BASF Chemical Emergency Medical Guidelines

Nitrogen dioxide (NO_2) C 1

Information and recommendations for doctors at hospitals/emergency departments

- **Patients whose clothing or skin is contaminated with nitrogen dioxide can cause secondary contamination of rescue and medical personnel by direct contact or through evaporation of nitrogen dioxide.**
- **Nitrogen dioxide and its vapor are rapidly corrosive when they come in contact with tissues such as the eyes, skin, and upper respiratory tract causing irritation, burns, coughing, chest pain and dyspnea. Laryngospasm and pulmonary edema (shortness of breath, cyanosis, expectoration, cough) may occur.**
- **Ingestion of nitrogen dioxide can cause severe corrosive injury to the lips, mouth, throat, esophagus, and stomach.**
- **There is no antidote to be administered to counteract the effects of nitrogen dioxide. Treatment consists of supportive measures.**

1. Substance information

Nitrogen dioxide (NO_2), CAS 10102-44-0
Synonyms: dinitrogen tetroxide, nitrogen peroxide, nitrogen tetroxide, and NTO.
Nitrogen dioxide is a colorless to yellow liquid at room temperature. Above 21°C (70°F) it is a gas. The concentrated gas has a dark violet to black color; when rarefied it becomes reddish-brown to yellow. Nitrogen dioxide has an irritating sharp odor at concentrations of 1-5 ppm. Upon contact with water it forms nitric acid. Nitrogen dioxide itself is nonflammable, but it can increase the flammability or cause the spontaneous combustion of other materials.
Nitrogen dioxide is formed naturally when fossil fuels like coal, oil or gas are burned and when stored grain ferments in storage silos. It is also part of airborne smog. Nitrogen dioxide is released in the reaction between nitric acid and any organic material. It is also formed whenever nitric acid acts upon metals, as in bright dipping, pickling, and etching.

2. Routes of exposure

Inhalation

Nitrogen dioxide's odor and irritant properties generally provide adequate warning of acutely hazardous concentrations.

Skin/eye contact

Direct contact with liquid nitrogen dioxide or concentrated vapor on wet or moist skin causes severe chemical burns. Nitrogen dioxide is poorly absorbed through the skin.

Ingestion

Ingestion of nitrogen dioxide can cause severe corrosive injury to the lips, mouth, throat, esophagus, and stomach.

3. Acute health effects

Respiratory

Nitrogen dioxide exposure usually causes dryness of the nose and throat, and coughing. Inhalation of very high concentrations may result in laryngospasm and eventually in obstruction of the airways and death. Development of respiratory distress with chest pain, dyspnea and pulmonary edema (shortness of breath, cyanosis, expectoration) may occur as late as 24 hours after exposure.

Exposure to nitrogen oxides results in acute and chronic changes of the pulmonary system including pulmonary edema, pneumonitis, bronchitis, bronchiolitis, emphysema, and possibly methemoglobinemia. Usually, no initial symptoms occur, except a slight cough, fatigue and nausea. However, potentially fatal pulmonary edema can occur following minimal early symptoms.

	Acute effects may or may not develop within one to two hours after exposure, and include tachypnea, tachycardia, fine crackles and wheezing, and cyanosis. Another acute scenario involves dyspnea and coughing which subside over two to three weeks. The second stage involves abrupt development of fever and chills, more severe dyspnea, cyanosis, and pulmonary edema. There is no correlation between severity of the first and second stages.
Hematologic	Only after high-dose exposure methemoglobinemia may result, but usually to an extent that does not require treatment. For further information on methemoglobinemia see BASF Chemical Emergency Medical Guideline for ANILINE.
Gastrointestinal	Epigastric pain, nausea, and vomiting may occur. In cases of ingestion diffuse corrosive mucosal injury can involve the entire intestinal tract.
Renal	Acid-base imbalance and acute renal failure may occur.
Dermal	Deep burns of the skin and mucous membranes may be caused by contact with concentrated nitrogen dioxide; sometimes yellowing of the skin results. Contact with less concentrated nitrogen dioxide vapor can cause burning pain, redness, and inflammation.
Ocular	Severe eye burns with clouding of the surface, perforation of the globe, and ensuing blindness may occur from exposure to liquid nitrogen dioxide. Low concentrations of vapor cause burning discomfort, spasmodic blinking or involuntary closing of the eyelids, redness, and tearing.
Dose-effect relationships	Dose-effect relationships are as follows:

Nitrogen dioxide concentration		Effect
1-5 ppm	-	Odor detection (some tolerance develops)
5-10 ppm	-	Mild mucous membrane irritation
25 ppm	-	Immediate chest pain, dyspnea, coughing, bronchitis, usually full recovery
50-150 ppm	-	Bronchiolitis, focal pneumonitis, may cause irreversible lung lesions
>100 ppm	-	Pulmonary edema possible
1000 ppm	-	Fatal within a few minutes

Potential sequelae	Skin, eye, and mucous membrane damage caused by chemical burns may be irreversible, e. g. gangrene, blindness, or narrowing of the esophagus. After inhalation, complete recovery is usual; however, symptoms and pulmonary deficits may persist. Permanent restrictive and obstructive lung disease may occur from bronchiolar damage. Pulmonary tissue destruction and scarring may result in chronic dilation of the bronchi and increased susceptibility to infection. Yellow discoloration or erosion of teeth can occur from prolonged exposure.

4. Actions

Self-protection	Patients whose clothing or skin is contaminated with nitrogen dioxide can secondarily contaminate other people by direct contact or nitrogen dioxide vapor.
Decontamination	Patients exposed only to nitrogen dioxide vapor who have no evidence of skin or eye irritation do not need decontamination. All others require decontamination. Patients who are able and cooperative may assist with their own decontamination. If the exposure involved liquid nitrogen dioxide and if clothing is contaminated, remove and double-bag the clothing. **Assure that exposed or irritated eyes have been irrigated with plain water or saline for at least 20 minutes, and that the pH of the conjunctival fluid has returned to normal (7.0)**. If not, continue eye irrigation during other basic care and transport. If eye irrigation is

impaired by blepharospasm, one to two drops of oxybuprocaine 0.4% may be instilled into affected eyes to allow adequate irrigation.
Remove contact lenses if present and easily removable without additional trauma to the eye.
Assure that exposed skin and hair have been flushed with plain water for at least 15 minutes. If not, continue flushing during other basic care and transport. Protect eyes during flushing of skin and hair.

Initial treatment

Therapy will be empiric; there is no specific antidote to be administered to counteract the effects of nitrogen dioxide.
The following measures are recommended if the airborne exposure dose is 10 ppm or greater, if symptoms, e. g. eye irritation or pulmonary symptoms have developed, or if no exposure dose can be estimated but exposure has possibly occurred.

- **Administration of oxygen**
- **Administration of 8 puffs of beclomethasone (800 µg beclomethasone dipropionate) from a metered dose inhaler.**

Patients with severe clinical respiratory symptoms (e.g. bronchospasms, stridor) should be treated as follows:
a) Nebulization of adrenaline (epinephrine): 2 mg adrenaline (2 ml) with 3 ml NaCl 0.9% and inhale through a nebulizer mask.

b) Administration of a ß2-selective adrenoceptor agonist, e.g., four strokes of terbutaline or salbutamol or fenoterol (one stroke usually contains 0.25 mg of terbutaline sulfate; or 0.1 mg of salbutamol; or 0.2 mg of fenoterol); this may be repeated once after 10 minutes.
Alternatively, 2.5 mg salbutamol and 0.5 mg atrovent may be administered by nebulizer mask.
If inhalation is not possible, administration of terbutaline sulfate (0.25 mg to 0.5 mg) subcutaneously or salbutamol (0.2 mg to 0.4 mg over 15 minutes) intravenously.

c) Intravenous administration of 250 mg methylprednisolone (or equivalent steroid dose).

Patients with clinical signs of a toxic lung edema (e.g. foamy sputum, wet crackles) should be treated as follows:
a) Start CPAP-therapy (Continuous Positive Airway Pressure Ventilation).
b) Intravenous administration of 1000 mg methylprednisolone (or an equivalent steroid dose) is recommended.

Intubation of the trachea or an alternative airway management should be considered in cases of respiratory compromise. When the patient's condition precludes this, consider cricothyrotomy if equipped and trained to do so.

Note: Efficacy of corticosteroid administration has not yet been proven in controlled clinical studies.
If nitrogen dioxide was in contact with the skin, chemical burns may result; treat as thermal burns: adequate fluid resuscitation and administration of analgesics, maintenance of the body temperature, covering of the burn with a sterile pad or clean sheet.
After eye exposure chemical burns may result; treat as thermal burns. Immediately consult an ophthalmologist.
Note: Any facial exposure to liquid nitrogen dioxide should be considered as a serious exposure.
In case of ingestion of nitrogen dioxide, **do not induce emesis. If signs or symptoms of esophageal irritation or burns are present, consider endoscopy to determine the extent of the injury; in severe cases**

surgical intervention should be considered if gastrointestinal necrosis or perforation is suspected.
Only **if a large dose has been ingested less than 30 minutes before evaluation** of the patient's condition and if a perforation can be excluded, consider immediate gastric lavage with a small-bore tube.

Further evaluation and treatment

To the standard intake history, physical examination, and vital signs add pulse oximetry monitoring and a PA chest X-ray.
Spirometry should be performed. Routine laboratory studies should include a complete blood count, blood glucose and electrolyte determinations. Arterial blood gases and methemoglobin concentrations should be used to assess for the presence of acidosis and methemoglobinemia in symptomatic patients.

Evidence of pulmonary edema - hilar enlargement and ill-defined, central-patch infiltrates on chest radiography - **is a late finding that may occur as late as 24 hours after exposure. The chest X-ray is typically normal on first presentation to the emergency department even with severe exposures.**
Patients who have possible exposure or who develop serious signs or symptoms should be observed for a minimum of 24 hours and reexamined frequently before confirming the absence of toxic effects. Delayed effects are unlikely in patients who have minor upper respiratory symptoms (mild burning or a slight cough) that resolve quickly.
If oxygen saturation is less than 90 % or if it appears to drop, immediately check arterial blood gases and repeat the chest X-ray.
If blood gasses begin to show deterioration and/or if the chest X-ray begins to show pulmonary edema start oxygen supplementation.
In case of worsening clinical signs (especially tachypnea >30/min with a simultaneous decrease of the partial pressure of carbon dioxide) CPAP-therapy (Continuous Positive Airway Pressure Ventilation) should be started within the first 24 hours after exposure.
In case of a pulmonary edema fluid intake/output and electrolytes should be monitored closely. Avoid net positive fluid balance. Central line or Swan-Ganz catheterization might be considered, to optimize fluid management.
As long as signs of pulmonary edema are present, intravenous administration of methylprednisolone (or an equivalent steroid) should be continued in intervals of 8-12 hours.

Prophylactic antibiotics are not routinely recommended but may be used based on the results of sputum cultures. Pneumonia can complicate severe pulmonary edema.

Patient release/ follow-up instructions

Clinically asymptomatic patients exposed to a concentration of **less than 10 ppm** (depending on the period of time exposed) **as well as patients who have a normal clinical examination and no signs or symptoms of toxicity may be discharged after an appropriate observation period in the following circumstances:**

a) The evaluating physician is experienced in the evaluation of individuals with nitrogen dioxide exposures.
b) Information and recommendations for patients with follow-up instructions are provided verbally and in writing. Patients are advised to seek medical care promptly if symptoms develop or recur.
c) The physician is comfortable that the patient understands the health effects of nitrogen dioxide.
d) Site medical is notified, so that the patient may be contacted at regular intervals in the 24-hour period following release from the emergency department.
e) Heavy physical work should be precluded for up to 24 hours. Patients who have serious skin or eye injuries should be reexamined in 24 hours.

f) Exposure to cigarette smoke should be avoided for 72 hours; the smoke may worsen the condition of the lungs.

Patients who have serious skin or eye injuries should be reexamined in 24 hours.
Post discharge spirometry should be repeated until values return to the patient's baseline values.

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