Diseases Caused by Respiratory Irritants and Toxic Chemicals

Authors: Rom, William N., Ryon, David L.S.


The presence of respiratory irritants in the workplace can be unpleasant and distracting, leading to poor morale and decreased productivity. Certain exposures are dangerous, even lethal. In either extreme, the problem of respiratory irritants and inhaled toxic chemicals is common; many workers face a daily threat of exposure. These compounds cause harm by a variety of different mechanisms, and the extent of injury can vary widely, depending on the degree of exposure and on the biochemical properties of the inhalant. However, they all have the characteristic of nonspecificity; that is, above a certain level of exposure virtually all persons experience a threat to their health.

There are other inhaled substances that cause only susceptible individuals to develop respiratory problems; such complaints are most appropriately approached as diseases of allergic and immunological origin. Certain compounds, such as isocyanates, acid anhydrides and epoxy resins, can act not only as non-specific irritants in high concentrations, but can also predispose certain subjects to allergic sensitization. These compounds provoke respiratory symptoms in sensitized individuals at very low concentrations.

Respiratory irritants include substances that cause inflammation of the airways after they are inhaled. Damage may occur in the upper and lower airways. More dangerous is acute inflammation of the pulmonary parenchyma, as in chemical pneumonitis or non-cardiogenic pulmonary oedema. Compounds that can cause parenchymal damage are considered toxic chemicals. Many inhaled toxic chemicals also act as respiratory irritants, warning us of their danger with their noxious odour and symptoms of nose and throat irritation and cough. Most respiratory irritants are also toxic to the lung parenchyma if inhaled in sufficient amount.

Many inhaled substances have systemic toxic effects after being absorbed by inhalation. Inflammatory effects on the lung may be absent, as in the case of lead, carbon monoxide or hydrogen cyanide. Minimal lung inflammation is normally seen in the inhalation fevers (e.g., organic dust toxic syndrome, metal fume fever and polymer fume fever). Severe lung and distal organ damage occurs with significant exposure to toxins such as cadmium and mercury.

The physical properties of inhaled substances predict the site of deposition; irritants will produce symptoms at these sites. Large particles (10 to 20mm) deposit in the nose and upper airways, smaller particles (5 to 10mm) deposit in the trachea and bronchi, and particles less than 5mm in size may reach the alveoli. Particles less than 0.5mm are so small they behave like gases. Toxic gases deposit according to their solubility. A water-soluble gas will be adsorbed by the moist mucosa of the upper airway; less soluble gases will deposit more randomly throughout the respiratory tract.

Respiratory Irritants

Respiratory irritants cause non-specific inflammation of the lung after being inhaled. These substances, their sources of exposure, physical and other properties, and effects on the victim are outlined in Table 1. Irritant gases tend to be more water soluble than gases more toxic to the lung parenchyma. Toxic fumes are more dangerous when they have a high irritant threshold; that is, there is little warning that the fume is being inhaled because there is little irritation.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Sources of exposure</th>
<th>Important properties</th>
<th>Injury produced</th>
<th>Dangerous</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Substance</th>
<th>Source of exposure</th>
<th>Properties</th>
<th>Health effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde</td>
<td>Plastics, synthetic rubber industry, combustion products</td>
<td>High vapour pressure; high water solubility</td>
<td>Upper airway injury; rarely causes delayed pulmonary oedema</td>
</tr>
<tr>
<td>Acetic acid, organic acids</td>
<td>Chemical industry, electronics, combustion products</td>
<td>Water soluble</td>
<td>Ocular and upper airway injury</td>
</tr>
<tr>
<td>Acid anhydrides</td>
<td>Chemicals, paints, and plastics industries; components of epoxy resins</td>
<td>Water soluble, highly reactive, may cause allergic sensitization</td>
<td>Ocular, upper airway injury, bronchospasm; pulmonary haemorrhage after massive exposure</td>
</tr>
<tr>
<td>Acrolein</td>
<td>Plastics, textiles, pharmaceutical manufacturing, combustion products</td>
<td>High vapour pressure, intermediate water solubility, extremely irritating</td>
<td>Diffuse airway and parenchymal injury</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Fertilizers, animal feeds, chemicals, and pharmaceuticals manufacturing</td>
<td>Alkaline gas, very high water solubility</td>
<td>Primarily ocular and upper airway burn; massive exposure may cause bronchiectasis</td>
</tr>
<tr>
<td>Antimony trichloride, antimony pentachloride</td>
<td>Alloys, organic catalysts</td>
<td>Poorly soluble, injury likely due to halide ion</td>
<td>Pneumonitis, non-cardiogenic pulmonary oedema</td>
</tr>
<tr>
<td>Beryllium</td>
<td>Alloys (with copper), ceramics; electronics, aerospace and nuclear reactor equipment</td>
<td>Irritant metal, also acts as an antigen to promote a long-term granulomatous response</td>
<td>Acute upper airway injury, tracheobronchitis, chemical pneumonitis</td>
</tr>
<tr>
<td>Boranes (diborane)</td>
<td>Aircraft fuel, fungicide manufacturing</td>
<td>Water soluble gas</td>
<td>Upper airway injury, pneumonitis with massive exposure</td>
</tr>
<tr>
<td>Hydrogen bromide</td>
<td>Petroleum refining</td>
<td></td>
<td>Upper airway injury, pneumonitis with massive exposure</td>
</tr>
<tr>
<td>Methyl bromide</td>
<td>Refrigeration, produce fumigation</td>
<td>Moderately soluble gas</td>
<td>Upper and lower airway injury, pneumonitis, CNS depression and seizures</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Alloys with Zn and Pb, electroplating, batteries, insecticides</td>
<td>Acute and chronic respiratory effects</td>
<td>Tracheobronchitis, pulmonary oedema (often delayed onset over 24–48 hours); chronic low level exposure leads to inflammatory changes and emphysema</td>
</tr>
<tr>
<td>Calcium oxide, calcium hydroxide</td>
<td>Lime, photography, tanning, insecticides</td>
<td>Moderately caustic, very high doses required for toxicity</td>
<td>Upper and lower airway inflammation, pneumonitis</td>
</tr>
<tr>
<td>Chlorine</td>
<td>Bleaching, formation of chlorinated compounds, household cleaners</td>
<td>Intermediate water solubility</td>
<td>Upper and lower airway inflammation, pneumonitis and non-cardiogenic pulmonary oedema</td>
</tr>
<tr>
<td>Chloroacetophenone</td>
<td>Crowd control agent, “tear gas”</td>
<td>Irritant qualities are used to incapacitate; alkylating agent</td>
<td>Ocular and upper airway inflammation, lower airway and parenchymal injury with massive exposure</td>
</tr>
<tr>
<td>o-Chlorobenzonitrite</td>
<td>Crowd control agent, “tear gas”</td>
<td>Irritant qualities are used to incapacitate</td>
<td>Ocular and upper airway inflammation, lower airway injury with massive exposure</td>
</tr>
<tr>
<td>Compound</td>
<td>Source/Use</td>
<td>Health effects</td>
<td>Limit/Level</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Chloromethyl ethers</td>
<td>Solvents, used in manufacture of other organic compounds</td>
<td>Upper and lower airway irritation, also a respiratory tract carcinogen</td>
<td></td>
</tr>
<tr>
<td>Chloropicrin</td>
<td>Chemical manufacturing, fumigant component</td>
<td>Former First World War gas</td>
<td>Upper and lower airway inflammation</td>
</tr>
<tr>
<td>Chromic acid (Cr(IV))</td>
<td>Welding, plating</td>
<td>Water soluble irritant, allergic sensitizer</td>
<td>Nasal inflammation and ulceration, rhinitis, pneumonitis with massive exposure</td>
</tr>
<tr>
<td>Cobalt</td>
<td>High temperature alloys, permanent magnets, hard metal tools (with tungsten carbide)</td>
<td>Non-specific irritant, also allergic sensitizer</td>
<td>Acute bronchospasm and/or pneumonitis; chronic exposure can cause lung fibrosis</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Manufacture of foam insulation, plywood, textiles, paper, fertilizers, resins; embalming agents; combustion products</td>
<td>Highly water soluble, rapidly metabolized; primarily acts via sensory nerve stimulation; sensitization reported</td>
<td>Ocular and upper airway irritation; bronchospasm in severe exposure; contact dermatitis in sensitized persons</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>Metal refining, rubber manufacturing, organic compound manufacture, photographic materials</td>
<td>Highly water soluble</td>
<td>Ocular and upper airway inflammation, lower airway inflammation only with massive exposure</td>
</tr>
<tr>
<td>Hydrofluoric acid</td>
<td>Chemical catalyst, pesticides, bleaching, welding, etching</td>
<td>Highly water soluble</td>
<td>Ocular and upper airway inflammation, tracheobronchitis and pneumonitis with massive exposure</td>
</tr>
<tr>
<td>Isocyanates</td>
<td>Polyurethane production; paints; herbicide and insecticide products; laminating, furniture, enamelling, resin work</td>
<td>Low molecular weight organic compounds, irritants, cause sensitization in susceptible persons</td>
<td>Ocular, upper and lower inflammation; asthma, hypersensitivity pneumonitis in sensitized persons</td>
</tr>
<tr>
<td>Lithium hydride</td>
<td>Alloys, ceramics, electronics, chemical catalysts</td>
<td>Low solubility, highly reactive</td>
<td>Pneumonitis, non-cardiogenic pulmonary oedema</td>
</tr>
<tr>
<td>Mercury</td>
<td>Electrolysis, ore and amalgam extraction, electronics manufacture</td>
<td>No respiratory symptoms with low level, chronic exposure</td>
<td>Ocular and respiratory tract inflammation, pneumonitis, CNS, kidney and systemic effects</td>
</tr>
<tr>
<td>Nickel carbonyl</td>
<td>Nickel refining, electroplating, chemical reagents</td>
<td>Potent toxin</td>
<td>Lower respiratory irritation, pneumonitis, delayed systemic toxic effects</td>
</tr>
<tr>
<td>Nitrogen dioxide</td>
<td>Silos after new grain storage, fertilizer making, arc welding, combustion products</td>
<td>Low water solubility, brown gas at high concentration</td>
<td>Ocular and upper airway inflammation, non-cardiogenic pulmonary oedema, delayed onset bronchiolitis</td>
</tr>
<tr>
<td>Nitrogen mustards; sulphur mustard</td>
<td>Military gases</td>
<td>Causes severe injury, vesicant properties</td>
<td>Ocular, upper and lower airway inflammation, pneumonitis</td>
</tr>
<tr>
<td>Osmium tetroxide</td>
<td>Copper refining, alloy with iridium, catalyst for steroid synthesis and ammonia formation</td>
<td>Metallic osmium is inert, tetroxide forms when heated in air</td>
<td>Severe ocular and upper airway irritation; transient renal damage</td>
</tr>
<tr>
<td>Ozone</td>
<td>Arc welding, copy machines, paper bleaching</td>
<td>Sweet smelling gas, moderate water solubility</td>
<td>Upper and lower airway inflammation; asthmatics more susceptible</td>
</tr>
<tr>
<td>Phosgene</td>
<td>Pesticide and other chemical manufacture,</td>
<td>Poorly water soluble, does not irritate airways</td>
<td>Upper airway inflammation and pneumonitis; delayed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance</td>
<td>Description</td>
<td>Properties</td>
<td>Effects</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Phosphoric sulphides</td>
<td>Production of insecticides, ignition compounds, matches</td>
<td>Form phosphoric acid and hydrochloric acid on contact with mucosal surfaces</td>
<td>Ocular and upper airway inflammation</td>
</tr>
<tr>
<td>Phosphoric chlorides</td>
<td>Manufacture of chlorinated organic compounds, dyes, gasoline additives</td>
<td>Strong vescissant, forms selenious acid (HSeO₃) on mucosal surfaces</td>
<td>Ocular and upper airway inflammation, pulmonary oedema in massive exposure</td>
</tr>
<tr>
<td>Selenium dioxide</td>
<td>Copper or nickel smelting, heating of selenium alloys</td>
<td>Highly water soluble; exposure to selenium compounds gives rise to garlic odour breath</td>
<td>Ocular and upper airway inflammation, delayed pulmonary oedema</td>
</tr>
<tr>
<td>Hydrogen selenide</td>
<td>Copper refining, sulphuric acid production</td>
<td>Highly irritating</td>
<td>Ocular, upper and lower airway inflammation, neurological impairments</td>
</tr>
<tr>
<td>Styrene</td>
<td>Manufacture of polystyrene and resins, polymers</td>
<td>Highly irritating</td>
<td>Ocular, upper and lower airway inflammation, bronchospasm, pneumonitis</td>
</tr>
<tr>
<td>Sulphur dioxide</td>
<td>Petroleum refining, pulp mills, refrigeration plants, manufacturing of sodium sulphite</td>
<td>Chloride ions form HCl on mucosa</td>
<td>Upper airway injury</td>
</tr>
<tr>
<td>Titanium tetrachloride</td>
<td>Dyes, pigments, sky writing</td>
<td>Toxicity likely from chloride ions</td>
<td>Upper and lower airway injury, bronchospasm, pneumonitis</td>
</tr>
<tr>
<td>Uranium hexafluoride</td>
<td>Metal coat removers, floor sealants, spray paints</td>
<td>More severe than zinc oxide exposure</td>
<td>Upper and lower airway irritation, fever, delayed onset pneumonitis</td>
</tr>
<tr>
<td>Vanadium pentoxide</td>
<td>Cleaning oil tanks, metallurgy</td>
<td>Ocular, upper and lower airway symptoms</td>
<td></td>
</tr>
<tr>
<td>Zinc chloride</td>
<td>Smoke grenades, artillery</td>
<td>Ocular, upper and lower airway symptoms</td>
<td></td>
</tr>
<tr>
<td>Zirconium tetrachloride</td>
<td>Pigments, catalysts</td>
<td>Chloride ion toxicity</td>
<td>Upper and lower airway irritation, pneumonitis</td>
</tr>
</tbody>
</table>

This condition is thought to result from persistent inflammation with reduction of epithelial cell layer permeability or reduced conductance threshold for subepithelial nerve endings. Adapted from Sheppard 1988; Graham 1994; Rom 1992; Blanc and Schwartz 1994; Nemery 1990; Skornik 1988.

The nature and extent of the reaction to an irritant depends on the physical properties of the gas or aerosol, the concentration and time of exposure, and on other variables as well, such as temperature, humidity and the presence of pathogens or other gases (Man and Hulbert 1988). Host factors such as age (Cabral-Anderson, Evans and Freeman 1977; Evans, Cabral-Anderson and Freeman 1977), prior exposure (Tyler, Tyler and Last 1988), level of antioxidants (McMillan and Boyd 1982) and presence of infection may play a role in determining the pathological changes seen. This wide range of factors has made it difficult to study the pathogenic effects of respiratory irritants in a systematic way.

The best understood irritants are those which inflict oxidative injury. The majority of inhaled irritants, including the major pollutants, act by oxidation or give rise to compounds that act in this way. Most metal fumes are actually oxides of the heated metal; these oxides cause oxidative injury. Oxidants damage cells primarily by lipid peroxidation, and there may be other mechanisms. On a cellular level, there is initially a fairly specific loss of ciliated cells of the airway epithelium and of Type I alveolar epithelial cells, with subsequent violation of the tight junction interface between epithelial cells (Man and Hulbert 1988; Gordon, Salano and Kleinerman 1986; Stephens et al. 1974). This leads to
subepithelial and submucosal damage, with stimulation of smooth muscle and parasympathetic sensory afferent nerve endings causing bronchoconstriction (Holgate, Beasley and Twentyman 1987; Boucher 1981). An inflammatory response follows (Hogg 1981), and the neutrophils and eosinophils release mediators that cause further oxidative injury (Castleman et al. 1980). Type II pneumocytes and cuboidal cells act as stem cells for repair (Keenan, Combs and McDowell 1982; Keenan, Wilson and McDowell 1983).

Other mechanisms of lung injury eventually involve the oxidative pathway of cellular damage, particularly after damage to the protective epithelial cell layer has occurred and an inflammatory response has been elicited. The most commonly described mechanisms are outlined in Table 2.

Table 2. Mechanisms of lung injury by inhaled substances

<table>
<thead>
<tr>
<th>Mechanism of injury</th>
<th>Example compounds</th>
<th>Damage that occurs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation</td>
<td>Ozone, nitrogen dioxide, sulphur dioxide, chlorine, oxides</td>
<td>Patchy airway epithelial damage, with increased permeability and exposure of nerve fibre endings; loss of cilia from ciliated cells; necrosis of type I pneumocytes; free radical formation and subsequent protein binding and lipid peroxidation</td>
</tr>
<tr>
<td>Acid formation</td>
<td>Sulphur dioxide, chlorine, halides</td>
<td>Gas dissolves in water to form acid that damages epithelial cells via oxidation; action mainly on upper airway</td>
</tr>
<tr>
<td>Alkali formation</td>
<td>Ammonia, calcium oxide, hydroxides</td>
<td>Gas dissolves in water to form alkaline solution that may cause tissue liquefaction; predominant upper airway damage, lower airway in heavy exposures</td>
</tr>
<tr>
<td>Protein binding</td>
<td>Formaldehyde</td>
<td>Reactions with amino acids lead to toxic intermediates with damage to the epithelial cell layer</td>
</tr>
<tr>
<td>Afferent nerve stimulation</td>
<td>Ammonia, formaldehyde</td>
<td>Direct nerve ending stimulation provokes symptoms</td>
</tr>
<tr>
<td>Antigenicity</td>
<td>Platinum, acid anhydrides</td>
<td>Low molecular weight molecules serve as haptons in sensitized persons</td>
</tr>
<tr>
<td>Stimulation of host inflammatory response</td>
<td>Copper and zinc oxides, lipoproteins</td>
<td>Stimulation of cytokines and inflammatory mediators without apparent direct cellular damage</td>
</tr>
<tr>
<td>Free radical formation</td>
<td>Paraquat</td>
<td>Promotion of formation or retardation of clearance of superoxide radicals, leading to lipid peroxidation and oxidative damage</td>
</tr>
<tr>
<td>Delayed particle clearance</td>
<td>Any prolonged inhalation of mineral dust</td>
<td>Overwhelming of mucociliary escalators and alveolar macrophage systems with particles, leading to a non-specific inflammatory response</td>
</tr>
</tbody>
</table>

Workers exposed to low levels of respiratory irritants may have subclinical symptoms traceable to mucous membrane irritation, such as watery eyes, sore throat, runny nose and cough. With significant exposure, the added feeling of shortness of breath will often prompt medical attention. It is important to secure a good medical history in order to determine the likely composition of the exposure, the quantity of exposure, and the period of time during which the exposure took place. Signs of laryngeal oedema, including hoarseness and stridor, should be sought, and the lungs should be examined for signs of lower airway or parenchymal involvement. Assessment of the airway and lung function, together with chest radiography, are important in short-term management. Laryngoscopy may be indicated to evaluate the airway.

If the airway is threatened, the patient should undergo intubation and supportive care. Patients with signs of laryngeal oedema should be observed for at least 12 hours to insure that the process is self-limited. Bronchospasm should be treated with β-agonists and, if refractory, intravenous corticosteroids. Irritated oral and ocular mucosa should be thoroughly irrigated. Patients with crackles on examination or chest radiograph abnormalities should be hospitalized for observation in view of the possibility of pneumonitis or pulmonary oedema. Such patients are at risk of bacterial superinfection; nevertheless, no benefit has been demonstrated by using prophylactic antibiotics.
The overwhelming majority of patients who survive the initial insult recover fully from irritant exposures. The chances for long-term sequelae are more likely with greater initial injury. The term reactive airway dysfunction syndrome (RADS) has been applied to the persistence of asthma-like symptoms following acute exposure to respiratory irritants (Brooks, Weiss and Bernstein 1985).

High-level exposures to alkalis and acids can cause upper and lower respiratory tract burns that lead to chronic disease. Ammonia is known to cause bronchiectasis (Kass et al. 1972); chlorine gas (which becomes HCl in the mucosa) is reported to cause obstructive lung disease (Donelly and Fitzgerald 1990; Das and Blanc 1993). Chronic low-level exposures to irritants may cause continued ocular and upper airway symptoms (Korn, Dockery and Speizer 1987), but deterioration of lung function has not been conclusively documented. Studies of the effects of chronic low-level irritants on airway function are hampered by a lack of long-term follow-up, confounding by cigarette smoking, the “healthy worker effect,” and the minimal, if any, actual clinical effect (Brooks and Kalica 1987).

After a patient recovers from the initial injury, regular follow-up by a physician is needed. Clearly, there should be an effort to investigate the workplace and evaluate respiratory precautions, ventilation and containment of the culprit irritants.

**Toxic Chemicals**

Chemicals toxic to the lung include most of the respiratory irritants given enough high exposure, but there are many chemicals that cause significant parenchymal lung injury despite possessing low to moderate irritant properties.

These compounds work their effects by mechanisms reviewed in Table 3 and discussed above. Pulmonary toxins tend to be less water soluble than upper airway irritants. Examples of lung toxins and their sources of exposure are reviewed in table 3.

**Table 3. Compounds capable of lung toxicity after low to moderate exposure**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Sources of exposure</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrolein</td>
<td>Plastics, textiles, pharmaceutical manufacturing, combustion products</td>
<td>Diffuse airway and parenchymal injury</td>
</tr>
<tr>
<td>Antimony trichloride;</td>
<td>Alloys, organic catalysts</td>
<td>Pneumonitis, non-cardiogenic pulmonary oedema</td>
</tr>
<tr>
<td>Antimony pentachloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>Alloys with zinc and lead, electroplating, batteries, insecticides</td>
<td>Tracheobronchitis, pulmonary oedema (often delayed onset over 24–48 hours), kidney damage: tubule proteinuria</td>
</tr>
<tr>
<td>Chloropicrin</td>
<td>Chemical manufacturing, fumigant components</td>
<td>Upper and lower airway inflammation</td>
</tr>
<tr>
<td>Chlorine</td>
<td>Bleaching, formation of chlorinated compounds, household cleaners</td>
<td>Upper and lower airway inflammation, pneumonitis and non-cardiogenic pulmonary oedema</td>
</tr>
<tr>
<td>Hydrogen sulphide</td>
<td>Natural gas wells, mines, manure</td>
<td>Ocular, upper and lower airway irritation, delayed pulmonary oedema, asphyxiation from systemic tissue hypoxia</td>
</tr>
<tr>
<td>Lithium hydride</td>
<td>Alloys, ceramics, electronics, chemical catalysts</td>
<td>Pneumonitis, non-cardiogenic pulmonary oedema</td>
</tr>
<tr>
<td>Methyl isocyanate</td>
<td>Pesticide synthesis</td>
<td>Upper and lower respiratory tract irritation, pulmonary oedema</td>
</tr>
<tr>
<td>Mercury</td>
<td>Electrolysis, ore and amalgam extraction, electronics manufacture</td>
<td>Ocular and respiratory tract inflammation, pneumonitis, CNS, kidney and systemic effects</td>
</tr>
<tr>
<td>Nickel carbonyl</td>
<td>Nickel refining, electroplating, chemical reagents</td>
<td>Lower respiratory irritation, pneumonitis, delayed systemic toxic effects</td>
</tr>
<tr>
<td>Nitrogen dioxide</td>
<td>Silos after new grain storage, fertilizer making, arc welding; combustion products</td>
<td>Ocular and upper airway inflammation, non-cardiogenic pulmonary oedema, delayed onset bronchiolitis</td>
</tr>
<tr>
<td>Nitrogen mustards, sulphur mustards</td>
<td>Military agents, vesicants</td>
<td>Ocular and respiratory tract inflammation, pneumonitis</td>
</tr>
<tr>
<td>Paraquat</td>
<td>Herbicides (ingested)</td>
<td>Selective damage to type-2 pneumocytes leading to</td>
</tr>
</tbody>
</table>
One group of inhalable toxins are termed *asphyxiants*. When present in high enough concentrations, the asphyxiants, carbon dioxide, methane and nitrogen, displace oxygen and in effect suffocate the victim. Hydrogen cyanide, carbon monoxide and hydrogen sulphide act by inhibiting cellular respiration despite adequate delivery of oxygen to the lung. Non-asphyxiant inhaled toxins damage target organs, causing a wide variety of health problems and mortality. The medical management of inhaled lung toxins is similar to the management of respiratory irritants. These toxins often do not elicit their peak clinical effect for several hours after exposure; overnight monitoring may be indicated for compounds known to cause delayed onset pulmonary oedema. Since the therapy of systemic toxins is beyond the scope of this chapter, the reader is referred to discussions of the individual toxins elsewhere in this *Encyclopaedia* and in further texts on the subject (Goldfrank et al. 1990; Ellenhorn and Barceloux 1988).

**Inhalation Fevers**

Certain inhalation exposures occurring in a variety of different occupational settings may result in debilitating flu-like illnesses lasting a few hours. These are collectively referred to as inhalation fevers. Despite the severity of the symptoms, the toxicity seems to be self-limited in most cases, and there are few data to suggest long-term sequelae. Massive exposure to inciting compounds can cause a more severe reaction involving pneumonitis and pulmonary oedema; these uncommon cases are considered more complicated than simple inhalation fever.

The inhalation fevers have in common the feature of nonspecificity: the syndrome can be produced in nearly anyone, given adequate exposure to the inciting agent. Sensitization is not required, and no previous exposure is necessary. Some of the syndromes exhibit the phenomenon of tolerance; that is, with regular repeated exposure the symptoms do not occur. This effect is thought to be related to an increased activity of clearance mechanisms, but has not been adequately studied.

**Organic Dust Toxic Syndrome**

*Organic dust toxic syndrome* (ODTS) is a broad term denoting the self-limited flu-like symptoms that occur following heavy exposure to organic dusts. The syndrome encompasses a wide range of acute febrile illnesses that have names derived from the specific tasks that lead to dust exposure. Symptoms occur only after a massive exposure to organic dust, and most individuals so exposed will develop the syndrome.

Organic dust toxic syndrome has previously been called *pulmonary mycotoxicosis*, owing to its putative aetiology in the action of mould spores and *actinomycetes*. With some patients, one can culture species of *Aspergillus*, *Penicillium*, and mesophilic and thermophilic *actinomycetes* (Emmanuel, Marx and Ault 1975; Emmanuel, Marx and Ault 1989). More recently, bacterial endotoxins have been proposed to play at least as large a role. The syndrome has been provoked experimentally by inhalation of endotoxin derived from *Enterobacter agglomerans*, a major component of organic dust (Rylander, Bake and Fischer 1989). Endotoxin levels have been measured in the farm environment, with levels ranging from 0.01 to 100μg/m³. Many samples had a level greater than 0.2μg/m³, which is the level where clinical effects are known to occur (May, Stallones and Darrow 1989). There is speculation that cytokines, such as IL-1, may mediate the systemic effects, given what is already known about the release of IL-1 from alveolar macrophages in the presence of endotoxin (Richerson 1990). Allergic mechanisms are unlikely given the lack of need for sensitization and the requirement for high dust exposure.
Clinically, the patient will usually present symptoms 2 to 8 hours after exposure to (usually mouldy) grain, hay, cotton, flax, hemp or wood chips, or upon manipulation of pigs (Do Pico 1992). Often symptoms begin with eye and mucus membrane irritation with dry cough, progressing to fever, and malaise, chest tightness, myalgias and headache. The patient appears ill but otherwise normal upon physical examination. Leukocytosis frequently occurs, with levels as high as 25,000 white blood corpuscles (WBC)/mm^3. The chest radiograph is almost always normal. Spirometry may reveal a modest obstructive defect. In cases where fibre optic bronchoscopy was performed and bronchial washings were obtained, an elevation of leukocytes was found in the lavage fluid. The percentage of neutrophils was significantly higher than normal (Emmanuel, Marx and Ault 1989; Lecours, Laviolette and Cormier 1986). Bronchoscopy 1 to 4 weeks after the event shows a persistently high cellularity, predominantly lymphocytes. Depending on the nature of the exposure, the differential diagnosis may include toxic gas (such as nitrogen dioxide or ammonia) exposure, particularly if the episode occurred in a silo. Hypersensitivity pneumonitis should be considered, especially if there are significant chest radiograph or pulmonary function test abnormalities. The distinction between hypersensitivity pneumonitis (HP) and ODT is important: HP will require strict exposure avoidance and has a worse prognosis, whereas ODT has a benign and self-limited course. ODT is also distinguished from HP because it occurs more frequently, requires higher levels of dust exposure, does not induce the release of serum precipitating antibodies, and (initially) does not give rise to the lymphocytic alveolitis that is characteristic of HP. Cases are managed with antipyretics. A role for steroids has not been advocated given the self-limited nature of the illness. Patients should be educated about massive exposure avoidance. The long-term effect of repeated occurrences is thought to be negligible; however, this question has not been adequately studied.

**Metal Fume Fever**

Metal fume fever (MFF) is another self-limited, flu-like illness that develops after inhalation exposure, in this instance to metal fumes. The syndrome most commonly develops after zinc oxide inhalation, as occurs in brass foundries, and in smelting or welding galvanized metal. Oxides of copper and iron also cause MFF, and vapours of aluminium, arsenic, cadmium, mercury, cobalt, chromium, silver, manganese, selenium and tin have been occasionally implicated (Rose 1992). Workers develop tachyphalaxis; that is, symptoms appear only when the exposure occurs after several days without exposure, not when there are regular repeated exposures. An eight-hour TLV of 5 mg/m^3 for zinc oxide has been established by the US Occupational Safety and Health Administration (OSHA), but symptoms have been elicited experimentally after a two-hour exposure at this concentration (Gordon et al. 1992). The pathogenesis of MFF remains unclear. The reproducible onset of symptoms regardless of the individual exposed argues against a specific immune or allergic sensitization. The lack of symptoms associated with histamine release (flushing, itching, wheezing, hives) also militates against the likelihood of an allergic mechanism. Paul Blanc and co-workers have developed a model implicating cytokine release (Blanc et al. 1991; Blanc et al. 1993). They measured the levels of tumour necrosis factor (TNF), and of the interleukins IL-1, IL-4, IL-6 and IL-8 in the fluid lavaged from the lungs of 23 volunteers experimentally exposed to zinc oxide fumes (Blanc et al. 1993). The volunteers developed elevated levels of TNF in their bronchoalveolar lavage (BAL) fluid 3 hours after exposure. Twenty hours later, high BAL fluid levels of IL-8 (a potent neutrophil attractant) and an impressive neutrophilic alveolitis were observed. TNF, a cytokine capable of causing fever and stimulating immune cells, has been shown to be released from monocytes in culture that are exposed to zinc (Scuderi 1990). Accordingly, the presence of increased TNF in the lung accounts for the onset of symptoms observed in MFF. TNF is known to stimulate the release of both IL-6 and IL-8, in a time period that correlated with the peaks of the cytokines in these volunteers’ BAL fluid. The recruitment of these cytokines may account for the ensuing neutrophil alveolitis and flu-like symptoms that characterize MFF. Why the alveolitis resolves so quickly remains a mystery.
Symptoms begin 3 to 10 hours after exposure. Initially, there may be a sweet metallic taste in the mouth, accompanied by a worsening dry cough and shortness of breath. Fever and shaking chills often develop, and the worker feels ill. The physical examination is otherwise unremarkable. Laboratory evaluation shows a leukocytosis and a normal chest radiograph. Pulmonary function studies may show a slightly reduced $\text{FEF}_{25-75}$ and DLCO levels (Nemery 1990; Rose 1992).

With a good history the diagnosis is readily established and the worker can be treated symptomatically with antipyretics. Symptoms and clinical abnormalities resolve within 24 to 48 hours. Otherwise, bacterial and viral aetiologies of the symptoms must be considered. In cases of extreme exposure, or exposures involving contamination by toxins such as zinc chloride, cadmium or mercury, MFF may be a harbinger of a clinical chemical pneumonitis that will evolve over the next 2 days (Blount 1990). Such cases can exhibit diffuse infiltrates on a chest radiograph and signs of pulmonary oedema and respiratory failure. While this possibility should be considered in the initial evaluation of an exposed patient, such a fulminant course is unusual and not characteristic of uncomplicated MFF.

MFF does not require a specific sensitivity of the individual for the metal fumes; rather, it indicates inadequate environmental control. The exposure problem should be addressed to prevent recurrent symptoms. Although the syndrome is considered benign, the long-term effects of repeated bouts of MFF have not been adequately investigated.

**Polymer Fume Fever**

Polymer fume fever is a self-limited febrile illness similar to MFF, but caused by inhaled pyrolysis products of fluoropolymers, including polytetrafluoroethylene (PTFE; trade names Teflon, Fluon, Halon). PTFE is widely used for its lubricant, thermal stability and electrical insulative properties. It is harmless unless heated above 30°C, when it starts to release degradation products (Shusterman 1993). This situation occurs when welding materials coated with PTFE, heating PTFE with a tool edge during high speed machining, operating moulding or extruding machines (Rose 1992) and rarely during endotracheal laser surgery (Rom 1992a).

A common cause of polymer fume fever was elicited after a period of classic public health detective work in the early 1970s (Wegman and Peters 1974; Kuntz and McCord 1974). Textile workers were developing self-limited febrile illnesses with exposures to formaldehyde, ammonia and nylon fibre; they did not have exposure to fluoropolymer fumes but handled crushed polymer. After finding that exposure levels of the other possible aetiological agents were within acceptable limits, the fluoropolymer work was examined more closely. As it turned out, only cigarette smokers working with the fluoropolymer were symptomatic. It was hypothesized that the cigarettes were being contaminated with fluoropolymer on the worker's hands, then the product was combusted on the cigarette when it was smoked, exposing the worker to toxic fumes. After banning cigarette smoking in the workplace and setting strict handwashing rules, no further illnesses were reported (Wegman and Peters 1974). Since then, this phenomenon has been reported after working with waterproofing compounds, mould-release compounds (Albrecht and Bryant 1987) and after using certain kinds of ski wax (Strom and Alexandersen 1990).

The pathogenesis of polymer fume fever is not known. It is thought to be similar to the other inhalation fevers owing to its similar presentation and apparently non-specific immune response. There have been no human experimental studies; however, rats and birds both develop severe alveolar epithelial damage on exposure to PTFE pyrolysis products (Wells, Slocombe and Trapp 1982; Blandford et al. 1975). Accurate measurement of pulmonary function or BAL fluid changes has not been done.

Symptoms appear several hours after exposure, and a tolerance or tachyphalaxis effect is not there as seen in MFF. Weakness and myalgias are followed by fever and chills. Often there is chest tightness and cough. Physical
examination is usually otherwise normal. Leukocytosis is often seen, and the chest radiograph is usually normal. Symptoms resolve spontaneously in 12 to 48 hours. There have been a few cases of persons developing pulmonary oedema after exposure; in general, PTFE fumes are thought to be more toxic than zinc or copper fumes in causing MFF (Shusterman 1993; Brubaker 1977). Chronic airways dysfunction has been reported in persons who have had multiple episodes of polymer fume fever (Williams, Atkinson and Patchefsky 1974). The diagnosis of polymer fume fever requires a careful history with high clinical suspicion. After ascertaining the source of the PTFE pyrolysis products, efforts must be made to prevent further exposure. Mandatory handwashing rules and the elimination of smoking in the workplace has effectively eliminated cases related to contaminated cigarettes. Workers who have had multiple episodes of polymer fume fever or associated pulmonary oedema should have long-term medical follow-up.

Drug-induced pulmonary disease is not a single disorder, but rather a common clinical problem in which a patient without previous pulmonary disease develops respiratory symptoms, chest x-ray changes, deterioration of pulmonary function, histologic changes, or several of these findings in association with drug therapy. Over 150 drugs or categories of drugs have been reported to cause pulmonary disease; the mechanism is rarely known, but many drugs are thought to provoke a hypersensitivity response. Some drugs (eg, nitrofurantoin) can cause different injury patterns in different patients.

Depending on the drug, drug-induced syndromes can cause interstitial fibrosis, organizing pneumonia, asthma, noncardiogenic pulmonary edema, pleural effusions, pulmonary eosinophilia, pulmonary hemorrhage, or veno-occlusive disease (see Substances With Toxic Pulmonary Effects).

### Substances With Toxic Pulmonary Effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug or Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td><strong>Aspirin</strong>, β-blockers (eg, timolol), cocaine, dipyridamole, IV hydrocortisone (rarely in aspirin-sensitive patients with asthma), IL-2, methylphenidate, nitrofurantoin, protamine, sulfasalazine, vinca alkaloids (with mitomycin-C)</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>Amiodarone, bleomycin, cocaine, cyclophosphamide, methotrexate, minocycline, mitomycin-</td>
</tr>
<tr>
<td></td>
<td>C, penicillamine, sulfasalazine, tetracycline</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
<td><strong>Azathioprine</strong> plus 6-mercaptopurine, busulfan, fluoxetine, radiation</td>
</tr>
<tr>
<td>Interstitial pneumonia or fibrosis</td>
<td>Amphotericin B, bleomycin, busulfan, carbamazepine, chlorambucil, cocaine, cyclophosphamide, diphenylhydantoin, flecainide, heroin, melphalan, methadone, methotrexate, methylphenidate, methysergide, mineral oil (via chronic microaspiration), nitrofurantoin, nitrosoureas, procarbazine, silicone (sc injection), tocainide, vinca alkaloids (with mitomycin-C)</td>
</tr>
<tr>
<td>Condition</td>
<td>Drug or Agent</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Noncardiac pulmonary edema</td>
<td>β-Adrenergic agonists (eg, ritodrine, terbutaline), chlorozideoxide, cocaine, cytarabine, ethiodized oil (IV, and via chronic microaspiration), gemcitabine, heroin, hydrochlorothiazide, methadone, mitomycin-C, phenothiazines, protamine, sulfasalazine, tocolytic agents, tricyclic antidepressants, tumor necrosis factor, vinca alkaloids (with mitomycin-C)</td>
</tr>
<tr>
<td>Parenchymal hemorrhage</td>
<td>Anticoagulants, azathioprine plus 6-mercaptopurine, cocaine, mineral oil (via chronic microaspiration), nitrofurantoin, radiation</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Amiodarone, anticoagulants, bleomycin, bromocriptine, busulfan, granulocyte-macrophage colony-stimulating factor, IL-2, methotrexate, methysergide, mitomycin-C, nitrofurantoin, para-aminosalicylic acid, procarbazine, radiation, tocolytic agents</td>
</tr>
<tr>
<td>Pulmonary infiltrate</td>
<td>Amiodarone, amphotericin B, bleomycin, carbamazepine, diphenylhydantoin, ethambutol, etoposide, granulocyte-macrophage colony-stimulating factor, isoniazid, methotrexate, minocycline, mitomycin-C, nitrofurantoin, para-aminosalicylic acid, procarbazine, radiation, sulfasalazine, sulfonamides, tetracycline, trazodone</td>
</tr>
<tr>
<td>Pulmonary vascular disease</td>
<td>Appetite suppressants (eg, dexfenfluramine, fenfluramine, phentermine), busulfan, cocaine, heroin, methadone, methylphenidate, nitrosoureas, radiation</td>
</tr>
</tbody>
</table>

Diagnosis is based on observation of responses to withdrawal from and, if practical, reintroduction to the suspected drug.

Treatment is stopping the drug. A screening pulmonary function test is commonly done in patients about to begin or already taking drugs with pulmonary toxicities, but the benefits of screening for prediction or early detection of toxicity are unproved.

- **Table 1**

  **Substances With Toxic Pulmonary Effects**

**Drugs causing disease**

- **Drug Name**

  **Select Trade**

  - **nitrofurantoin**

    FURADANTIN, MACROBID, MACRODANTIN
- **methadone**
  DOLOPHINE

- **gemcitabine**
  GEMZAR

- **cyclophosphamide**
  CYTOXAN (LYOPHILIZED)

- **phentermine**
  ADIPEX-P

- **minocycline**
  MINOCIN

- **tetracycline**
  ACHROMYCIN V

- **fluoxetine**
  PROZAC, SARAFEM

- **bleomycin**
  No US brand name

- **hydrochlorothiazide**
  MICROZIDE

- **trazodone**
  OLEPTRO
- **mitomycin**
  MITOSOL

- **melphalan**
  ALKERAN

- **mercaptopurine**
  PURINETHOL

- **dipyridamole**
  PERSANTINE

- **chlordiazepoxide**
  LIBRIUM

- **busulfan**
  MYLERAN

- **isoniazid**
  LANIAZID

- **chlorambucil**
  LEUKERAN

- **sulfasalazine**
  AZULFIDINE

- **Azathioprine**
  IMURAN
<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>CORDARONE</td>
</tr>
<tr>
<td>etoposide</td>
<td>ETOPOPHOS</td>
</tr>
<tr>
<td>timolol</td>
<td>TIMOPTIC</td>
</tr>
<tr>
<td>procarbazine</td>
<td>MATULANE</td>
</tr>
<tr>
<td>bromocriptine</td>
<td>PARLODEL</td>
</tr>
<tr>
<td>methotrexate</td>
<td>OTREXUP</td>
</tr>
<tr>
<td>penicillamine</td>
<td>CUPRIMINE</td>
</tr>
<tr>
<td>ethambutol</td>
<td>MYAMUBTOL</td>
</tr>
<tr>
<td>methylphenidate</td>
<td>CONCERTA, RITALIN</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>TEGRETOL</td>
</tr>
</tbody>
</table>
Prof Nelson - Desiré

Towards a new Safe and Effective truly Modern Medicine

Dr. János (Hans) Selye

This is a new common sense method of modern medicine, that is Health motivated not just symptom control. We respect the complexity and the whole body, and respect the Natural process of health

<table>
<thead>
<tr>
<th>Lack of Awareness or Lack of Education</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>Trauma Injury</td>
</tr>
<tr>
<td>Heredity</td>
<td>Pathogens (microorganisms, bacteria, fungus, virus, prions, worms, etc.)</td>
</tr>
<tr>
<td>Mental Factors</td>
<td>Perverse Energy (heat, cold, wind, dryness, radiation, magnetic, etc.)</td>
</tr>
<tr>
<td>(Greed, anger, delusion arrogance etc)</td>
<td>Deficiency or Excess of Nutrients</td>
</tr>
<tr>
<td>Allergy</td>
<td></td>
</tr>
<tr>
<td>Bad Posture</td>
<td></td>
</tr>
</tbody>
</table>

Nelson Method of Medicine

1. Reduce the Causes of Disease, Change Behavior, get patients to Care, get the nail out of the tire
2. Repair the organs weakened by the Causes. Restore Health. Fix the Tire
3. Unblock the Blockages to energy, nutrition, Oxygen, waste, Parana, acupuncture, neural FLOW
4. Treat the symptoms with natural means before resorting to Synthetic. Use foods, exercise, herbs, homeopathics any and all natural means before resulting to Synthetics
5. Balance the metabolic typing or Constitutional Imbalances. Treat the patient as an Individual Whole

Selye Pathway of Disease

**Health then enter stressor (toxin etc)-enters**

1. **ALARM Stage**
   
   Symptoms are the alarm, not the enemy, symptoms at first are related to the Stressor, later the dysfunction
   
   If stressor continues then
   
   2. **ADAPTATION Stage**
      
      Symptoms go away as we adapt, the distress + disease penetrates deeper. You can have no symptoms and be very very sick.
      
      Being symptom free is not an indicator of Health
      
      If stressor continues then
      
      3. **EXHAUSTION Stage**
         
         The stressors burden the weakest organs
      
      If stressor continues then
         
         a. **FUNCTIONAL**
            
            First the stressor effect the weakest organ function
         
      If stressor continues then
         
         b. **ORGANIC**
            
            Then the weak organs start to swell or shrink
         
      If stressor continues then
         
         4. **DEATH**
            
            Cellular, organ, organ system, organism death

Since the body's weakest link is prone to disease from the stressors, any disease will improve with reduction of the stressors. If there is good nutrition and no excess or deficiency of nutrients, the body's repair system improves. With stress reduction the Parasympathetic system becomes free to boost digestion and immunity as well as cellular repair. Some stressors can have more specific target diseases, such as cigarettes target the lungs primarily. But with the lack of systemic oxygen, any other weak link in the body from genetics or from life will be involved. Thus stress reduction is a universal therapy for all diseases. Reductionism of diseases via inaccurate and expensive current medical diagnostic means, are archaic, inaccurate, overly complex, non-productive, expensive, unsafe, risky and most often ineffective. Add to this the risk of side effects from SYNthetic drugs and we see the poor history of medicine. Nelson and Selye have plotted out a safe, inexpensive and effective new more modern medicine.
Table 1. Drugs and Other Factors Increasing Susceptibility to Interstitial Lung Disease

**Age:** Considerably more likely to affect adults, although infants and children may be affected; IIPs increase with advancing age

**Antibiotics:** e.g., nitrofurantoin, sulfasalazine

**Anti-inflammatory agents:** e.g., infliximab, etanercept

**Chemotherapy agents:** e.g., bleomycin, busulfan, carmustine, cyclophosphamide, methotrexate

**Cardiovascular drugs:** e.g., amiodarone

**Illicit drugs**

**Occupational and environmental toxins:** e.g., asbestos fibers, silica dust, coal dust, cotton dust, grain dust, bird and animal droppings, and other toxins found in mining, farming, and construction

**Oxygen:** i.e., continuous inhalation of very high levels of therapeutic oxygen for more than 48 hours

**Paraquat**

**Radiation:** e.g., of the lung or breast—based on the extent of lung exposed, quantity of radiation, whether adjunct chemotherapy was used, and the presence of underlying lung disease

**Smoking:** A history of smoking or active smoking may exacerbate some forms of interstitial lung disease or cause it to be more severe

*IID: idiopathic interstitial pneumonias*

*Source: References 1, 2, 4, 5, 9-13.*

<table>
<thead>
<tr>
<th>ILD of known cause or association</th>
<th>ILD of unknown cause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure</strong></td>
<td><strong>Systemic disease</strong></td>
</tr>
<tr>
<td>Occupation Environment</td>
<td>CTD</td>
</tr>
<tr>
<td>Avocation Medication</td>
<td>IBD</td>
</tr>
<tr>
<td>Drug Radiation</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Smoking</td>
<td>HPS</td>
</tr>
</tbody>
</table>
Table 2. Drug-Induced Pulmonary Disorders

<table>
<thead>
<tr>
<th>Pulmonary Syndrome</th>
<th>Chest Film Findings</th>
<th>Other Diagnostic Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar hemorrhage</td>
<td>Diffuse bilateral alveolar infiltrates</td>
<td>Dyspnea, fever, acute respiratory failure, hemoptysis</td>
</tr>
<tr>
<td>Alveolar hypoventilation</td>
<td>Normal or atelectatic changes</td>
<td>Unexplained hypercapnic respiratory failure, difficulty in weaning from mechanical ventilation, Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>Normal or hyperinflated lung fields, localized acinar or nodular infiltrates</td>
<td>Dyspnea, cough, fever, hypoxia, hypocapnia, high-pitched inspiratory squeak, expiratory wheeze, obstruction unresponsive to bronchodilator therapy, increased lung volumes, decreased $D_{l,CO}$</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Normal or hyperinflated lung fields</td>
<td>Dyspnea, wheezing, cough, occasionally other allergic signs (i.e., angioedema, urticaria, conjunctival injection, rhinitis)</td>
</tr>
<tr>
<td>Hypersensitivity lung disease</td>
<td>Acinar or mixed acinar-interstitial pattern of infiltrates, frequent pleural effusions</td>
<td>Subacute onset and progression of dyspnea, fever, nonproductive cough, chest pain, rash, myalgia, eosinophilia, restrictive ventilatory defect with decreased $D_{l,CO}$</td>
</tr>
<tr>
<td>Noncardiogenic pulmonary edema</td>
<td>Diffuse acinar infiltrates, pleural effusions may be present</td>
<td>Rapid onset and progression of dyspnea and tachypnea; normal LV filling pressures and systolic function</td>
</tr>
<tr>
<td>Pneumonitis/ fibrosis</td>
<td>Bilateral reticular or reticulonodular infiltrates; pleural effusions may be present</td>
<td>Slow onset and progression of dyspnea, nonproductive cough, fever, weight loss, clubbing, restrictive ventilatory defect with decreased $D_{l,CO}$</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Normal or prominent pulmonary arteries with right ventricular enlargement</td>
<td>Progressive dyspnea, exertional chest pain, presyncope, physical exam findings of right heart failure</td>
</tr>
<tr>
<td>Pulmonary infiltrates and eosinophilia</td>
<td>Patchy alveolar infiltrates that rapidly migrate (acute disease) or diffuse interstitial infiltrates (chronic disease)</td>
<td>Fever, dyspnea, nonproductive cough, wheezing</td>
</tr>
<tr>
<td>Pulmonary-renal syndrome</td>
<td>Diffuse acinar or reticular infiltrates</td>
<td>Acute onset dyspnea, nonproductive cough, hemoptysis, hematuria; syndrome resembles Goodpasture's syndrome, but circulating antiglomerular basement membrane antibody is absent</td>
</tr>
<tr>
<td>SLE</td>
<td>Pleural effusion; rarely interstitial and acinar infiltrates, atelectatic changes</td>
<td>Systemic complaints, arthralgias, polyarthritis, pleuritic chest pain, presence of antinuclear antibodies</td>
</tr>
</tbody>
</table>


Source: References 1, 2, 4, 5, 7, 8, 24.
**Drugs that Cause Lung Disease**

<table>
<thead>
<tr>
<th>Chemotherapeutic Agents</th>
<th>Nonchemotherapeutic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Azathioprine</td>
<td>• Amiodarone&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>• BCNU</td>
<td>• Anti-TNF-&lt;sub&gt;α&lt;/sub&gt;-targeted therapy</td>
</tr>
<tr>
<td>• Bleomycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• Cocaine</td>
</tr>
<tr>
<td>• Busulfan</td>
<td>• Gold</td>
</tr>
<tr>
<td>• Chlorambucil</td>
<td>• Heroin</td>
</tr>
<tr>
<td>• Cyclophosphamide</td>
<td>• Methysergide</td>
</tr>
<tr>
<td>• Fludarabine</td>
<td>• Nitrofurantoin</td>
</tr>
<tr>
<td>• Gemcitabine</td>
<td>• Penicillamine</td>
</tr>
<tr>
<td>• 6-Mercaptopurine</td>
<td>• Phenytoin</td>
</tr>
<tr>
<td>• Methotrexate</td>
<td>• Sirolimus</td>
</tr>
<tr>
<td>• Mitomycin C</td>
<td>• Statins</td>
</tr>
<tr>
<td>• Taxanes (paclitaxel/docetaxel)</td>
<td>• Sulfasalazine</td>
</tr>
<tr>
<td>• Tyrosine kinase inhibitors (imatinib)</td>
<td>• Tocainide</td>
</tr>
</tbody>
</table>


<sup>a</sup>Most commonly implicated.

**SINthetic drugs can cause Lung disease.**
Causes of COPD Exacerbations

Pathogen factors
- Antimicrobial resistance
- Ability to persist in respiratory tract
  - Invasion of bronchial tissue
  - Biofilm formation

Host factors
- Exposure to common respiratory pathogens
- Institutionalization
- Exposure to children in day care
- Defects in host immunity
  - Nonspecific
    - Salivary lysozyme
    - Immunodeficient states
    - Human immunodeficiency virus (HIV) infection
  - Specific
    - Lymphocyte proliferation
    - Antibody production
- Comorbid conditions
  - Cardiac disease
  - Diabetes mellitus
- Airway inflammation
  - Increased airway inflammation at baseline
  - Exaggerated inflammatory response to infection
- Chronic sinusitis
- Airway hyperreactivity
- Noncompliance with medication
- Recurrent aspiration

Treatment factors
- Inadequate antimicrobial therapy
- Inadequate anti-inflammatory therapy
References:


—. 1991a. Chlorinated drinking-water; Chlorination by-products; Some other halogenated compounds; Cobalt and cobalt compounds. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 52. Lyon: IARC.


—. 1992. Occupational exposures to mists and vapours from sulfuric acid, other strong inorganic acids and other industrial chemicals. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 54. Lyon: IARC.


