Inorganic Compounds that Affect the Lungs  

V. Beasley

Department of Veterinary Biosciences, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA.

Direct Effects on the Lungs
Toxicants that selectively affect the lungs include gaseous and small particulate compounds and mixtures that are able to bypass the scrubbing capabilities of the upper respiratory tract, trachea and larger bronchi. Included in many agents associated with work place hazards such as mineral dust (pneumoconiosis), coal dust (anthracosis or anthracosilicosis [blacklung]), silica (silicosis) asbestosis (asbestosis), cotton dust (byssinosis), sugar cane dust (bagassosis), coliform bacteria (asthma and other respiratory problems in some workers), nitrogen oxides (silo filler's disease), as well as tobacco smoke (emphysema, bronchogenic carcinoma). Also included are low molecular hydrocarbons such as kerosene, gasoline, light crude oil, and mineral seal oil that tend to be aspirated into the lungs during and shortly after ingestion.

A few toxicants, such as the herbicide parathion are selectively taken by the lung. In addition parathion is bioactivated by lung P450 in Clara cells of the lung which results in toxicity. Several other agents bioactivated by lung P450s that have a furan ring and cause a cute bovine pulmonary edema and emphysema include the amino acid tryptophan (in corn and lush pastures), perilla ketone in the purple mint plant (Perilla futescens) and the mycotoxin ipomeanol produced by the mold Fusarium solani on sweet potatoes (Ipomea batatas).

Indirect Effects on the Lungs
A range of other toxicants affect the lungs by altering bronchial smooth muscle tone or secretions. The cholinesterase-inhibitors are of major importance as they often affect lung function in this way and they may also depress respiratory drive from the medulla and potentially cause paralysis of the muscles of respiration. All of these are the result of the buildups of excess acetylcholine. Hemorrhage is another problem sometimes caused by toxicants, and it may cause pulmonary failure when bleeding into the lung is involved. Many compounds that affect the action of the heart may secondarily result in pulmonary edema and/or compensatory tachypnea either of which might initially suggest a potential primary lung effect. Compounds that cause severe hypoproteinemia may affect the hygroscopic pressure of the blood to the point that pulmonary edema may become more likely. Anemia, carboxyhemoglobinemia, or methemoglobinemia related to a number of etiologies may reduce the oxygen-carrying capacity of the blood resulting in respiratory compensation.

Inhaled Toxicants and Respiratory Tract Dosimetry

Definitions related to inhalation of particulate toxic substances -

Deposition - Implies removal of particles from inhaled air because of impact with and retention by an airway surface
Clearance - Implies elimination of deposited particles from their initial deposition site
Retention - Pertains to quantity of particles that remain in the respiratory tract at a particular time after exposure.

Retention = Deposition - Clearance

Particle deposition is influenced by features of the particle and the host.

- Particle features include: size, shape, density, electrical charge, and hygroscopicity.
- Host features include: aspects of the respiratory tract anatomy, breathing rate, and breathing pattern.
- Airway branching points are major sites of particle impact and, therefore, deposition.
In dogs, larger particles (greater than 1 µm) are deposited mainly in the upper respiratory tract. Approximately 10 - 15% of smaller particles are deposited in the tracheobronchial tree; and approximately 20 to 30% are deposited in the alveolar region.

With regard to clearance, the assumption is that the most rapidly cleared particles are those that were deposited in the tracheobronchial region.

Particulate toxicants deposited in the anterior nasal passage may move to the exterior, but most of the material deposited in the nasal area overall is likely to be swallowed.

Similarly, particles deposited in the tracheobronchial tree tend to be moved by the "mucociliary escalator" to the pharynx where they are swallowed.

**Tracheobronchial mucociliary clearance is influenced by:**

- **Age** - The rate increases from childhood to adulthood and then may decline as the animal grows older.
- **Exercise** - May increase rate.
- **Disease** - Certain lung diseases decreased rate (e.g., respiratory infection, asthma, chronic bronchitis).
- Deposited particles that are retained may be phagocytized by alveolar macrophages.
- If the particles penetrate through the epithelial cells they may be phagocytized by interstitial macrophages.
- Solubilized poisons able to penetrate the epithelium may react with local calls or may be cleared via the blood or lymph.
- Dog pulmonary macrophages seem to patrol a smaller region than the pulmonary macrophage of rodents and even humans. Also, clearance of insoluble and slowly soluble particles from the dog lung to the lymph nodes is slower than in rats and mice.

---

### Nitrogen Oxides (Silo Filler's Disease)

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Inorganic Compounds that Affect the Lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most species</td>
<td>Minutes to hours</td>
<td>Hours to permanent damage, potentially lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Sources**

- Nitrogen dioxide is formed when nitric oxide in fresh silage comes in contact with oxygen in the air.
- Toxicosis is primarily seen when people (and sometimes animals) are near silos shortly after they are filled. The risk is highest when feedstuffs are high in nitrates (drought years), since in the ensiling process these form nitric acid as the silage reacts with oxygen in the air.
- Gas production is greatest in alfalfa silage, reaching a peak in 24 hours and apparently ending in 2 or 3 days. Concentrations as great as 1500 ppm can be reached during the first 48 hours after filling a silo.
- Nitrogen dioxide usually is seen as a yellowish-brown haze if any amount of it has been formed. Other toxic by-products such as NO or N₂O₄ are colorless and odorless.
  - This gas has an irritating odor similar to laundry bleach. It is heavier than air and therefore remains in the silo below the upper edge of the last door or settles down through the chute to the silo room and into the barn.
  - Oxides of nitrogen play a very important role in air pollution because in urban areas, large quantities of these oxides are constantly being generated from such sources as automobiles, diesel engines, thermal power plants, boilers, industrial gaseous wastes, etc.
  - Combustion of x-ray films results in the production of nitrogen dioxide.
  - Plastic plants also have the potential of giving off this gas.
  - Exposure to nitrogen tetroxide in the missile industry can produce symptoms identical to those from nitrogen dioxide and should be treated in a similar fashion.

**Mechanism of Action**

- Nitrogen dioxide dissolves in water to form a mixture of nitric and nitrous acids, both of which are very irritating and corrosive to the mucous membranes. Due to its relatively low solubility in water, however, the transient passage of nitrogen dioxide through the upper respiratory tract may not cause significant signs but may result in considerable damage to the lower respiratory tract, where the duration of contact and the amount of moisture are greater.
- The acid is only slowly absorbed and removed from the lung. The ultimate effect is one of local irritation which results in pulmonary edema. Because of a short residency time, the upper airways are generally less affected. Prior exposure can produce a degree of tolerance to subsequent inhalation of comparatively high concentrations of nitrogen oxides.
- NO₂ also acts by causing lipid peroxidation, which is maximal at 24 hours after exposure and lasts at least 24 hours thereafter. Vitamin E deficiency increases susceptibility to nitrogen dioxide. Nitrogen dioxides, in turn, increase the susceptibility to infection by decreasing the ability of the lung to remove pathogenic microorganisms.
Toxicity

- "Silo-filler's disease", or silage gas poisoning, also called bronchiolitis fibrosa obliterans due to inhalation of nitrogen dioxide, is especially hazardous for agricultural workers.
- Inhalation of low concentrations of the oxides of nitrogen may cause little or no discomfort of the upper respiratory tract but may result in death hours later due to pulmonary edema. A brief exposure to 200 ppm can be fatal.
- Though it is an invisible gas in smaller concentrations, it is still dangerous. Humans are able to detect NO2 at levels as low as 0.1 - 0.2 ppm in the air.
- In laboratory animals, a short exposure to only 0.5 ppm of nitrogen dioxide for 4 hours leads to histologic alterations. These mild lesions are reversible.
- In humans exposed for 10 minutes to 5 ppm of nitrogen dioxide, there was a 92% increase in airway resistance, and this response was delayed until 30 minutes after exposure.
- When laboratory animals were exposed for 2 hours to 50 ppm nitrogen dioxide, pulmonary edema occurred. Even after 1 hour exposure to only 1 ppm, there were alterations in the configuration of collagen and elastin.

Signs

- The clinical manifestations vary according to the intensity of exposure and the period of inhalation.
- In man, the clinical features and chest x-rays of this condition closely resemble sarcoidosis, miliary tuberculosis, histoplasmosis, etc.
- Inhalation of nitrogen dioxide can produce serious respiratory symptoms with feeling of suffocation in the chest, dyspnea, cyanosis, syncope, pulmonary edema and death.
- An increase in respiratory rate, a decrease in compliance and an increase in airway resistance occurs.

Lesions

- Extent of pathological changes in the lungs corresponds to the degree of exposure.
- Cyanosis.
- Pulmonary mast cells are ruptured, and degranulated and the alveoli become markedly expanded.
- Pulmonary congestion, edema.
- Emphysema.

Diagnosis

KI starch papers are available commercially--turn dark when exposed to NO2 gas.

Treatment

- Treatment consists of immediate administration of oxygen and artificial respiration if necessary.
- Corticosteroids have been found very effective in relieving the pulmonary edema and symptoms.
- Additional supportive care includes controlling pulmonary edema and administering broad-spectrum antibiotics for bronchopneumonia.
- Recovery may require from 1 - 6 months. Some emphysematous changes may persist indefinitely.

Prevention

- Education of the farmer to the dangers of toxic silo gas, as well as the safety measures that should be carried out to prevent undue exposure and inhalation by both humans and animals, is paramount in the elimination of this serious type of poisoning.
- This hazard of farming can be avoided simply by not entering a silo during filling and for a week or 10 days after completion thereof. Animals should not be allowed to gather in a barn near the base of a silo shortly after filling.
Gaseous Ammonia

Sources

- This section deals primarily with the local effects of inhaled ammonia as a result of its release from decaying animal wastes.
- Although hydrogen sulfide is probably responsible for more acute deaths in animals in confinement, ammonia is the toxic air pollutant most frequently present in high concentrations in animal facilities.
- Ammonia is present especially when animals are held in an area in which feces and other wastes are allowed to accumulate and decompose on a solid floor.
- Concentrations increase due to agitation of manure. Ammonia is lighter than air, and will rise from a manure pit or pack.
- Usually concentrations in enclosed animal facilities remain below 30 ppm when ventilation systems are operational, but it is not unusual to find 50 ppm or higher in spite of normal function of these systems.
- Anhydrous ammonia gas, commonly used from compressed gas tanks, is a potentially dangerous source for animals and especially man. Because of the pressure involved, breakage of hoses, failure of valves or human error when transferring ammonia from dealer tanks (nurse-tanks) to farmer tanks can result in a serious degree of exposure.

Structure of Ammonia

NH₃.

Mechanism of Action

- Ammonia is highly soluble in water. As a result, ammonia tends to go into solution in the aqueous layer on the surface of the eye and upper airways, resulting in irritation in these areas.
- Ammonia may irritate the respiratory mucosa from the nose to the lungs, depending upon the concentration present and the time of exposure.
- At concentrations usually found in animal environments (less than 100 ppm), the primary mechanism is chronic stress on the respiratory tract as a result of the continual irritation.

Toxicity

- Humans can detect the pungent odor at about 10 ppm.
- Signs are seen primarily when birds are exposed to 75 - 100 ppm or more.

Signs

- Shallow breathing, excessive lacrimation, clear or purulent nasal discharge, reduced production.
- Chickens on deep litter may exhibit keratoconjunctivitis, corneal opacity and tracheitis. They may keep their eyes closed most of the time, become listless and eat less than normal.
- An increase in secondary respiratory infections, including an increase in severity of atrophic rhinitis may occur in ammonia exposed animals. In one study, the prevalence of the lesion was unaffected despite increased severity of lesions in the affected animals.
- Poultry may often experience corneal opacity which may correlate with listlessness and reduced feed intake, perhaps a result of blindness.
- Permanent loss or impairment of eyesight, respiratory problems and skin burns result from exposure to anhydrous ammonia. The material should be handled only by persons wearing tight fitting goggles. When exposure has occurred, first aid is comprised of continuous irrigation of the exposed surface with water for 15 - 20 minutes.

Lesions

- Because of the high solubility of ammonia, when lesions occur, they tend to be present in the eyes and upper air passages.
- Apart from the keratitis, corneal opacities and tracheitis in chickens and the increased severity of atrophic rhinitis in swine, the lesions associated with ammonia are usually mild and usually confined to the upper respiratory tract.
  - Increased secretion of mucus in the respiratory tract.
  - Hyperplasia of the bronchiolar and alveolar epithelium has been reported.

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Inorganic Compounds that Affect the Lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most species</td>
<td>Minutes to chronic</td>
<td>Hours to permanent damage due to infection (usually upper respiratory), rarely lethal</td>
<td></td>
</tr>
</tbody>
</table>

Major Species

<table>
<thead>
<tr>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Inorganic Compounds that Affect the Lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minutes to chronic</td>
<td>Hours to permanent damage due to infection (usually upper respiratory), rarely lethal</td>
<td></td>
</tr>
</tbody>
</table>
## Overheated Polytetrafluoroethylene - Teflon or Silverstone

### Sources
- Polytetrafluoroethylene is a synthetic polymer used to make Teflon® and Silverstone® non-stick cookware. When pans or skillets are left on a range and become overheated (above 280°C or 530°F) pyrolysis products capable of causing toxic effects are produced. Empty PTFE cookware on burner set on high can reach > 750°F. A recently developed product is PTFE coated drip pans, which can be dangerous to birds under conditions of normal usage. The temperature of the drip pan can exceed 650°F after 5 minutes if the burner is on high and > 1,000°F after 10 minutes.
- The polymer coating is known to break down forming, in the process, particulates and acidic volatile gasses. Toxicoses have been reproduced in birds exposed to air from a pan heated to 400°C.
- Some heat lamps may have a Teflon coating which may break down with excessive heat.

### Toxic Principle
- Toxic breakdown products in heated Teflon or Silverstone include the following:
  - Carbonyl fluoride.*
  - Perfluoroisobutylene.*
  - Hexafluorocyclobutylene.*
  - Carbon tetrafluoride (CF₄).
  - Hydrofluoric acid.
  - Monomeric tetrafluoroethylene.

### Toxicity
- Acute, severe toxicosis occurs in pet birds.
- Mice and guinea pigs tolerated fumes lethal to birds.
- In humans, the condition is known as polymer fume fever and is comprised of a well-documented, transient flu-like syndrome.

### Signs
- In birds, including cockatiels, parrots, budgerigars and finches as well as quail, the condition is generally a rapidly fatal one. Signs include acute pulmonary distress with noisy respiration and dyspnea.
- These signs are shortly followed by "rocking movements", eyelid blinking sometimes described as somnolence and agonal convulsions (in some cases), followed by death.

### Lesions
- Extensive pulmonary hemorrhage and congestion.
- Particles may be seen in some lung sections.
- Particles similar to those found on air filters in the contaminated enclosure have been found in the lungs of affected birds. It is believed that the toxic effects arise as a result of the combined actions of toxic constituents carried on these particles and the acidic gasses (also) produced.

### Differential Diagnosis
- Carbon monoxide, methane, other toxic gasses. Acute pneumonia if a single bird is involved.

### Treatment
- Birds often found dead.
- Remove from further exposure.
- Symptomatic care - steroids, warm humid environment, fluids, antibiotics if bronchopneumonia is present.
Additional Toxicants

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Doses of Selenium and Selenium Containing Plants (Acute)</td>
<td>See Metals and Metalloids that Affect the Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochloric acid (HCl)</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to 2 days, potentially lethal</td>
</tr>
<tr>
<td>Hydrofluoric acid (HF)</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours, poisoning very rare</td>
</tr>
<tr>
<td>Zinc phosphide (rodenticide) or aluminum phosphide (fumigant and general biocide)</td>
<td>See Toxicants Associated with CNS Stimulation or Seizures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References

**Toxicants that Affect the Lungs**


**Overheated Polytetrafluoroethylene - Teflon or Silverstone**

1. AJVR 43(7):1238 and 1242, 1982.

All rights reserved. This document is available on-line at www.ivis.org. Document No. A2646.0899.