in ppm. The chromatogram produced by the GC-FID during a calibration run is shown in Figure 6. Each peak is a chemical compound, other than one of the xylene peaks, the larger one, has 2 of the 3 types of xylene compounds at the same location on the abscissa. The specific chemical identity of other peaks generated during COV samples were not identified or quantified. They were only recorded and tracked to determine if the oil vapor composition was changing during the duration of the study.

Results

Feedback control performance

The computer-controlled exposure system had three automatic feedback loops controlling the following exposure chamber conditions: (1) TVOC concentration, (2) relative humidity, and (3) pressure. Figure 7 shows the TVOC concentration during one of the early test runs in which tuning of the feedback controller was being optimized. Several ramp-up tests are shown; for each test the initial pump speed was set to 30 ml/min. The first ramp-up was without feedback control enabled, and it reached approximately 300 ppm in 40 min. The next 4 tests were done with feedback control enabled. After each test, modifications were made to the PID values of the controller in the software. The third ramp-up test showed a controller that was too aggressive and was going to overshoot the target of 300 ppm by a significant amount, and so it was ended. The last two step tests showed the PID values were starting to result in an acceptable exposure

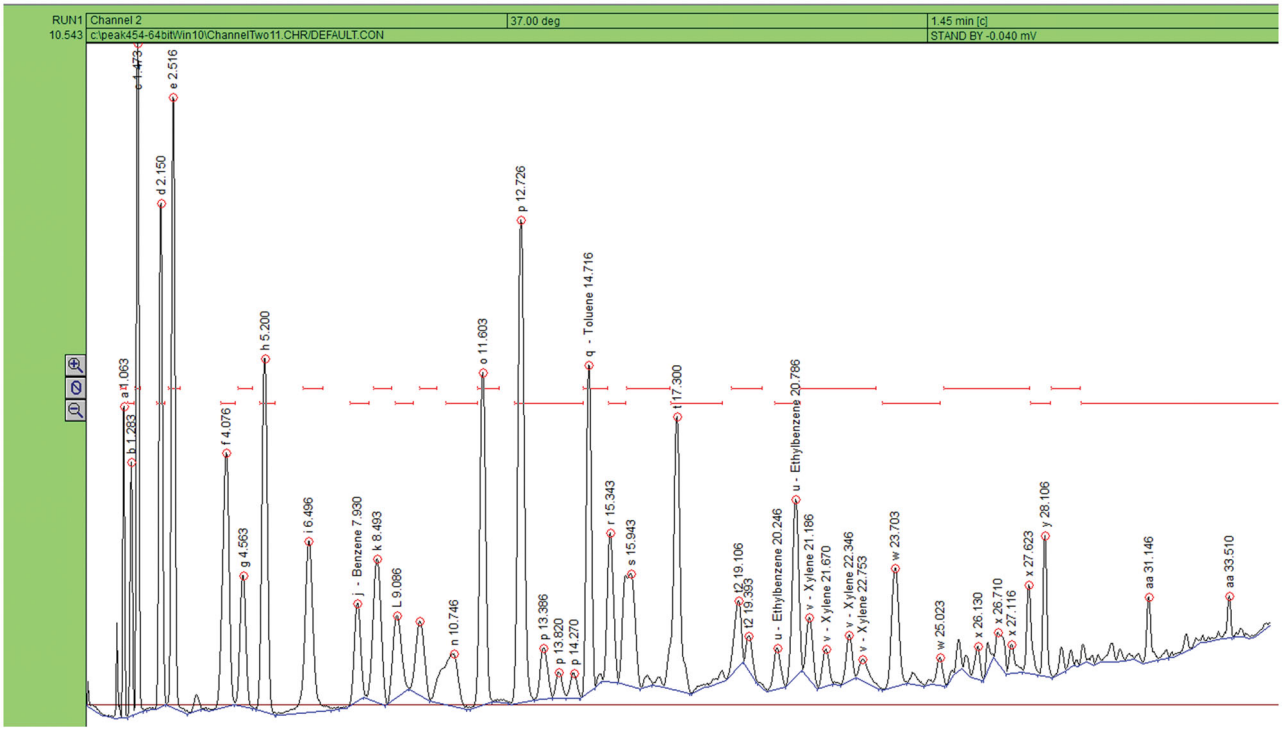

Figure 5. GC-FID spectrum output from a typical crude oil vapor reading at 300 ppm TVOC.

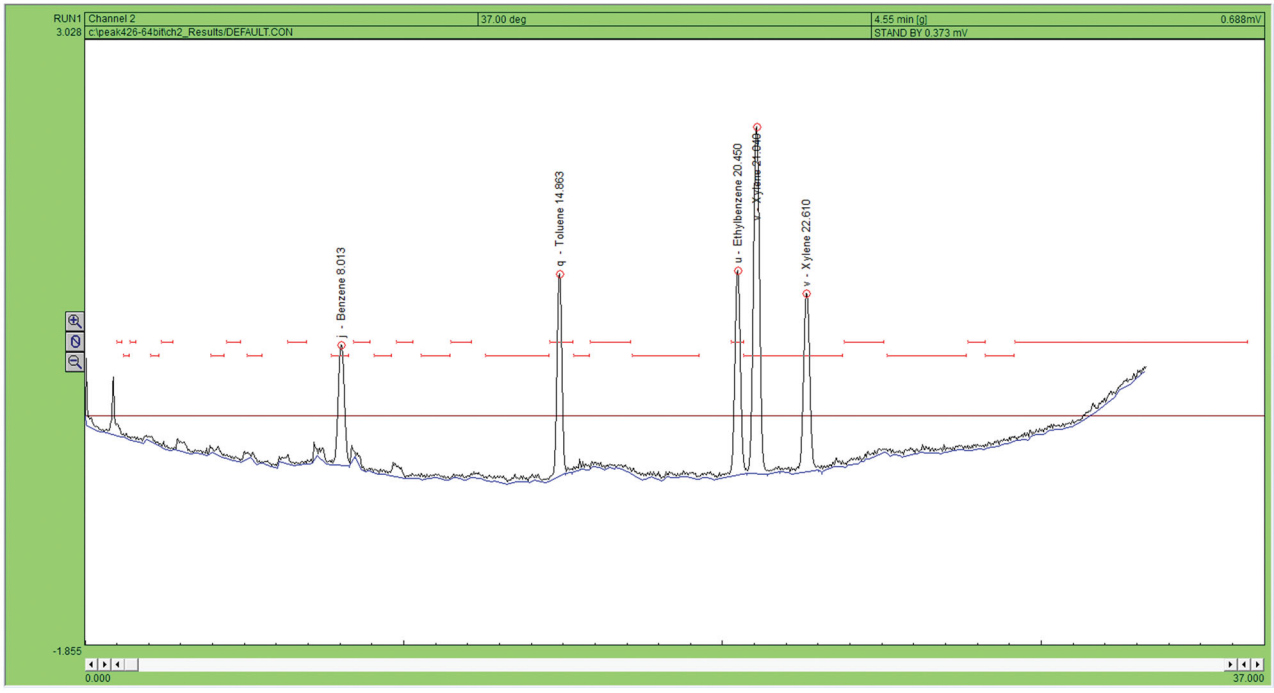

Figure 6. CG-FID spectrum output from BTEX calibration gas.

controller. Many more short-duration tests were conducted before the 1st exposure of animals, and several full 6-h tests were performed.

Figure 8(A) shows typical exposure chamber TVOC concentration during a 6-h exposure with a target concentration of 300 ppm. The system's control software would reach 90% of the target concentration in less than 15 mins and would have peak overshoot values of less than 315 ppm, i.e. less than 5% overshoot. After the initial rise transient response from 0 to 300 ppm the system was able to maintain TVOC concentrations to within ±4 ppm of the target 300 ppm setpoint. When the system

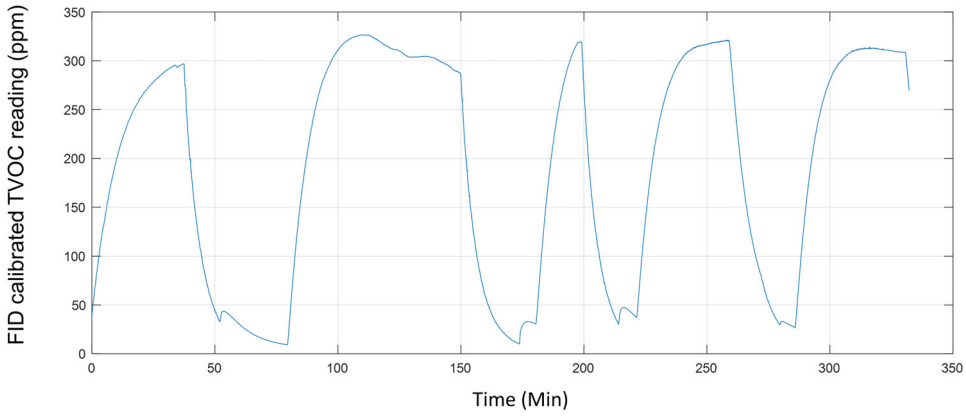

Figure 7. Exposure chamber TVOC during feedback tuning.

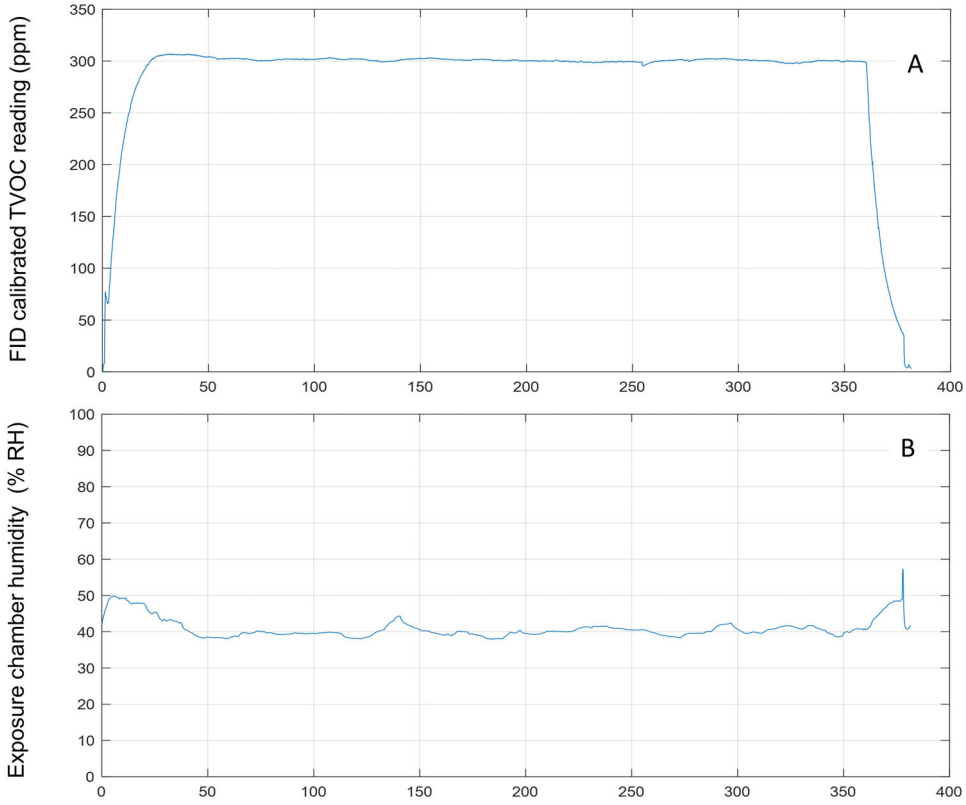

Figure 8. (A). Typical exposure chamber TVOC concentration (A) and relative humidity (B) plots during a 6 h exposure.

was set to purge mode the TVOC concentration would drop from 300 ppm to a safe level in less than 15 min.

The performance of the exposure chamber relative humidity controller is shown in Figure 8(B). The target humidity was 40% for all exposure runs. The humidity was slightly higher than target at the start of this exposure because the chamber was at equilibrium with lab room air during loading of animals into the chamber. Also, when animals were more active during the start of an exposure, they generate humidity. This effect can also be noted at the end of the exposure when the system entered purge mode. During the steady state portion of the exposures, humidity was well controlled to within ±5 of the 40% target.

The exposure chamber pressure controller could maintain the pressure at 0 inch-H_2O differential pressure with respect to the room pressure. This pressure difference never increased or decreased more than 0.1 inch H_2O.

Exposure chamber temperature and CO_2 levels vs. time

Exposure chamber temperature and CO_2 levels were not directly controlled by feedback loops but were monitored in real-time during all exposures to ensure adequate ventilation. Figure 9(A) shows the temperature during a 6-h exposure run. The fluctuations are likely from laboratory room temperature fluctuations. The exposure chamber temperatures ranged from 71 to 75 °F. The exposure chamber CO_2 levels during a typical 6-h exposure is shown in Figure 9(B). The CO_2 concentration would quickly rise to around

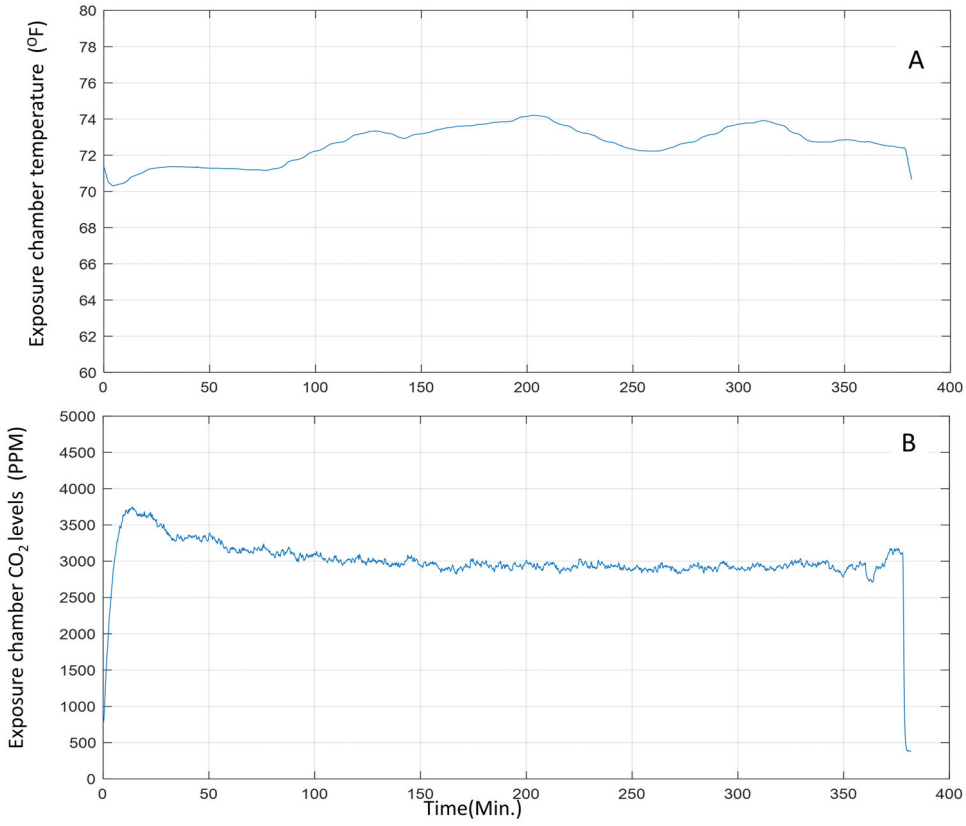

Figure 9. Typical exposure chamber temperature (A) and CO2 levels (B) during a 6 h exposure.

Table 3. Vapor concentrations during exposures.

Measurement	6-h average (ppm)	Daily standard deviation
TVOC	299.7	1.78
Benzene	6.9	1.2
Toluene	14.7	2.3
Ethylbenzene	2.0	0.2
Xylenes	12.9	1.9

3700 ppm during the beginning of an exposure then level off at around 3000 ppm as the animals became less active. The exposure chamber temperature and CO_2 levels were always within the acceptable range required by the Institutional Animal Care and Use Committee.

Crude oil vapor during exposures

The target concentration for all exposures was 300 ppm TVOC calibrated to a BTEX standard. TVOC readings were recorded by the custom software every 2 sec, and BTEX were recorded at two time points during the steady state portion of each exposure. Table 3 gives the mean and standard deviations of all exposure days for the studies that used this system. There were 2 exposure protocols, i.e. a single day exposure and 4 days a week exposure lasting 4 weeks (16 exposure days total). Each exposure would last 6 hours. The single-day exposure was conducted 11 times total to accommodate the needs of the study. The 4 weeks exposure was also conducted 11 times total. Animals in the single-day exposure protocol were never exposed more than one day, and the animals in the 4-week exposure protocol were never exposed more than 16 days. The total number of days the system was run with animals was 187. The number of animals in the chamber ranged from 12 to 24 to meet the experimental requirements.

A VOC reading was taken from the air control chamber using a full chamber of 24 rats with the same air flow rate as the COV exposure chamber. The FID had a stable reading of 1.4 ppm during these tests. This level was considered low enough (less than 0.5% of the target 300 ppm) to be negligible for our studies. The primary gasses generated by rats are ammonia from their urine and CO_2 from their breathing. Ammonia and CO_2 are not detected by an FID instrument so they did not show up as a VOC.

The overall pattern and heights of the peaks detected by the GC-FID during each exposure were consistent with the spectrum shown in Figure 5. There were not any detectable trends of changing COV composition over the duration of the studies.

Discussion

A computer-controlled system for exposing small laboratory animals to COV was designed, fabricated, performance-tested and employed. The system met or exceeded all the design objectives. The target concentration for studies at NIOSH using this system was 300 ppm but the system operated well with any target concentration ranging from 20 and 600 ppm COV without modification. This exposure system was developed for COV; however, the system would likely work with a wide variety of volatile liquid mixtures. It is

also possible that the exposure system could be scaled up with minimal difficulty to accommodate much larger exposure chambers that can house more animals which would be required for long-term and/or lower concentration inhalation studies. The system provided a valuable tool for NIOSH researchers to study the health effects of inhaled COVs (Fedan et al. 2022; 2022; Investigative Team 2022; Krajnak et al. 2022, Weatherly et al. 2022; Sriram et al. 2022).

Disclosure statement

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 PreventionMention of any company or product does not constitute endorsement by NIOSH/CDC.

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