
Information and recommendations for doctors at hospitals/emergency departments

- Patients whose clothing or skin is contaminated with solid acid anhydrides or their dusts can cause secondary contamination of rescue and medical personnel by direct contact.
 - Acid anhydrides and their dusts and vapors are irritating when they come in contact with the eyes, skin, and upper respiratory tract causing coughing, sore throat and wheezing. Obstruction of the airways and respiratory distress with chest pain and dyspnea may occur. Skin and pulmonary sensitization is possible.
 - Ingestion of acid anhydrides can cause irritation to the lips, mouth, throat, esophagus, and stomach.
 - Immediate decontamination (first removal of solid acid anhydrides, thereafter extensive flushing of contaminated eyes, skin, and hair) is crucial.
 - There is no antidote to be administered to counteract the effects of acid anhydrides. Treatment consists of supportive measures.
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1. Substance information

Maleic anhydride (C₄H₂O₃), CAS 108-31-6

Synonyms: 2,5-furandione, maleic acid anhydride, phthalic acid anhydride

At room temperature, maleic anhydride is a white crystalline solid with an acrid odor. Maleic anhydride is soluble in water, acetone, ethyl acetate, chloroform, and benzene. Vapor pressure is 25 Pa at 25°C. In presence of water maleic anhydride hydrolyzes to maleic acid.

Use of maleic anhydride includes the manufacture of polyester and alkyd coating resins, fumaric and tartaric acids and maleic hydrazide, a herbicide.

Phthalic anhydride (C₈H₄O₃), CAS 85-44-9

Synonyms: 1,2-benzenedicarboxylic anhydride, phthalic acid anhydride.

At room temperature, phthalic anhydride appears as white crystalline needles with a characteristic, suffocating odor. Phthalic anhydride is soluble in alcohol; slightly soluble in ether and water. Vapor pressure is < 0.3 Pa at 20°C. In presence of water phthalic anhydride converts to phthalic acid.

Phthalic anhydride is widely used in organic syntheses for the manufacture of many resins, polyesters, dyes, pharmaceuticals, plasticizers, and fungicides.

2. Routes of exposure

Inhalation

Inhalation of dust and vapor is a relevant route of exposure. Acid anhydrides' irritant properties do not generally provide adequate warning of acutely hazardous concentrations. Sensitized, allergic individuals may react to very low concentrations of acid anhydrides.

Skin/eye contact

Most exposures to acid anhydrides occur by skin contact. Direct contact with solid acid anhydrides or dusts on eyes or skin causes irritation.

Ingestion

Ingestion of acid anhydrides can cause irritation to the lips, mouth, throat, esophagus, and stomach.

3. Acute health effects

Respiratory

Acid anhydrides exposure usually causes coughing, sore throat and wheezing. Inhalation may result in obstruction of the airways and

respiratory distress with chest pain and dyspnea. Several cases of occupational asthma have been reported.

Dermal

Irritation, redness and pain of the skin and mucous membranes may be caused by contact with acid anhydrides. Skin sensitization with occasional urticaria and eczematous response may occur.

Ocular

Eye irritation with burning discomfort, spasmodic blinking or involuntary closing of the eyelids, redness, and tearing may be caused by contact with acid anhydrides.

Gastrointestinal

Abdominal pain, nausea, and vomiting may occur. In cases of ingestion, diffuse irritation can involve the entire intestinal tract.

Hematologic

Hemolytic anemia and pulmonary hemorrhage has been observed after exposure, but the actual relationship of maleic anhydride to autoimmune hemolytic anemia is unclear.

Dose-effect relationships

Dose-effect relationships are as follows:

Maleic anhydride concentration	Effect
1 mg/m ³	- TLV-TWA (USA, NIOSH)
1.0 mg/m ³	- Odor threshold
1.5 mg/m ³	- Mucous membrane irritation
2.5 mg/m ³	- Extremely irritating
10 mg/m ³	- IDLH (USA, NIOSH)

Phthalic anhydride concentration	Effect
0.32 mg/m ³	- Odor threshold
6 mg/m ³	- TLV_TWA (USA; NIOSH)
25 mg/m ³	- Mucous membrane irritation
30 mg/m ³	- Conjunctivitis
60 mg/m ³	- IDLH (UUS, NIOSH)

Potential sequelae

Skin and pulmonary sensitization may occur.

4. Actions

Self-protection

Patients whose clothing or skin is contaminated with solid acid anhydrides or their dusts can cause secondary contamination of rescue and medical personnel by direct contact.

Decontamination

Patients exposed only to acid anhydride vapors 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 solid acid anhydrides or dusts and if clothing is contaminated, remove and double-bag the clothing.

If any solid acid anhydrides or dusts are present on the patient's skin, hair or clothes, brush it away before flushing. Protect yourself and the patient's eyes.

Assure that exposed or irritated eyes have been irrigated with plain water or saline for at least 15 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 counteract the effects of acid anhydrides.

The following measures are recommended if the airborne exposure concentration is 1.5 mg/m³ maleic anhydride or greater or 30 mg/m³

phthalic anhydride or greater, if symptoms, e. g. eye irritation or pulmonary symptoms have developed, or if no exposure concentration 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 β 2-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 acid anhydrides were in contact with the skin, irritation may result; apply supportive measures.

After eye exposure chemical irritation may result; apply support measures. Consult an ophthalmologist.

In case of ingestion of acid anhydrides, do not induce emesis, apply supportive measures. After large doses consider lavage.

If signs or symptoms of esophageal irritation are present, consider endoscopy to determine the extent of the injury.

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, liver function and electrolyte determinations. Evidence of pulmonary edema - hilar enlargement and ill-defined, central-patch infiltrates on chest radiography - is a late finding that may occur 6 to 8 hours or later after exposure. The chest X-ray is typically normal on first presentation to the emergency department even with severe exposures.

Further evaluation and treatment

Patients who have possible exposure to higher concentrations 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 gasses 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.

Should it become clear that pulmonary edema is worsening, positive end-expiratory pressure (PEEP) therapy should be started within the first 24 hours after exposure even if oxygenation can be maintained by mask.

Early indication for PEEP therapy is tachypnea (>30/min) with a simultaneous decrease of the partial pressure of carbon dioxide.

An inadequate increase or a relative decrease of the partial pressure of oxygen despite hyperventilation indicates the development of 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 1 g methylprednisolone (or an equivalent steroid dose) 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 0.4 mg/m³ maleic anhydride or 6 mg/m³ phthalic anhydride** (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 acid anhydrides or irritant dust exposure.
- 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 acid anhydrides.
- d) Site physician is informed, 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.
- 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.

In this document BASF has made a diligent effort to ensure the accuracy and currency of the information presented but makes no claim that the document comprehensively addresses all possible situations related to this topic. This document is intended as an additional resource for doctors at hospitals/emergency departments in assessing the condition and managing the treatment of patients exposed to acid anhydrides. It is not, however, a substitute for the professional judgement of a doctor and must be interpreted in the light of specific information regarding the patient available to such a doctor and in conjunction with other sources of authority.

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