General Toxicology

Toxic Responses of the Respiratory System

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HISTORICAL PERSPECTIVE

- Toxic substances can disrupt the respiratory system and distant organs after chemicals enter the body by means of inhalation.

- Blood borne agents also can cause pathological changes in the respiratory tract.

- Inhalation toxicology refers to the route of exposure, whereas respiratory toxicology refers to target organ toxicity.

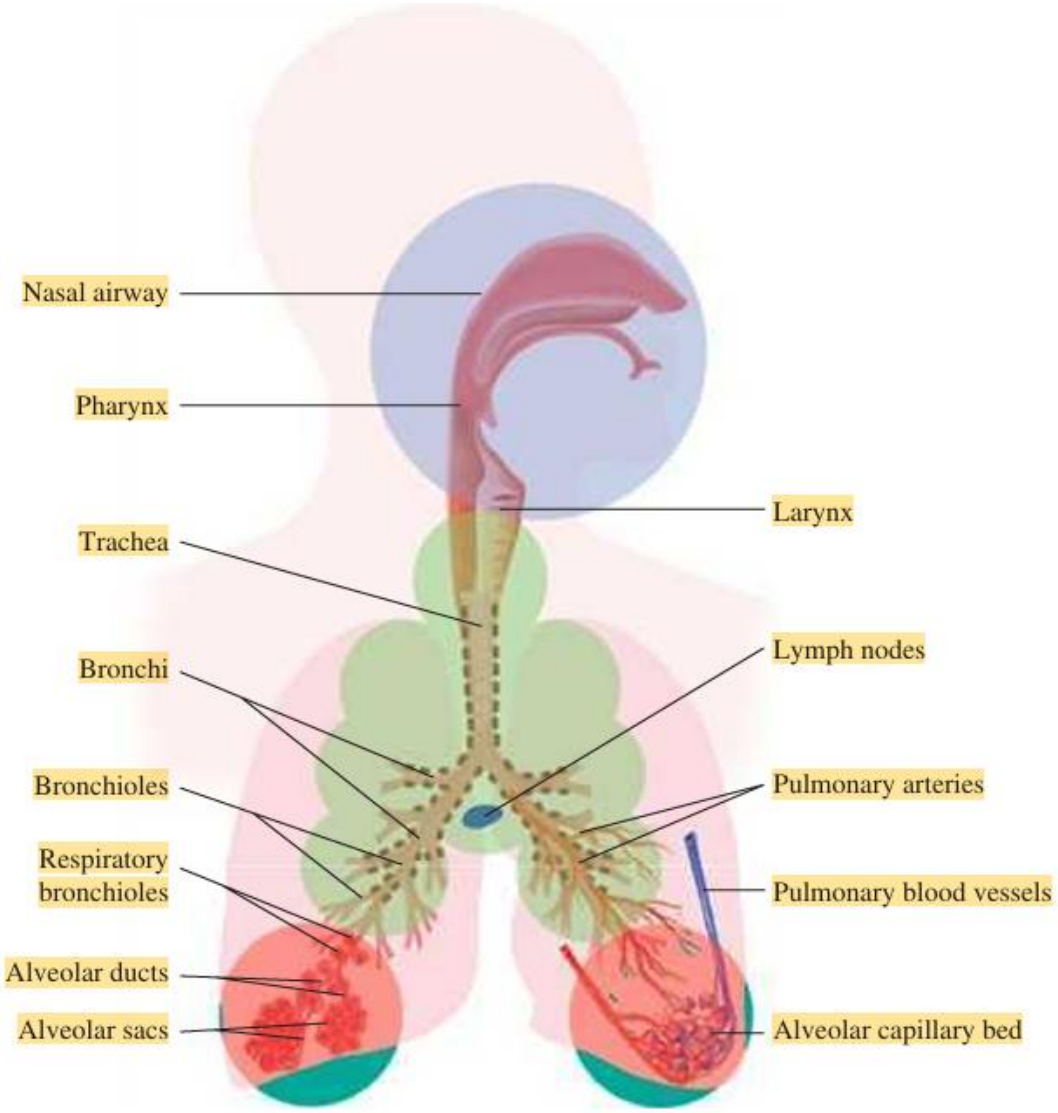
RESPIRATORY TRACT STRUCTURE AND FUNCTION

Oronasal Passages

Structure:

- The respiratory tract is divided into the **upper respiratory tract** (extrathoracic airway passages above the neck) and **lower respiratory tract** (airway passages and lung parenchyma below the pharynx).

- The upper respiratory tract reaches from the nostril or mouth to the pharynx and functions to conduct, heat, humidify, filter, and chemosense incoming air.



Major regions of the respiratory tract and predicted fractional deposition of inhaled particles in the extrathoracic, bronchial, and alveolar region of the human respiratory tract during (solid line) oral or (dashed) nasal breathing.

- The nasal passages are lined with stratified squamous epithelium in the anterior vestibule, nonciliated cuboidal/columnar epithelium in the anterior chamber, and ciliated pseudostratified respiratory epithelium in the remainder of the passage including the turbinates.

Sensory Functions:

- In addition to conducting, conditioning, and filtering air flowing to the lower respiratory tract, a major function of the oronasal passage is chemosensory.

- Nasal epithelia can metabolize many foreign compounds by cytochrome P450 and other enzymes.

- Humans can distinguish between more than 5000 odors. The detection of odor can be protective and can induce avoidance behaviors.

- The olfactory epithelium contains specialized chemosensory olfactory neurons located above the superior turbinates.

- Olfactory receptors are 7-transmembrane domain G-protein–coupled receptors that mediate transduction of odorant signals through formation of cyclic adenosine monophosphate (cAMP).

Irritant, Thermosensory, and Mechanosensory Functions:

- The main nerve endings that perceive irritants, the chemical nociceptors, also discern temperature and mechanical stress.

- Two protein families, the transient receptor potential (TRP) channels and the taste (TAS) receptors, perform these functions in the upper respiratory tract.

- Transient receptor potential (TRP) channels are ion channels that are permeable to cations, including calcium, magnesium, and sodium.

- TRPA1 and TRPV1 are the major irritant receptors in the nasal passage and are primarily within the trigeminal nerve.

- TRPA1 is responsive to a variety of natural ingredients including:

allyl isothiocyanate (in mustard and wasabi),
cinnamaldehyde (in cinnamon),
allicin and allyl sulfides (in garlic and onion).

- TRPA1 is also responsive to pain stimuli, cold (≤17°C), stretch, and a wide range of chemical irritants.

- TRPV1 is responsive to capsaicin (in chili pepper) or moderate heat (≥43°C),

- TRPV2 is responsive to higher heat (≥52°C).

Conducting Airways

Structure:

- The conducting airways of the lower respiratory tract can be divided into proximal (trachea and bronchi) and distal regions (bronchioles).

- Conducting airways have a bifurcating structure, with successive airway generations containing about twice the number of bronchi progressively decreasing in internal diameter.

- Airflow is faster in the larger diameter proximal airways, whereas airflow is slower in the smaller distal airways

- The airflow is also altered by airway smooth muscle that surrounds the airways and is under autonomic innervation via the vagus nerve. Vagal nerve endings release acetylcholine, which contracts smooth muscle and induces mucus secretion.

- The contraction of airway smooth muscle can be reversed by adrenergic stimulation either by circulating epinephrine or by inhaled bronchodilators that stimulate adrenergic receptors beta 2 on airway smooth muscle.

- In the bronchiolar epithelium, mucus-producing cells and glands give way to bronchiolar secretoglobin cells (BSCs).

Gas Exchange Region

Structure

- The gas exchange region consists of terminal bronchioles, respiratory bronchioles, alveolar ducts, alveoli, blood vessels, and lung interstitium.

- Human lung has five lobes: the superior and inferior left lobes and the superior, middle, and inferior right lobes.

- Gas exchange occurs in the alveoli, which comprise ~85% of the total parenchymal lung volume. Adult human lungs contain an estimated 300 to 500 million alveoli.

- The alveolar epithelium consists of two cells, the alveolar type I and type II cell.

- Alveolar type I cells cover ~95% of the alveolar surface and therefore are susceptible to damage by noxious agents that penetrate to the alveolus. Alveolar type I cells have an attenuated cytoplasm to enhance gas exchange.

- Alveolar type II cells are cuboidal and have abundant perinuclear cytoplasm, extensive secretory capacity. They produce surfactant, a mixture of lipids, and four surfactant associated proteins and can undergo mitotic division and replace damaged type I cells.

- The mesenchymal interstitial cell population consists of fibroblasts and myofibroblasts that produce collagen and elastin as well as other cell matrix components and various effector molecules.

ACUTE RESPONSES OF THE RESPIRATORY TRACT TO INJURY

Trigeminally Mediated Airway Reflexes to Inhaled Chemicals

- Inhaled toxic chemicals or particles can come into contact with cells lining the respiratory tract from the nostrils to the gas-exchanging region.

- The sites of deposition in the respiratory tract have important implications in evaluating the risks posed by inhalants.

- Nasal and airway irritation represents a common response to inspired toxic compounds.

- Nasal irritation is mediated by irritant receptors (e.g., TRPA1) that trigger trigeminal nerve responses characterized by tickling, itching, and painful nasal sensations.

- TRPA1 is sensitive to several irritants including acrolein, allyl isothiocyanate, chlorine.

- One of the consequences of nasal irritation is nasal mucus secretion that can dilute the irritant.

- Some chemicals can produce severe irritation at concentrations below those that induce a toxic response upon chronic exposure.

- Nasal irritation could be a limiting factor in human exposures, and thus the chronic effects are less likely to occur.

- If continued exposure cannot be avoided, many irritants will produce cell necrosis and increase permeability of the airway epithelium.

Bronchoconstriction, Airway Hyperreactivity, and Neurogenic Inflammation

- Substances that penetrate the nasal passage or are inhaled orally can trigger irritant receptors in the airways.
- Large diameter airways are surrounded by collagen and bronchial smooth muscle, which helps maintain airway tone and diameter during expansion and contraction of the lung.
- Bronchoconstriction can be evoked by irritants (acrolein, etc.), cigarette smoke, or air pollutants, and by cholinergic drugs such as acetylcholine. Bronchoconstriction causes a decrease in airway diameter and a corresponding increase in resistance to airflow.

- Bronchoconstriction can also be accompanied by an accumulation of thick mucus in the airway lumen. Characteristics of bronchoconstriction include the associated signs of coughing, wheezing, and rapid shallow breathing, and the associated symptoms of a sensation of chest tightness, substernal pain, and dyspnea.

- In addition to inducing an acute bronchoconstriction, irritants can prime the autonomic response by lowering the threshold dose of acetylcholine needed to induce bronchoconstriction. A lower threshold of acetylcholine-mediated bronchoconstriction is called airway hyperreactivity (or hyperresponsiveness).

- important bronchoconstrictive substances include histamine, various eicosanoids (including PGs [mainly PGF2 α and PGD2] thromboxane A2 , leukotrienes C4 and D4], and adenosine.

- In addition to bronchoconstriction, cough, and airway hyperreactivity, irritants can stimulate TRP channels (especially TRPA1 and TRPV1) that cause neurogenic inflammation.

- Mediated by neuropeptides (including tachykinins) released from nociceptive nerve terminals, neurogenic inflammation also includes vasodilatation, plasma protein extravasation, and leukocyte adhesion to the vascular endothelium.

Acute Lung Injury and Pulmonary Edema

- Initiated by numerous factors, acute lung injury (adult or infant respiratory distress syndrome) is marked by alveolar epithelial and endothelial cell perturbation and inflammatory cell influx that leads to surfactant disruption, pulmonary edema, and atelectasis(collapse of alveoli).

- Pulmonary edema produces a thickening of the alveolar capillary barrier and thereby limits O2 and CO2 exchange.

- During acute lung injury, profibrotic growth factors, TGFB1 and platelet-derived growth factor (PDGF), are activated and can initiate epithelial–mesenchymal transition (EMT)

- When inhaled in high concentrations, acrolein, HCl, NO2 , NH3 , or phosgene may produce immediate alveolar damage leading to a rapid death. However, these gases inhaled in lower concentrations may produce very little apparent damage in the respiratory tract.

CHRONIC RESPONSES OF THE LUNG TO INJURY

Asthma

- Asthma is defined by sporadic bouts of airflow obstruction, leading to dyspnea.
- Airflow obstruction is measured as increased air way resistance.
- In asthma, resting levels of airway resistance can be normal or slightly increased, which typically is reversible with bronchodilators. The hallmark of asthma is a persistent or recurrent airway hyperreactivity.

- Airway hyperreactivity can be specific, as in allergic asthma, and induced by exposure to a single known irritant or antigen.

- Responses to a methacholine or histamine challenge can vary with severity of the disease.
- The response in mild asthma is marked by a greater sensitivity.
- In more severe asthma, greater sensitivity is accompanied by a greater maximal response than observed in healthy subjects.
- This may be due to additional increases in airway smooth contractility, thickening of the airway wall, and decreased lung elastic load.

- The pathogenesis of asthma involves the adaptive and innate immune systems.

- **In allergic asthma**, previous exposure to an antigen typically leads to the **generation of immunoglobin E (IgE) molecules** that have molecular recognition sites specific to the antigen.

- Upon reexposure, the antigen causes cross-linking of IgE molecules and activation of (lymphocytes, eosinophils, macrophages, and mast cells), with elaboration and release of an array of (cytokines, chemokines, eicosanoids, histamine, tachykinins, and other mediators).

- Together, these mediators induce smooth muscle constriction, vascular leakage, mucus secretion, and inflammatory cell recruitment.

- These processes lead to airway obstruction, airway edema, formation of intraluminal mucus and plugging, and neutrophil recruitment with additional mediator release, respectively.

- **In irritant-induced (non allergic) asthma**, the inflammatory cascade is not initiated by an inhaled antigen but many of the same mediators and effector pathways are activated.
- Asthma has been associated with a number of occupations.

- Occupational asthma can involve adaptive immunity induced by high-molecular-weight and some low-molecular-weight substances.

- High-molecular-weight agents, including flour-, cereals-, latex-, or animal-derived proteins and enzymes, **cause sensitization through an IgE-mediated mechanism**, such as in common atopic asthma.

- Low-molecular-weight agents include chemicals like acid anhydrides and platinum salts that induce asthma **through an IgE mechanism**. However, most low-molecular weight agents involve an **uncertain mechanism of induction**.

- A portion of low-molecular-weight chemicals can **cross-link biological macromolecules.**

- The latter chemicals include metals (e.g., nickel, vanadium, chromium, cobalt, zinc, cadmium, or aluminum), diisocyanates (e.g., toluene diisocyanate), cleaning agents, wood dusts, soldering fluxes, pesticides, pharmaceuticals, and reactive dyes.

- Low-molecular-weight chemicals may act **as haptens** that combine with endogenous proteins to form a complex that is recognized as an antigen by the immune system.

Chronic Obstructive Pulmonary Disease

- Characterized by a progressive airflow obstruction, COPD involves an airway (bronchitis) and an alveolar (emphysema) pathology.

- COPD is the fourth leading cause of death.

- The major risk factor for COPD is tobacco smoking and about 20% of smokers will develop COPD.

- **Chronic bronchitis** is defined by the presence of sputum production and cough for at least 3 months in each of 2 consecutive years.

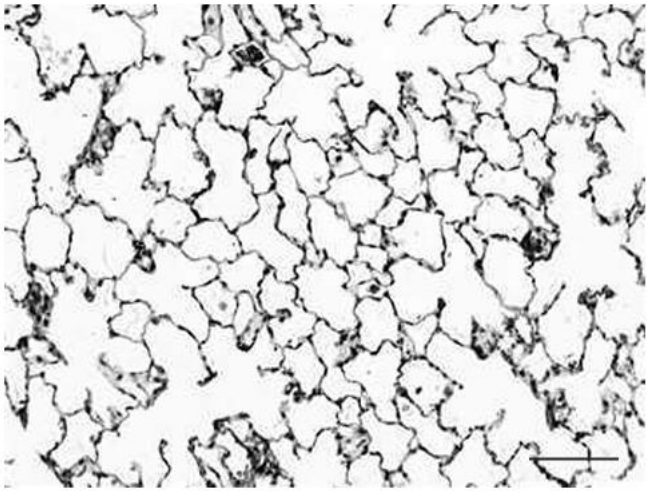
- Bronchitis in COPD involves airway inflammation with excessive mucus production from surface epithelial (goblet) cells and submucosal glands.

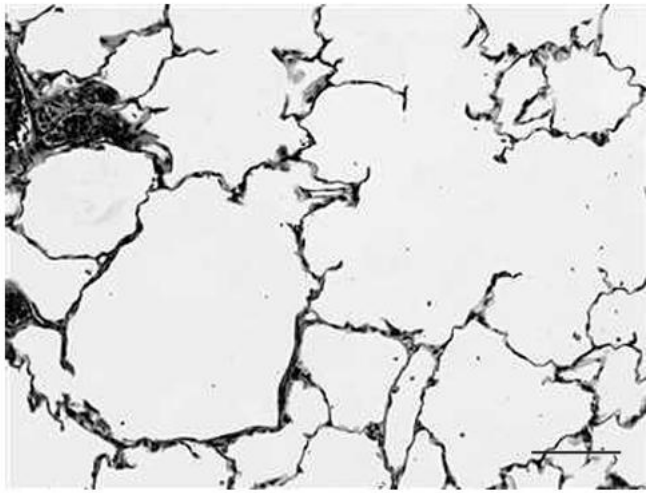
- Acrolein can increase mucin overproduction and can be formed endogenously in the airways during COPD.

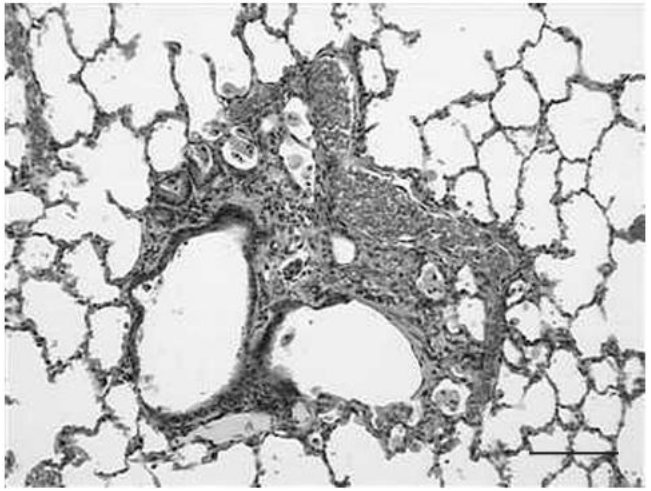
- Frequent coughing in COPD can be exacerbated by respiratory infections, and many viruses and bacteria induce cough to move from host to host.

- **Emphysema** is physiologically defined by airflow obstruction that leads to dyspnea (especially on exertion) accompanied by diminished FEV1(Forced Expiratory Volume in 1 second).

- Destruction of the gas exchanging surface area results in a distended, hyperinflated lung that no longer effectively exchanges oxygen and carbon dioxide as a result of both loss of tissue and air trapping.







Airspace enlargement induced by tobacco smoke and pulmonary fibrosis induced by asbestos in rat lung.

Lung Cancer

- The main factor responsible for smoking dependence is nicotine, a ligand for the nicotinic acetylcholine receptor α subunit, which makes up 0.3% to 5% of tobacco plant and accumulates in the tobacco leaf during curing.

- The increased risk of developing lung cancer for average smokers compared with nonsmokers is 8- to 10-fold and for heavy smokers about 20- to 40-fold.

- The global burden is ~1.2 million cancer deaths per year, with 85% of lung cancer cases in men and 47% of lung cancer cases in women being attributable to tobacco use.

- Many chemical exposures encountered in industrial settings also pose a lung cancer risk. Arsenic, asbestos, beryllium, cadmium, chromium, and nickel have been associated with cancer of the respiratory tract.

- Human lung cancers may have a latency period of 20 to 40 years, making the relationship to specific exposures difficult to establish.

- The two major forms of lung cancer are **non–small-cell lung cancer** (NSCLC; which accounts for ~85% of all lung cancer cases) and **SCLC** (which accounts for ~15% of all lung cancer cases).

- Cigarette smoke contains high quantities of reactive oxygen species and acrolein.

- Additional oxidative stress may be placed on the lung tissue of smokers by the release of reactive oxygen/ nitrogen species formed by activated macrophages and other inflammatory leukocytes.

- In addition, diminished DNA repair and loss of enzymes that maintain chromosomal integrity.

Pulmonary Fibrosis

- The pathological hallmark of pulmonary fibrosis is increased focal staining of collagen fibers in the alveolar interstitium.

- Excess lung collagen is usually observed not only in the alveolar interstitium but also throughout the centriacinar region, including the alveolar ducts and respiratory bronchioles.

- The foci(small localized areas of disease) can coalesce to form large masses of noncompliant lung. These foci can contain the inducing material including asbestos, silica.

- Ultimately the lung is unable to inflate or deflate properly and thus is restricted. Restrictive lung disease can be detected by a decrease in the predicted FVC(total air exhaled), with or without a change in the FEV1.

- The pathogenesis of pulmonary fibrosis involves epithelial cell injury and macrophage activation produced by a wide range of **toxic insults**.

- For example, macrophages can be activated by phagocytosis of crystalline silica or crocidolite asbestos, which activate inflammasome receptor-mediated TNF and IL1B formation.

- Epithelial cells and macrophages also release chemokines that recruit and activate other inflammatory cells including neutrophils and T cells.

- These cells combine to produce excessive TGF-B1, TNF, IL1B, IL13, and IL17.
- Of these, TNF and TGF-B1 are major mediators in pulmonary fibrosis because fibrosis can be diminished experimentally by inhibition of TNF.

- The migration, proliferation, and activation of myofibroblasts contribute to excessive extracellular matrix deposition that has altered collagen cross-linking.

- A feature of fibrogenesis is the oxidation of lysines in the extracellular matrix (ECM), mainly in collagen, to the aldehyde, allysine by lysyl-oxidase (LOX) enzymes.

- The consequence of this process is disorderly repair and substained fibrogenesis, which leads to progressive stiffness of the fibrotic lung.

AGENTS KNOWN TO PRODUCE RESPIRATORY DISEASE IN HUMANS

Inhalation Hazards

Acrolein

- As an α–β-unsaturated aldehyde, acrolein (2-propenal) is volatile at room temperature and is highly irritating to the upper and lower respiratory tract.
- Acrolein can be formed by heating cooking oils and fats above 300°C.
- Acrolein also can be formed in cigarette smoke, environmental tobacco smoke, domestic cooking.

- Acrolein contains a reactive carbonyl group and an electrophilic α-carbon and thus is highly reactive (often forming cross links) with biological macromolecules.

- Irritant stimuli, of which acrolein is one of the most potent, activate respiratory sensory nerve endings, especially TRPA1.
- Acrolein is also generated endogenously at sites of lung injury, and excessive breath levels.

- Because of its high reactivity, acrolein alters gene regulation, increases inflammation, decreases mucociliary transport, and diminishes alveolar-capillary barrier integrity.

- **In laboratory animals**, high acrolein exposures have led to acute lung injury and pulmonary edema similar to that produced by smoke inhalation, whereas lower concentrations have produced bronchial hyperreactivity, excessive mucus production, and alveolar enlargement.

- acrolein contributes to the morbidity and mortality associated with acute lung injury and COPD, and possibly asthma and lung cancer.

Asbestos

- Asbestos refers to a group of silicate minerals in fiber form.

- Exposure to asbestos fibers occurs in mining operations and in the construction and shipbuilding industries, where asbestos was at one time widely used for its insulating and fireproofing properties.

- Asbestos causes three forms of lung disease: **asbestosis, lung cancer, and malignant mesothelioma**.

- Asbestosis is a form of pulmonary fibrosis with characteristically diffuse collagen foci and the **presence of asbestos fibers**, either free or coated with a proteinaceous material (**asbestos bodies**).

- Alveolar macrophage clearance is critical to the prevention of asbestosis and depends on fiber length, biopersistance, and dose.

- Long fibers cannot be fully engulfed by a macrophage and cause “frustrated phagocytosis.” High fiber concentrations (dose) can produce particle overload, thereby augmenting inflammation, and lead to failure of the macrophages to clear particles.

- Asbestosis can produce characteristic nodular localized lesions of macrophages and asbestos fibers.

- Lung cancer develops in workers in the asbestos mining industry and smoking of cigarettes greatly enhances the risk.

- Malignant mesothelioma is a rare form of cancer that develops mainly in the pleural mesothelium, the protective lining that covers the lungs, diaphragm, and interior of the chest wall.

- Unlike lung cancer, mesothelioma is not associated with smoking history.

- Health hazards associated with asbestos exposure depend on fiber shape, length, and surface properties.

- **Chrysolite asbestos** are curved fibers and tend to be **less toxic** than crocidolite fibers that are long and thin, straight fibers.

- The surface proper ties of asbestos fibers also contribute to toxicity. **Crocidolite contains more iron** (including ferrous iron [Fe2+] that may **participate in Fenton chemistry to generate reactive oxygen species**) than chrysolite.

- The interaction of iron on the surface of asbestos fibers with oxygen may lead to the production of hydrogen peroxide and the highly reactive hydroxyl radical events that have been associated with asbestos toxicity.

- Once asbestos fibers have been deposited in the lung, they may become phagocytized by alveolar macrophages.

- Short fibers are completely ingested and subsequently removed via the mucociliary escalator. Longer fibers are incompletely ingested, and the macrophages become unable to leave the alveoli.

- Activated by the fibers, macrophages release mediators such as cytokine, chemokines, and growth factors, which in turn attract immunocompetent cells or stimulate collagen production.

Naphthalene

- Naphthalene occurs in cigarette smoke, tars, petroleum and is a precursor in the chemical synthesis of tanning agents, phthalic acid anhydride.

- **In laboratory animals**, inhaled or parenterally administered naphthalene produces extensive necrosis in the bronchiolar epithelium of the mouse but much less necrosis in the airways of rats, hamsters, or monkeys.

- The primary target in the surface epithelium is the bronchiolar secretoglobin cells. These cells were thought to be very important because they contain a stem cell subpopulation.

- They were once thought to be capable of cellular maintenance of the epithelium in bronchi, bronchioles, and alveolar regions.

- **In mice**, naphthalene is metabolized to naphthalene oxide primarily through CYP2F enzymes, especially CYP2F2.

- The toxic metabolite thus can be used to remove bronchiolar secretoglobin cells. **In rats and other species,** including monkeys, metabolism of naphthalene is less stereospecific and the rates of formation of the epoxide are much slower than in mice.

- Naphthalene epoxides may subsequently be conjugated with glutathione and form adducts that are eliminated as mercapturic acids.

- The epoxides can undergo rearrangement to **1-naphthol** with subsequent metabolism to **quinones**, which are potentially **toxic compounds**.

Silica

- Inhaled particles of silicon dioxide (silica) cause a characteristic human lung disease silicosis. Crystalline silica is a major component of the earth's crust; silicon is only second to oxygen as the most common element.

- Silicosis may be acute or chronic with distinct pathological consequences.

- **Acute silicosis** occurs only in subjects exposed to a very high levels of silica (most often quartz or sand), small enough to be respirable (usually <5μm) over a relatively short period, generally a few months or years.

- These patients have worsening dyspnea, fever, cough, and weight loss that can rapidly progress to respiratory failure, usually ending in death within two years.

- **Chronic silicosis** has a long latency period, usually >10 years and can be divided into simple and complicated silicosis.

- Even after radiographic changes, simple silicosis may be asymptomatic (i.e., no dyspnea) with little change in pulmonary function.

- The x-ray presents fibrotic nodules, generally in the apical portion of lung. The hilar lymph nodes have peripheral calcifications known **as egg shell calcifications.**

- Simple silicosis may progress into complicated silicosis, which is defined as the presence of conglomerate nodules larger than 1 cm in diameter. These nodules usually occur in the upper and mid-lung zones.

- **In advanced stages**, the nodules may be surrounded by emphysematous bullae. Chronic silicosis is associated with an increased incidence of tuberculosis.

- The role of pulmonary alveolar macrophages in the ingestion of silica is an initiating event.

- Macrophages phagocytose silica particles into phagosomes that fuse with endosomes during the internalization process.

- In contrast to microorganisms, silica particles cannot be degraded and macrophages undergo cell death, releasing these particles that are engulfed by other macrophages, thus perpetuating the process of phagocytosis and cell death.

- This leads to elevated mediator release (TGFB1, TNF, etc.), epithelial-mesenchymal transition, and initiates and maintains myofibroblast collagen.

Blood-Borne Agents That Cause Pulmonary Toxicity in Humans

- A number of compounds administered systematically can enter the lung through the pulmonary circulation and cause lung injury and disease.

- For example, **intraparenteral naphthalene** has marked lung toxicity in the mouse, probably due to an enrichment of an activating enzyme (CYP2F) in a specific cell in the lung epithelium.

- Another example is **that the ingestion of arsenic** has been associated with lung cancer. Below are three examples that have had toxicological significance in clinical settings.

1,3 Bis (2-Chloroethyl)-1-Nitrosourea (BCNU)

- A **chemotherapeutic drug** that has pulmonary fibrosis as a complication is carmustine (BCNU).

- BCNU exerts its antitumor properties by reacting with cellular macromolecules and forms inter- and intra-strand cross-links with DNA.

- In humans, a dose-related pulmonary toxicity is often noticed first by a decrease in diffusion capacity, which can develop into fatal pulmonary fibrosis.

- The mechanism of action is not entirely clear. It is possible that BCNU inhibits pulmonary glutathione disulfide reductase, an event that may lead to a disturbed GSH/GSSG state in pulmonary cells.

- Eventually, this state leaves the cell unable to cope with oxidant stress.

- High concentrations of oxygen in the inspired air may enhance the pulmonary toxicity of BCNU and also that of the other anticancer drugs known to affect lung tissue: bleomycin and cyclophosphamide.

Bleomycin

- Bleomycin is a cancer chemotherapeutic drug with a major complication—pulmonary fibrosis that can be fatal.

- Bleomycin produces a sequence of injury and necrosis to capillary endothelial cells and alveolar type I cells.

- This, in turn, leads to edema formation and hemorrhage, delayed (after 1 to 2 weeks) proliferation, and apoptosis of alveolar type II cells.

- Eventually the alveolar walls are thickened by fibrotic changes. **In many tissues**, the cytosolic enzyme bleomycin hydrolase inactivates bleomycin.

- **In lung and skin**, two target organs for bleomycin toxicity, the activity of this enzyme is low compared with that in other organs.

- **Cyclophosphamide** A number of chemotherapeutic drugs can produce lung damage and pulmonary toxicity in patients treated with these drugs.

- Cyclophosphamide is widely used as an anticancer and immunosuppressive drug.

- The undesirable side effects include hemorrhagic cystitis and pulmonary fibrosis.

- Cyclophosphamide is metabolized by cytochrome P450 to two highly reactive metabolites: acrolein and phosphoramide mustard.

- Although the exact mechanism of action for causing lung damage has not been established,

- studies with isolated lung microsomes have shown that cyclophosphamide and its metabolite acrolein initiate lipid peroxidation.

Thank you