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RESEARCH ARTICLE

Computer controlled multi-walled carbon nanotube inhalation exposure system

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Abstract

Inhalation exposure systems are necessary tools for determining the dose–response relationship of inhaled toxicants under a variety of exposure conditions. The objective of this project was to develop an automated computer controlled system to expose small laboratory animals to precise concentrations of airborne multi-walled carbon nanotubes (MWCNT). An aerosol generator was developed which was capable of suspending a respirable fraction of multi-walled carbon nanotubes from bulk material. The output of the generator was used to expose small laboratory animals to constant aerosol concentrations up to 12 mg/m³. Particle distribution and morphology of the MWCNT aerosol delivered to the exposure chamber were measured and compared to samples previously taken from air inside a facility that produces MWCNT. The comparison showed the MWCNT generator was producing particles similar in size and shape to those found in a work environment. The inhalation exposure system combined air flow controllers, particle monitors, data acquisition devices, and custom software with automatic feedback control to achieve constant and repeatable exposure chamber temperature, relative humidity, pressure, aerosol concentration, and particle size distribution. The automatic control algorithm was capable of maintaining the mean aerosol concentration to within 0.1 mg/m³ of the selected target value, and it could reach 95% of the target value in less than 10 minutes during the start-up of an inhalation exposure. One of the major advantages of this system was that once the exposure parameters were selected, a minimum amount of operator intervention was required over the exposure period.

Keywords: Carbon nanotube; inhalation exposure; exposure system; computer control; particle generation; particle distribution; feedback control

Introduction

There is rapidly expanding interest in the field of nanotechnology, which involves the synthesis of nanoparticles having at least one dimension between 1 and 100 nanometers. Nanostructures are finding applications in the manufacturing of medical products, drug delivery systems, consumer goods, and miniature electrical components. Carbon nanotubes exhibit exceptional thermal and electrical conductivity properties and are promising candidates for use in chemical sensors and catalysts. Some nanotubes have been used in medicine to deliver therapeutic agents to both the brain (Oberdorster et al., 2004) and cancer tumors (Liu et al., 2006; Chakravarty et al., 2008).

Even though multi-walled carbon nanotubes (MWCNT) appear to have great potential for industrial and medical applications, there is very little information concerning their

adverse toxicological effects on workers who are involved in the production and use of these products. It has been suggested that workers may be at risk for exposure to nanosized particles during the manufacture, handling, and cleanup of engineered nanomaterials (Maynard et al., 2004; Oberdorster et al., 2005a & b). Because of their atypical physical and chemical characteristics, nanoparticles may provoke unique biological responses that are different from those found for fine-sized particles of the same composition (Oberdorster et al., 2005a & b; Maynard & Kuempel, 2005). Previous studies have indicated that low-solubility nanoparticles appear to be more toxic than larger particles of the same material on an equal mass basis (Oberdorster et al., 2005a & b). As a result, it is important to conduct toxicological investigations of manufactured nanosized particles before workers exposed to aerosols of those materials develop disease.

During the past few years several investigators have developed and described methods for aerosolizing carbon nanotubes to evaluate their health effects. In a recent publication (Mitchell et al., 2007) a method of generating multi-walled carbon nanotubes to expose mice was described. Their system employed a screw feeder, jet mill, and cut-point cyclone to produce a respirable aerosol. The system was capable of producing low concentrations of nanotubes between 0.1 and 1 mg/m³. This method of generating carbon nanotubes separates the fibers by injecting them into a turbulent air stream where they undergo high velocity collisions with other carbon nanotubes. In the past, this process has often been used to pulverize materials such as silica to form small particles. Questions have arisen, however, as to whether the energy associated with this separation process alters the physical properties of the aerosolized carbon fibers compared with those found in the air of a carbon nanotube production facility.

A second method employs an ultra high-speed knife mill to chop single walled carbon nanotubes to form small particles (Baron et al., 2008). The system produces aerosols that can be used for inhalation studies, although it generates considerable noise, which may cause additional stresses to the animals in the exposure chamber. It also requires continuous adjustments by a well-trained technician.

The overall objective of this study was to develop a generator and incorporate it into an exposure system which was capable of exposing small animals to constant concentrations of multi-walled carbon nanotubes. This paper focuses on the design and testing of that system. The computer controlled multi-walled carbon nanotube inhalation exposure system was designed to meet the following specific requirements: (1) the generator must produce airborne particles continuously for long periods of exposure time (5 or more hours), (2) the physical characteristics of the aerosolized multi-walled carbon nanotubes should mimic what has been found airborne in the workplace, (3) the exposure concentration, up to a level of 12 mg/m³, should be maintained automatically by the system with minimal fluctuations during an exposure period, (4) the size distribution of the airborne exposure particles should remain constant during consecutive exposure periods, (5) the exposure concentration response time must be minimal after the animals have been placed into the chamber, (6) the overshoot in exposure concentration during the initial rise transient should be minimal, and (7) the system should be computer controlled and require little, if any, operator intervention over the exposure period.

Materials and methods

The MWCNT exposure system hardware

A block diagram of the complete computer controlled multi-walled carbon nanotube inhalation exposure system is shown in Figure 1. Air from a water seal compressor was conditioned by passing it through a dryer, a charcoal filter, and then a high efficiency particulate air (HEPA) filter. The clean air was regulated with two mass flow controllers (Aalborg,

model GPC373S). The first mass flow controller supplied air at a flow rate of 6 liters per minute (LPM) to the acoustical particle generator, and the second mass flow controller supplied a variable flow, from 0 to 20 LPM, to the generator's enclosure box. This mass flow controller was placed in a feedback loop that was automatically controlled by the computer to keep the pressure differential across the generator's flexible diaphragms at a constant +0.1 inches of H₂O. The acoustical generator itself is discussed in full detail in the following section. The output air of the particle generator was introduced into a modified 20-liter metabolism chamber that held an animal cage capable of accommodating 12 mice. An instrument based on light scattering properties of aerosols (Thermo Electron DataRAM 4) was used to monitor the mass concentration of carbon nanotubes in the exposure chamber. Samples from the DataRAM were read continuously by the computer and used to adjust the voltage signal driving the particle generator's speaker to maintain the desired exposure aerosol concentration. In addition, aerosol concentrations were determined gravimetrically with 37-mm cassettes and Teflon filters over an exposure period and were used to calibrate and verify the DataRAM readings. An example of the calibration data is shown in Figure 2. After the MWCNT

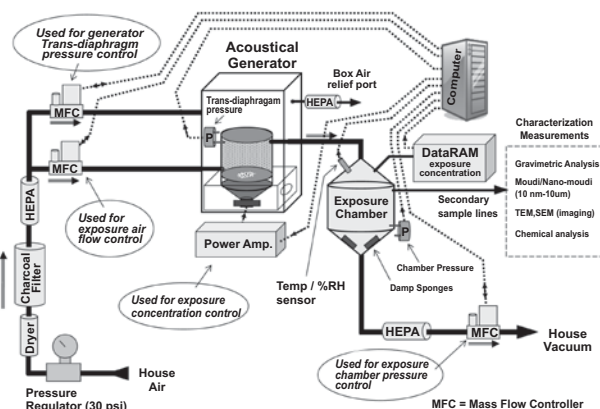


Figure 1. The computer controlled multi-walled carbon nanotube (MWCNT) inhalation exposure system.

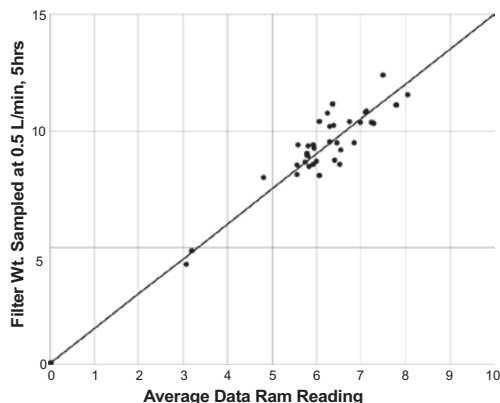


Figure 2. DataRAM calibration data.

aerosol exited the exposure chamber, it was filtered through a HEPA filter and the air was exhausted through a third mass flow controller to a vacuum system. Pressure inside the exposure chamber was measured continuously with a pressure transducer (Setra, model 264). The exposure system's software was designed to automatically make adjustments to this mass flow controller to keep the exposure chamber at a negative pressure of -0.02 inches of H_2O . This slight negative pressure was maintained to minimize the effects of air leaks and to aid in preventing the aerosol from escaping the exposure chamber into the ambient.

The temperature and humidity of the air inside the exposure chamber were continuously measured with a temperature/humidity sensor (Vaisala, model 234). Damp sponges were placed in the bottom of the exposure chamber before each exposure period, which resulted in a stable relative humidity of about 35% over a 5-hour exposure period. Particle distribution and morphology of the MWCNT aerosol inside the exposure chamber was determined with a micro-orifice uniform deposit impactor (MOUDI; model 110), a nano-MOUDI (model 115), a transmission electron microscope (TEM; Jeol 1220; Jeol Inc., Tokyo, Japan) and a scanning electron microscope (SEM; Jeol 6400; JEOL, Inc.).

The MWCNT aerosol generator

The MWCNT bulk material was provided by Mitsui & Co. (MWCNT-7, lot 061220-31; Ibaraki, Japan). The nanotubes were catalytically grown by chemical vapor deposition processes. The powder was conductive and contained fiber particles. According to the vendor's description, the average width of the particles was between 40 and 90 nm, while the length varied up to several micrometers.

The multi-walled carbon nanotube aerosol generator is illustrated in Figure 3. A major component of the generator was a large cylindrical acrylic chamber. The chamber was 18 inches in height with a 14-inch diameter. Both ends of the cylinder were enclosed with flexible latex rubber diaphragms to form a drum-like structure. The diaphragms were 0.02 inches thick and were held tightly in place with rubber o-rings. The walls of the acrylic cylinder, excluding a viewing port, were lined with conductive foil tape and were electrically grounded to prevent the build-up of static electrical charge. The cylinder was mounted vertically above a base containing a high compliance 15-inch loudspeaker (Ciare, model 15.00SW). The speaker faced upward, and without making physical contact was acoustically coupled to the bottom diaphragm of the acrylic cylinder. During operation, bulk samples of multi-walled carbon nanotubes (5 grams) were placed inside the cylinder onto the lower diaphragm. The speaker was driven with a computer generated analog signal fed through an audio amplifier (Butt Kicker, model BKA-1000-4A). The signal used to excite the speaker consisted of a variable frequency sine wave that gradually swept back and forth between 10 and 18 Hz over a 20-second period. This signal was chosen because it generated frequencies above and below the resonant frequency of the acrylic cylinder and flexible diaphragm combination. The resonance frequency

of the generator is primarily a function of the acrylic cylinder dimensions and the flexible diaphragms on each end. How tightly the flexible diaphragms are stretched over the cylinder can effect the resonance frequency. A sweeping voltage signal proved useful because when the resonance frequency changed slightly the driving signal still swept through the new resonance frequency. Thus, slight changes in the actual resonance frequency (± 3 Hz) of the generator had minimal effects on the overall output efficiency of the generator. Tests verified that this type of signal was highly efficient in aerosolizing the bulk MWCNT material. The output concentration of the generator was controlled by varying the amplitude of the signal used to drive the speaker. The relationship between the root mean square (RMS) voltage of the speaker excitation and the generator aerosol output concentration is shown in Figure 4. Each data point in Figure 4 represents the mean concentration at the set RMS voltage over a 30-minute run period. The error bars indicate the standard deviation of the concentration over the test period. As shown in Figure 3, clean dry air entered the generator on the lower left hand side of the acrylic chamber, and exited the cylinder on the upper right hand side. The chamber acted as a vertical elutriator allowing only small airborne particles to escape the cylinder. The larger particles consisting of agglomerated fibers and bundles tended to stay in the lower portion of the cylinder

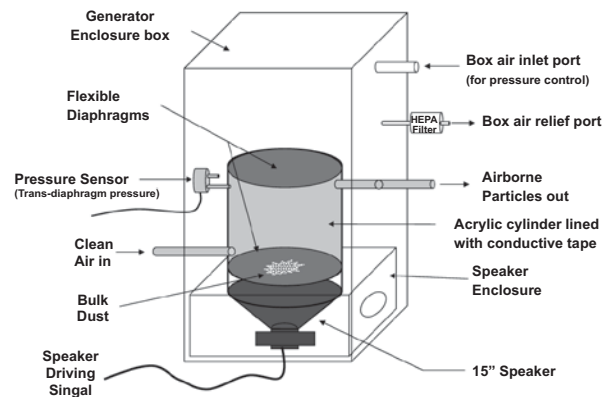


Figure 3. The MWCNT aerosol generator.

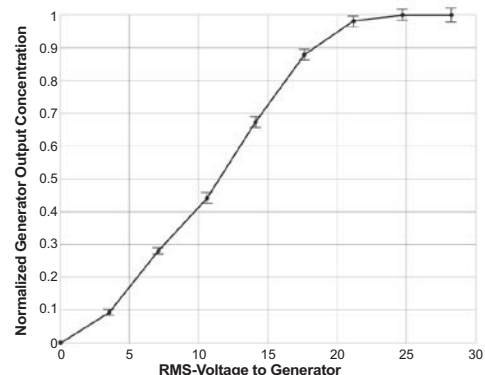


Figure 4. MWCNT generator energy vs. generator output concentration.

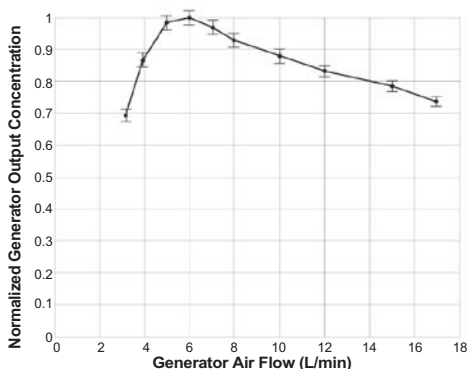


Figure 5. MWCNT generator air flow vs. generator output concentration.

until they were dispersed. When the generator air flow rate was increased to excessively high levels, it was possible to entrain larger particles which could exit the generator and distort the desired aerosol size distribution. In order to keep the larger agglomerated bundles from escaping the generator it was determined that the generator air flow should not exceed 15 LPM.

The relationship between acceptable generator air flows and generator output concentration is shown in Figure 5. Each data point in Figure 5 represents the mean concentration at the set generator air flow rate over a 30-minute run period. The error bars indicate the standard deviation of the concentration over the test period. When the air flow through the generator was very low the output dropped off quickly, and when the flow was too high, the concentration became diluted by the excess air. In order to maximize the generator's performance, it was typically operated at 6 LPM.

The acrylic cylinder, latex diaphragms, and loud-speaker assembly were placed within a large enclosure box (48 × 20 × 20 inches) with a small air pressure inlet port, and air relief port. The purpose of the box was to: (1) muffle the acoustic noise produced by the loudspeaker, (2) form a barrier to protect operators from aerosols that escaped from the generator due to a leak or ruptured diaphragm, and (3) precisely control the pressure differential across the flexible diaphragms on the ends of the cylinder.

The pressure inside the generator's cylindrical chamber was capable of rising quickly as air flowed through it, through several feet of tubing, through the exposure chamber, and finally through a HEPA filter before it was exhausted. This pressure, if uncontrolled, would cause the two flexible membranes on the ends to bulge outward. This deformation of the diaphragms induced the bulk material to collect at the center of the lower diaphragm. Since most of the displacement energy was delivered to that portion of the diaphragm, a slightly positive pressure across the flexible diaphragms was desirable to increase generator performance. If the positive pressure became excessive, however, the flexible diaphragms became overly stretched

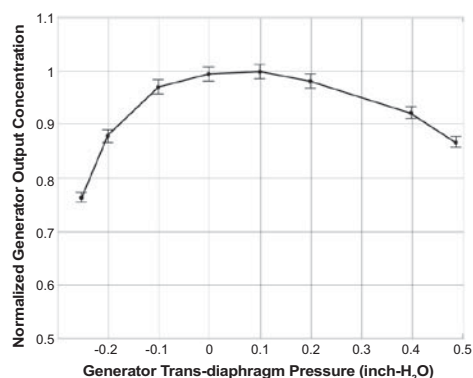


Figure 6. MWCNT generator cylinder pressure vs. generator output concentration.

and less compliant, resulting in a reduction in generator efficiency. By regulating the pressure inside the chamber holding the generator cylinder, the adverse effects of the pressure differential acting on the flexible diaphragms could be controlled. This helped to maximize the generator's performance. The relationship between the pressure difference across the flexible membranes, measured with a pressure transducer (Setra, model 264), and the generator aerosol output concentration is shown in Figure 6. Each data point in Figure 6 represents the mean concentration at the set trans-diaphragm pressure over a 30-minute run period. The error bars indicate the standard deviation of the concentration over the test period. When the pressure difference became negative the flexible diaphragms were pulled inward, causing the bulk material, on the lower diaphragm, to migrate toward the edges of the cylinder. This resulted in a decrease in the aerosol output concentration. The MWCNT system used a computer controlled automated feedback loop to maintain the trans-diaphragm pressure at its optimal value of +0.1 inches of H₂O. This ensured that the generator would be operating near its maximum effectiveness and eliminated pressure-related fluctuations in the output concentration. The details of the pressure feedback control loop are discussed in a later section.

Computer software user interface

A computer software interface for the MWCNT exposure system was implemented using the LabVIEW 7.1 programming environment. The interface was in the form of a virtual instrument and is shown in Figure 7. A graphical display on the lower portion of the virtual instrument continuously displayed the exposure concentration, the desired exposure concentration, and the output voltage driving the power amplifier of the acoustical generator. Three mouse-activated virtual buttons in the upper right hand corner of the user interface provided the main controls for the MWCNT exposure system. After animals had been placed into the exposure chamber the top button, labeled "Start the exposure," was pressed, which immediately changed

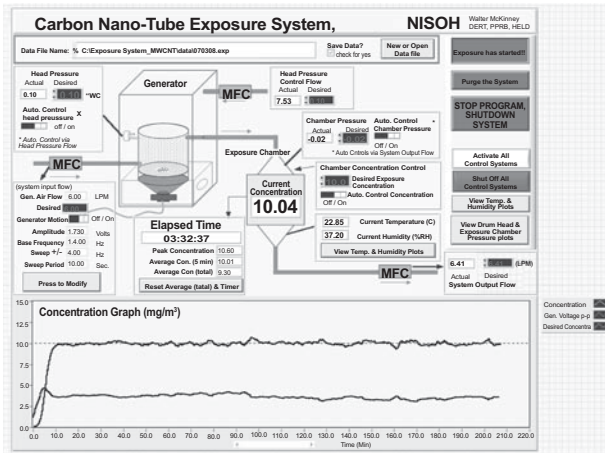


Figure 7. The exposure system interface and control screen.

that button's label to "Exposure has started!!" The virtual instrument then prompted the user to select a data file name and the desired exposure concentration. After entering those parameters, all feedback control systems were enabled, and average MWCNT concentration over the entire exposure period, the peak concentration, the last 5-minute average concentration, and the total elapsed time displays were reset to zero. The time and exposure averages were continuously displayed by the virtual instrument while the system was running.

The computer saved the history of the following exposure parameters in the selected data file at 2-second intervals: the elapsed exposure time (seconds), the generator excitation (volts), the air flow through the generator (LPM), the generator trans-diaphragm pressure (inches of H_2O), the exposure chamber MWCNT mass concentration (mg/m^3), the exposure chamber temperature ($^{\circ}C$), the exposure chamber relative humidity (%), and the exposure chamber trans-diaphragm pressure (inches of H_2O). During the inhalation exposure period the computer automatically controlled the air flow through the generator and exposure chamber, the exposure chamber pressure, the generator trans-diaphragm pressure, and the voltage driving the generator speaker, to maintain a constant MWCNT inhalation exposure. The system operator would periodically check the exposure system parameters only to verify the system was operating properly and to collect filter samples via the sample port in the exposure chamber. When the desired exposure period was completed, the operator pressed the second main virtual button labeled "Purge the system." This disabled the particle generator drive and raised the air flow rate into the exposure chamber to 15 LPM, quickly reducing the exposure chamber aerosol concentration. When the concentration dropped below $0.05 mg/m^3$, a window appeared on the computer screen indicating that the exposure was complete and it was safe to remove the animals from the chamber. At the same time the data file that saved all the exposure data was closed, and the feedback control loops were deactivated. After the animals were removed from the exposure

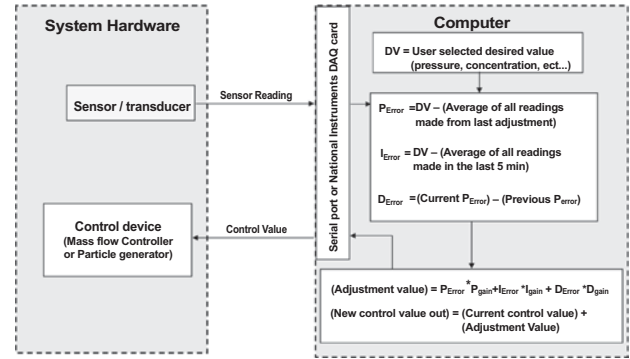


Figure 8. Diagram of proportional-integral-derivative (PID) feedback control loop.

chamber, the operator pressed the third main virtual button labeled "Stop program, shutdown system," which set all the mass flow controllers to zero flow and closed the software program.

Automated feedback control

The computer controlled MWCNT exposure system employed three different feedback loops to control the exposure concentration, the exposure chamber pressure, and the generator's trans-diaphragm pressure. The exposure concentration was maintained at a constant value by making adjustments every 20 seconds to the amplitude of the particle generator's excitation voltage based on readings made from the DataRAM. Typical desired exposure concentrations ranged between 5 and $12 mg/m^3$. The exposure chamber pressure was regulated by making corrections once every 2 seconds to the exposure chamber exhaust flow, based on readings from a Setra pressure transducer (see Figure 3). This pressure was typically held constant at a slight negative value of -0.02 inches of H_2O . The generator diaphragm pressure differential was automatically controlled by making adjustments to the amount of air entering the generator enclosure box, which also had a small air relief port (see Figure 3). A correction was made every 2 seconds based on the output of the Setra pressure transducer within the enclosure box. The pressure differential across the generator diaphragms was typically held constant at $+0.1$ inches of H_2O to yield maximum generator output efficiency (see Figure 6). A proportional-integral-derivative (PID) control algorithm (Nise, 1995) was implemented for each feedback control loop employed by the MWCNT exposure system. A block diagram of the feedback control algorithm is shown in Figure 8. The constants P_{gain} , I_{gain} , and D_{gain} used by each PID control loop were found using basic control tuning methods described by Nise (1995).

Results (system testing and validation)

Han et al. (2008) collected samples from the breathing zones of a workplace producing MWCNT by drawing the aerosol

through 35-mm filters at a rate of 1.5 LPM. These investigators provided an electron micrograph of a typical filter sample in their publication. The workplace sample was compared with those obtained from the exposure chamber of the MWCNT inhalation system. The exposure chamber samples were collected by drawing aerosol from the chamber through 47-mm polycarbonate filters (Whatman, Clinton, PA) at a rate of 1 LPM. These filters were then analyzed by transmission electron microscopy and scanning electron microscopy. The results are shown in Figure 9. Both the images of Han et al. (2008) and those illustrated in Figure 9 show many small particles having nearly circular dimensions with diameters in the 100–300-nm range. These small particles appear to be composed of tangled knots of fibers. In addition to these particles, a distribution of dispersed and lightly agglomerated MWCNT ranging in lengths from 1 to 6 μm were present on both the workplace and exposure system samples. The particle size and shape appeared to be nearly

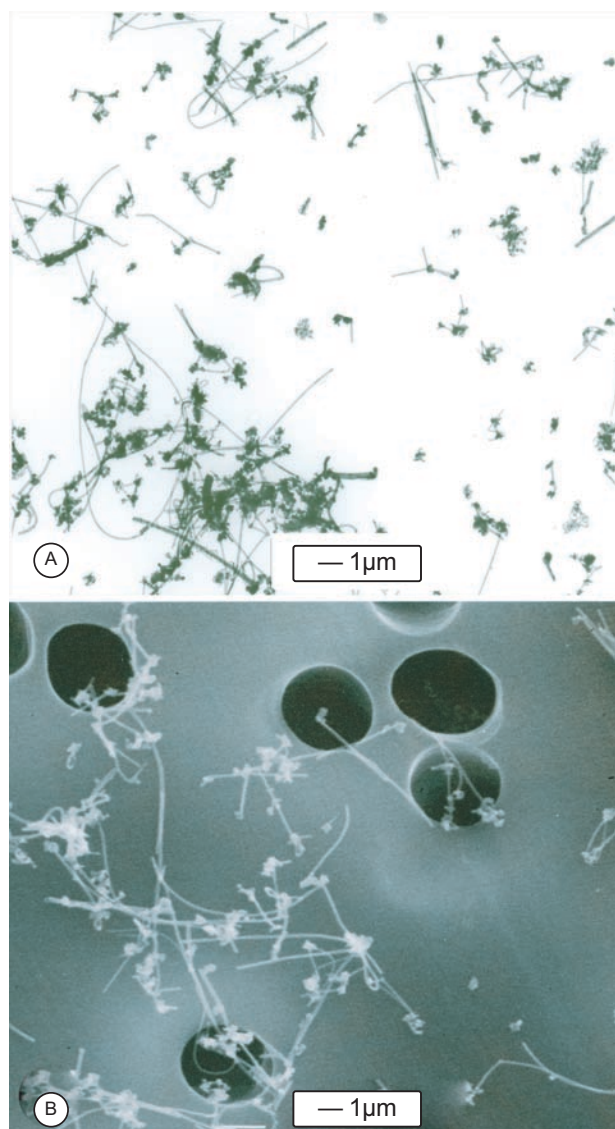


Figure 9. MWCNT sampled from the exposure chamber and viewed by (A) TEM, (B) SEM.

identical for samples collected in the workplace and in the exposure chamber.

Ideally, the particle size distribution of the MWCNT in the exposure chamber should remain constant at all times to ensure that the same conditions can be reproduced during each exposure period. The only variable associated with exposures should be the user-selected concentration (mg/m^3). Two types of experiments were conducted to determine the particle size distribution of the output of the MWCNT generator under different operating conditions. The first of these tests compared the size distribution of an aerosol generated with fresh bulk powder (5 grams) with the size distribution of an aerosol generated with the same powder after it had been used to produce a constant concentration of $10 \text{ mg}/\text{m}^3$ for 25 hours. There were concerns that the smaller particles might be released by the generator during the early stages of an exposure period, thus shifting the particle size distribution with respect to time. A second set of tests compared the particle size distribution of the generator output operating with a low energy signal (5.5 volts RMS, 25W) versus a high energy signal (24 volts RMS, 100W). This was important because the exposure concentration was controlled by varying the voltage delivered to the generator's speaker (see Figure 4). Particle size distributions were determined using a micro-orifice uniform deposit impactor (MOUDI model 110) and a nano-MOUDI (model 115) to take exposure chamber samples during each test run. The results of the particle size distribution measurements are shown in Figure 10. Surprisingly, there was not a significant difference between the four test samples. All samples had a mass median aerodynamic diameter of $1.5 \mu\text{m}$. The particle distribution data could be characterized by lognormal curves, and the geometric standard deviations of all four curves were about 1.7. The particle count aerodynamic diameter mode was found to be approximately $0.40 \mu\text{m}$, by visually inspecting the MOUDI filters under a scanning electron microscope.

The final test of the generator was to determine how often a typical bulk sample of MWCNT material (5 grams) needed to be replaced before the output aerosol concentration could no longer be controlled at the desired level. Results showed

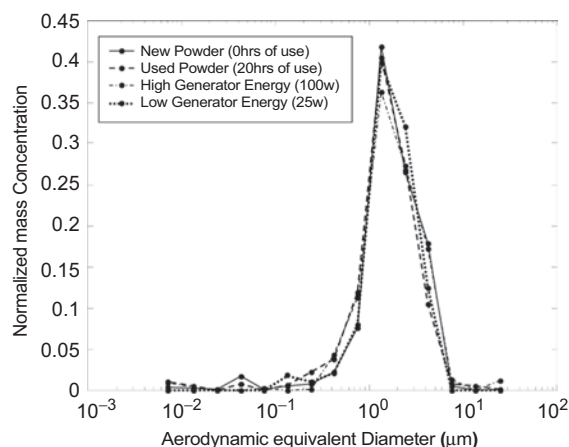


Figure 10. MWCNT particle distributions under various generator operating conditions.

that the generator could produce a stable concentration of 10 mg/m³ for a period up to 30 hours. After 30 hours the generator was operating at its maximum energy level (26 volts RMS, 113 W) and producing concentrations slightly lower than 10 mg/m³. Maintaining lower exposure chamber concentrations would enable the MWCNT bulk material to produce a constant aerosol concentration over a longer period.

In order to test the performance of the exposure system concentration feedback control loop, the system was operated for two 360-minute runs with and without the exposure concentration feedback control loop activated. The remaining two additional feedback control loops that controlled exposure chamber pressure and generator cylinder pressure were enabled during both runs. The results of these tests are

shown in Figure 11. The target concentration in both cases was 10 mg/m³. The automated control algorithm reduced the difference between the desired concentration and the median concentration by a factor of 19 (from 0.19 to 0.01), minimized the fluctuation from the desired concentration by a factor of 3.6 (from 0.65 to 0.18), and reduced both rise and fall times at the start and end of the exposure period by several minutes.

To verify that the computer controlled MWCNT inhalation exposure system could automatically hold exposure levels at various user-selected concentrations without an operator's assistance, three runs were conducted with target concentrations of 6, 10, and 12 mg/m³. The results of these test exposures are shown in Figure 12.

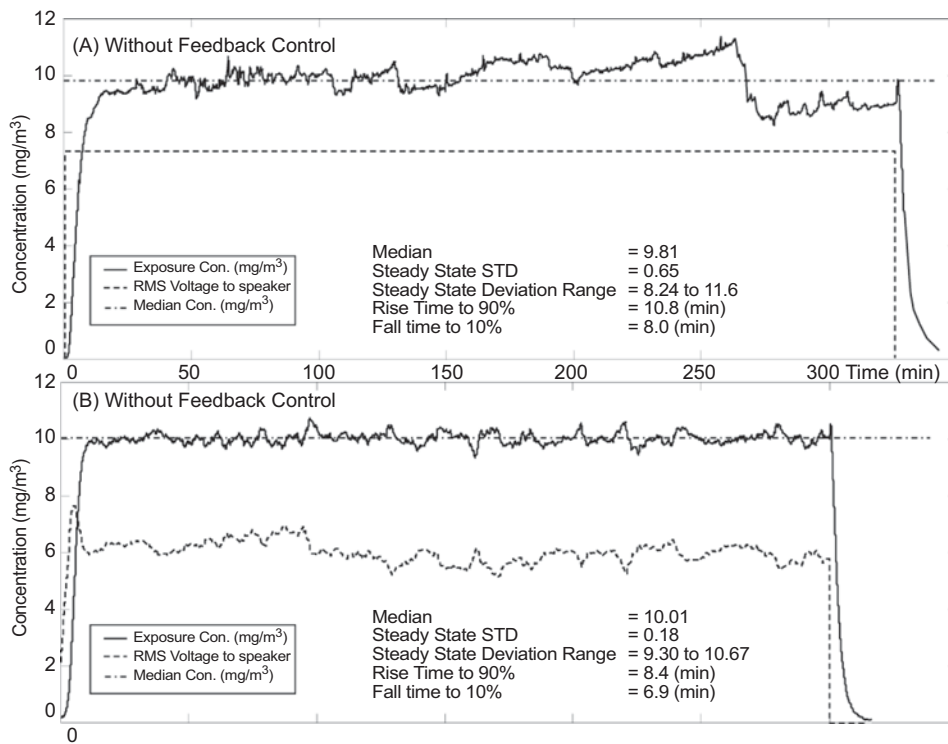


Figure 11. MWCNT exposure concentrations (A) without and (B) with automated feedback.

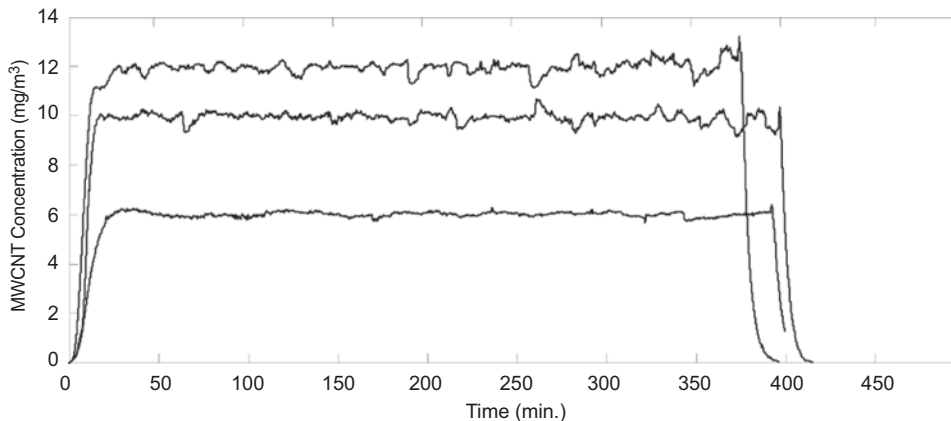


Figure 12. Automatic exposure level control with target concentrations of 12, 10, and 6 mg/m³.

In addition to controlling the inhalation exposure concentration, the MWCNT exposure system automatically controlled exposure chamber pressure and the pressure difference across the generator cylinder diaphragms. The pressure inside the exposure chamber was typically held constant at -0.02 inches of H_2O and the generator cylinder pressure difference was normally held constant at 0.10 inches of H_2O . The pressure measurements over an exposure period that lasted about 300 minutes are shown in Figure 13. The system was capable of automatically holding both pressures at very precise levels with a standard deviation of less than 0.003 . The small blips on the exposure chamber pressure graph were a result of sample pumps being turned on and off during an exposure run as filters were being changed. It can be seen that the automatic control system quickly compensated for the variation in air flow leaving the exposure chamber during a filter change to bring the pressure back to the desired value.

The temperature and relative humidity inside the exposure chamber were not under feedback control; however, they were monitored and continuously logged during each exposure run. Figure 14 shows the temperature and humidity data for a typical exposure run lasting about 300 minutes. The damp sponges placed in the lower portion of the exposure chamber (see Figure 1) provided the chamber with a

humidity level of around 35%. The exposure chamber air flow rate that was maintained at 6 LPM provided good ventilation, resulting in a stable temperature that matched the temperature of the laboratory.

Discussion and conclusion

A computer controlled MWCNT inhalation exposure system was successfully designed, constructed, and tested. The MWCNT particle generator consisted of an improved and optimized acoustical dust generator. Through the use of this generator and the custom computer software that controlled the exposure system, all the project objectives were accomplished. (1) The generator produced airborne particles continuously for long periods of time. The generator would produce 10 mg/m^3 mass concentration for 35 hours before the typical 5 grams of bulk material would need to be replaced. (2) The physical characteristics of the aerosolized multi-walled carbon nanotubes mimicked what was previously found airborne in a work environment. (3) The exposure system had the ability to expose animals to a range of inhalation exposure doses up to 12 mg/m^3 , with minimal fluctuations during an exposure period. (4) The data showed that the particle size distribution was repeatable between exposures and various

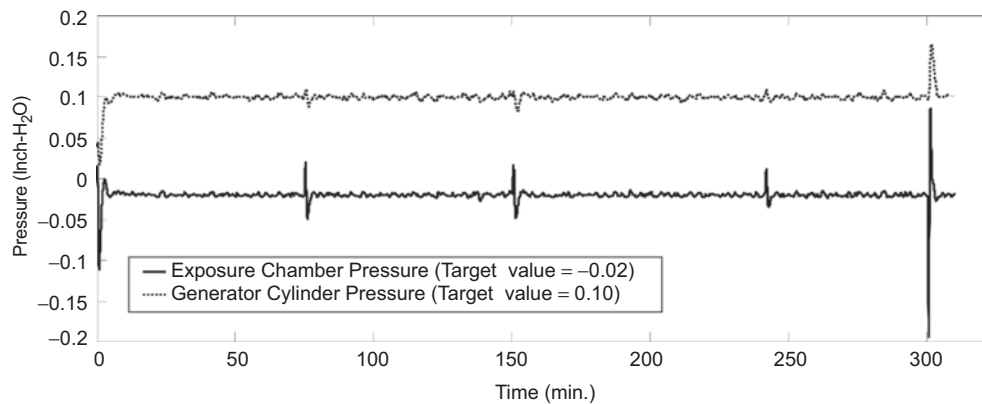


Figure 13. Automatic control of exposure chamber pressure and generator cylinder pressure.

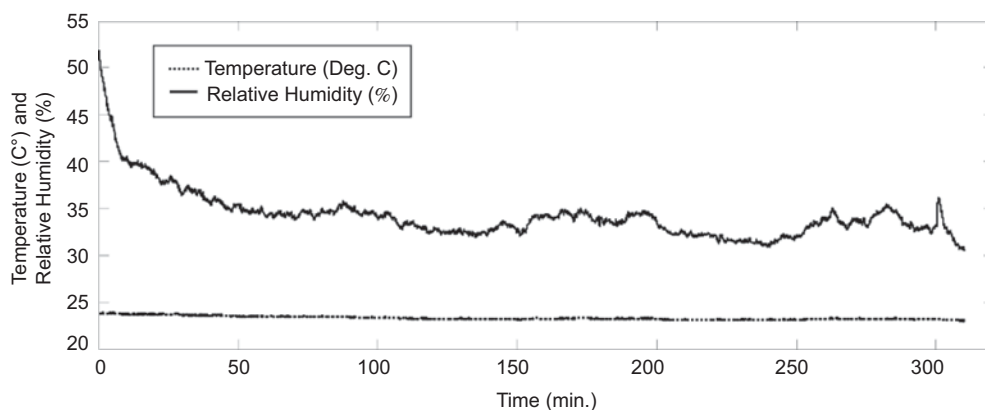


Figure 14. Exposure chamber temperature and relative humidity plots.

operating conditions, with a mass median aerodynamic diameter of about $1.5 \mu\text{m}$ and a geometric standard deviation of 1.7. The count aerodynamic diameter mode was about $0.40 \mu\text{m}$. The size distribution of the airborne exposure particles did not change over long exposure runs, and remained constant over all generator energy levels. (5) The exposure concentration response time, after animals were placed into the exposure chamber, was minimized to less than 9 minutes by employing a feedback control loop. (6) The overshoot in exposure concentration during the initial rise transient was minimal at less than $0.5 \text{mg}/\text{m}^3$. The animals did not receive a spike in exposure concentration that sometimes results when using a feedback control loop. (7) The system was computer automated and required little operator intervention over the exposure period. The computer controlled MWCNT inhalation exposure system is currently being used to assist NIOSH investigators in determining potential adverse toxicological effects from inhalation exposure to MWCNT.

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Declaration of interest: 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.

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