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Respiratory tract toxicology:

Respiratory tract is the target organ for xenobiotic toxicity, and the abnormal changes in the respiratory tract produced by airborne.

There are many mechanisms protect the epithelial cells in conducting airways and pulmonary tract from toxicants:

- ✓ Cytochrome P450 isozymes have been localized in the nose in several species ,in addition two important cytosolic enzymes in lung cell involved in xenobiotic metabolism are glutathione S-transferases and glutathione peroxidase.
- ✓ The epithelium coated with a viscoelastic sticky protective layer that traps pollutants and cell debris, upon which a mucus layer may be floated.
- ✓ The mucus layer is also thought to have antioxidant, acid-neutralizing, and free radical scavenging functions.
- ✓ The action of the respiratory tract cilia is removed the foreign body from respiratory system by swallowing or expectoration.
- ✓ Particles may be phagocytized by macrophage or alveolar macrophages and removed via the lymphatic drainage.
- ✓ Materials may dissolve and be removed via the bloodstream or lymphatics such as small particles may directly penetrate epithelial membranes.

Mechanisms of impact of xenobiotic on Gas-Exchange Region:

1- The certain gases and vapors caused sites interaction by stimulate nerve endings in the nose, particularly those of the trigeminal nerve. The result is holding of the breath or changes in breathing patterns to avoid or reduce further exposure.

2- May causes variety of abnormal processes may thicken the alveolar septum and adversely affect the diffusion of oxygen to the erythrocytes.

3- May causes collection of liquid in the alveolar space.The epithelial barrier in the alveolar zone, after a latency period of several hours, begins to leak, flooding the alveoli and producing a delayed pulmonary Edema that is often fatal.

4- May caused abnormal thickening of the pulmonary vessels epithelium,

5- May causes increased formation and deposition of extracellular substances such as collagen.

6- The continued exposure for many acidic or alkaline irritants produced cell necrosis and increased permeability of the alveolar walls. Other inhaled agents can be more insidious; inhalation of HCL, NO_2, NH_3, or phosgene, may at first is produce apparent damage in the respiratory tract.

7- The highly reactive molecules (OH, O, H_2O_2,) are involved in the pathogenesis of lung injury.

The deposition of gases in the respiratory tract

Water solubility is the critical factor in determining how deeply a given gas penetrates into the lung. Highly soluble gases such as SO_2 do not penetrate farther than the nose unless doses are very high, and are therefore relatively nontoxic. Relatively insoluble gases such as ozone and NO_2 penetrate deeply into the lung can elicit toxic responses. Insoluble gases such as CO and H_2S efficiently pass through the respiratory tract and distributed throughout the body.

Particle Deposition:

Particle size is usually the critical factor that determines the regions of the respiratory tract in which a particle or an aerosol will be deposited. Large particles (larger than 5 Km) are usually trapped in the upper respiratory tract.Whereas the smaller particles (0.2 -5μm) can be transported to the smaller airways and the alveoli.

Nanotoxicology:

Are particles with diameters less than 100 nm. Ultrafine particles of this size range are increasingly being used in manufactured product, and increased release of particles of this size to the environment, and exposure of individuals increasing exponentially

The Nanotoxicology concerns reflect three major issues:

1- The enormous surface area of these particles relative to their mass, and the presence of reactive metals on their surfaces.

2- Commercially important forms of nanoparticles include nanotubes, more toxic than spheres of the same mass.

3- It can be readily transported through and out of the lung to other tissues via pathways that are not normally accessible to larger particles.

Important factors participate in particle deposition:

• The pattern of breathing: when larger volumes are inhaled at higher velocities, deposition in airways increases, such as a large proportion of the inhaled particles may be exhaled during exercise.

• Factors that modify the diameter of the conducting airways can alter particle deposition. In patients with chronic bronchitis, the mucous layer is greatly thickened and extended peripherally and may partially block the airways in some areas and partially occluded airways have the potential to increase the deposition of particles by impaction and diffusion in the small airways.

• Irritant materials that produce bronchoconstriction tend to increase the tracheobronchial deposition of particles. Cigarette smoking has been shown experimentally to produce such an effect.

Biomarkers of Lung Toxicity:

Interleukin (IL IL-2, LL-5, IL-8, and IL-13) to be essential components of the lung's response to epithelial cell injury. The transforming growth factor (TGF-beta), and tumor necrosis factor (TNF-

alpha) were participating in the cascade of reactions that are responsible for the pathogenesis of pulmonary fibrosis. In addition various specific prostaglandin especially PGE2 have roles of cell surface adhesion molecules and their interaction with cell matrix components and with control of inflammatory cell migration (particularly neutrophil influx to the lung).

Oxidative Burden:

Is mediated by free radicals such as those generated by ozone, NO_2, tobacco smoke, and lung defense cells can directly and indirectly cause lung damage. Lung oxidant toxicity by the formation of unstable free radicals and active oxygen species.
Subsequent chain reactions can lead to uncontrolled destructive oxidation. Beside that the roles of superoxide, nitric oxide, peroxynitrate, hydroxyl radicals, & hydrogen peroxide are act as mediators for tissue damage.

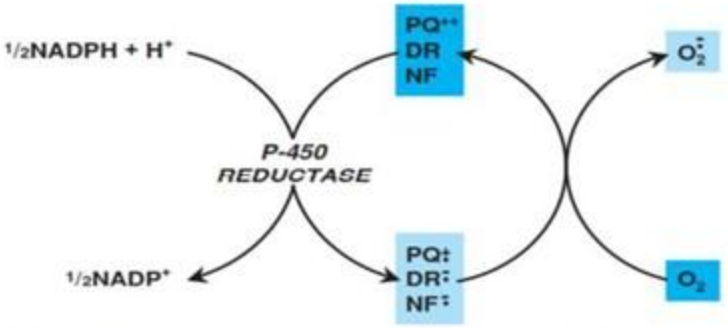


Figure 3-3. Production of superoxide anion radical ($O_2^{\bullet}$) by paraquat (PQ^{++}), doxorubicin (DR), and nitrofurantoin (NF).

Airway Reactivity:

Bronchoconstriction occurred because increased production of acetylcholine, histamine, various prostaglandins and leukotrienes, substances P and nitric oxide. It happens because irritant of cigarette smoke and air pollutants and by consumption cholinergic drugs. Bronchoconstriction causes a decrease in airway diameter corresponding increase in resistance to airflow. Characteristic associated symptoms include wheezing, coughing, a sensation of chest tightness, and dyspnea, the exercise potentiates these problems.

Pulmonary Edema:

Toxic pulmonary edema represents an acute, exudative phase of lung injury was distinguished by thickening of the alveolar-capillary barrier. Edema that generally produces a fluid alters ventilation-perfusion relationships and limits diffusive transfer of O_2 and CO_2. After exposure to some toxic chemicals in which the alveolar-capillary surface is denuded (such as alloxan), recovery is unlikely, in more modest injury (such as histamine administration) full recovery is readily achievable.
Accumulation and turnover of inflammatory cells and related immune responses in an edematous lung probably play a role in eliciting both mitogenic activity and fibrogenic responses.

Emphysema:

Is "an abnormal enlargement of the airspaces distal to the terminal bronchiole accompanied by destruction of the walls without obvious fibrosis" The major cause of human emphysema is cigarette smoke inhalation, although other toxicants also can elicit this response.

The toxicants-induce severe or recurrent inflammation was causes alpha- l-antiprotease deficiency. Toxicants that cause inflammatory cell influx and thus increase the burden of neutrophil elastase can accelerate this process. The neutrophil elastase or with other proteolytic enzymes that can digest

elastin which result the characteristics of emphysema, including destruction of alveolar walls and airspace enlargement in the lung parenchyma. As an individual ages, an accumulation of random elastolytic events can cause the emphysematous changes in the lungs that are normally associated with aging

Fibrosis:

A fibrotic lung is increased amounts 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.

In lungs damaged by toxicants, the response in adult is being chronic interstitial fibrosis. Types 1 and III collagen are major lung interstitial components, that are found in the normal lungs of all mammals in an approximate ratio of 2:1. Type III collagen is more compliant than type I, when increasing type I relative to type III collagen may result in a stiffer lung have been observed acute pulmonary fibrosis.

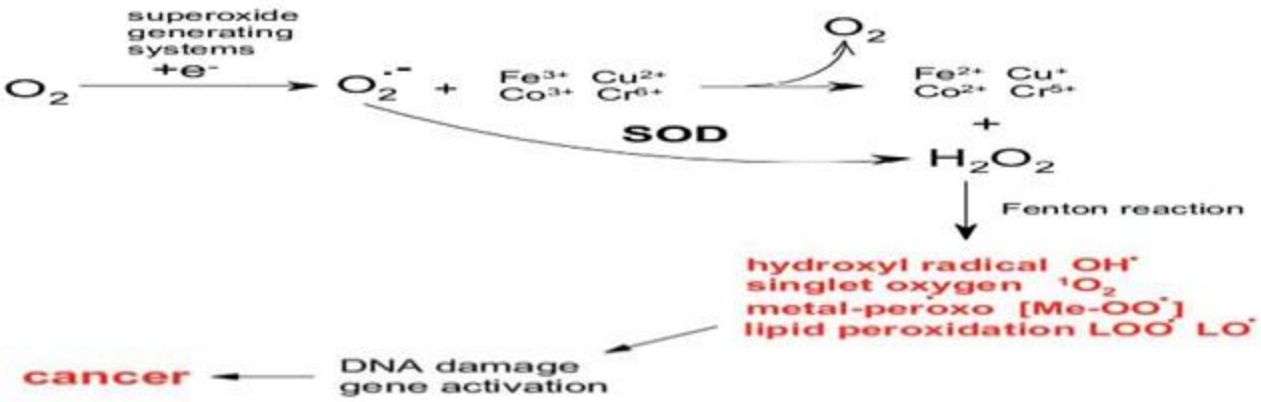
Asthma:

Characterized clinically by attacks of shortness of breath, because increased airway reactivity in response to exposure to irritants. The occupational or environmental exposure to antigens or to chemicals that can act as haptens and the pathogenesis of asthma (especially ultrafine particulate air pollution).There may be common mechanisms, which are shared between asthma and fibrosis, especially with regard to the role of recurrent or chronic pulmonary inflammation in disease pathogenesis.

Lung Cancer:

The exposure for many chemicals in industrial settings poses a lung cancer risk. Inhalation of asbestos fibers and metallic dusts or fumes, such as arsenic, beryllium, cadmium, chromium, and nickel, encountered in smelting and manufacturing operations has been associated with cancer of the respiratory tract , workers who manufacture chloromethyl ether or mustard gas have an increased risk of developing lung cancers, as do workers exposed to effluent gases from coke ovens. Radon gases and Formaldehyde are human respiratory carcinogens. Silica, human-made fibers, and welding fumes are suspected carcinogens. Common air pollutants such as ozone, nitrogen dioxide, sulfur dioxide, and fumes emanating from power plants, oil refineries, and from diesel fuel powered trucks and cars contribute to the development of lung cancer in the general population.

Damage to DNA is thought to be a key mechanism. An activated metabolic product, such as alkyldiazonium ions derived from N-nitrosamines, may interact with DNA. Carcinogenesis where DNA damage caused by active oxygen species is another potentially important mechanism. Ionizing radiation the lead to formation of superoxide, converted through the action superoxide dismutase to hydrogen peroxide. In the presence of Fe and other transition metals, hydroxyl radicals may be formed which then cause DNA strand breaks. Cigarette smoke contains high quantities of active oxygen species and other free radicals. Additional oxidative stress may be placed on the lung tissue of smokers by the release of superoxide anions and hydrogen peroxide by activated macrophages, metabolism of carcinogens, and lipid peroxidation caused by reactive aldehydes.



Airborne Agents That Produce Lung Injury in humans

Asbestos

The term asbestos describes silicate minerals in fiber form. Exposure to asbestos fibers occurs mining operations and the construction and shipbuilding industries. In humans, asbestos causes three forms of lung disease: asbestosis, lung cancer, and malignant mesothelioma. The hazards of asbestos exposure depend on fiber length. Fibers 2μm in length may produce asbestosis, but the mesothelioma is associated with fibers 5μm long, and lung cancer with fibers larger than 10 μm. The development of mesothelioma (a rare tumor of the cells covering the surface of the visceral and parietal pleura), may be translocated from their site of deposition via the lymphatics to other organs, including the pleural surface. 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. The Longer fibers are incompletely ingested and the macrophages become unable to leave alveoli. Activated by the fibers macrophages release mediators such as lymphokines and growth factors cells which in turn attract immune-competent cells or stimulate collagen production.

Asbestos-triggering of an inflammatory sequence of events or the production of changes that eventually lead to the initiation (DNA damage caused by reactive molecular species) or promotion (increase rate of cell turnover in the lung) of the carcinogenic process.

Naphthalene:

Is obtained from either coal tar or petroleum and is a widely used for synthetic tanning agents, phthalic acid anhydride, carbaryl, and 2-naphthol. It is present in ambient air. Smokers inhale substantial amounts of naphthalene in cigarette smoke.

Naphthalene epoxides may subsequently be conjugated with glutathione and form adducts that are eliminated as mercapturic acids. The rearrangement naphthalene to 1- naphthol with subsequent metabolism to quinones, which are potentially toxic compounds. Naphthalene metabolites bind covalently to cellular proteins that are important in normal cellular homeostasis and protein folding.

Bleomycin:

Used as cancer chemotherapeutic agent. After exposure increased the risk pulmonary fibrosis because have damage impact that includes necrosis of capillary endothelial and type I alveolar cells, delayed proliferation of type II epithelial cells, formation edema and hemorrhage, and eventually thickening of the alveolar walls 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. Bleomycin stimulates the production of collagen in the lung, and subsequent to a bleomycin-mediated release of cytokines such as TGF beta (Transforming growth factor beta) and TNF alpha. Bleomycin also combines double-strand breaks are produced by a free radical reaction.

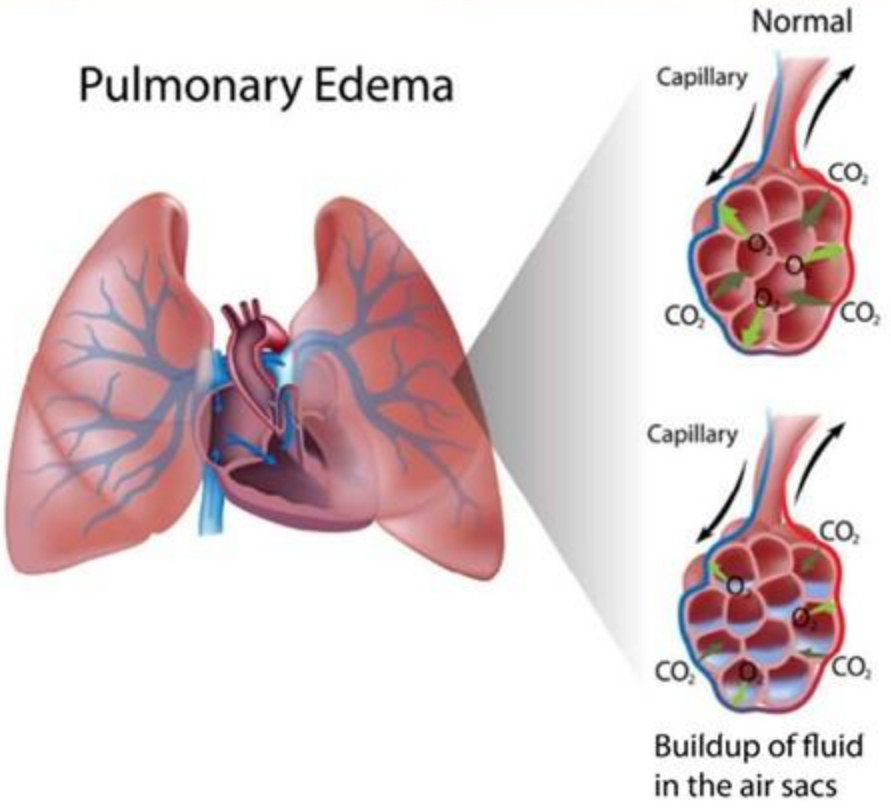
Cyclophosphamide:

It is an anticancer and immunosuppressive drug. The undesirable side effects include hemorrhagic cystitis and pulmonary fibrosis. Cyclophosphamide is metabolized by the cytochrome P-450 system to two highly reactive metabolites: acrolein and phosphoramide mustard. Cyclophosphamide and its metabolite acrolein initiate lipid peroxidation.

Industrial Toxicants That Produce Lung Disease

TOXICANT	COMMON NAME OF DISEASE	OCCUPATIONAL SOURCE	ACUTE EFFECT	CHRONIC EFFECT
Asbestos	Asbestosis	Mining, construction, shipbuilding, manufacture of asbestos-containing material		Fibrosis, pleural calcification, lung cancer, pleural mesothelioma
Aluminum dust	Aluminosis	Manufacture of aluminum products, fireworks, ceramics, paints, electrical goods, abrasives	Cough, shortness of breath	Interstitial fibrosis
Aluminum abrasives	Shaver's disease, corundum smelter's lung, bauxite lung	Manufacture of abrasives, smelting	Alveolar edema	Interstitial fibrosis, emphysema
Ammonia		Ammonia production, manufacture of fertilizers, chemical production, explosives	Upper and lower respiratory tract irritation, edema	Chronic bronchitis
Arsenic		Manufacture of pesticides, pigments, glass, alloys	Bronchitis	Lung cancer, bronchitis, laryngitis
Beryllium	Berylliosis	Ore extraction, manufacture of alloys, ceramics	Severe pulmonary edema, pneumonia	Fibrosis, progressive dyspnea, interstitial granulomatosis, lung cancer, cor pulmonale
Cadmium oxide		Welding, manufacture of	Cough, pneumonia	Emphysema, cor pulmonale

		electrical equipment, alloys, pigments, smelting		
Carbides of tungsten, titanium, tantalum	Hard metal disease	Manufacture of cutting edges on tools	Hyperplasia and metaplasia of bronchial epithelium	Peribronchial and perivascular fibrosis
Chlorine		Manufacture of pulp and paper, plastics, chlorinated chemicals	Cough, hemoptysis, dyspnea, tracheobronchitis, bronchopneumonia	
Chromium (VI)		Production of Cr compounds, paint pigments, reduction of chromite ore	Nasal irritation, bronchitis	Lung cancer, fibrosis
Coal dust	Pneumoconiosis	Coal mining		Fibrosis
Cotton dust	Byssinosis	Manufacture of textiles	Chest tightness, wheezing, dyspnea	Reduced pulmonary function, chronic bronchitis
Hydrogen fluoride		Manufacture of chemicals, photographic film, solvents, plastics	Respiratory irritation, hemorrhagic pulmonary edema	
Iron oxides	Siderotic lung disease; silver finisher's lung, hematite miner's lung, arc welder's lung	Welding, foundry work, steel manufacture, hematite mining, jewelry making	Cough	Silver finisher's lung: subpleural and perivascular aggregations of macrophages; hematite miner's lung: diffuse fibrosislike pneumoconiosis; arc welder's lung: bronchitis
Isocyanates		Manufacture of plastics,	Airway irritation,	Asthma, reduced pulmonary




Elastic Fibers
Air Sacs
Small airway & air sacs
in normal lung


Elastic Fibers
become strained
Inflamation
causes
the airways
to narrow
Fibers break and
the small the small
airways pull away
from the air sacs
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and the
walls of the
air sacs
collapse
Small airway narrowing and air sac damage
in emphysema