Nitrogen oxides

Updated: December 2015

Nitrogen oxides are reactive substances commonly understood to encompass nitric oxide (NO), nitrogen dioxide (NO_2) , and dinitrogen tetroxide (N_2O_4), referred to together under the label "NOx" (in air pollution literature), or "nitrous fume" (in the older occupational literature) [1]. The high process temperature causes oxygen and nitrogen in the air to combine, forming nitric oxide (NO). Where NO levels are high the gas rapidly oxidizes into nitrogen dioxide (NO_2). Conversely, if NO levels are low oxidation takes place very slowly resulting in the formation of only low levels of NO_2 ($2NO + O_2 \rightarrow 2NO_2$).

Two of the most toxicologically significant nitrogen oxides are nitric oxide and nitrogen dioxide, the latter exists in equilibrium with its dimmer, nitrogen tetroxide ($2\ NO_2 \leftrightarrow N_2O_4$).

Nitric oxide or nitrogen oxide (NO) is a colorless, sharp, sweet-smelling gas that is water soluble at room temperature.

Nitrogen dioxide (NO_2) is a liquid below 21°C, but inhalation of the gas is the most common route of toxic exposure. NO_2 has a strong, harsh odor and reacts with water to form a mixture of nitric and nitrous acids.

Dinitrogen tetroxide (N_2O_4) is a colorless liquid but can appear as a brownish yellowliquid due to the presence of NO2 according to the following equilibrium: $N_2O_4 \rightleftharpoons 2NO_2$.It is yellowish-brown liquid or reddish-brown gas (above 21°C) with a pungent, acrid odor. It is a solid form below -9°C [2]. Higher temperatures push the equilibrium towards nitrogen dioxide. Inevitably, some dinitrogen tetroxide is a component of smog containing nitrogen dioxide. Nitrogen tetroxide is used as an

oxidizer in one of the more important rocket propellants because it can be stored as a liquid at room temperature, and by the late 1950s it became the storable oxidizer of choice for many rockets.

Nitrogen oxides are broken down rapidly in the atmosphere by reacting with other substances commonly found in the air. The reaction of nitrogen dioxide with chemicals produced by sunlight leads to the formation of nitric acid, which is a major constituent of acid rain. Nitrogen dioxide also reacts with sunlight, which leads to the formation of ozone and smog conditions in the air we breathe. Small amounts of nitrogen oxides may evaporate from water, but most of it will react with water and form nitric acid. When released from the soil, small amounts of nitrogen oxides may evaporate into air. However, most of it will be converted to nitric acid or other compounds.

Reports estimate that about 300,000 tons of NOx are produced each year from industrial processes; combustion of fossil fuels (coal, oil) adds 10 million tons to that number [3].

Exposure

- Combustion of fossil fuels
- Nitric acid production and transportation
- Manufacture of lacquers and dyes
- Manufacture or use of explosives
- Manufacture of fertilizer
- Agriculture (silo filling)
- Mining
- Arc welding
- Firefighting
- Nitration of organic chemicals. May be evolved from silage [4].

Although regulatory attention has focused on outdoor concentrations of NOx, greater human exposure occurs indoors. Indoor sources include gas cooking stoves, gas furnaces and kerosene space heaters [5].

Routes of exposure: Inhalation, ingestion, skin and/or eye contact.

Nitrogen oxides are irritating to the upper respiratory tract and lungs even at low concentrations. Only one or two breaths of a very high concentration can cause severe toxicity. Odor is generally an adequate warning property for acute exposures. Nitrogen dioxide is heavier than air, such that exposure in poorly ventilated, enclosed, or low-lying areas can result in asphyxiation. Exposure to relatively high air concentrations can produce eye irritation and inflammation. Both nitrogen dioxide and nitric oxide are gases at room temperature. However, nitrogen dioxide exists as a liquid below 21ºC and, if ingested, will cause gastrointestinal irritation or burns.

Metabolism

The health effects associated with exposure to nitrogen oxides are due to the formation of nitric acid when the nitrogen dioxide reacts with water on the skin, in the eyes, or along the respiratory tract. The pulmonary and respiratory systems were most commonly identified with effects from nitrogen dioxide exposure. Symptoms usually develop after a 1 to 24 hour delay from the actual exposure; the chemical conversion of nitrogen dioxide into nitric acid in the body is relatively slow.

NO_2 reacts with intrapulmonary water to form nitric and nitrous acids. When NO_2 is absorbed onto the moist surface of the respiratory tract, it can be hydrolyzed to evolve acidic species such as HONO (nitrous acid) and HNO_3 (nitric acid).The potential for NO_2 to cause the local generation of hydrogen ions in the airways may be an important feature of its toxicity [6].

NO has an affinity for hemoglobin that is several thousand times higher than that of carbon monoxide [Sullivan].

Health effects

Cases of marked illness from nitrogen dioxide have been from accidental exposures to arc or gas welding (in confined spaces), in unventilated farm silos, following explosions, using nitrogen-containing explosives and with the use of nitric acid [7].

Acute exposure

Most of the higher oxides of nitrogen are eye, skin, and respiratory tract irritants.

The severity of clinical effects depends primarily on the concentration of nitrogen oxides inhaled. Mild intoxication may induce transient nonspecific symptoms, including dyspnea, cough, headache, fatigue, nausea, vertigo, and somnolence. Exposure to massive concentrations of nitrogen oxides may cause sudden death from laryngospasm or asphyxiation.

Severe exposure to nitrogen oxides may result in methemoglobinemia, hypoxemia, pulmonary edema, lung inflammation and decreased pulmonary vascular resistance, particularly in patients with heart disease or pulmonary hypertension. Impairment of pulmonary function may occur in the absence of acute symptoms (Information notices).

After the interval of a few hours (usually 4-12), the exposed individual may present with chemical pneumonitis or pulmonary edema, with dyspnea, tachypnea, cyanosis, cough, hemoptysis, substernal pain, and tachycardia. After recovery from the acute illness, some patients may subsequently develop bronchiolitis obliterance approximately 10-30 days after the exposure [Sullivan].

Populations that may be particularly sensitive to nitrogen oxides include asthmatics and those with chronic obstructive pulmonary disease or heart disease.

Controlled exposure studies of subjects with asthma have demonstrated that NO_2 exposure can enhance airway responsiveness and enhanced bronchoconstrictor responses to inhaled allergen following NO_2 exposure [LaDou, 2014].

Higher nitrogen oxides are skin irritants and corrosives. Skin moisture in contact with liquid nitrogen dioxide or high concentrations of its vapor can result in nitric acid formation, which may lead to second- and third-degree skin burns. Nitric acid may also cause yellowing of the skin and erosion of dental enamel.

Liquid nitrogen oxides cause severe eye burns after brief contact. High concentrations of the gas cause irritation and, after prolonged exposure, may cause clouding of the eye surface and blindness.

Nitrogen dioxide is thought to damage lungs in three ways:

- it is converted to nitric and nitrous acids in the distal airways, which directly damages certain structural and functional lung cells;
- it initiates free radical generation, which results in protein oxidation, lipid peroxidation, and cell membrane damage;
- it reduces resistance to infection by altering macrophage and immune function, NO_2 also impairs the action of the cilia that line the bronchial airways and hence slows down the action of the mucociliary escalator.

Nitrogen monoxide molecules contain an unpaired electron and hence have free radical properties that confer chemically reactive properties. Nitrogen monoxide is less water-soluble than nitrogen dioxide and is known to have effects on the endothelial cells of the pulmonary capillaries. Low exposures to nitrogen monoxide cause the development of small holes in the alveolar walls (fenestrae) that were suggested to represent early stages in emphysema development.High-dose exposure may convert Fe+2 in hemoglobin to Fe+3, by virtue of the presence of nitric oxide (NO), causing methemoglobinemia and impaired oxygen transport [ATSDR].

Chronic exposure

Chronic exposure to low concentrations of nitrogen oxides may aggravate asthma and allergic conditions. Reduced pulmonary function including reduced vital capacity, reduced maximum breathing capacity, reduced lung compliance, and increased

residual volume has been documented. Chronic exposure to nitrogen oxides is associated with increased risk of respiratory infections in children. Permanent restrictive and obstructive lung disease from bronchiolar damage may occur. Special consideration regarding the exposure of pregnant women may be warranted, since nitrogen oxides have been shown to be mutagenic and clastogenic, and fetotoxic in rats; thus, medical counseling is recommended for the acutely exposed pregnant woman.

Nitrogen dioxide chronic exposure of experimental animals to high concentrations of NO_2 has caused emphysema-like changes and decreased resistance to bacterial infections. Nitrogen dioxide also causes DNA damage, mutations, sister chromatid exchanges, and other DNA aberrations [ATSDR].

The prospective 8-year study of children in California indicates that exposure to nitrogen dioxide associates with clinically and statistically significant deficits in the FEV1 [8].

The studies in London and Seoul test the effects of air pollution on the heart. Nitrogen dioxide has been implicated as a cause of adverse cardiovascular effect [9,10].

Both nitrogen dioxide and nitric oxide have been shown to have mutagenic potential, which raises possible concerns for lung cancer [HSE].

References

1.Sullivan J.B., Krieger G.R., eds.: Hazardous Materials Toxicology: Clinical Principles of Environmental Health. pp.430-431. Williams & Wilkins, 1992.

2. CDC. NIOSH Pocket Guide to Chemical Hazards. Nitrogen dioxide. <http://www.cdc.gov/niosh/npg/npgd0454.html>.Accessed 07/11/2015.

3. ATSDR. Medical management Guidelines (MMGs) for nitrogen oxides (NO, NO_2, and others). <http://www.atsdr.cdc.gov/mmg/mmg.asp?id=394&tid=69>. Accessed 07/11/2015.

4. Information notices on occupational diseases: a guide to diagnosis. European Commission 2009 p:47.
5. LaDou J.: Current Occupational and Environmental Medicine, 5th ed., McGraw Hill Education, 2014. pp 785-786.
6. LaDou J.: Occupational and Environmental Medicine, 2nd ed., pp.708-709. Appleton & Lange, Stamford, 1997.
7. Zenz C.: Occupational Medicine, 3rd ed., pp. 506-541. Mosby, 1994.
8. Gauderman W.J., Avol E., Gilliland F., Vora H.: The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 351: 1057-1067, 2004.
9. Routledge H.C., Ayres J.G.: Air pollution and the heart. Occup Med (Lond) 55: 439-447, 2005.
10. Kwon H.J., Cho S.H., Nyberg F.: Effects of ambient air pollution on daily mortality in a cohort of patients with congestive heart failure. Epidemiology 12(4):413-419, 2001.