Exposure of Intensive Care Unit Nurses to Nitric Oxide and Nitrogen Dioxide During Therapeutic Use of Inhaled Nitric Oxide in Adults With Acute Respiratory Distress Syndrome

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• BACKGROUND *Although low concentrations of inhaled nitric oxide may by therapeutic, both nitric oxide and its oxidation product nitrogen dioxide are potentially toxic. The threshold limits for time-weighted average concentrations of nitric oxide and nitrogen dioxide issued by the American Conference of Governmental Industrial Hygienists are 25 and 3 ppm, respectively. The concentrations of these gases in the breathing space of hospital personnel during administration of nitric oxide to adult patients have not been reported.*

• METHODS *Air was sampled from the breathing zone of intensive care unit nurses via collar-mounted tubes during the nurses' routine duties attending patients who were receiving inhaled nitric oxide at 5 or 20 ppm. The exhaust ports of the mechanical ventilators were left open to the room. Nitric oxide and nitrogen dioxide were chemically assayed as nitrite from sorbent tubes by using spectrophotometry. Ambient nitric oxide levels were measured at sequential distances from the ventilator by using chemiluminescence.*

• RESULTS *The time-weighted average concentrations of inspired gas for nurses during inhaled nitric oxide treatment were 0.45 ppm or less for nitric oxide and less than 0.29 ppm for nitrogen dioxide. Nitric oxide levels at the ventilator during delivery at 20 ppm were 9.2 ppm, but dropped off markedly beyond 0.6 m (2 ft), to a mean of about 30 ppb.*

• CONCLUSION *Inhaled nitric oxide therapy at doses up to 20 ppm does not appear to pose a risk of excessive occupational exposure to nitric oxide or nitrogen dioxide to nurses during routine delivery of critical care. (American Journal of Critical Care. 2002;11:147-153)*

Nitric oxide (NO) is a colorless, corrosive gas used industrially in the manufacture of nitric acid, bleaching of rayon, and preparation of nitrosyl halide compounds. It spontaneously combines with oxygen to form nitrogen dioxide (NO_2), a fuming yellow liquid (principally as the dimer, N_2O_4) at temperatures lower than 21°C and a reddish brown gas at higher temperatures.[1-5] NO_2 is also produced when nitric acid contacts organic material or certain metals (eg, during industrial acid dipping) and by combustion of nitrogen-containing materials, such as diesel fuel, in enclosed spaces. The odor threshold for NO_2 is between approximately 1 and 3 ppm, although broader ranges have been reported.[6,7] In air, NO and NO_2 exist in equilibrium; thus, mixtures of the 2 gases are often referred to collectively as nitro-

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gen oxides or NOx. Both gases are considered atmospheric pollutants with potentially toxic effects. Outdoors, the main source of this pollution is combustion of fossil fuels by industries and motor vehicles.

Occupationally, workers involved in the production of nitric oxide, manufacture of explosives, mining, agriculture, and fire fighting and those who work with ice resurfacing machines, boilers, and arc welders are potentially at risk for exposure to nitrogen oxides. Sources of nonoccupational exposures include unvented gas- and oil-fired household appliances, kerosene heaters, motor vehicle exhaust, and cigarette smoke.[2,5,8,9] NO_2, a more potent toxin and pulmonary irritant than NO, is the causative agent of silo filler's disease.

■ Nitric oxide, which is used at low concentrations to treat acute lung diseases, combines with oxygen to form nitrogen dioxide. Both nitric oxide and nitrogen dioxide can be toxic at higher concentrations. The amounts of these gases to which intensive care unit nurses may be exposed depends on the concentration of nitric oxide delivered to the patient, the patient's minute volume, the size of the room, ventilation in the room, baseline levels of those gases in the room, and the nurse's proximity to the ventilator's exhaust port.

The signs and symptoms of acute toxic exposure to exogenous NO or NO_2 depend on the concentration of the gas and the duration of exposure but can range from dyspnea, cough, headache, fatigue, nausea, vertigo, and somnolence to sudden death. Removal to fresh air of the person exposed may diminish or resolve these manifestations, although frank pulmonary edema, pneumonitis, bronchiolitis obliterans, laryngospasm, bronchospasm, asphyxiation, and death can occur.[2,4,5,7,8,10]

Therapeutic use of low concentrations of inhaled NO in patients with acute lung diseases associated with pulmonary hypertension, including children and adults with acute respiratory failure, acute respiratory distress syndrome,[11-19] and acute lung injury,[20] has been examined in clinical trials. Therapeutic use has also been studied in premature and full-term neonates with persistent pulmonary hypertension[21,22]; infant and adult cardiac surgery patients,[23-25] including patients with pulmonary hypertension after heart or lung transplantation[26,27]; and patients with pulmonary embolism,[28] sickle cell anemia,[29] pulmonary edema after pneumonectomy,[30] status asthmaticus,[31] and primary pulmonary hypertension.[32] Inhaled NO diffuses rapidly from lung tissue into adjacent blood vessels, resulting in pulmonary vasodilatation, decreased pulmonary vascular resistance, and lowering of pulmonary artery pressure. NO is rapidly deactivated by reaction with hemoglobin to form nitrosylhemoglobin, methemoglobin, nitrite, and nitrate.

Because of the toxicity of NO and NO_2, questions have been raised about occupational exposure of healthcare workers to these gases.[33-35] To our knowledge, occupational hygiene methods have not been used to determine the time-weighted average (TWA) concentrations of NO and NO_2 in the breathing space of hospital personnel during the therapeutic administration of inhaled NO to adult patients. We evaluated exposure of intensive care unit (ICU) nursing personnel to these gases during NO treatment of adult patients with acute respiratory distress syndrome.

Methods

The study took place at Detroit Receiving Hospital, was approved by the Wayne State University Human Investigation Committee, and conformed to the standards set forth in the Helsinki Declaration of 1975. Written informed consent was obtained from participating patients (or their authorized representative) and from the nurses who were subjects in the study. Patients met standard criteria for acute respiratory distress syndrome associated with pneumonia and were treated with mechanical ventilation plus investigational treatment with inhaled NO at 5 ppm or 20 ppm. The system used for administration of NO consisted of a commercially manufactured device with an integral mass flow controller (Nitric Oxide Delivery System, Ohmeda, Inc, Madison, Wis) for delivery of inhaled NO and a conventional mechanical ventilator (Servo 900C, Siemens Elema, Lund, Sweden). NO was introduced from compressed gas cylinders containing 400 ppm NO (the balance was nitrogen; BOC Special Gases, Murray Hill, NJ) into the ventilatory circuit during the inspiratory phase. The flow rate was controlled by the delivery device to ensure a constant concentration of NO. Patients' vital signs, arterial blood gases, and methemoglobin levels

■ A collar-mounted sampling tube and a belt-mounted aspiration pump were used to measure the levels of nitric oxide and nitrogen dioxide in the air that the nurses were breathing. Air samples were obtained while the nurses were caring for patients treated with 2 different levels of nitric oxide. Nitric oxide levels in the room were also measured at various distances from the ventilator. All patients were in closed isolation, negative-pressure rooms.

were monitored intermittently. Concentrations of oxygen, NO, and NO_2 in the inspiratory limb of the ventilator circuit were monitored continuously during the period of NO administration by using a series of electrochemical gas analyzers incorporating numerical displays and alarms.[36] The exhaust ports of the mechanical ventilators were open to the patients' rooms; that is, no special venting, chemical sorbent traps, or other exhaust scavenging equipment was used.

Each nurse participating in the study was the primary ICU nurse caring for one of the patients receiving inhaled NO treatment. Under the direction of a certified industrial hygienist, air in the zone of air breathed by healthcare personnel[37] was sampled via a collar-mounted sampling tube and belt-mounted portable aspiration pump (model 224-30, SKC, Inc, Eighty Four, Pa) that each participating nurse wore while he or she carried out routine duties attending a single patient receiving inhaled NO therapy. No other patients in the unit received inhaled NO therapy during the period of study. The flow rate of the aspiration pump used for sampling the breathing space was measured by using a timed volumetric calibration device (Mini Buck Calibrator, AP Buck, Inc, Orlando, Fla) before and after each sampling period to ensure a constant flow rate.

For measurements of the exposure of healthcare personnel to NO and NO_2, the gases were chemically assayed as nitrite from sorbent tubes containing triethanolamine-treated molecular-sieve media, with and without preoxidation, by using visible absorption spectrophotometry.[38] The lower mass limit of detection with this standard method is 2 μg. However, the limit of the concentration that can be detected varies with the cumulative volume of air sampled, as reflected by the sampling interval and pump flow rate. The TWA concentrations of NO and NO_2 inspired by the healthcare personnel were determined from the sampling intervals, pump flow rates, and the mass results obtained from NO and NO_2 assays and corresponding blanks.[38]

Samples of ambient air in each patient's room were obtained at 8 sequential, horizontal, linear distances from the ventilator exhaust port and were assayed for NO by using a calibrated on-line chemiluminescence monitor (series 2108, Dasibi Environmental Corp, Glendale, Calif; US Environmental Protection Agency reference method RFNA-1192-089). After the displayed value reached a plateau, the mean of at least quadruplicate measurements was determined during a period of approximately 2 minutes at each position. Samples of ambient air just outside each patient's room were also obtained and assayed. Hourly outdoor environmental concentrations of NO and NO_2 during the intervals of the personnel study were obtained from measurements reported by the Wayne County Department of Environment Air Quality Management Division, Detroit, Mich.

Results

A total of 2 patients and 4 nurses participated in the study. The breathing spaces of the 4 nurses were sampled while the nurses provided care to the 2 patients treated with inhaled NO. The patients received mechanical ventilation via volume-cycled and pressure-control modes, fractions of inspired oxygen between 0.60 and 1.00, ventilator-set rates of 12 and 30 breaths/min (neither of the patients was overbreathing the ventilator during the study period), and positive end-expiratory pressure of 10 and 16 cm H_2O. Tidal volumes ranged from 550 mL to 950 mL. Neither patient had any tube thoracostomy drains in place. The rooms used to treat the 2 patients were closed isolation rooms (room volume, 47 m^3 for nurses 1 and 2 and 38 m^3 for nurses 3 and 4) maintained under negative-pressure (0.018 and 0.030 cm H_2O, respectively) ventilation (13.8 and 19.4 air changes per hour, respectively), and directly exhausted to the outside. The highest blood fractional methemoglobin level in the patients during study treatment with inhaled NO was 0.022.

■ Levels of nitric oxide and nitrogen dioxide detected in the air that nurses were breathing were well below legally permissible exposure limits mandated by the Occupational Safety and Health Administration, regardless of the amount of nitric oxide administered to the patient. Much higher levels of nitric oxide were found at the ventilator's exhaust port, but levels were markedly lower 2 feet away from the port.

The nurses' exposure time during sampling ranged from 3.8 to 7 hours, and they remained asymptomatic throughout their period of study (see Table). The flow rate of the sampling pump before and after treatment remained constant at 26 mL/min. The TWA concentration of inspired NO for one of the nurses caring for the patient treated with 5 ppm inhaled NO was 0.26 ppm. For the other nurse involved in this patient's care, the TWA concentration was less than the limit of detection for the assay (0.44 ppm). Corresponding TWA concentrations of NO_2 for these nurses were less than the limits of detection (0.17 ppm for one nurse and 0.29 ppm for the other). For the 2 nurses caring for the patient treated with inhaled NO at 20 ppm, the TWA concentrations of inspired gases were 0.44 and 0.45 ppm for NO and 0.28 and 0.27 ppm for NO_2, respectively.

Ambient NO concentrations measured at selected distances from the ventilator exhaust port for one

Monitored occupational exposure times, patients' therapy level of inhaled nitric oxide (NO), occupational time-weighted average (TWA) concentrations of NO and nitrogen dioxide (NO_2) inspired by nurses, and corresponding outdoor ambient NO and NO_2 levels during the healthcare personnel study periods*

Nurse	Exposure time, hours	Patients' therapy level of inhaled NO, ppm	TWA concentration of inspired NO, ppm	TWA concentration of inspired NO_2, ppm	Estimated outdoor concentration of NO, ppb†	Measured outdoor concentration of ambient NO_2, ppb‡
1	3.8	5	<0.44	<0.29	4-30	12-90
2	7.0	5	0.26	<0.17	6-22	17-68
3	4.5	20	0.44	0.28	5-6	14-18
4	6.0	20	0.45	0.27	6-13	17-38

*Outdoor ambient NO and NO_2 levels taken from hourly determinations provided by the Air Quality Management Division, Wayne County Department of Environment, Detroit, MI. Numbers after the < symbol indicate lower detection limit of assay.
†Based on modeling guideline followed by the Air Quality Management Division, Wayne County Department of Environment, Detroit, Mich.
‡For comparison, the primary national ambient air quality standard of the Environmental Protection Agency to protect against adverse health effects is 53 ppb (100 μg/m^3), calculated as an annual arithmetic mean.

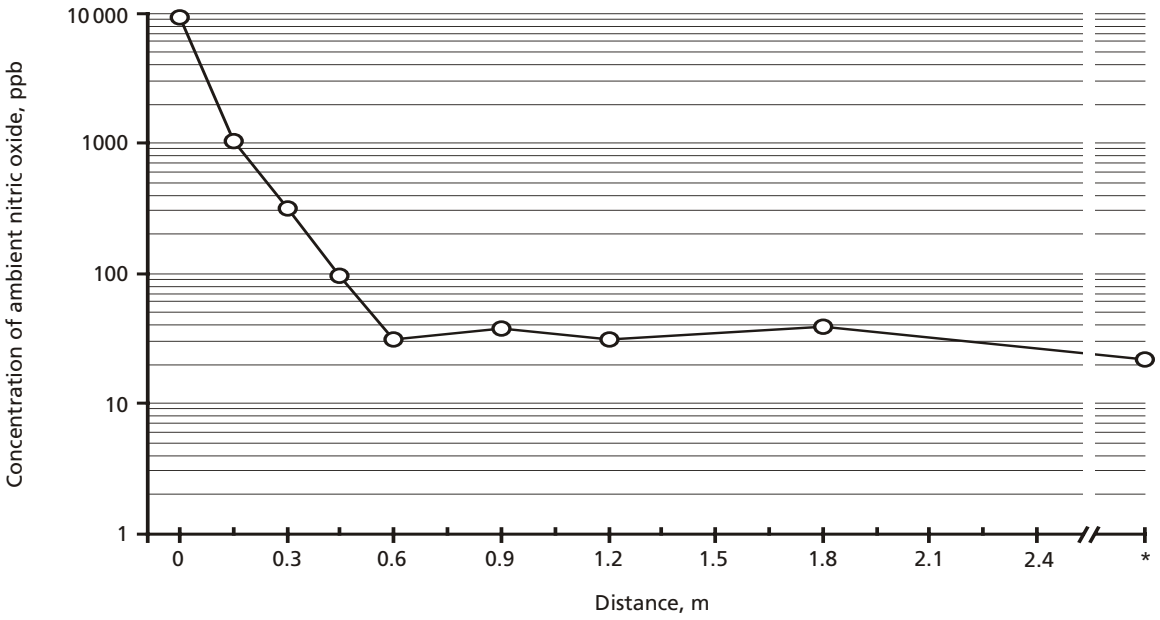
patient are shown in the Figure. Concentrations of NO outdoors during the periods of study, as reported by the county in which the study was conducted, are indicated in the Table.

Discussion

NO is naturally produced in the body by the enzyme NO synthase, which converts L-arginine to L-citrulline and NO in the presence of oxygen and certain cofactors. Both constitutive and inducible forms of NO synthase are present in endothelium and various other tissues.[39-41] NO has several important physiological roles, including involvement in smooth muscle relaxation, neurotransmission, host defense responses, and platelet function. NO produced by the vascular endothelium causes local vasodilatation, thereby regulating vasomotor tone. Circulating NO is present in only picomolar amounts and is rapidly inactivated by reaction with hemoglobin. Because of this short circulating half-life (3-5 seconds), inhalation of subtoxic levels of NO causes vasodilatation of the pulmonary vasculature with little or no systemic vasodilatation. Therapeutic administration of NO by inhalation thus provides a means of selectively lowering pulmonary arterial blood pressure, potentially improving hemodynamic status and gas exchange.[11-13,15,17,18,23]

Inhaled NO has been widely studied in adults with pulmonary hypertension and acute lung injury, and it is currently approved by the Food and Drug Administration for treatment of hypoxic respiratory failure in neonates with pulmonary hypertension. Three potential hazards associated with inhaled NO therapy are recognized: (1) direct pulmonary toxic effects of NO, (2) pulmonary toxic effects due to NO_2 produced by oxidation of NO, and (3) development of methemoglobinemia. Studies of exposure to toxic levels of NO and NO_2 in various species indicated that high concentrations of these gases can be lethal. Pulmonary edema, hypoxemia, acidosis, and hypotension developed in dogs exposed to 0.5% to 2% NO or NO_2, and most animals died within 7 to 50 minutes of exposure.[42] In rats, inhaled NO_2 concentrations of 127 ppm were lethal within 30 minutes in 50% of animals (LC_{50}).[43] The LC_{50} in primates exposed to NO_2 for 30 to 60 minutes is 100 to 200 ppm.[43] Methemoglobinemia is detectable by measurement of blood levels of methemoglobin and is manifested clinically as cyanosis and hypoxia. Methemoglobinemia developed in animals exposed to high concentrations of NO or NO_2, although not uniformly. In one instance, a methemoglobin level of 1.00 developed in a dog exposed to 2% NO for 50 minutes.[42] In humans, NO at 10 to 20 ppm can cause irritation of the eyes and nose, 25 ppm can be irritating to the respiratory tract and cause chest pain, 50 ppm can cause pulmonary edema, and 100 ppm can be fatal.[1,4]

Legally permissible exposure limits for NO and NO_2 have been issued by the Occupational Safety and Health Administration. For NO, this threshold is 25 ppm (30 mg/m^3), averaged over an 8-hour work shift.[10] This value corresponds to the threshold limit value promulgated by the American Conference of Governmental Industrial Hygienists.[2] Adherence to this limit is thought to provide adequate protection against methemoglobinemia and other toxic effects. Concentrations of 100 ppm and higher (30-minute mean) are deemed to be an immediate threat to life and health by the National



Semilogarithmic plot of ambient concentration of nitric oxide measured by using on-line chemiluminescence analysis vs linear distance from ventilator exhaust port in an intensive care unit isolation room of a patient treated with 20 ppm nitric oxide. Each point represents the mean of at least quadruplicate measurements of nitric oxide. The farthest distance (*) was 0.6 m (2 ft) outside the room, with the door open.

Institute for Occupational Safety and Health.[44] The Occupational Safety and Health Administration ceiling limit for NO_2 is 1 ppm (1.8 mg/m^3), and this limit is not to be exceeded at any time during the work shift.[10] The threshold limit for TWA concentration of NO_2 issued by the American Conference of Governmental Industrial Hygienists is 3 ppm,[2] and the National Institute for Occupational Safety and Health requires that NO_2 exposures not exceed 1 ppm.[10,44]

These threshold values are thought to represent maximum concentrations to which nearly all workers can be exposed on a regular basis without adverse effects. Nevertheless, evidence suggests that lower levels of exposure can have deleterious effects. For example, irreversible emphysematous changes to the lungs occurred in beagles exposed to 0.6 ppm NO_2 for 16 h/d for 68 months and then to clean air for 32 to 36 months.[45] In a study of exposure of humans to NO at 1.0 ppm, small but significant increases in airway resistance occurred in half the subjects.[46] Similarly, inhalation of NO_2 at 0.7 to 2 ppm for 10 minutes increased airflow resistance in healthy subjects.[1] Exposure to NO_2 at 2.3 ppm for 5 hours reportedly altered alveolar permeability in humans.[47] Brief exposure to NO_2 levels as low as 0.4 ppm may augment the response to challenge with specific allergens, and exposure to 0.1 to 0.5 ppm may affect pulmonary function in patients with asthma or chronic obstructive lung disease.[1,5,7,48,49]

Limited information is available on occupational exposure to NO in the healthcare setting. Using stationary chemiluminescence monitoring, Mourgeon et al[50] determined ambient concentrations of NO and NO_2 in the main corridor of an ICU. They found that mean ambient NO concentrations within the ICU were 0.237 ppm (SD 0.147 ppm) during the therapeutic use of inhaled NO at 5 ppm or less in 1 or more patients and 0.289 ppm (SD 0.147 ppm) during times when inhaled NO therapy was not used. The institution where this study[50] was performed is located on a main street in Paris, and Mourgeon et al concluded that the ICU corridor values were entirely dependent on prevailing outdoor concentrations. Markhorst et al[51] examined ambient levels of NO and NO_2 in well-ventilated and poorly ventilated pediatric ICU rooms in which administration of inhaled NO at 20 ppm was simulated. As in the study by Mourgeon et al, sampling was done from a stationary position (in the study by Markhorst et al, 65 cm from the high-frequency oscillator used) at a height of 150 cm. During the simulation, maximum NO and NO_2 levels were 0.462 and 0.064 ppm, respectively. Phillips et al[52] used occupational hygiene techniques similar to those we used to examine exposure levels in medical personnel during

administration of inhaled NO to 6 patients in a pediatric ICU. In all instances, TWA concentrations were less than the limits of detection for the assay used. The patients' sizes and minute volumes were not specified, although 3 of the patients were classified as neonatal.

We examined the occupational exposure of ICU nurses to NO during NO therapy at delivery levels of 5 and 20 ppm in adult patients with acute respiratory distress syndrome. The maximum TWA exposures in our study were 0.45 ppm for NO and 0.28 ppm for NO_2, well below the legally permissible exposure limits mandated by the Occupational Safety and Health Administration, and the involved nurses reported no respiratory or other signs or symptoms. The maximum outdoor background concentrations of NO and NO_2 in our county during the periods of study ranged from 0.006 to 0.030 ppm for NO and 0.018 to 0.090 ppm for NO_2. For comparison, the primary national ambient air quality standard issued by the Environmental Protection Agency is 0.053 ppm (100 μg/m^3), calculated as an annual arithmetic mean.[53] We did not assess methemoglobin levels in the nurses; however, methemoglobinemia did not develop in the treated patients. Marked methemoglobinemia is uncommon in patients treated with inhaled NO at concentrations similar to those used in our study.[11,12,15,16,18,23]

■ Nitric oxide therapy does not appear to expose nurses to excessive levels of nitric oxide or nitrogen dioxide during routine patient care in the ICU.

In the simulation study of Markhorst et al,[51] ambient NO concentrations were measured at distances of 15 to 200 cm from a high-frequency oscillator, yielding levels ranging from 1.2 to 0.4 ppm. Our measurements yielded similar results (see Figure); however, in our study, NO levels at the ventilator exhaust port were nearly 10 times higher (9.2 ppm) than those 15 cm away (1.0 ppm). NO concentrations decreased rapidly; the mean was about 0.030 ppm in the area between 0.6 m from the ventilator and 0.6 m outside the patient's room. For comparison, in homes with gas cooking stoves, ambient NOx levels of 0.025 to 0.075 ppm are typical.[9]

A number of factors determine the concentrations of NO and NO_2 to which personnel are exposed during the therapeutic use of inhaled NO. These include the concentration of NO delivered to the patient, the patient's minute volume, room size, room ventilation, and whether special ventilator exhaust routing or chemical scavenging devices are used. Baseline ambient levels of NO and NO_2 depend on outdoor environmental factors such as proximity to motor vehicle traffic or heavy industry, climate, wind, and sky clarity.[50] Depending on the mode of administration, the actual concentration of NO delivered to a patient can fluctuate from the intended level. Continuous delivery during the entire respiratory cycle can produce more atmospheric contamination than does sequential administration limited to the inspiratory phase.[54] The amount of NO_2 formed during NO therapy varies according to the concentrations of oxygen and NO delivered, the time the 2 gases remain in contact, total gas flow, and minute volume.[55] Thus, higher fractions of inspired oxygen will lead to increased formation of NO_2 during inhaled NO therapy.

Because of differences in minute volume, therapeutic administration of inhaled NO to adult patients will result in substantially greater release of NO than will administration to infants or children. For example, to achieve a delivered NO concentration of 20 ppm, the required flow from a 1000-ppm NO source varies from 20 mL/min for a minute volume of 1 L/min to more than 200 mL/min for a minute volume of 11 L/min[19] (our patients' minute volumes exceeded 11 L/min). Simultaneous treatment of multiple patients in the same room or unit might increase exposure levels. The time spent by healthcare providers in the patient's room and their average exposure distance from the ventilator exhaust port are also important factors. Room ventilation is clearly a factor. Ventilation in our negative-pressure isolation rooms exceeded that mandated by the Centers for Disease Control and Prevention (ie, ≥6 air changes per hour for existing rooms and ≥12 air changes per hour where possible and in new hospital construction).[56] Our study design did not allow analysis of the effects of any of these factors; however, the methods we used provide data for real-world examples of ICU nurses caring for typical adult patients receiving inhaled NO. These techniques also constitute the standard method for evaluations of occupational exposure to toxic gases. Studies in which these methods are used, but involving larger samples of nurses and patients in various settings, would allow better definition of variance and the effects that factors such as room ventilation have on exposure to ambient NO and NO_2.

In summary, we found that inhaled NO therapy at doses up to 20 ppm does not appear to pose a risk of excessive occupational exposure to NO or NO_2 to healthcare workers during the routine delivery of critical care nursing in typical adult ICU settings. These findings lend support to the occupational safety of this therapeutic modality.

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