

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20845

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

**ENVIRONMENTAL ASSESSMENT
AND
FINDING OF NO SIGNIFICANT IMPACT
FOR
NITRIC OXIDE FOR INHALATION
(400 ppm in Nitrogen)**

NDA 20-845

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS
(HFD-110)**

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-845

NITRIC OXIDE FOR INHALATION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new orphan drug application for Nitric Oxide for Inhalation, Ohmeda Pharmaceutical Products Division Inc (Ohmeda PPD), Liberty Corner, New Jersey 07938-0804 prepared an environmental assessment (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product. The format for the environmental assessment for an orphan drug NDA, defined in 21 CFR 25.31a (b) (3), is the same as the Tier 0 format.

The combustion of fossil fuels results in the emission of millions of tons of nitric oxide into the atmosphere. The quantities used for medical purposes are very small by comparison. Furthermore, precautions used in manufacturing and administration to patients are designed to minimize atmospheric emissions related to this NDA.

Nitric oxide is a synthetic gaseous drug substance. It is diluted in nitrogen, specifically, 400 ppm NO in nitrogen. It is administered to term and near term infants in conjunction with mechanical ventilation for the treatment of respiratory hypoxia. The drug substance, nitric oxide, and the drug product, Nitric Oxide for Inhalation, are manufactured, packaged, tested and labeled by BOC Gases, Port Allen, LA 70767. Both Ohmeda PPD and BOC Gases are operating divisions of The BOC Group Inc. Chemical waste is collected and shipped from Port Allen by a licensed chemical waste disposal company. All facilities are certified to operate in accord with applicable environmental regulations.

The drug product, Nitric Oxide for Inhalation, will be used primarily in hospitals and secondarily, in ambulatory transport.

Nitric oxide must be administered through the I-NOvent (or equivalent) delivery device to minimize escape of nitrogen oxides into the environment. The amount of inhaled nitric oxide that is absorbed by a patient is variable, however some nitric oxide rapidly diffuses into the vascular bed where it induces vasodilatation and undergoes rapid inactivation by reaction with hemoglobin to produce methemoglobin and the nitrate and nitrite ions. Nitric oxide absorbed by the patient is not excreted into the environment.

Acid waste from the drug substance manufacturing operations is neutralized to pH 7, analyzed and disposed into the municipal storm sewers.

Residual nitric oxide (drug substance) contained in reusable aluminum alloy compressed gas cylinders with a stainless steel valve with Teflon O-Ring, is disposed by BOC Gases at the Port Allen site. The contents of compressed gas cylinders containing less than 10% nitric oxide may vented to the atmosphere according to the Small Source Exemption for Air Emission issued by the State of Louisiana to BOC Gases, on December 14, 1994. Alternatively, the cylinders may be shipped to a licensed chemical waste disposal company. This includes all rejected, used (empty), unused (partially full) or expired drug product cylinders.

The contents of compressed gas cylinders containing more than 10% nitric oxide are treated with oxygen to form higher oxides of nitrogen, scrubbed with caustic solution and disposed by

Supplies not returned by American hospitals, pharmacies and clinics will be disposed according to their procedures.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the drug substance and the drug product are expected to minimize occupational exposures and environmental release.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

July 21, 1997
Date

IS/
PREPARED BY: Florian Zielinski, Review Chemist
Division of New Drug Chemistry I

7/21/97
Date

IS/
DIVISION CONCURRENCE: Robert Wolters
Division of New Drug Chemistry I

7/26/97
Date

IS/
APPROVED: Nancy B. Sager, Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

- Attachments: Environmental Assessment, pages 332 to 356
Material Safety Data Sheets
a) Nitric Oxide, pages 344 to 350
b) Nitric Oxide in Nitrogen, 0.00001% to 1%, pages 351 to 356

- Original: NDA 20-845.
HFD-357 FONSI File [NDA 20-845]
HFD-357 Docket File
HFD-205 FOI COPY
HFD-110 Division File
HFD-110 CSO, Zelda McDonald
HFD-110 Review Chemist, Florian Zielinski

1. **Date of preparation**

February 21, 1997.

2. **Name of Applicant/Petitioner**

Ohmeda Pharmaceutical Products Division (PPD) Inc
The BOC Group of Companies

3. **Address**

110 Allen Road
Liberty Corner, NJ 07938, USA

4. **Description of Proposed Action**

a. **Requested Approval**

Pursuant to section 505 (b)(2) of the Act, Ohmeda PPD is submitting an NDA for an orphan drug, I-NO™ (Nitric Oxide) for Inhalation, 400 ppm (in nitrogen), packaged in a seamless aluminum compressed gas cylinder with a stainless steel valve and Teflon gasket. An environmental assessment (EA), prepared according to the Tier 0 approach, is being submitted pursuant to 21 CFR 25.25a(b)(5) and the FDA EA guideline.

b. **Need For Action**

Approval for this orphan drug is sought for the treatment for respiratory hypoxia in conjunction with mechanical ventilation in term and near-term infants (≥ 34 weeks gestation), which may be caused by such conditions as persistent pulmonary hypertension, respiratory distress syndrome (RDS), meconium aspiration, pneumonia/sepsis, and congenital diaphragmatic hernia.² This is a new therapy for the

² The product is delivered *via* an approved ventilator system at a recommended concentration of 20 ppm.

treatment of respiratory hypoxia in infants and can provide significant advantages over the existing therapies.

c. Production Location

Both Ohmeda PPD Inc, the NDA holder, and BOC Gases, the manufacturer of the drug substance/product (listed below), are operating divisions/subsidiaries of The BOC Group Inc.

The drug substance (NO) and drug product (Nitric Oxide for Inhalation) will be manufactured, packaged, tested, and labeled at the facility listed below (also known as the Port Allen site).

BOC Gases
1075 Cinclare Drive
Port Allen, LA 70767, USA

Port Allen is a suburb of Baton Rouge, Louisiana and is located on the opposite bank of the Mississippi River (within about 2 miles.) The BOC Gases facility is located in an industrial zone. The region is flat and the climate is temperate.

d. Locations Of Use

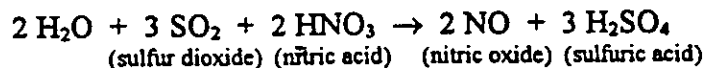
Nitric Oxide for Inhalation will be used primarily in hospitals and secondarily in ambulatory transport.

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e. **Disposal Sites**

i. **DISPOSAL OF SYNTHESIS BY-PRODUCTS**

Nitric oxide (NO) is synthesized in a one step process according to the chemical reaction listed below.



The by-products of the drug synthesis are sulfuric acid, a reaction by-product, and nitric acid, which is reacted in excess.

Prior to disposal, sulfuric and nitric acids are neutralized with caustic solution to pH 7, in accordance with the regulations of the City of Port Allen. [The neutralized waste is analyzed by an independent laboratory,

contracted by BOC Gases, in order to monitor long-term sulfate and nitrate salt output.] The neutralized solution then is released into the municipal storm sewers, as permitted by the City of Port Allen (BOC Gases Waste Generators Permit No. LAD094178050).

Any residual SO₂ is scrubbed with a caustic solution, and the exhausted scrubber solution is collected and shipped from the Port Allen site by

to a licensed chemical waste disposal company

ii. **DISPOSAL OF NITRIC OXIDE DRUG SUBSTANCE AND DRUG PRODUCT**

As the drug product, which is packaged in a reusable aluminum alloy compressed gas cylinder with a stainless steel valve and Teflon O-ring is 'loaned' to the health care provider, all used, unused or expired drug product cylinders are expected to be returned from the user to Port Allen for disposal as described below. If any supplies

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are not returned by US hospitals, pharmacies or clinics, they will be disposed of according to hospital, pharmacy or clinic procedures.

Returned, expired, drug product or rejected drug substance and/or drug product will be disposed of either by BOC Gases at the Port Allen site, or shipped to a licensed chemical waste disposal company.

The contents of compressed gas cylinders containing nitric oxide at concentrations less than 10% may be vented to the atmosphere, as permitted by the Small Source Exemption for Air Emission issued by the State of Louisiana to BOC Gases on 12/14/94.

The contents of compressed gas cylinders containing nitric oxide at concentrations greater than 10% are treated with oxygen (to form higher oxides of nitrogen), and then scrubbed with a caustic solution (to form water soluble nitrates). The oxidized/scrubbed waste is shipped to

5. Identification of Chemical Substances that are the Subject of the Proposed Action

a. Nomenclature

i. ESTABLISHED NAME (US ADOPTED NAME - USAN)

none

ii. BRAND/PROPRIETARY NAME

I-NO™ (nitric oxide) for Inhalation

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iii. CHEMICAL NAMES

(1) Chemical Abstracts Service (CAS) Name

nitric oxide

(2) Systematic Chemical Name

nitric oxide; nitrogen(II) oxide; mononitrogen monoxide; nitrogen monoxide

b. Chemical Abstracts Service (CAS) Registration Number

[10102-43-9]

c. Molecular Formula

NO

d. Molecular Weight

30.01

e. Structural Formula



f. Physical Description

Nitric oxide is a colorless gas at room temperature.

g. Additives

The drug substance nitric oxide contains no additives of any kind.

The drug product Nitric Oxide for Inhalation contains nitrogen (N₂) as the sole inactive ingredient. The CAS number for nitrogen is [7727-37-9]. Since nitrogen is

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the principal component of breathable air (~78% by volume), the impact on the environment as a result of its incorporation in the drug product is nil.

h. Impurities

There are no individual impurities in the drug substance or drug product at levels greater than 1%.

6. Introduction of Substances into the Environment

a. Substances Expected To Be Emitted

The substances expected to be emitted are described in EA format item 4.e "Disposal Sites".

b. Control Exercised

Information on the control/treatment of emitted substances is provided in EA format item 4.e "Disposal Sites".

c. Citation Of And Statement Of Compliance With Applicable Emission Requirements

BOC Gases, Port Allen, LA, complies with all of the applicable Federal, Local and State of Louisiana emission requirements, and holds the following permits at the facility:

- Small Source Exemption for Air Emission issued by the state of Louisiana on 12/14/94
- A Permit for Water Discharge, State Permit WP2987. BOC Gases currently is awaiting renewal information from the state of Louisiana.
- An EPA permit for water discharge, No. LA0086797
- A Radioactive Materials License issued by the State of Louisiana Department of Environmental Qualitative Radiological Protection Division, No. LA2926L01

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- A Waste Generators Permit from the State of Louisiana, No. LAD094178050.

The Material Safety Data Sheet, for both drug substance and drug product, is included in non-confidential Appendix 15.a

d. Discussion Of The Effect Of Approval On Compliance With Current Emission Requirements

Based upon the estimated sales volume in the fifth year of marketing after approval of the Nitric Oxide NDA, production of nitric oxide at the Port Allen facility will not adversely affect compliance with applicable environmental regulations, permits, and requirements.

Expected Introduction Concentrations From Use And Disposal

The potential concentration of nitric oxide introduced into the atmosphere as a result of manufacture, use, and disposal is expected to be less than 1 ppb, as explained in confidential appendix 15.b.

7. Fate Of Emitted Substances In The Environment
8. Environmental Effects Of Emitted Substances
9. Use of Resources and Energy
10. Mitigation Measures
11. Alternatives To The Proposed Action

EA format items 7-11 listed above are omitted, since nitric oxide is an Orphan Drug (Application No. 93-744, approved 6/22/93) and the EA follows the Tier 0 approach. The justification for the Tier 0 approach is provided in confidential Appendix 15.b.

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12. List of Preparers

Brian E. Wildstein, Associate Drug Regulatory Affairs

- B.S. Chemistry, State University of New York, Stony Brook, NY
- M.S. Chemistry, The Pennsylvania State University, College Park, PA
- Four years experience in the pharmaceutical industry including medicinal chemistry and regulatory affairs (CMC).

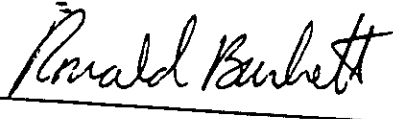
David L. Ziering, Ph.D., Assistant Director Drug Regulatory Affairs (CMC)

- B.S. Chemistry, Seton Hall University, South Orange, NJ
- M.A. Chemistry, Princeton University, Princeton, NJ
- Ph.D. Chemistry, Princeton University, Princeton, NJ
- Thirteen years experience in the pharmaceutical industry including analytical chemistry and regulatory affairs (CMC).

13. Certification

The undersigned official certifies that the information presented is true, accurate and complete to the best of the knowledge of the firm or agency responsible for preparation of the EA.

Additionally, the undersigned official certifies that EA format items 1, 2, 3, 4, 5, 6, 12, 13, 14, and 15a contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR 150.6.6.



Ronald Burkett

Director Environmental Affairs, Ohmeda Inc.

14. References (available upon request)

- Hutzler, M. J.; Andersen, A. T. "Emissions of Greenhouse Gases in the United States 1987-1994"; Energy Information Administration, U.S. Department of Energy. U.S. Government Printing Office: Washington, DC, 1995; DE/EIA-0573(94).
- Butler, J. D.; *Air Pollution Chemistry*; Academic: New York, 1979; pp. 37-38, 76-78, 273-275.
- Brown, T. L.; Lemay, H. E., Jr.; Bursten, B. E. "The Chemistry of Atmospheric Pollutants" in *Chemistry, The Central Science*; Prentice Hall: Englewood Cliffs, 1991.
- Office of Air Pollution. "Air Quality Trends - 1994: Six Principal Pollutants"; document # EPA-454/F-95-003; US Environmental Protection Agency: National Technical Information Services, 1995.

15. Appendix

a. Non-Confidential Information

The Material Safety Data Sheet, for both nitric oxide drug substance and drug product, is provided on the pages which follow.

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BOC GASES

MATERIAL SAFETY DATA SHEET

PRODUCT NAME: NITRIC OXIDE

1. Chemical Product and Company Identification

BOC Gases,
Division of,
The BOC Group, Inc
575 Mountain Avenue
Murray Hill, NJ 07974

BOC Gases
Division of,
BOC Canada Ltd.
5975 Falbourne Street, Unit 2
Mississauga, Ontario L5R 3W6

TELEPHONE NUMBER: (908) 464-8100
24-HOUR EMERGENCY TELEPHONE
NUMBER: CHEMTREC (800) 424-9300

TELEPHONE NUMBER: (905) 501-1700
24-HOUR EMERGENCY TELEPHONE
NUMBER: (905) 949-3777
EMERGENCY RESPONSE PLAN NO: 20101

PRODUCT NAME: NITRIC OXIDE
CHEMICAL NAME: Nitric Oxide
COMMON NAMES/SYNONYMS: Nitrogen Monoxide
TDG (Canada) CLASSIFICATION: 2.3 (5.1, 8)
WHMIS CLASSIFICATION: A, C, D1A, E, D2B

PREPARED BY: Loss Control (908)464-8100/(905)273-7700
PREPARATION DATE: 6/1/95
REVIEW DATES: 6/7/96

2. Composition, Information on Ingredients

INGREDIENT	% VOLUME	PEL-OSHA ¹	TLV-ACGIH ²	LD ₅₀ or LC ₅₀ Route/Species
Nitric Oxide FORMULA: NO CAS: 10102-43-9 RTECS #: QX0525000	100	25 ppm TWA	25 ppm TWA	LC ₅₀ 1068 mg/m ³ (rat)

¹ As stated in 29 CFR 1910, Subpart Z (revised July 1, 1993)

² As stated in the ACGIH 1994-95 Threshold Limit Values for Chemical Substances and Physical Agents

3. Hazards Identification

EMERGENCY OVERVIEW

Nitric Oxide is severely irritating to eyes and respiratory system. Effects may be delayed for several hours following exposure. Corrosive. Inhalation may result in chemical pneumonitis and pulmonary edema. Nonflammable. Oxidizer. This product accelerates the combustion of combustible material.

PRODUCT NAME: NITRIC OXIDE

ROUTE OF ENTRY:

Skin Contact Yes	Skin Absorption No	Eye Contact Yes	Inhalation Yes	Ingestion No
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HEALTH EFFECTS:

Exposure Limits Yes	Irritant Yes	Sensitization No
Teratogen No	Reproductive Hazard No	Mutagen No
Synergistic Effects None Reported		

Carcinogenicity: -- NTP: No IARC: No OSHA: No

EYE EFFECTS:

Severely irritating to the eyes.

SKIN EFFECTS:

Severely irritating to dermal tissues.

INGESTION EFFECTS:

None. This product is a gas and cannot be ingested.

INHALATION EFFECTS:

Nitric oxide vapors are a strong irritant to the pulmonary tract. At high concentrations initial symptoms of inhalation may be moderate and include irritation to the throat, tightness of the chest, headache, nausea and gradual loss of strength. Severe symptoms may be delayed (possible for several hours) and include cyanosis, increased difficulty in breathing, irregular respiration, lassitude and possible eventual death due to pulmonary edema in untreated cases.

NFPA HAZARD CODES

Health: 3
Flammability: 0
Reactivity: 0
OXIDIZER

HMIS HAZARD CODES

Health: 3
Flammability: 0
Reactivity: 0

RATINGS SYSTEM

0 = No Hazard
1 = Slight Hazard
2 = Moderate Hazard
3 = Serious Hazard
4 = Severe Hazard

4. First Aid Measures

EYES:

Immediately flush with tepid water in large quantities, or with a sterile saline solution. Seek medical attention as soon as possible.

SKIN:

Immediately flush with tepid water in large quantities, or with a sterile saline solution. Seek medical attention if blisters or other reactions develop.

INGESTION:

Not required.

MSDS: G-60

Revised: 6/7/96

0345

PRODUCT NAME: NITRIC OXIDE

INHALATION:

PROMPT MEDICAL ATTENTION IS MANDATORY IN ALL CASES OF OVEREXPOSURE. RESCUE PERSONNEL SHOULD BE EQUIPPED WITH SELF-CONTAINED BREATHING APPARATUS. Conscious victims should be **CARRIED** (not assisted) to an uncontaminated area and inhale fresh air with supplemental oxygen. Quick removal from the contaminated area is most important. Keep the patient warm, quiet and under competent medical observation until the danger of delayed pulmonary edema has passed (at least 72 hours). Any physical exertion during this period should be discouraged as it may increase the severity of the pulmonary edema or chemical pneumonitis. Bed rest is indicated. Unconscious persons should be moved to an uncontaminated area, and if breathing has stopped, administer artificial resuscitation and supplemental oxygen. Once respiration has been restored they should be treated as above.

5. Fire Fighting Measures

Conditions of Flammability: Not flammable, Oxidizer		
Flash point: None	Method: Not Applicable	Autoignition Temperature: None
LEL(%): None	UEL(%): None	
Hazardous combustion products: Oxides of nitrogen		
Sensitivity to mechanical shock: None		
Sensitivity to static discharge: None		

FIRE AND EXPLOSION HAZARDS:

Nitric oxide is nonflammable but will support combustion. As examples: In NO, hydrogen has a LEL of 13.5% and an UEL of 49% Methane 9-22% and Butane 7.5-12.5%.

EXTINGUISHING MEDIA:

Not Applicable. Use media appropriate for surrounding materials. Nitric oxide hydrolyzes to nitric acid in the presence of moisture.

FIRE FIGHTING INSTRUCTIONS:

Cut off the flow of gas if possible.

6. Accidental Release Measures

Evacuate all personnel from affected area. Use appropriate protective equipment. If leak is in user's equipment, be certain to purge piping with inert gas prior to attempting repairs. If leak is in container or container valve, contact the appropriate emergency telephone number listed in Section 1 or call your closest BOC location.

7. Handling and Storage

Electrical Classification:

Nonhazardous.

Nitric oxide is noncorrosive and may be used with most common structural materials. However, in the presence of moisture and oxygen, corrosive conditions will develop as a result of the formation of nitric and nitrous acids. Prior to use, systems to contain nitric oxide must first be purged with an inert gas. Where air contamination cannot be eliminated, stainless steel materials should be used.

PRODUCT NAME: NITRIC OXIDE

Use only in well-ventilated areas. Valve protection caps must remain in place unless container is secured with valve outlet piped to use point. Do not drag, slide or roll cylinders. Use a suitable hand truck for cylinder movement. Use a pressure reducing regulator when connecting cylinder to lower pressure (<3000 psig) piping or systems. Do not heat cylinder by any means to increase the discharge rate of product from the cylinder. Use a check valve or trap in the discharge line to prevent hazardous back flow into the system.

Protect cylinders from physical damage. Store in cool, dry, well-ventilated area away from heavily trafficked areas and emergency exits. Do not allow the temperature where cylinders are stored to exceed 130 °F (54 °C). Cylinders should be stored upright and firmly secured to prevent falling or being knocked over. Full and empty cylinders should be segregated. Use a "first in-first out" inventory system to prevent full cylinders being stored for excessive periods of time.

Never carry a compressed gas cylinder or a container of a gas in cryogenic liquid form in an enclosed space such as a car trunk, van or station wagon. A leak can result in a fire, explosion, asphyxiation or a toxic exposure.

8. Exposure Controls, Personal Protection

EXPOSURE LIMITS¹:

INGREDIENT	% VOLUME	PEL-OSHA ²	TLV-ACGIH ³	LD ₅₀ or LC ₅₀ Route/Species
Nitric Oxide FORMULA: NO CAS: 10102-43-9 RTECS #: QX0525000	98.0 to 99.995	25 ppm TWA	25 ppm TWA	LC ₅₀ 1068 mg/m ³ (rat)

¹ Refer to individual state or provincial regulations, as applicable, for limits which may be more stringent than those listed here.

² As stated in 29 CFR 1910, Subpart Z (revised July 1, 1993)

³ As stated in the ACGIH 1994-1995 Threshold Limit Values for Chemical Substances and Physical Agents.

IDLH (Nitric Oxide): 100 ppm

ENGINEERING CONTROLS:

Local exhaust to prevent accumulation of NO above the exposure limit.

EYE/FACE PROTECTION:

Gas-tight safety goggles or full-face respirator.

SKIN PROTECTION:

Protective gloves of Rubber or Teflon ®.

RESPIRATORY PROTECTION:

Positive pressure air line with full-face mask and escape bottle or self-contained breathing apparatus should be available for emergency use.

OTHER/GENERAL PROTECTION:

Safety shoes and eyewash.

PRODUCT NAME: NITRIC OXIDE

9. Physical and Chemical Properties

PARAMETER	VALUE	UNITS
Physical state (gas, liquid, solid)	: Gas	
Vapor pressure	: above critical temp.	
Vapor density at STP (Air = 1)	: 1.04	
Evaporation point	: Not Available	
Boiling point	: -241.2	°F
	: -151.9	°C
Freezing point	: -262.5	°F
	: -163.6	°C
pH	: Not Applicable	
Specific gravity	: Not Available	
Oil/water partition coefficient	: Not Available	
Solubility (H ₂ O)	: Negligible	
Odor threshold	: Not Applicable	
Odor and appearance	: Colorless gas with suffocating odor, reddish brown in air	

10. Stability and Reactivity

STABILITY:

Stable

INCOMPATIBLE MATERIALS:

Oxidizing agents, halides, hydrocarbons and oxygen. Reacts vigorously with fluorine, fluorine oxides and chlorine in the presence of moisture.

HAZARDOUS DECOMPOSITION PRODUCTS:

Oxidizes in air to form nitrogen dioxide, which is extremely reactive and a strong oxidizer. Upon contact with moisture and oxygen, it produces nitrous and nitric acids.

HAZARDOUS POLYMERIZATION:

Will not occur.

11. Toxicological Information

MUTAGENIC:

There is unspecified mutagenic data for nitric oxide (SAX/RTECS).

OTHER:

Chronic or repeated exposure may cause permanent decrements in pulmonary function (Silo Filler's Disease). The absence of marked acute irritation of nitric oxide limits its warning properties.

12. Ecological Information

No data given.

MSDS: G-60
Revised: 6/7/96

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PRODUCT NAME: NITRIC OXIDE

13. Disposal Considerations

Do not attempt to dispose of residual waste or unused quantities. Return in the shipping container PROPERLY LABELED, WITH ANY VALVE OUTLET PLUGS OR CAPS SECURED AND VALVE PROTECTION CAP IN PLACE to BOC Gases or authorized distributor for proper disposal.

14. Transport Information

PARAMETER	United States DOT	Canada TDG
PROPER SHIPPING NAME:	Nitric Oxide	Nitric Oxide
HAZARD CLASS:	2.3	2.3 (5.1, 8)
IDENTIFICATION NUMBER:	UN 1660	UN 1660
SHIPPING LABEL:	POISON GAS, OXIDIZER, CORROSIVE	POISON GAS, OXIDIZER, CORROSIVE

Additional Marking Requirement: "Inhalation Hazard"

Additional Shipping Paper Description Requirement: "Poison-Inhalation Hazard, Zone B"

15. Regulatory Information

Nitric oxide is listed under the accident prevention provisions of section 112(r) of the Clean Air Act (CAA) with a threshold quantity (TQ) of 10,000 pounds.

SARA TITLE III NOTIFICATIONS AND INFORMATION

Nitric oxide is listed as an extremely hazardous substance (EHS) subject to state and local reporting under Section 304 of SARA Title III (EPCRA).

The presence of nitric oxide in quantities in excess of the threshold planning quantity (TPQ) of 100 pounds requires certain emergency planning activities to be conducted.

Releases of nitric oxide in quantities equal to or greater than the reportable quantity (RQ) of 10 pounds are subject to reporting to the National Response Center under CERCLA, Section 304 SARA Title III.

SARA TITLE III - HAZARD CLASSES:

- Acute Health Hazard
- Chronic Health Hazard
- Sudden Release of Pressure Hazard
- Reactivity Hazard

PRODUCT NAME: NITRIC OXIDE

16. Other Information

Compressed gas cylinders shall not be refilled without the express written permission of the owner. Shipment of a compressed gas cylinder which has not been filled by the owner or with his/her (written) consent is a violation of transportation regulations.

DISCLAIMER OF EXPRESSED AND IMPLIED WARRANTIES:

Although reasonable care has been taken in the preparation of this document, we extend no warranties and make no representations as to the accuracy or completeness of the information contained herein, and assume no responsibility regarding the suitability of this information for the user's intended purposes or for the consequences of its use. Each individual should make a determination as to the suitability of the information for their particular purpose(s).

BOC GASES

MATERIAL SAFETY DATA SHEET

PRODUCT NAME: NITRIC OXIDE IN NITROGEN 0.00001% TO 1%

1. Chemical Product and Company Identification

BOC Gases,
Division of,
The BOC Group, Inc
575 Mountain Avenue
Murray Hill, NJ 07974

BOC Gases
Division of,
BOC Canada Ltd.
5975 Falbourne Street, Unit 2
Mississauga, Ontario L5R 3W6

TELEPHONE NUMBER: (908) 464-8100 =
24-HOUR EMERGENCY TELEPHONE
NUMBER: CHEMTREC (800) 424-9300

TELEPHONE NUMBER: (905) 501-1700
24-HOUR EMERGENCY TELEPHONE
NUMBER: (905) 949-3777
EMERGENCY RESPONSE PLAN NO: 20101

PRODUCT NAME: NITRIC OXIDE IN NITROGEN 0.00001% TO 1%

CHEMICAL NAME: Nitric Oxide in Nitrogen

COMMON NAMES/SYNONYMS: Not Applicable

TDG (Canada) CLASSIFICATION: 2.2

WHMIS CLASSIFICATION: A, D2B

PREPARED BY: Loss Control (908)464-8100/(905)273-7700

PREPARATION DATE: 6/1/95

REVIEW DATES: 6/7/96

2. Composition, Information on Ingredients

INGREDIENT	% VOLUME	PEL-OSHA ¹	TLV-ACGIH ²	LD ₅₀ or LC ₅₀ Route/Species
Nitric Oxide FORMULA: NO CAS: 10102-43-9 RTECS #: QX0525000	0.00001 to 1.0	25 ppm TWA	25 ppm TWA	LC ₅₀ 1068 mg/m ³ (rat)
Nitrogen FORMULA: N ₂ CAS: 7727-37-9 RTECS #: QW9700000	99.0 to 99.9999	Simple Asphyxiant	Simple Asphyxiant	Not Available

¹ As stated in 29 CFR 1910, Subpart Z (revised July 1, 1993)

² As stated in the ACGIH 1994-95 Threshold Limit Values for Chemical Substances and Physical Agents

3. Hazards Identification

EMERGENCY OVERVIEW

Nitric Oxide is severely irritating to eyes and respiratory system. Effects may be delayed for several hours following exposure. Inhalation of high concentrations may result in chemical pneumonitis and pulmonary edema. Nitrogen is a simple asphyxiant.

MSDS: G-153
Revised: 6/7/96

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PRODUCT NAME: NITRIC OXIDE IN NITROGEN 0.00001% TO 1%

ROUTE OF ENTRY:

Skin Contact No	Skin Absorption No	Eye Contact Yes	Inhalation Yes	Ingestion No
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HEALTH EFFECTS:

Exposure Limits Yes	Irritant Yes	Sensitization No
Teratogen No	Reproductive Hazard No	Mutagen Unknown
Synergistic Effects Other agents that irritate the respiratory system		

Carcinogenicity: - NTP: No IARC: No² OSHA: No

EYE EFFECTS:

Irritation of the eyes in moderate concentrations.

SKIN EFFECTS: =

None.

INGESTION EFFECTS:

None. This product is a gas and cannot be ingested.

INHALATION EFFECTS:

Effects of oxygen deficiency resulting from simple asphyxiants may include: rapid breathing, diminished mental alertness, impaired muscular coordination, faulty judgement, depression of all sensations, emotional instability, and fatigue. As asphyxiation progresses, nausea, vomiting, prostration, and loss of consciousness may result, eventually leading to convulsions, coma, and death.

Oxygen deficiency during pregnancy has produced developmental abnormalities in humans and experimental animals.

Nitric oxide vapors are a strong irritant to the pulmonary tract. At high concentrations initial symptoms of inhalation may be moderate and include irritation to the throat, tightness of the chest, headache, nausea and gradual loss of strength. Severe symptoms may be delayed (possibly for several hours) and include cyanosis, increased difficulty in breathing, irregular respiration, lassitude and possible eventual death due to pulmonary edema in untreated cases.

NFPA HAZARD CODES

Health: 1
Flammability: 0
Reactivity: 0

HMIS HAZARD CODES

Health: 1
Flammability: 0
Reactivity: 0

RATINGS SYSTEM

0 = No Hazard
1 = Slight Hazard
2 = Moderate Hazard
3 = Serious Hazard
4 = Severe Hazard

4. First Aid Measures

EYES:

Immediately flush with tepid water in large quantities, or with a sterile saline solution. Seek medical attention as soon as possible.

MSDS: G-153
Revised: 6/7/96

0352

PRODUCT NAME: NITRIC OXIDE IN NITROGEN 0.00001% TO 1%

SKIN:

None normally required.

INGESTION:

None normally required.

INHALATION:

PROMPT MEDICAL ATTENTION IS MANDATORY IN ALL CASES OF OVEREXPOSURE. RESCUE PERSONNEL SHOULD BE EQUIPPED WITH SELF-CONTAINED BREATHING APPARATUS. Conscious victims should be CARRIED (not assisted) to an uncontaminated area and inhale fresh air with supplemental oxygen. Quick removal from the contaminated area is most important. Keep the patient warm, quiet and under competent medical observation until the danger of delayed pulmonary edema has passed (at least 72 hours). Any physical exertion during this period should be discouraged as it may increase the severity of the pulmonary edema or chemical pneumonitis. Bed rest is indicated. Unconscious persons should be moved to an uncontaminated area, and if breathing has stopped, administer artificial resuscitation and supplemental oxygen. Once respiration has been restored they should be treated as above.

5. Fire Fighting Measures

Conditions of Flammability: Not flammable		
Flash point: None	Method: Not Applicable	Autoignition Temperature: None
LEL(%): None	UEL(%): None	
Hazardous combustion products: Oxides of nitrogen		
Sensitivity to mechanical shock: None		
Sensitivity to static discharge: None		

FIRE AND EXPLOSION HAZARDS:

Nitric oxide is nonflammable but will support combustion.

EXTINGUISHING MEDIA:

Not Applicable. Nonflammable product.

FIRE FIGHTING INSTRUCTIONS:

Not Applicable.

6. Accidental Release Measures

Evacuate all personnel from affected area. Use appropriate protective equipment. If leak is in user's equipment, be certain to purge piping with inert gas prior to attempting repairs. If leak is in container or container valve, contact the appropriate emergency telephone number listed in Section 1 or call your closest BOC location.

7. Handling and Storage

Electrical Classification:

Nonhazardous.

MSDS: G-153

Revised: 6/7/96

0353

PRODUCT NAME: NITRIC OXIDE IN NITROGEN 0.00001% TO 1%

Nitric oxide and nitrogen is non-corrosive and may be used with any common structural material. Corrosive conditions can exist in the presence of moisture, i.e. Nitric Acid.

Use only in well-ventilated areas. Valve protection caps must remain in place unless container is secured with valve outlet piped to use point. Do not drag, slide or roll cylinders. Use a suitable hand truck for cylinder movement. Use a pressure reducing regulator when connecting cylinder to lower pressure (<3000 psig) piping or systems. Do not heat cylinder by any means to increase the discharge rate of product from the cylinder. Use a check valve or trap in the discharge line to prevent hazardous back flow into the system.

Protect cylinders from physical damage. Store in cool, dry, well-ventilated area away from heavily trafficked areas and emergency exits. Do not allow the temperature where cylinders are stored to exceed 130°F (54°C). Cylinders should be stored upright and firmly secured to prevent falling or being knocked over. Full and empty cylinders should be segregated. Use a "first in-first out" inventory system to prevent full cylinders being stored for excessive periods of time.

Never carry a compressed gas cylinder or a container of a gas in cryogenic liquid form in an enclosed space such as a car trunk, van or station wagon. A leak can result in a fire, explosion, asphyxiation or a toxic exposure.

8. Exposure Controls, Personal Protection

EXPOSURE LIMITS¹:

INGREDIENT	% VOLUME	PEL-OSHA ²	TLV-ACGIH ³	LD ₅₀ or LC ₅₀ Route/Species
Nitric Oxide FORMULA: NO CAS: 10102-43-9 RTECS #: QX0525000	0.00001 to 1.0	25 ppm TWA	25 ppm TWA	LC ₅₀ 1068 mg/m ³ (rat)
Nitrogen FORMULA: N ₂ CAS: 7727-37-9 RTECS #: QW9700000	Balance	Simple Asphyxiant	Simple Asphyxiant	Not Available

¹ As stated in 29 CFR 1910, Subpart Z (revised July 1, 1993)

² Refer to individual state of provincial regulations, as applicable, for limits which may be more stringent than those listed here.

³ As stated in the ACGIH 1994-1995 Threshold Limit Values for Chemical Substances and Physical Agents.

IDLH (Nitric Oxide): 100 ppm

ENGINEERING CONTROLS:

Local exhaust to prevent accumulation of high concentrations so as to reduce the oxygen level in the air to less than 19.5% and to prevent NO accumulation above the exposure limit.

EYE/FACE PROTECTION:

Safety goggles or glasses and face shield.

SKIN PROTECTION:

Protective gloves of any material, (Rubber or teflon).

RESPIRATORY PROTECTION:

Positive pressure air line with full-face mask and escape bottle or self-contained breathing apparatus should be available for emergency use.

PRODUCT NAME: NITRIC OXIDE IN NITROGEN 0.00001% TO 1%

OTHER/GENERAL PROTECTION:

Safety shoes and eyewash.

9. Physical and Chemical Properties

PARAMETER	VALUE	UNITS
Physical state (gas, liquid, solid)	: Gas	
Vapor pressure	: Not Available	
Vapor density (Air = 1)	: Not Available	
Evaporation point	: Not Available	
Boiling point	: Not Available	
Freezing point	: Not Available	
pH	: Not Available	
Specific gravity	: Not Applicable	
Oil/water partition coefficient	: Not Available	
Solubility (H ₂ O)	: Not Available	
Odor threshold	: Very slightly soluble	
Odor and appearance	: Not Applicable	
	: Colorless, odorless gas	

10. Stability and Reactivity

STABILITY:

Stable

INCOMPATIBLE MATERIALS:

Oxidizing agents, halides, hydrocarbons and oxygen. Reacts vigorously with fluorine, fluorine oxides and chlorine in the presence of moisture.

HAZARDOUS DECOMPOSITION PRODUCTS:

Oxidizes in air to form nitrogen dioxide, which is extremely reactive and a strong oxidizer. Upon contact with moisture and oxygen, it produces nitrous and nitric acids.

HAZARDOUS POLYMERIZATION:

Will not occur.

11. Toxicological Information

MUTAGENIC:

There is unspecified mutagenic data for nitric oxide (SAX/RTECS).

OTHER:

Chronic or repeated exposure may cause permanent decrements in pulmonary function (Silo Filler's Disease). The absence of marked acute irritation of nitric oxide limits its warning properties.

PRODUCT NAME: NITRIC OXIDE IN NITROGEN 0.00001% TO 1%

12. Ecological Information

No data given.

13. Disposal Considerations

Do not attempt to dispose of residual waste or unused quantities. Return in the shipping container **PROPERLY LABELED, WITH ANY VALVE OUTLET PLUGS OR CAPS SECURED AND VALVE PROTECTION CAP IN PLACE** to BOC Gases or authorized distributor for proper disposal.

14. Transport Information

PARAMETER	United States DOT	Canada TDG
PROPER SHIPPING NAME:	Compressed Gases, n.o.s. (nitric oxide in nitrogen)	Compressed Gas, n.o.s. (nitric oxide in nitrogen)
HAZARD CLASS:	2.2	2.2
IDENTIFICATION NUMBER:	UN 1956	UN 1956
SHIPPING LABEL:	NONFLAMMABLE GAS	NONFLAMMABLE GAS

15. Regulatory Information

Nitric oxide is listed under the accident prevention provisions of section 112(r) of the Clean Air Act (CAA) with a threshold quantity (TQ) of 10,000 pounds.

SARA TITLE III NOTIFICATIONS AND INFORMATION

SARA TITLE III - HAZARD CLASSES:

Sudden Release of Pressure Hazard

Nitric oxide is listed as an extremely hazardous substance (EHS). The presence of nitric oxide in excess of the Threshold Planning Quantity (TPQ) of 100 pounds requires certain emergency planning activities to be conducted.

Releases of nitric oxide in quantities equal to or greater than the reportable quantity (RQ) of 10 pounds are subject to reporting to the National Response Center under CERCLA, Section 304 SARA Title III.

16. Other Information

Compressed gas cylinders shall not be refilled without the express written permission of the owner. Shipment of a compressed gas cylinder which has not been filled by the owner or with his/her (written) consent is a violation of transportation regulations.

DISCLAIMER OF EXPRESSED AND IMPLIED WARRANTIES:

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