HETA 99-0313-2802
The Children's Hospital of Denver
Denver, Colorado

Lisa J. Delaney, M.S.

PREFACE

The Hazard Evaluations and Technical Assistance Branch (HETAB) of the National Institute for Occupational Safety and Health (NIOSH) conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health (OSHA) Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found.

HETAB also provides, upon request, technical and consultative assistance to Federal, State, and local agencies; labor; industry; and other groups or individuals to control occupational health hazards and to prevent related trauma and disease. Mention of company names or products does not constitute endorsement by NIOSH.

ACKNOWLEDGMENTS AND AVAILABILITY OF REPORT

This report was prepared by Lisa J. Delaney, of HETAB, Division of Surveillance, Hazard Evaluations and Field Studies (DSHEFS). Field assistance was provided by Jane McCammon, Ken Martinez, and Kristin Gwin, HETAB. Analytical support was provided by Ardith A. Grote, NIOSH, Division of Applied Research and Technology, and Penny A. Foote and Ciro S. Parraga of Data Chem Laboratories. Desktop publishing was performed by Denise Ratliff. Review and preparation for printing were performed by Penny Arthur.

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Highlights of the NIOSH Health Hazard Evaluation

Exposures During Inhaled Nitric Oxide Therapy

NIOSH conducted a health hazard evaluation at The Children's Hospital of Denver, Colorado, to look at exposures to substances during INO (inhaled nitric oxide) treatment.

What NIOSH Did

Took air samples for nitric oxide (NO), nitrogen dioxide, and nitric acid.
Looked at the ventilation in the closets used to store the NO tanks.
Talked with employees about how they prepare and use the NO therapy.

What NIOSH Found

No measurable amounts of nitrogen dioxide or nitric acid were found in the workplace.
Nitric oxide levels were low.
Ventilation was poor in the NO tank storage closet.

What The Children's Hospital Managers Can Do

Improve the ventilation in the NO tank storage closet and install monitors to warn of leaks.
Install scavenging systems on ventilators to capture the patient's exhaled breath.
Take air samples when training therapists on how to use the INO treatment.

What the Respiratory Therapists and Nurses Can Do

Follow standard operating procedures when preparing and using NO.

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CENTERS FOR DISEASE CONTROL AND PREVENTION

What To Do For More Information:
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NIOSH National Institute for Occupational Safety and Health

Health Hazard Evaluation Report 99-0313-2802
The Children's Hospital of Denver
Denver, Colorado
April 2000

Lisa J. Delaney, M.S.

SUMMARY

On August 11, 1999, the National Institute for Occupational Safety and Health (NIOSH) received a request for a health hazard evaluation (HHE) from the management of The Children's Hospital of Denver (TCH), to evaluate employees' potential health hazards encountered during inhaled nitric oxide (INO) therapy. NIOSH investigators conducted two site visits to meet with management and observe the use of INO during therapy. During a third visit, personal breathing zone (PBZ) samples and general area (GA) samples were collected for nitric oxide (NO), nitrogen dioxide (NO_2), and nitric acid (HNO_3). The ventilation system was assessed in the two closets where the NO cylinders are stored, and in the treatment area.

All of the PBZ and GA samples collected for NO, NO_2, and HNO_3 were well below the relevant evaluation criteria for occupational exposures. The respiratory care storage closet and the pediatric intensive care unit (PICU) had adequate ventilation in controlling the low concentrations of NO produced from INO therapy. The PICU had 8-10 air exchanges per hour. A need for ventilation was identified in the NO compressed gas storage closet, which had only a duct leading to the outside of the building.

The industrial hygiene sampling data indicate that employees were not overexposed to NO, NO_2, or HNO_3 at The Children's Hospital of Denver during inhaled nitric oxide therapy. Ventilation was adequate in the pediatric intensive care unit and the respiratory care closet. Recommendations for improved ventilation in the compressed gas storage closet are given in the recommendations section of this report.

Keywords: SIC: 8069 (Specialty Hospitals, Except Psychiatric), Nitric oxide, nitrogen dioxide, nitric acid, pediatric hospital

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INTRODUCTION

On August 11, 1999, the National Institute for Occupational Safety and Health (NIOSH) received a request for a health hazard evaluation (HHE) from the management of The Children's Hospital of Denver (TCH), to evaluate employees' potential health hazards from the storage and use of nitric oxide (NO). The request concerned employee exposures to the gas during inhaled nitric oxide (INO) treatment and the proper storage and handling of the NO cylinders.

In August and December 1999, NIOSH investigators toured the NO compressed gas tank storage areas and observed the INO therapy in use. During a third site visit (February 29-March 1, 2000) a ventilation system assessment and air sampling for NO, nitrogen dioxide (NO_2), and nitric acid (HNO_3) were conducted.

BACKGROUND

TCH was founded in 1908 and is a private, not-for-profit pediatric health care facility. TCH currently employees more than 1,000 pediatric specialists and 1,700 full-time employees. The hospital operates 24 hours a day, 7 days per week. The nursing staff typically works 12-hour shifts.

For nearly ten years, TCH of Denver has had an Investigational New Drug Number from the U.S. Food and Drug Admin-istration (FDA) for administration of an inhaled nitric oxide therapy to treat respiratory failure in infants and young children. In December 1999, the FDA approved this therapy for use.

INOmax™ is the trade name used to describe the drug that is administered to patients by inhalation. INOmax consists of a mixture of NO (0.8 percent [%]) and nitrogen (N_2 [99.2%]) and is stored as a compressed gas in an aluminum cylinder under 2000 pounds per square gauge (psig). The drug is administered via the I-NOvent Delivery System which consists of three components: (1) a delivery system, (2) a bag system for manual deliver, and (3) an in-line analyzer to measure NO, NO_2, and oxygen (O_2). To prepare the INOmax for delivery, a respiratory therapist (RT) attaches the INOmax system to an O_2 supplying ventilator. The RT purges the high pressure line of the cylinder to rid it of NO_2 before attaching it to the I-NOvent. The pressure of the line decreases from 2000 psig to 50 psig in approximately 20 seconds. The purge inlet is attached to a piece of tubing which redirects the NO_2 build up in the line to the floor. The cylinder is then opened to permit the flow of INOmax and the RT sets the dosage to be delivered to the patient. The recom-mended dose of INOmax is 20 parts per million (ppm), but a dose of 0-80 ppm can be delivered. The RT preps the line first in the respiratory storage closet before transporting the I-NOvent Delivery System to the patient's bedside. The I-NOvent can also be prepared for use in the NO compressed gas cylinder storage closet. The line is prepped a second time at bedside.

The I-NOvent can be attached to either a continu-ous or non-continuous flow ventilator, which supplies O_2 to the patient. A pneumotach injector module regulates NO injection into the ventilator circuit which then mixes with oxygen at the inspiratory limb of the ventilator prior to humidification. A photochemical analyzer, measuring NO, NO_2, and O_2 is located downstream of the humidifier in the inspiratory limb. Exhaled breath is returned to the ventilator via the expiratory limb. The air is filtered through a high-efficiency filter before it is exhausted into the ambient air.

TCH management contacted the Denver Fire Department regarding the requirements for storage of the NO cylinders. The Denver Fire Department initially was concerned about the amount of NO that was being stored and used within the hospital. They later determined that no additional ventilation was needed in the areas where NO was used due to the low concentration of NO in the cylinders. Additionally, one of the plastic pneumotach modules that reportedly had 5000 hours of use was discolored, which raised concerns that the plastic may be decomposing in the presence of the INOmax.

METHODS

During the third NIOSH visit (February/March 2000), full-shift personal breathing zone (PBZ) samples were collected for NO, NO_2 , and HNO_3 on 2 employees in the Pediatric Intensive Care Unit (PICU) while the employees cared for a child receiving INOmax treatment. Full-shift general area (GA) samples were also collected for NO, NO_2, and HNO_3 by the patient's bedside and at a nursing station 30 feet from the bedside. Short-term PBZ samples for NO_2 and HNO_3 were collected on one employee during line priming in the NO cylinder storage closet and the respiratory care storage closet. GA samples at the ventilator exhaust were collected for NO_2 and NO. Volatile organic compounds (VOCs) were sampled with the pneumotach module in line to determine if any reaction between the NO/NO_2 and the plastic occurred. NO, NO_2, and HNO_3 samples were collected using personal air sampling pumps drawing air at a measured sampling rate of 0.025 to 0.750 liters per minute (Lpm). Sampling rates varied depending on the type of contaminant sampled and the duration of sampling. Full-shift NO and NO_2 samples were collected simultaneously and were changed out after 4 hours of sampling due to the maximum volume limitation of the method.

Using NIOSH Method 6014 for NO and NO_2, samples were collected on a sorbent tube of oxidizer + triethanolamine-treated molecular sieve and quantitatively analyzed by visible absorption spectrophotometry.[1] Using NIOSH Method 7903, samples were collected on a solid sorbent tube of washed silica gel, 400 milligrams (mg)/200mg with glass fiber filter plug and quantitatively analyzed using ion chromatography for nitric acid.[1] Short-term and full-shift GA samples for NO were collected with Biosystems, Inc. Toxi Ultra personal NO monitors equipped with electrochemical sensors. These units were set to record NO levels every minute and store the results in a data logger. The monitor measures NO concentrations from 0-100 ppm. The accu-racy of measurements at low levels is $\pm$ 1 ppm. The data were downloaded to a computer and the results printed. Calibration of these monitors was accomplished before and after sampling according to the manufacturer's specifications. Lastly, two thermal desorption tube area samples were collected using NIOSH Method 2549 to screen VOCs that may potentially be in the ventilator exhaust stream.[1]

EVALUATION CRITERIA

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH field staff employ environmental evaluation criteria for the assessment of a number of chemical and physical agents. These criteria are intended to suggest levels of exposure to which most workers may be exposed up to 10 hours per day, 40 hours per week for a working lifetime without experiencing adverse health effects. It is, however, important to note that not all workers will be protected from adverse health effects even though their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a pre-existing medical condition, and/or a hypersensitivity (allergy). In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the worker to produce health effects even if the occupational exposures are controlled at the level set by the criterion. These combined effects are often not considered in the evaluation criteria. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus potentially increases the overall exposure. Finally, evaluation criteria may change over the years as new information on the toxic effects of an agent become available.

The primary sources of environmental evaluation criteria for the workplace are: (1) NIOSH Recommended Exposure Limits (RELs),[2] (2) the American Conference of Governmental Industrial Hygienists' (ACGIH®) Threshold Limit Values (TLVs®),[3] and (3) the U.S. Department of Labor, Occupational Safety and Health Admin-istration (OSHA) Permissible Exposure Limits (PELs).[4] Employers are encouraged to follow the OSHA limits, the NIOSH RELs, the ACGIH TLVs, or whichever are the more protective criterion.

OSHA requires an employer to furnish employees a place of employment that is free from recognized hazards that are causing or are likely to cause death or serious physical harm [Occupational Safety and Health Act of 1970, Public Law 91–596, sec. 5.(a)(1)]. Thus, employers should understand that not all hazardous chemicals have specific OSHA exposure limits such as PELs and short-term exposure limits (STELs). An employer is still required by OSHA to protect their employees from hazards, even in the absence of a specific OSHA PEL.

A time-weighted average (TWA) exposure refers to the average airborne concentration of a substance during a normal 8- to 10-hour workday. Some substances have recommended STELs or ceiling values which are intended to supplement the TWA where there are recognized toxic effects from higher exposures over the short-term. Ceiling concentrations should not be exceeded during any part of the workday.

Nitric Oxide

Nitric oxide is a colorless gas that coverts spontaneously in air to NO_2. The oxidation rate occurs more rapidly at higher NO concentrations.[5] Therefore, it is difficult to identify the effects of NO exposures without considering the concomitant effects of NO_2. It is a component of photochemical smog with concentrations reaching as high as 2.65 ppm.[6] The most common occupational exposures to NO occur when NO is formed as a by-product in the preparation of nitrosylcarbonyls and HNO_3, tobacco smoke, and from combustion of propane, diesel, and gasoline engines.[7] In humans exposed to NO between 10 and 40 ppm, significant lung vasodilation effects were observed.[8] A com-parative analysis of inhaled and exhaled breath in humans after exposure to NO at concentrations of 5, 1, 0.5 and 0.33 ppm showed 85 to 93% retention in the body.[5]

Animal studies indicate that nitric oxide has an affinity for ferrous hemoglobin, which normally transports oxygen in the blood; the two substances react to form nitrosyl hemoglobin, a compound that is incapable of oxygen transport.[7] This toxic action resembles that of carbon monoxide. Exposures in mice to 5000 ppm for 6 to 8 minutes and to 2500 ppm for 12 minutes were lethal.[8]

Both NIOSH and OSHA have established an exposure criterion of 25 ppm (30 milligrams per cubic meter [mg/m^3]) for NO.[2,4,7] The NIOSH REL is based on a limited amount of scientific literature concerned with effects in humans or animals exposed to NO at low levels.[7] The ACGIH has also recommended an 8-hour TLV-TWA of 25 ppm.[3] The ACGIH limit is based on animal data that indicated NO was about one-fifth as toxic as NO_2, which has a TLV-STEL of 5 ppm (9 mg/m^3).[5]

Nitrogen Dioxide

Nitrogen dioxide gas is an irritant to the mucous membranes and its inhalation may cause severe coughing, which can be accompanied by mild or transient headache. The following health effects were observed in humans exposed to NO_2 for 60 minutes: at 100 ppm, pulmonary edema and death; at 50 ppm, pulmonary edema, with possible subacute or chronic lesions in the lungs; and, at 25 ppm, respiratory irritation and chest pain.[7,8] The effects of chronic low concentration exposures are not well characterized in humans. NO_2 would be expected to have an irritant effect upon the general mucosal surfaces and on the lower respiratory tract.[7] Chronic exposures to 0.2 ppm with daily excursions to 0.8 ppm in mice was shown to cause decreased pulmonary function. NO_2 has not been shown to have teratogenic, mutagenic, or directly carcinogenic effects.[8] The NIOSH REL for NO_2 is 1 ppm (1.8 mg/m^3) as a 15 minute STEL.[2] The OSHA ceiling concentration is 5 ppm (9 mg/m^3).[4] The ACGIH TLV-TWA is 3 ppm (5.4 mg/m^3) and the TLV-STEL is 5 ppm.[3]

Nitric Acid

Nitric acid is a corrosive chemical that decomposes in the presence of air or organic matter to oxides of nitrogen including NO and the more hazardous NO_2.[8] It is unclear whether the observed health effects from exposure are due to HNO_3 or oxides of nitrogen. Health effects after acute exposure to HNO_3 and a mixture of oxides of nitrogen include irritation of the upper respiratory tract leading to dryness of throat and

nose, cough, chest pain, and dyspnea.[9,10] The lethal concentration for rats exposed to HNO_3 (containing less than 0.5% dissolved NO_2) for 30 minutes is 334 ppm.[9] Both NIOSH and OSHA have established a full-shift TWA limit of 2 ppm (5 mg/m^3).[2,4] The NIOSH STEL is 4 ppm (10 mg/m^3). The ACGIH TLV-TWA is 2 ppm (5 mg/m^3) and the STEL is 4 ppm (10 mg/m^3).[3]

RESULTS

Environmental

All of the PBZ sample concentrations measured for NO were below detection. All but one of the area sample concentrations measured for NO were below detection. One area sample, located by the ventilator exhaust at the patient's bedside, measured 0.26 mg/m^3. The concentration was between the minimum detectable concentration (MDC) of 0.16 mg/m^3 and the minimum quantifiable concentration (MQC) of 0.61 mg/m^3, assuming a sample volume of 5.1 L. The MDC and MQC are the minimum concentrations that can be detected and quantified respectively, based upon sample volume and analytical sensitivity.

The results from direct reading measurements for NO are presented in Figures 1 and 2. The full-shift TWA GA concentrations measured in the PICU by instantaneous sampling ranged from 1-4 ppm (1.23-4.9 mg/m^3). Instantaneous sam-pling in the NO cylinder storage closet, when the line was primed twice, measured a peak concentration of 11 ppm (13.5 mg/m^3). Figure 2 shows the results from this sampling. These values show that peak concentrations occurred during line priming at 11:37 a.m. and again at 11:42 a.m.

All of the sample concentrations of NO_2 were below detection. The MDC for full-shift sampling was 0.25 mg/m^3, assuming a sample volume of 5.1 liters (L). The MDC for short-term sampling was 0.4 mg/m^3 assuming a sample volume of 3 L.

The results of the PBZ and GA concentrations measured for nitric acid were all non-detectable. The MDC for full-shift sampling was 0.004 mg/m^3 assuming a sample volume of 94.4 L. The MDC for short-term sampling was 0.04 mg/m^3 assuming a sample volume of 11.25 L.

Analysis of thermal tube samples showed only trace amounts of any volatile organic compounds (VOCs). Isopropanol and acetone were the major compounds detected, plus smaller amounts of limonene and toluene.

DISCUSSION AND CONCLUSIONS

The sampling results indicated that none of the sampled chemicals were detected at concentrations exceeding occupational exposure limits. Therefore, an inhalation health hazard to those compounds did not exist at the time of the NIOSH visit. All of the sample concentrations for NO_2 were below detection. Results from VOC analysis did not show any unusual compounds that might have been present if a chemical reaction occurred between the NO/NO_2 mixture and the plastic pneumotach module.

Based on instantaneous sampling, respiratory technicians are exposed to concentrations of 10-11 ppm of NO for approximately 2-4 minutes during line priming. No short-term exposure limits have been established for NO. Results indicate a short duration high exposure which quickly diffuses into the room and converts to NO_2. Simultaneous short-term sampling for NO_2 resulted in levels below detection.

Although concentrations of NO were low, proper storage of the NO compressed gas cylinders is imperative to control possible INOmax (NO/N_2 mixture) leaks due to the asphyxiant properties of nitrogen. On the day of the survey, both the respiratory care storage closet and the NO cylinder storage closet were under negative pressure. However, the hospital's heating, ven-tilating, and air-conditioning (HVAC) system in the NO cylinder storage closet is not connected to the HVAC system. Instead, a single duct connects directly to the outside. Depending on weather conditions outside, the room could be under positive or

negative pressure. According to TCH management, the PICU ventilation system operates at 8-10 air exchanges per hour which is adequate in controlling the low concentrations of NO produced from INO therapy.

RECOMMENDATIONS

Since the INO therapy is a relatively new treatment, the following recommendations are offered as an added measure of caution to reduce the potential hazards involved in its use:

1. To evaluate all potential exposure scenarios associated with the use of INO therapy, personal breathing zone samples should be collected during respiratory therapist training. The respiratory therapist must train other RTs on the preparation and use of the I-NOvent. During training, there is a potential for higher exposures due to the numerous line priming activities.

2. As a precautionary measure, install an anaesthetic gas scavenging system, which collects exhaust gases from ventilators, to prevent the release of the exhaled gas to the ambient air during NO treatment. A specialist should be consulted for installation to ensure the scavenging system does not affect the function of the ventilator.

3. There is always the possibility of a compressed gas cylinder leak. A release of nitro-gen gas could displace the ambient air and reduce the oxygen level in the environment. To protect employees in this situation, the ventilation should be improved to prevent airflow out of the room. A fan exhausting directly to the outside should be installed to maintain a negative pressure within the cylinder storage closet. The cylinders could also be placed either in a ventilated storage cabinet or closet or under a ventilated hood. A ventilation engineer should be consulted to aid in the proper design and installation of the fan. Install a NO and N_2 monitoring system for continuous monitoring of NO and N_2 concentrations in the NO cylinder storage closet and the respiratory care closet to alert employees in case of an accidental release.

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Figure 1
Instantaneous NO Monitoring Results Measured by Patient Bedside in PICU
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Denver, Colorado
HETA 99-0313-2802
February 29, 2000

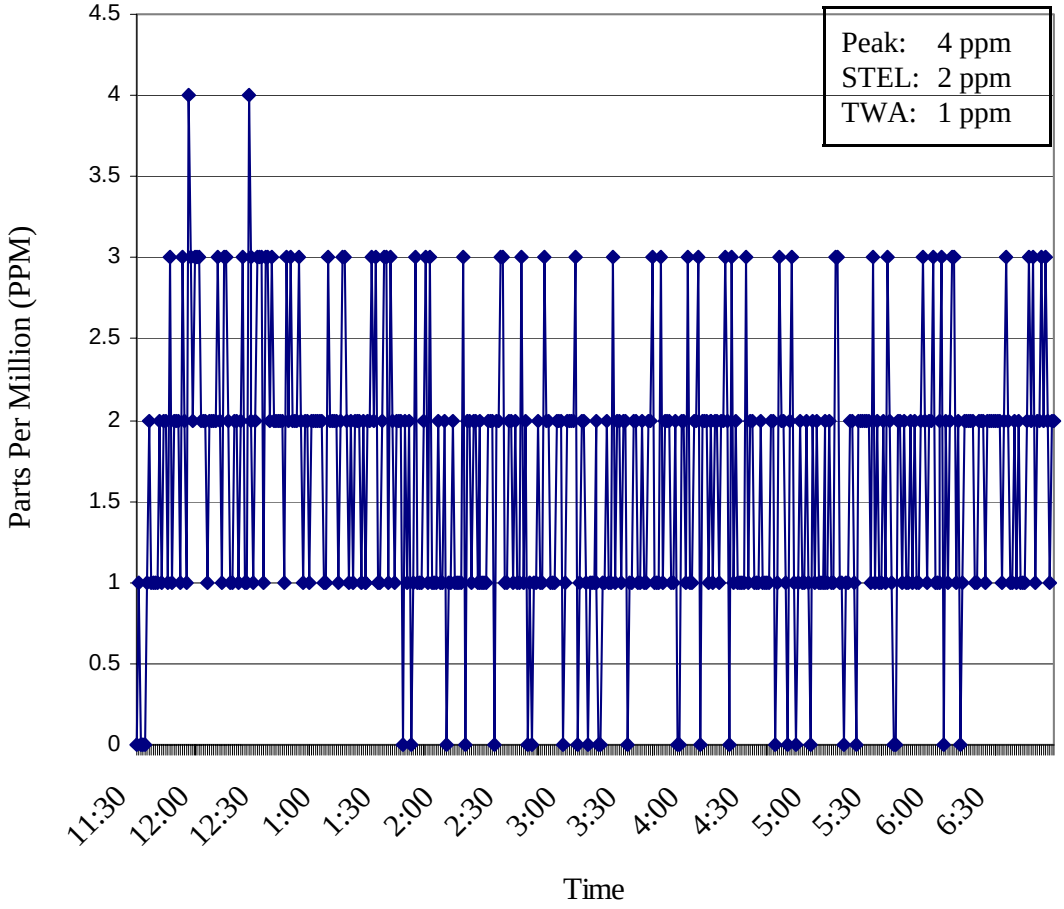
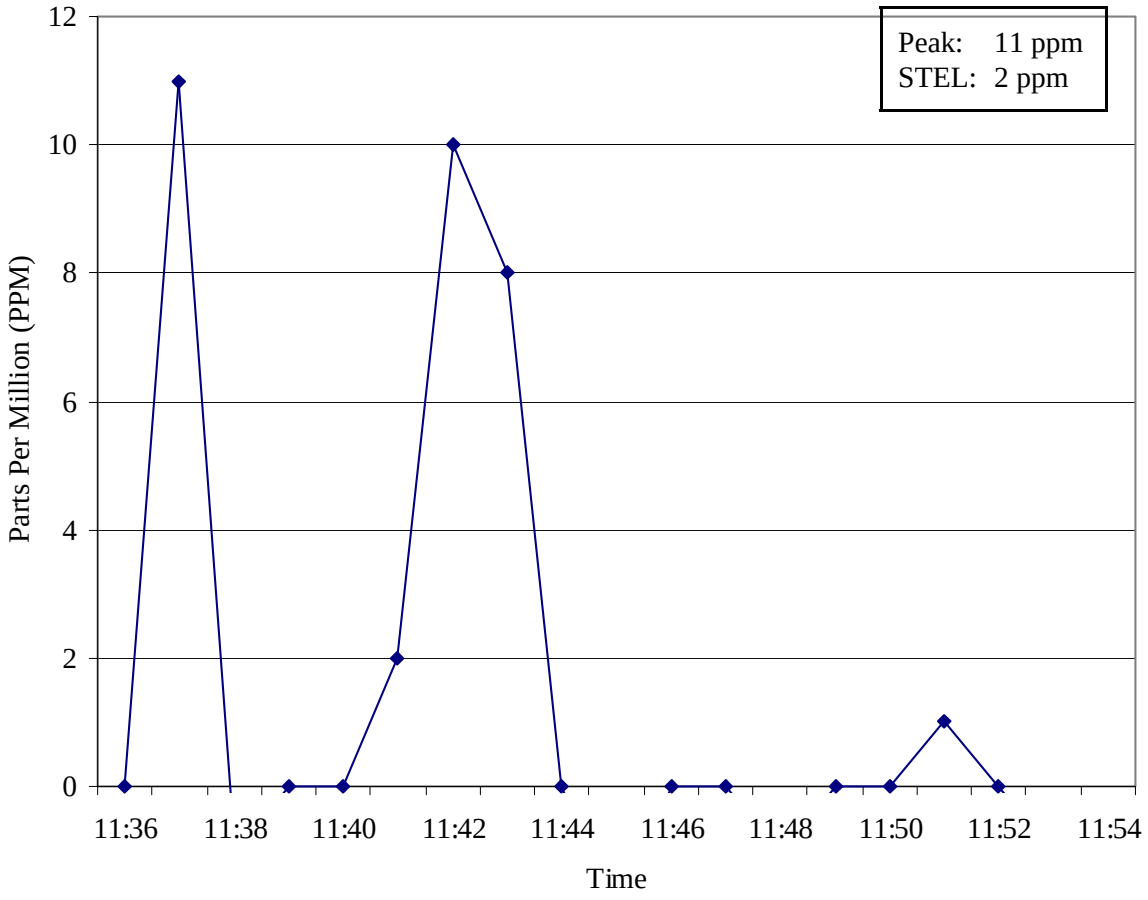


Figure 2
Instantaneous NO Monitoring Results Measured During Line Priming in NO Storage Closet
The Children's Hospital of Denver
Denver, Colorado
HETA 99-0313-2802
February 29, 2000



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