

**AN INDUSTRIAL HYGIENE SURVEY OF ACETONITRILE USING A
MINIATURE QUADRUPOLE MASS SPECTROMETER**

A Thesis

by

STACY M. BRUSS

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

December 1999

Major Subject: Industrial Hygiene

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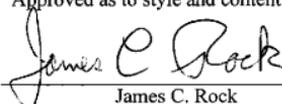
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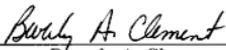
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ABSTRACT

An Industrial Hygiene Survey of Acetonitrile Using a Miniature Quadrupole Mass Spectrometer. (December 1999)

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Charcoal tubes are an industry standard for the collection and concentration of airborne chemicals in the field for later analysis in a laboratory. There are a few drawbacks in using charcoal tubes, including the time delay before results are returned, breakthrough potential, and interferences. It is often impractical or impossible to observe a time history of contamination concentration. New technological advances have made it possible to miniaturize instruments typically found in the laboratory, such as the mass spectrometer. These advances include recent development of a miniature multipole mass spectrometer that may be useful for direct measurement of contamination in the field.

Two goals were achieved in this research. First, the potential for worker exposure to acetonitrile vapors during the cleaning of a DNA-synthesizing process was demonstrated. Second, acetonitrile concentrations were measured from Tedlar bags filled in an organics-contaminated work environment and other bags with synthetic atmospheres. A miniature multipole mass spectrometer is compared with NIOSH method 1606 analysis of charcoal tubes through which the contaminated air passed while the bags were emptied.

Workplace air samples, along with studies of the ventilation patterns, showed potentially unacceptable worker exposure to acetonitrile. The hazardous DNA-synthesis process was shut down pending process improvements. The multipole mass spectrometer provided readings that did not have a consistent relationship with their associated charcoal tube readings. Background readings, which included varying concentrations of environmental contaminants, needed to be subtracted, increasing variance in readings due to the high variance observed in the background readings.

ACKNOWLEDGEMENTS

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I would like to thank my committee chair, Dr. James C. Rock, in giving support and guidance throughout the course of this work. I would also like to thank Dr. Vahid Majidi and his group at Los Alamos National Laboratory for their assistance in performing the research for this work, as well as the processing of charcoal tube samples. Thanks also goes out to my other committee members, Dr. Ian S. Hamilton and Dr. Beverly A. Clement, for their guidance and time.

I would also like to thank my parents for their support in getting me to where I am today. Their love and support while in school encouraged me to continue my education to graduate school. I would also like to thank Ken Krieger, whose love and support helped me to complete this thesis during the fall semester.

TABLE OF CONTENTS

	Page
ABSTRACT	iii
ACKNOWLEDGEMENTS.....	v
TABLE OF CONTENTS	vi
LIST OF FIGURES	vii
LIST OF TABLES.....	viii
INTRODUCTION	1
Acetonitrile Hazards	2
DNA Synthesis Process	4
Charcoal Tube.....	5
Mass Spectrometry	7
Verification of Method.....	16
EXPERIMENTAL METHODS AND MATERIALS	18
Materials	18
Methods	20
RESULTS AND DISCUSSION.....	23
CONCLUSIONS	32
REFERENCES	33
APPENDIX 1.....	36
APPENDIX 2.....	40
APPENDIX 3.....	43
APPENDIX 4.....	45
VITA.....	48

LIST OF FIGURES

	Page
Figure 1. The MerMade	5
Figure 2. Charcoal Tube	6
Figure 3. Schematic of Micropole Mass Filter	10
Figure 4. Electric Potential on a Quadrupole Array	11
Figure 5. Stability Diagram	12
Figure 6. Sensitivity vs. Resolution.....	13
Figure 7. Mass Spectrum for Acetonitrile by Electron Ionization ⁽¹¹⁾	15
Figure 8. Location of Sampling Devices (Top view of MerMade)	21
Figure 9. Vapor Flow from Enclosed Area	23
Figure 10. Mass Spectrometer Readings, Associated Background Readings, and 68% Confidence Limits of Each	26
Figure 11. Mass Spectrometer Readings Valid for Analysis and Associated Charcoal Tube Readings, Including 95% Confidence Limits.....	28

LIST OF TABLES

	Page
Table I. Characteristics of the Three Common MS Instruments	9
Table II. Compounds with Ions of Mass 39 to 41 AMU	15
Table III. Micropole System Components	18
Table IV. Charcoal Tube Results for Samples Taken at the MerMade.....	24
Table V. Test for Validity of Classical Statistics.....	30

INTRODUCTION

There are many types of instruments and analytical techniques available for industrial hygiene surveys for the measurement and analysis of workplace air. Instruments may measure contamination qualitatively, identifying the compound that is present, or quantitatively, identifying the amount of that compound present. Most instruments are developed to detect a certain compound or family of compounds. By using correction factors these instruments may be used to detect other compounds, however, the results will likely be only a qualitative measurement. Some common industrial hygiene measurement and analytical techniques involve the use of a sorbent media, usually charcoal tubes, to collect airborne contaminants for later analysis in a laboratory using a mass spectrometer and/or gas chromatograph. The charcoal tube is the industry standard used to collect airborne contaminants.

The use of sorbent tubes to concentrate contaminants for precise analysis has several drawbacks. The time delay before results are returned is chief among them. To process a charcoal tube at an accredited laboratory, results will take days to weeks to return. Other drawbacks include breakthrough potential or interferences. It is often expensive to screen a charcoal tube for more than one contaminant, and impractical or impossible to observe a time history of contamination concentration.

This thesis follows the style and format of *American Industrial Hygiene Association Journal*.

The goal of this research is twofold. First, to determine the potential for worker exposure to acetonitrile vapors during the cleaning of a DNA-synthesizing process (MerMade). This process has yet to be evaluated for worker exposure to the potentially harmful vapors. The second goal of this research is to quantify acetonitrile concentrations in an organics-contaminated work environment and created atmospheres using a field-deployable mass spectrometer, the Ferran Scientific Micropole system (Micropole). The mass spectrometer results will be compared to the results from charcoal tubes exposed to the same contaminated environment.

The use of a mass spectrometer should solve the drawbacks of breakthrough potential, interferences, and result return time. If successful, this mass spectrometer may be easily modified to make it a portable industrial hygiene tool, able to solve other drawbacks of screening for more than one contaminant, and time functions of contamination. Although much work has been reported with portable gas chromatograph/mass spectrometer (GC/MS) instruments, there has yet to be a published evaluation of a field-deployable mass spectrometer-only instrument as an industrial hygiene tool.⁽¹⁾

Acetonitrile Hazards

Acetonitrile is used extensively in many different chemical processes. It is used primarily as a solvent in extractive distillation, crystallization of pharmaceuticals, agricultural products, and as a catalyst in chemical reactions. Acetonitrile is used as a chemical intermediate in pesticide manufacture. This chemical is used extensively in

chemistry reactions wherever a polar solvent having a rather high dielectric constant is required, and as a solvent for both inorganic and organic compounds, including polymers.⁽²⁾

The occupational hazard from acetonitrile is believed to be controlled by the occupational exposure limits set by major rulemaking bodies. The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) and the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV-TWA) are set at 40 ppm, while National Institute for Occupational Safety and Health (NIOSH) has set its recommended exposure limit (REL) value to 20 ppm, all on the basis of an 8-hour exposure. ACGIH has set a Short-Term (15 minutes) Exposure Limit (TLV-STEL) of 60 ppm.^(3,4) Odor thresholds have been determined by various studies, but as is their nature, the estimates have high variance. It has been reported to be from 40 to 90 ppm.⁽²⁾ This suggests, however, that if acetonitrile odor can be smelled, that the exposure is above the exposure levels set for an 8 hour exposure, and is comparable to the recommended 15-minute exposure limit.

The major route of exposure to acetonitrile is inhalation of vapor, with skin absorption of liquid as the next most prominent route. Brief inhalation can result in irritation of the nose and throat. Heavier exposure, above 160 ppm, can cause nausea, dizziness, and respiratory depression.⁽⁵⁾ Chronic exposure at levels above the TLV-TWA may result in damage to the liver and kidneys. Contact of liquid acetonitrile with the skin results in irritation, as well as permeation through the skin to produce similar chronic health effects to those resulting from inhalation. Cyanide can be formed in the

body as a byproduct of acetonitrile metabolizing in the body, creating more health hazards.

The effects on health, as well as the low occupational exposure levels, illustrate the importance of quick and accurate air sampling for acetonitrile to reduce exposure.

DNA Synthesis Process

The process studied in the field is a DNA-synthesizing process, called the MerMade. This instrument manufactures strands of DNA for use in biological experiments. There are many organic chemicals used in small quantities during the production of the DNA strands. The solvent to all these chemicals is acetonitrile, used to clear the process between the application of each chemical. As a result, over four liters of acetonitrile, with large amounts of vapor produced, are used in the process every day. Additionally, the equipment requires a 20 to 40 minute cleaning by hand scrubbing, liberally using acetonitrile on a daily basis. The potential for inhalation exposure to acetonitrile vapors and skin exposure to liquid is greatest during this cleaning procedure.

The MerMade has an open-sided hood, depicted in Figure 1. Creation of DNA is accomplished in the enclosed process area. The cleaning procedure involves the cleaning of this normally enclosed area, through an open access panel.

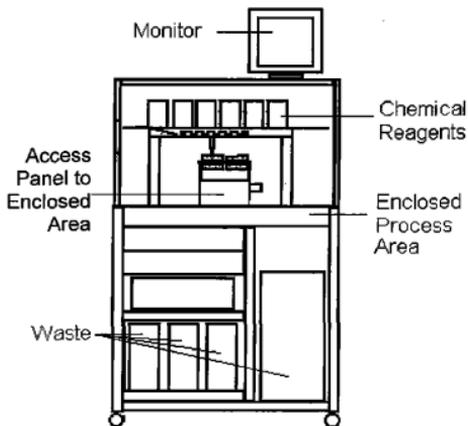


Figure 1. The MerMade

Charcoal Tube

The charcoal tube is a physical method for concentrating trace airborne chemicals for later analysis at a laboratory, without changing their chemical nature. A typical charcoal tube consists of a glass tube packed with two sections of charcoal granules separated by a foam plug (see Figure 2). As can be seen, the sorbent layer has twice the charcoal found in the backup sorbent layer.

As contaminated air is drawn through the charcoal tube, chemical contaminants are adsorbed on the surface and in the pores of the charcoal. Breakthrough occurs when

over five percent of the chemicals reach the backup sorbent layer, potentially affecting the accuracy of the sample.

The charcoal tube is sent to a laboratory for processing. Adsorbed chemicals are removed from the charcoal by a solvent desorption process. This involves the immersion of the contaminated charcoal in a solution of chemicals that readily displaces the contaminant from the charcoal. This desorption solution is usually specific to the contaminant to be analyzed. The charcoal is removed from the solution after a time, then the solution is analyzed using a specified analytical instrument, such as a gas chromatograph.

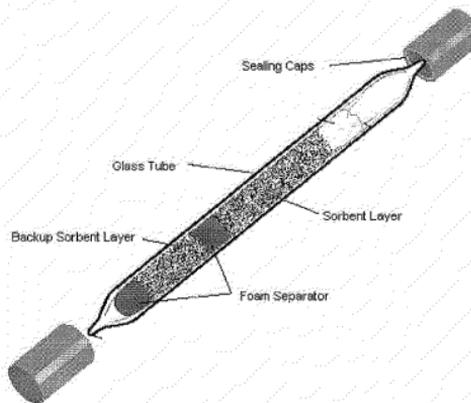


Figure 2. Charcoal Tube

The method currently recommended for acetonitrile sampling and analysis requires use of a charcoal tube. The NIOSH method for the detection of acetonitrile is method 1606.⁽⁶⁾ In this method, air is drawn through large (400/200mg) coconut shell charcoal tubes. The charcoal is desorbed using a methanol/methylene chloride solution, and the desorbed contaminant is analyzed using flame ionization gas chromatography. Large charcoal tubes are required for analyte collection, to reduce breakthrough potential. As well, samples containing more than fifteen percent methanol or similar alcohols may interfere with accurate sampling, due to the ability of methanol to displace acetonitrile from available binding sites on the charcoal.

Mass Spectrometry

Mass spectrometers are one tool that can rapidly determine chemical constituents of mixtures and the concentrations of specific compounds, on the basis of their molecular mass and ion charge. Traditionally, these instruments are found in a laboratory. However, recent advances in mass spectrometer (MS) technology have resulted in smaller, lighter units that may be deployed for use in the field. These units can perform the same functions as their laboratory counterparts, but require less space and energy. In the field, an MS may be used to directly sample and analyze workplace air, without the use of sorbent media or other intermediate steps.

There are three common types of MS instruments: magnetic sector, time-of-flight, and quadrupole.⁽⁷⁾ Table I shows a comparison of the three instrument types. Magnetic sector instruments use an electric field to accelerate ions to high energies

before they enter an orthogonal magnetic field to separate ions based on their momentum. This type of instrument has the highest resolution of the three types, and requires the largest amount of energy to accelerate ions (several thousand volts). Magnetic sector instruments may scan a range of masses if several detectors are used, or the magnetic field is varied to bring ions into focus at a single detector. However, fluctuations in ion abundance during the scan result in fluctuations in the ion spectrum. If ion abundance fluctuates, it is best to use the magnetic sector to scan a single ion peak.

Time-of-flight (TOF) instruments separate ions using velocity differences after experiencing acceleration through a common potential, usually hundreds to thousands of volts. TOF instruments have a short response time and theoretically no detectable mass range limitation, but low resolution. The size of a TOF instrument will vary based on individual instrument design. The TOF instrument can only be used in pulse mode. That is, following ion injection, all ions must be detected before the next group may be injected. The time-of-flight instrument always scans all mass numbers, so cannot be used to selectively scan mass units.

The quadrupole is more robust and, in general, cheaper than the other instruments. This type of instrument filters ions based on their mass-to-charge ratio by varying the direct current (DC) and radiofrequency (RF) voltages applied to rod arrays. It requires much smaller amounts of energy for acceleration (volts) than the other two. Disadvantages of the quadrupole are that its detectable mass range is smaller than the other two instruments, and its mass resolution is low. The quadrupole scans only one mass at a time, so it is best suited for continuous monitoring of process conditions. Like

the magnetic sector instrument, the quadrupole may scan over a range of mass numbers only if the ion abundance is kept consistent throughout the scan.

TABLE I
Characteristics of the Three Common MS Instruments

Type	Accel. Pot.	Resolution	Size	Det. Mass Range	Best Application
Magnetic Sector	kV	High	Large	High	Continuous
Time of Flight	hV to kV	Low	Varies	High	Pulse
Quadrupole	V	Low	Small	Low	Continuous

The mass spectrometer used in this research is a multipole, a recent variation on the quadrupole. This device consists of sixteen rods arranged in a precise array to create nine quadrupole mass spectrometer units operating in parallel. Ions are created in an ionization chamber, then accelerated into the mass-filtering chamber containing the quadrupoles. An oscillating radiofrequency field applied to the quadrupoles filters singly charged ions based on their inertial masses. Ions are detected as electrical current at the bottom by a collection of Faraday plates (see Figure 3).⁽⁸⁾

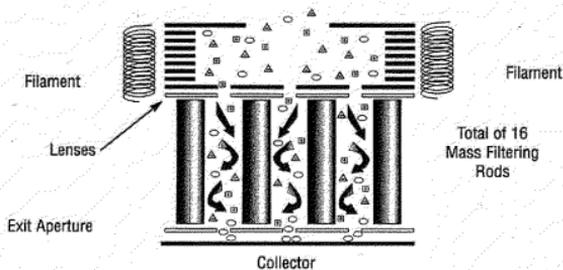


Figure 3. Schematic of Micropole Mass Filter

The Micropole uses electron ionization to ionize molecules. Electrons with energy of 45 eV are emitted from hot thorium-iridium filaments outside an ionization chamber, and injected into the chamber by use of repeller plates. These electrons impart energy to molecules, freeing valence electrons from their orbits and causing the parent molecules to become ions. The use of low (45 eV) energy electrons minimizes the formation of doubly charged ions. The created ions are accelerated into the quadrupole chamber by use of voltage 'lenses'. The lenses electrostatically focus primarily positive ions into the middle of each of the nine quadrupole units in the Micropole array.⁽⁸⁾

Quadrupole mass spectrometry, as mentioned earlier, uses varying DC and RF voltage to filter ions of different mass-charge ratios. Because the Micropole system eliminates doubly and multi-charged ions, the mass-charge ratio will be simply referred to as mass, or atomic mass unit (AMU), in this thesis. Between pairs of opposite and electrically connected rods, a DC voltage and superimposed RF potential are applied

(see Figure 4). Ions pass through the quadrupole chamber by following complex trajectories defined by these electric fields, described by the Mathieu equations:⁽⁹⁾

$$d^2x/dt^2 + (e/mr_0^2)[U-V\cos(2\pi ft)]x = 0$$

$$d^2y/dt^2 - (e/mr_0^2)[U-V\cos(2\pi ft)]y = 0$$

$$d^2z/dt^2 = 0 ; dz/dt = \text{constant}$$

where:

U = DC electric field amplitude

V = RF electric field amplitude

f = frequency [Hz]

r_0 = radius of inscribed circle tangent to all four rods [m].

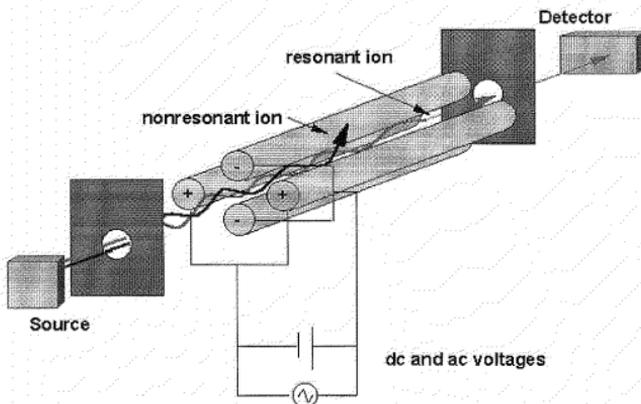


Figure 4. Electric Potential on a Quadrupole Array

Ions experience transverse acceleration when injected axially into the quadrupole region. For ions of any given mass/charge ratio, a stability region can be defined, as in Figure 5. An ion experiences a stable (resonant) trajectory if its helical path retains a finite diameter, so it can pass through the quadrupole region and deliver current to the ion detector. An ion is said to follow an unstable (nonresonant) path if it crashes into the poles, and is not detected. Although each mass-charge ratio has its own unique stability diagram, they all have topologically similar shapes.

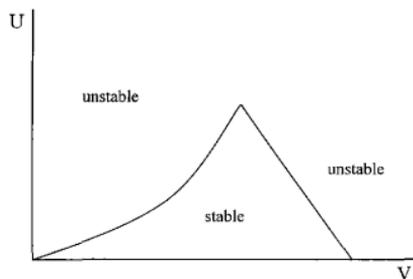


Figure 5. Stability Diagram

The Micropole uses a fixed U/V ratio and scans the size of both fields through the different masses. As the instrument scans along the U/V slope, it passes through different masses' stability regions (see Figure 6). By changing the U/V ratio, the sensitivity and resolution may be tuned. A smaller U/V ratio results in a greater

sensitivity, where more ions are detected in a wider range, with the scan line passing through more of the stability regions and more ions passing through the detector. The resolution of ions is compromised, however. A larger U/V ratio results in greater resolution, with the scan line specifically passing through the stability region of only one mass, but with lower sensitivity (see Figure 6).

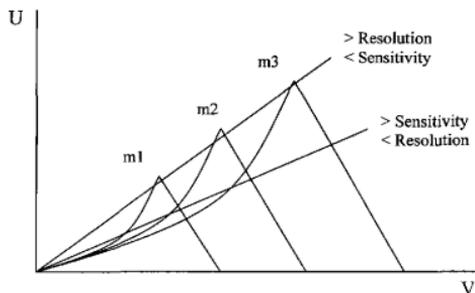


Figure 6. Sensitivity vs. Resolution

The Micropole has a benefit over standard quadrupoles in that it is able to operate at higher pressures. The rods in the Micropole are smaller in length and diameter. They range in length from 5 to 20mm, while the typical quadrupole is 100mm in length. This shorter length shortens the path of the ions through the analyzer, reducing the required mean free path, allowing higher operating pressures.⁽¹⁰⁾ However, shorter rods reduce the mass resolution of detection, affecting the mass range available. Mass resolution is directly related to the square of the length of the rods. As rods get shorter, either the mass resolution is decreased without a change in the applied RF

voltage, or the applied RF voltage must be increased to produce the same mass resolution. This increase in the RF voltage must be accompanied by a reduction in the diameter of the rods to maintain the same mass range. The diameter for the Micropole is around 0.5mm. The mass range of the Micropole ranges from 2-300 AMU for the shortest rods, with low resolution, to 2-45 AMU for the longest rods, with higher resolution.

Once ions with stable trajectories have passed through the analyzer, a Faraday cup collects them. The ions impinge on one of nine metal plates grounded through a resistor, one for each quadrupole unit.⁽⁸⁾ Neutralization of charge on the ions causes a current to flow through the resistor as the charge flows to ground. This current is collected and sent to data processing software.

For this experiment, the output of the Micropole is reported as a function of AMU, related in partial pressures in torr. The partial pressure reading at each AMU, usually called a peak, is a measure of the abundance of ions with that AMU mass.

When a molecule is ionized by the removal of a single electron, a molecular ion is formed.⁽⁷⁾ After the molecular ion is formed, the ion may possibly fragment into smaller ions. These fragments may further combine to form other ions.

The electron ionization of acetonitrile creates a mass spectrum as shown in Figure 7. The peak at 41 AMU is the molecular ion peak (base peak). The ion abundance at other peaks is mostly from the fragmentation and recombination of the molecular ion. Some of the ion abundance at the peaks, especially at 42 AMU, can be attributed to isotopic variations of carbon and nitrogen.

Compounds other than acetonitrile have ions of mass 39 to 41 AMU (see Table II). Argon, at 0.93 percent of the atmosphere, is the compound in this range most likely to be present in the samples taken during the experiment.

TABLE II
Compounds with Ions of Mass 39 to 41 AMU

Compound	Associated Ions [AMU]
Argon (Ar)	40
1,2-Propadiene	39, 40, 41
Propyne (C ₃ H ₄)	39, 40, 41
Methane, isocyano-	39, 40, 41

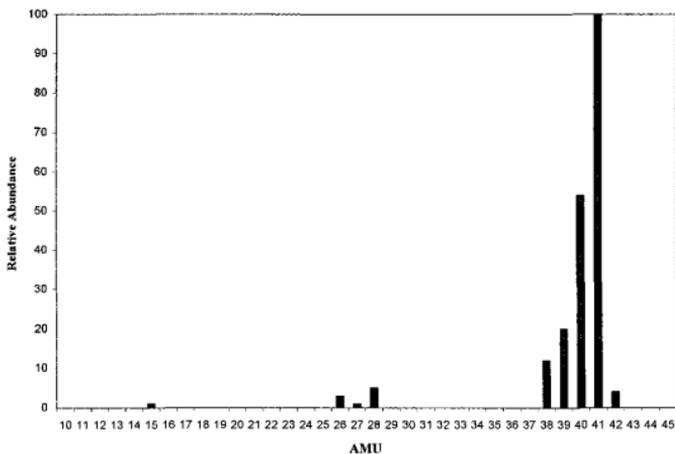


Figure 7. Mass Spectrum for Acetonitrile by Electron Ionization⁽¹¹⁾

All of the components of the Micropole come together to form a small, robust, weak-vacuum gas analyzer. This unit is able to bleed in air from its surroundings and analyze it. All these features make the Micropole an ideal unit for field-portable mass spectrometry.

Verification of Method

To verify that the mass spectrometer is able to replace charcoal tubes as a valid detection method, the NIOSH Development and Evaluation of Methods procedure should be followed.⁽¹²⁾

NIOSH stipulates statistical guidelines for new analytical methods to be considered acceptable. Results from the new analytical method should be, with 95 percent confidence, within ± 25 percent of the “true value,” as determined by an independent method. In this case, NIOSH method 1606 is used as the independent method of sampling acetonitrile concentrations.⁽⁶⁾ Since charcoal tubes have a stated error margin of ± 25 percent from the true value, the mass spectrometer results calculated from the data should not differ from the results from the charcoal tubes by more than 66 percent with a 95 percent confidence for the two methods to be considered equivalent for the detection of acetonitrile.⁽¹³⁾

The mass spectrometer should be evaluated between 0.1 and 2 times the threshold limit value. While it is not difficult to create low levels of acetonitrile contamination of 0.1 TLV, it is difficult to detect acetonitrile at these concentrations due to interference from ambient atmospheric background. Therefore, only a range of one-

quarter to two times the TLV was evaluated with the mass spectrometer in this experiment.

EXPERIMENTAL METHODS AND MATERIALS

Materials

The mass spectrometer used in this experiment is the Ferran Scientific Micropole. The model numbers of the different components follow in Table III.⁽⁸⁾

TABLE III
Micropole System Components

Description	Model #
High Pressure Gas Sampling Module	MMSDS-01
Mechanical Backing Pump	MMSDS-09
Micropole Analyzer	MPA-565C-3
WinMPA Software	Ver. 998330-SS

The high pressure gas sampling module contains a turbo-molecular pump, which draws pressure down within the quadrupole array, a manual micrometer valve inlet, and chamber for the Micropole analyzer. It also contains a spectra converter module and computer network logic interface, both of which serve as an interface between the Micropole analyzer and the computer. The mechanical backing pump is a dry pump used to bring the air pressure in the Micropole chamber down before the turbo-molecular pump draws it down to the final pressure.

The Micropole analyzer unit contains all of the necessary components for analysis of gases. The MPA-565C-3 unit was chosen for its ability to operate at

pressures up to 5 mtorr, yet still maintain a resolution of <1 AMU at the slowest scanning speed of very slow. This unit can detect a range of 2-65 AMU. The WinMPA software provides an interface between the MS and the user, providing data acquisition while controlling the scan parameters of the analyzer. The scan speed chosen for this experiment is fast, where the entire 2-65 AMU range may be scanned in 20 seconds. At slower scanning speeds, the resolution improves and noise is reduced.⁽⁸⁾

To calibrate the response of the Micropole to known concentrations, as well as provide data points for the second portion of the experiment, prepared concentrations of acetonitrile were created. This was done in 3L Tedlar sample bags using laboratory-grade acetonitrile. The 3L Tedlar sample bags were also used in the collection of samples in the field.

Large (400/200mg) charcoal tubes, were used to detect acetonitrile concentrations as well, as dictated by NIOSH method 1606.⁽⁶⁾ This type of charcoal tube is one of the commonly manufactured types; tubes used in this experiment were obtained from SKC [part #226-09]. These charcoal tubes have a limit of quantification below one-tenth the TLV-TWA, so the charcoal tubes are used above the limit of quantification for all readings. The charcoal tubes were attached in line with low-flow personal sampling pumps. Gillian Low-Flow pumps, used for the measurements, were calibrated using the appropriate Gillibrator cylinder.

Methods

Two types of samples were taken for each data point. Charcoal tube samples, as NIOSH method 1606 specifies, are an independent, approved method for sampling acetonitrile concentrations. Additional samples consist of Tedlar sample bags filled with workplace air and carried directly to the Micropole for analysis within a thirty minute time period. The Micropole also analyzed both the calibration mixture and the created air samples within thirty minutes of the time the bags were filled.

Each personal sampling pump used for charcoal tube measurements was calibrated to a flow rate of 0.2 L/min with a representative sample tube in line. Sampling procedures call for a blank charcoal tube of the same lot for each sample to be opened in the laboratory before sampling begins then immediately capped. This tube serves as an indication of any acetonitrile concentration in the batch of charcoal tube as a result of shipping and handling, exclusive of sampling. The actual sampling uses other charcoal tubes from the same batch, with between 1 and 25 liters of air needed to be drawn through it in the process of sampling.⁽⁶⁾

Tedlar sample bags were filled with workplace air through a low flow personal sampling pump operating at 0.1 L/min. The sample bag is attached to the exhaust port of the sampling pump, and filled with workplace air.

Calibration samples were created with known concentrations covering a range of 26 to 103 ppm. Appendix 1 lists the specific calibration protocol.

The fieldwork measured acetonitrile concentration arising from cleaning the MerMade. Measurements were taken inside the hood near the cleaning operation. To

assure that both the charcoal tube and the Micropole sample received the same concentration, the two personal sampling pumps were placed close to one another, but in a way that they would not affect the other's readings. The distance between inlets for the two systems was set at one inch. The two were also placed near the cleaning process so that the acetonitrile concentration was reasonably consistent (see Figure 8 for location). The sample bag, along with a blank sample of room air near the instrument, was immediately measured using the Micropole. The sample and blank charcoal tubes were refrigerated to preserve the sample, and later analyzed in a laboratory, using NIOSH method 1606.

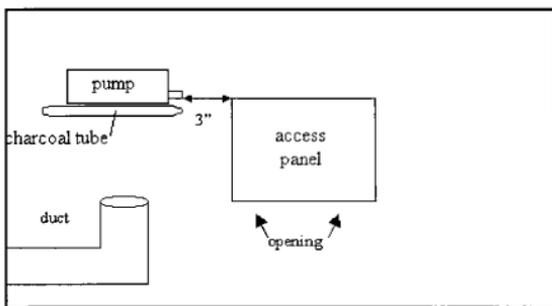


Figure 8. Location of Sampling Devices (Top view of MerMade)

Additional measurement sets, needed to test the hypothesis that the mass spectrometer results were comparable to charcoal tube results, consisted of prepared concentrations in sample bags. These sample bags were filled with a preset amount of

clean air, then acetonitrile liquid was injected from a microsyringe and allowed to evaporate to create a known concentration. The sample bags were processed through the Micropole, then drawn through charcoal tubes. The charcoal tubes were analyzed at a laboratory, using the same method stated earlier.

The analyses of all samples by the mass spectrometer were scanned using only the peaks at 40 and 41 AMU. These were scanned at the fast scanning speed, and then results were processed using a spreadsheet program to calculate a contaminant concentration.

RESULTS AND DISCUSSION

The flow of vapors from the enclosed area of the MerMade while the cleaning is taking place is shown in Figure 9. The majority of vapors, as shown below, flow towards the operator when the door is open. The ventilation duct placed near the opening only captures a small proportion of the evaporated vapors. Odors were obvious whenever the cleaning was taking place. Most times, these odors were sensed outside of the laboratory. This suggests unacceptable air flow out of the room as well as out of the hood, since laboratory rooms should operate at negative pressure compared to pedestrian hallways.⁽¹⁴⁾ The observed flow and presence of acetonitrile odors are indications of a potentially unhealthful worker exposure to acetonitrile vapors.

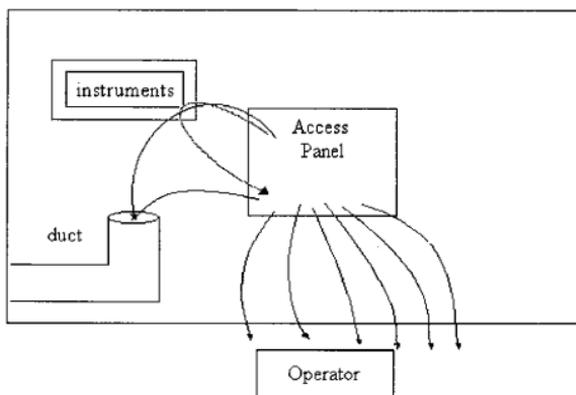


Figure 9. Vapor Flow from Enclosed Area

Other indications of potentially unhealthful worker exposure are the readings taken with charcoal tubes near the opening, as tabulated in Table IV. The high level of detected acetonitrile shows that the acetonitrile concentration has the potential to expose the worker to an unhealthy level, with three of the four samples reading at levels higher than the TLV-TWA.

TABLE IV
Charcoal Tube Results for Samples Taken at the MerMade

Date	CT reading [ppm]	Concentration/PEL
7/12	46	1.15
7/13	463	11.58
7/14	12	0.30
7/15	105	2.63

The tube with a reading of 463 ppm is a reasonable concentration and is not an outlier. The concentration may be a result of sampling liquid acetonitrile particles suspended in the air, or of vapor concentration. For example, one 5 μm particle of acetonitrile incorporated into a charcoal tube with four liters of air drawn through it will add an additional 3×10^{-7} ppm to the sample. A quantity of 1.36×10^9 particles of 5 μm size would result in a concentration of 463 ppm, over the average 54 ppm concentration. Alternately, the maximum possible acetonitrile vapor concentration at Los Alamos is 1.26×10^5 ppm at its equilibrium vapor pressure at 20° C. Therefore, a vapor concentration of 463 ppm is not unlikely.

The mass spectrum of acetonitrile when ionized by electron ionization has several peaks near its base peak at 41 AMU. In this study, the dominant peak at 41 AMU was used for both the calibration experiments and the analysis experiments. Each observation represents the mean of values observed in several scans, and each background measurement represents the mean value from several different scans. The mean background measurement is subtracted from the mean analytical reading, then, using the derived calibration equation, converted into part per million concentrations.

Known concentrations of 26, 52, and 103 ppm were analyzed using the mass spectrometer to create a calibration curve. It is assumed that these calibration standards are accurate with negligible error, shown below. The acetonitrile concentration in ppm is approximately related to mass spectrometer response at 41 AMU by the equation (see App. 1):

$$C_{\text{ppm}} = 4\text{E}+08*(41 \text{ AMU response}) - 5.0994$$

$$\sigma_c = 24 \text{ ppm}$$

Results for each data point collected are shown in Figure 10. The first four measurements (Sample #712-715) are from field measurements at the DNA-synthesizing process. The second group of measurements are the artificially created bag concentrations (Sample #101-802). Background is the background measurement for each data point, and reading is the mass spectrometer measurement for each data point. The upper and lower confidence limits, set at 68%, are shown for each data point.

Measured concentration of acetonitrile is the difference between the two bars. Tabulated data is included in Appendix 2.

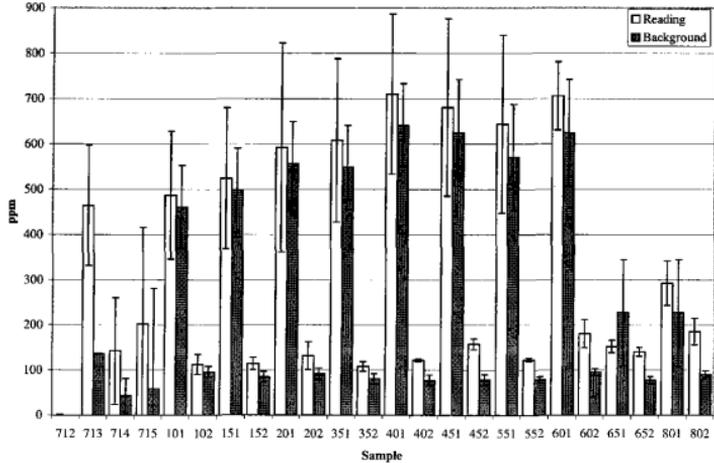


Figure 10. Mass Spectrometer Readings, Associated Background Readings, and 68% Confidence Limits of Each

The null and alternate hypotheses for this experiment are:

H_0 = The measurements as given by the mass spectrometer are within ± 66 percent of the charcoal tube measurements 95 percent of the measurements.

Ha = The measurements as given by the mass spectrometer are not within ± 66 percent of the charcoal tubes measurements, for more than 5 percent of the measurements.

Mass spectrometer measurements may be compared to the time weighted average values of the charcoal tube because of the sampling method. By collecting air samples in a sample bag, the air concentrations were time averaged. Therefore, the concentrations measured with the mass spectrometer are expected to be comparable with time-weighted average concentrations for the same sampling period measured with charcoal tubes. Two criteria are used to determine that a reading is valid for use in analysis. The first is that the background and mass spectrometer reading variance is low. The other is that the 68% lower confidence limit of the reading is greater than the 68% upper confidence limit of the background. The readings valid for analysis are shown with their corresponding charcoal tube measurement in Figure 11.

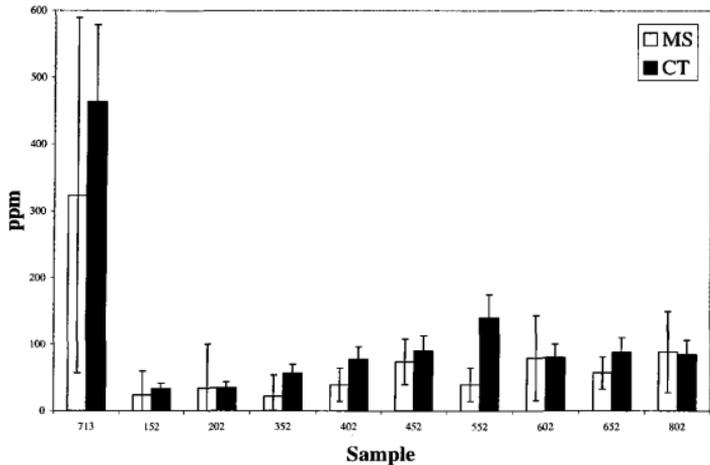


Figure 11. Mass Spectrometer Readings Valid for Analysis and Associated Charcoal Tube Readings, Including 95% Confidence Limits

The mass spectrometer gives measurements within 66 percent of the measurements as given by the charcoal tube for 69 percent of the measurements in Figure 11. This indicates that in this study the MS was not operated under a protocol that yields the accuracy needed to be a viable real-time survey instrument for acetonitrile.

There are several potential sources of error in the mass spectrometer readings. The most probable is the large variability of the background readings at 41 AMU. This variability may be associated with detection of the Argon-40 peak bleeding through at

greater than one AMU resolution to 41 AMU. Other background contaminants at 41 AMU include environmental contaminants arising from hydrocarbons, and Argon-41, a product of cosmic ray-generated neutrons activating atmospheric Argon into the radioisotope Argon-41. Commercial acetonitrile typically has contaminants of acetic acid and acetamide, both having major peaks at 41 AMU. During the operation of the MerMade, 0.5 L of tetrahydrofuran (THF) is used in several stages, flushed by acetonitrile into the waste area after each application. THF also has a major ion peak at 41 AMU. However, since THF is flushed by acetonitrile after each application, it is unlikely that its presence contributes to the error of mass spectrometer readings for acetonitrile.

Another source of error may be the assumption that the hypothesis testing may be used with the background data. Hypothesis testing requires that the data be independent, uncorrelated, and stationary. The Allen Variance was estimated for the discrete time series of measurements representing each background data set. This variance is compared to the classical variance, giving an indication whether it is safe to assume that a data set is valid for use in hypothesis testing.⁽¹⁵⁾ The ratio of classical variance to Allen Variance is compared to one plus the inverse of the square root of the number of measurements in the set (the test value). If the ratio is smaller than the test value, it is safe to assume that hypothesis testing is valid. If the ratio is larger, it is an indication that one of the assumptions required to use hypothesis testing might be invalid. Table V shows the classical variance to Allen Variance ratio, the test value, and whether it is valid to use hypothesis testing for each background data set. If it is shown that it is not

valid to use hypothesis testing with this test, it does not necessarily mean that hypothesis testing is invalid, but suggests that there might be time dependence and serial autocorrelation in the data set. The time dependence of some of the background data sets can be seen in Appendix 3, with a time-series plot of the background data.

TABLE V
Test for Validity of Classical Statistics

Date	Assoc. V/A Read.	Test value	Validity
7/12/99	712 1.23	1.50	SAFE
7/13/99	713 1.32	1.29	NO
7/14/99	714 1.26	1.58	SAFE
7/15/99	715 1.24	1.14	NO
8/9/99	101-401 1.15	1.24	SAFE
8/9/99	451-801 1.17	1.25	SAFE
8/9/99	102-452 1.66	1.35	NO
8/9/99	552-802,cal 1.34	1.10	NO

The errors specifically associated with the variability in the background measurements invalidated many of the mass spectrometer-derived data points. The time dependence, an unexplained serial dependence, in some of the background readings also reduces confidence in statistical analysis of the mass spectrometer readings. Because the background and the signal are taken at different times, and background readings have a definite time dependence, sample variance tends to its upper limits in the present experimental data.

In addition to the errors present in the data, there were several technical difficulties in the use of the Micropole, including reading of the spectrum, software glitches, and an inlet malfunction. These problems could only be resolved with the

assistance of individuals experienced in mass spectrometry. Even the normal operation of the MS requires a sophisticated operator with at least a basic background in mass spectrometry. These factors make the Micropole a difficult instrument for use by a typical operator.

CONCLUSIONS

The MerMade workstation was found to be poorly installed, and was shown to have the potential for unacceptable worker exposure to acetonitrile. Area monitoring measurements demonstrated acetonitrile concentrations well above STEL limits. Airflow studies showed that the contamination was inappropriately contained. The process was shut down to allow orderly evaluation of its safety and health concerns. Local exhaust ventilation deficiencies will be corrected before the process is restarted.

Future safety and health surveys, after production resumes, should include a complete workspace monitoring study to validate tolerable worker exposure to the acetonitrile vapors. The ventilation system should be commissioned and room ventilation patterns should be examined, to confirm successful capture of hazardous vapors.

The mass spectrometer itself could not be proved or disproved as an accurate real-time survey instrument on the basis of data collected under the protocol reported here. The measurements taken did not have the accuracy required to prove equivalence at this time, because an uncontrolled baseline shift invalidated the hypothesis test. A subset of data uncontaminated by baseline shift suggests the acetonitrile measurements with the response at 41 AMU are well within 66 percent uncertainty compared to the reference charcoal tube method. In this data subset, mass spectrometer readings are biased about 30% low of the charcoal tube readings.

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APPENDIX 1
CALIBRATION PROTOCOL AND DATA

Calibration Protocol

The protocol used to calibrate the response of the mass spectrometer follows;

1. Sample bags were filled with two liters clean air
2. A precise amount of acetonitrile is injected using a microsyringe to create a 60 ppm concentration
3. The sample is run through the mass spectrometer
4. One liter of air is removed from the sample bag, then one liter of clean air is filled into the sample bag to create a 30 ppm concentration, then run through the mass spectrometer
5. Another liter of air is removed, then one liter of clean air filled into the bag to create a 15 ppm concentration, then run through the mass spectrometer
6. The data is plotted to find a linear best-fit equation to correlate mass spectrometer response to acetonitrile concentration.

Calibration Data

TABLE A1-I
MS Readings at Calibration Concentrations

ppm	MS reading @ 41 AMU
26	6.98E-08
52	1.24E-07
103	2.41E-07

Calibration equation:

$$C_{\text{ppm}} = 4 \times 10^8 * (41 \text{ AMU response}) - 5.0994$$

$$R^2 = 0.9997$$

$$\sigma_c^2 = \frac{1}{N-2} \sum_{i=1}^N (y_i - A - Bx_i)^2$$

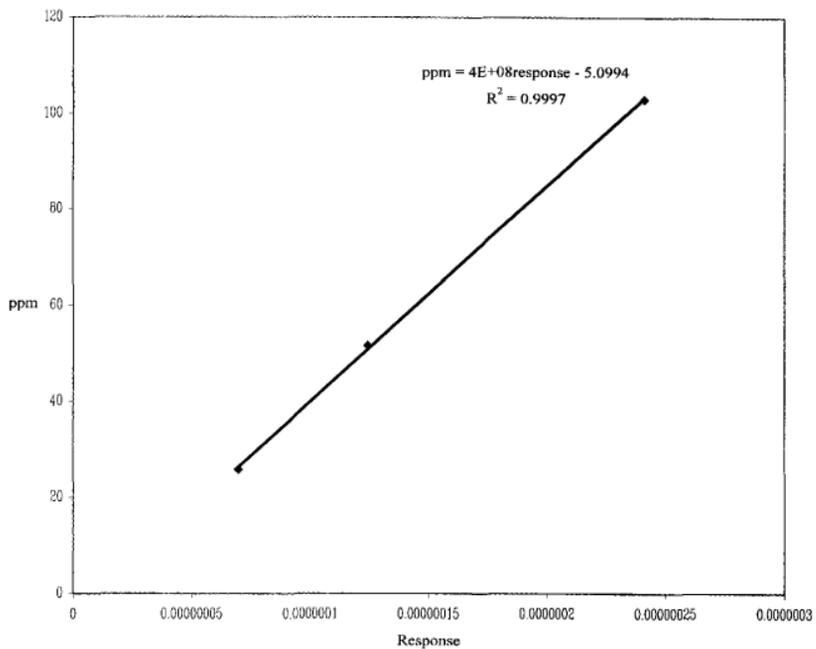


Figure A1-1. Calibration Line Fit

APPENDIX 2
CHARCOAL TUBE AND MASS SPECTROMETER DATA

TABLE A2-I
Results for Acetonitrile From Charcoal Tubes

Sample ID	Amount, mg/tube	Sample ID	Amount, mg/tube
7/12/99 Blank, front	ND	351, front	0.107
7/12/99 Blank, back	ND	351, back	ND
7/12/99 Sample, front	0.251	352, front	0.141
7/12/99 Sample, back	ND	352, back	ND**
7/13/99 Blank, front	ND	401, front	0.149
7/13/99 Blank, back	ND	401, back	ND
7/13/99 Sample, front	2.56*	402, front	0.194
7/13/99 Sample, back	0.236*	402, back	ND
7/14/99 Blank, front	ND	451, front	0.151
7/14/99 Blank, back	ND	451, back	ND
7/14/99 Sample, front	0.060	452, front	0.231
7/14/99 Sample, back	ND	452, back	ND
7/15/99 Blank, front	ND	551, front	0.143
7/15/99 Blank, back	ND	551, back	ND
7/15/99 Sample, front	0.510	552, front	0.344
7/15/99 Sample, back	ND	552, back	ND
Blank, front	ND	601, front	0.195
Blank, back	ND	601, back	ND
101, front	0.040	602, front	0.206
101, back	ND	602, back	ND
102, front	ND	651, front	0.157
102, back	ND	651, back	ND
151, front	0.043	652, front	0.203*
151, back	ND	652, back	0.025*
152, front	0.087	801, front	0.312*
152, back	ND	801, back	0.042*
201, front	0.053	802, front	0.217
201, back	ND	802, back	ND
202, front	0.088		
202, back	ND		

ND: <0.025mg based on lowest calibration point

* Breakthrough observed, sum front and back results for total for tube.

** Phase separation observed in ALS vial.

To get a ppm concentration:

$$C_{ppm} = \frac{\text{mg / tube}}{\text{air drawn through tube [m}^3\text{]} * 41.1} * \frac{RT}{P_{ATM}} * \frac{1}{P_{ATM}}$$

TABLE A2-II
Mass Spectrometer and Charcoal Tube Results

Sample #	MS background [torr]	MS reading [torr]	Difference [torr]	MS [ppm]	CT [ppm]	Error %
712	3.90E-09	1.26E-08	8.73E-09	ND	46	100
713	3.54E-07	1.17E-06	8.21E-07	323	463	-30
714	1.21E-07	3.68E-07	2.47E-07	94	12	709
715	1.59E-07	5.18E-07	3.59E-07	138	105	32
101	1.17E-06	1.23E-06	6.50E-08	21	16	32
102	2.54E-07	2.95E-07	4.10E-08	ND	ND	N/A
151	1.26E-06	1.32E-06	6.50E-08	21	17	24
152	2.26E-07	3.00E-07	7.35E-08	24	34	-28
201	1.41E-06	1.49E-06	8.75E-08	30	21	44
202	2.45E-07	3.43E-07	9.85E-08	34	35	-1
351	1.39E-06	1.53E-06	1.48E-07	54	42	28
352	2.15E-07	2.85E-07	6.73E-08	22	56	-61
401	1.62E-06	1.79E-06	1.73E-07	64	58	10
402	2.06E-07	3.17E-07	1.11E-07	39	77	-49
451	1.58E-06	1.72E-06	1.40E-07	51	60	-15
452	2.09E-07	4.06E-07	1.98E-07	74	90	-18
551	1.44E-06	1.62E-06	1.83E-07	68	55	24
552	2.09E-07	3.21E-07	1.12E-07	40	140	-72
601	1.58E-06	1.78E-06	2.03E-07	76	78	-2
602	2.52E-07	4.65E-07	2.13E-07	80	81	-1
651	5.80E-07	3.93E-07	-1.38E-07	ND	62	100
652	2.09E-07	3.65E-07	1.56E-07	57	88	-35
801	5.80E-07	7.44E-07	1.65E-07	61	140	-57
802	2.42E-07	4.77E-07	2.35E-07	89	85	5

ND= below limit of calibration

APPENDIX 3
TIME SERIES PLOT OF BACKGROUND DATA

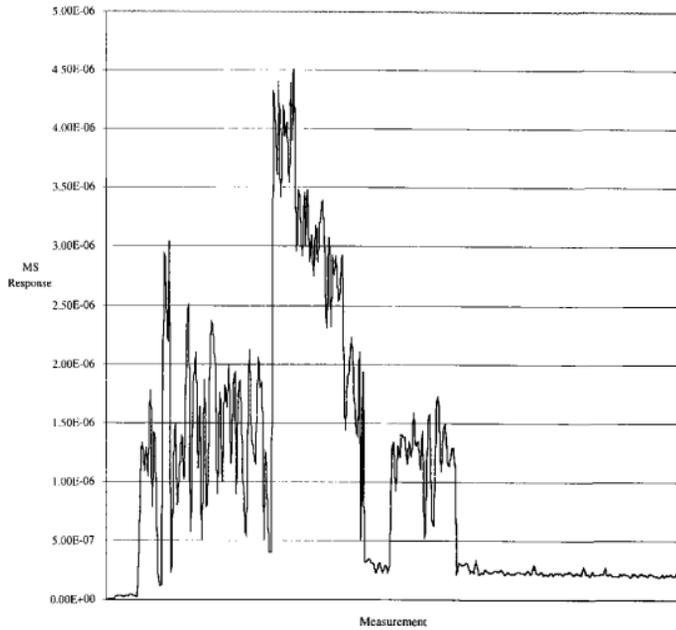


Figure A3-1. Time Series of
Background Measurement

APPENDIX 4
FUTURE WORK

Future work should be done to evaluate the effectiveness of the Micropole in other environments. It would be advisable to run the experiment again, scanning at a slower speed. This would increase the resolution, and may reduce the effect of Argon on acetonitrile detection. Another method for reducing the effect of other contaminants on acetonitrile detection would be to use the peak at 42 AMU, instead of 41. At this peak, there are no known environmental or process contaminants, nor should Argon be detected. Drift in background readings will be reduced if an individual background reading is taken for each sample reading.

Another method for reducing the effect of Argon on acetonitrile detection would be to do pre-analysis sample preparation before running the sample through the mass spectrometer. Since Argon is non-polar while acetonitrile is polar, a molecular sieve [SKC part # 226-40-02, Triethanolamine] should be able to capture the non-polar Argon before it reaches the MS. Running the sample through a silica gel tube would capture only the polar acetonitrile, and let the Argon pass through. The silica gel could then be desorbed, and the acetonitrile detected. However, these sample preparations will affect the timesaving and field portability benefits of the mass spectrometer, and the process begins to mirror a GC/MS instrument.

It would be advisable to use MSA tube #91624 in subsequent studies, which gives immediate short-term acetonitrile concentrations within a range of 10 to 150 ppm, to quantify hood improvements. This will provide for immediate analysis of results, where process changes may be tracked. Immediate results will also identify any need for changes to the hood improvements to further enhance health and safety.

The Micropole may be more effective on other contaminants, whose mass numbers do not have interferences in the environment. This would minimize the challenges of determining contaminant concentration as encountered in this experiment. Table A4-I shows a small portion of the chemicals that may be detected without interference from typical air components.

TABLE A4-I
Contaminants That May be Detected Without Interference in Ambient Air

Compound	Identifying peak(s) [AMU]
Nitric Oxide	30
Formaldehyde	29,30
Hydrogen Chloride	35,36
Ozone	48
Methyl Chloride	50,52
Acetone	43,58

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