The Respiratory System

• Responsible for:
  – Maintenance of life through gas exchange
    • Supplying O₂ to the body
    • Eliminating CO₂ from the body
  – Many non-respiratory functions like:
    • Immune system maintenance
    • Metabolism of environmental pollutants
    • Regulating body’s pH balance

• Toxicological importance:
  – Acts as early detection system for airborne toxicants (sense of smell)
  – Provides an exposure pathway for systemic exposures to many toxicants
  – Is a direct (and frequent) target of toxicity from exposures to many airborne chemicals
    • The average adult inhales approximately 12 kg of air daily (value increase dramatically with physical exertion)
    • Compare to average daily food intake (1.5 kg); or water intake (2 kg)
Functional Divisions of the Respiratory System

There are three functional divisions of the respiratory system:
- Nasopharyngeal
- Tracheobronchial
- Pulmonary (alveolar or gas exchange surfaces)

Inhalable pollutants settle in these regions by:
- Inertial impaction (nasopharyngeal)
- Sedimentation (trachea to bronchioles)
- Diffusion (alveoli)

Health Impact

Important AQ/toxicology episodes
- The accidental release of 40 tons of methyl isocyanate in Bhopal, India in 1984
  - 3800 deaths
  - Thousands of partial and/or permanent disabilities
- London, UK, 1952
  - Unusually cold weather → more coal burning
  - Typical emissions from local industries
  - A strong, persistent temperature inversion
  - Results
    - \([\text{PM}_{10}]\): 3000 – 14,000 \(\mu\text{g/m}^3\) (NAAQS: 150 \(\mu\text{g/m}^3\) 24h)
    - Approximately 12,000 deaths
Respiratory Exposure

- Inhaled air contains:
  - A variety of nonessential gases
  - Vapors
  - Aerosols
  - Particulates
- All may possess the capacity to induce local or systemic injury
- The respiratory system can provide a route for systemic toxicants in addition to those that target the system directly
  - For example, NO$_2$ can cause pulmonary fibrosis upon inhalation without producing systemic toxicity.

Systemic Toxicities Through Respiratory Exposure

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritants</td>
<td>NH$_3$, NO$_2$, SO$_2$, O$_3$, phosgene, halogens, aldehydes</td>
</tr>
<tr>
<td>Alkylcyanides</td>
<td>CO, CN, N$_2$, CH$_2$, CH$_3$, H$_2$, HCN</td>
</tr>
<tr>
<td>Central nervous system toxicants</td>
<td>Aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, acetone, ethyl ether, benzene, Cl$_2$, Hg, acrylamide, n-hexane, methyl n-butyl ketone</td>
</tr>
<tr>
<td>Hepatotoxicants</td>
<td>CCl$_4$, CCl$_3$, ethyl alcohol, bromobenzene</td>
</tr>
<tr>
<td>Nephrotoxicants</td>
<td>Heavy metals, CCl$_4$, chloroform, trichloroethylene</td>
</tr>
<tr>
<td>Hematotoxicants</td>
<td>CO, nitrobenzene, aniline, naphthalene</td>
</tr>
<tr>
<td>Carcinogens</td>
<td>Polycyclic aromatic hydrocarbons, vinyl chloride, 2-naphthylamine, bis(chloromethyl)ether</td>
</tr>
</tbody>
</table>

Nomenclature of Airborne Toxicants

- **Gases**
  - If water soluble (e.g., SO$_2$), absorption by nasal passages and upper airways
  - If insoluble (e.g., CO, NO$_2$), absorption by deeper airways and alveolar region
- **Vapors**
  - Normally a liquid or solid at STP
  - Volatilize due to high vapor pressure (e.g., alcohols, gasoline)
- **Aerosols**
  - Relatively stable suspensions of solids and/or liquid particles in air
- **Dusts**
  - Small particles produced by abrasive processes such as sanding, grinding, or milling (e.g., metals, silica, grains)
Nomenclature of Airborne Toxicants (2)

• **Fumes**
  - Produced by combustion, sublimation, or condensation of vaporized material
  - Size tends to be <0.3 μm (e.g., zinc vapors and metal fumes)

• **Smoke**
  - Particles produced by combustion of organic matter

• **Mists and fogs**
  - Condensation of moisture on particulate nuclei in air (e.g., the condensation of SO2 onto particles of ash)

• **Smog**
  - Mixture of smoke, particles, and gases (fog) produced by combustion processes and the action of sunlight on NOx and VOCs

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Respiratory System Injury

• Broad categories of respiratory response:
  - Irritative or inflammatory
    - Smoking, viruses, fumes, vapors
  - Bronchoconstrictive
    - Allergens
  - Fibrotic
    - Asbestos
  - Oncogenetic
    - Vinyl chloride
  - Necrotic
    - Bacteria

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Respiratory System Injury (2)

• The type and extent of injury depend on the:
  - Concentration of the pollutant
  - Dose
  - Duration of exposure
  - Physiochemical properties of the chemical
Exposures to Air Pollutants: 

$O_3$

- Epidemiologic studies have demonstrated a link between ozone and acute responses such as asthma exacerbation
  - Exposure to $O_3$ (one of the criteria pollutants) is known to induce increases in airway inflammation in non-asthmatics.
    - Low $O_3$ concentrations, even brief exposures, are thought capable of triggering this response.
  - In asthmatics the effect of $O_3$ is exaggerated
    - Exposure produces bronchoconstriction and increased sensitivity to allergens.
  - $O_3$ is found naturally in the stratosphere and in the troposphere as a component of air pollution.

Exposures to Air Pollutants: 

$O_3$ (2)

- Concentrations typically spike in the summer when NOx and VOCs react to form $O_3$
  - There are concurrent increases of other pollutants that may exacerbate the irritant effects of ozone on the respiratory system.
  - $O_3$ is less soluble than many other irritant gases and penetrates into the pulmonary regions more effectively

Exposures to Air Pollutants: 

$NO_x$

- Like $O_3$, $NO_x$ effectively penetrates deep into the respiratory system
  - Exposure to nitrogen oxides triggers pathological changes in alveolar regions of the respiratory system
  - Acute exposure to $NO_x$ can result in pulmonary edema
  - Chronic exposures may be linked to emphysema
Exposures to Air Pollutants:

**SO₂**

- Produced by the combustion of sulfur-containing fossil fuels like coal, oil, and kerosene
  - Primarily an upper airway irritant due to its high water solubility
    - Asthmatics are especially vulnerable
  - Prior exposures may result in increased bronchoconstriction in subsequent exposures and increase airways reactivity pollutants other than SO₂.

Exposures to Air Pollutants:

**Photolysis of VOCs/HCs**

- Photolysis yields a variety of aldehydes (e.g., HCHO and acrolein)
  - HCHO represents 50% of total aldehydes
    - It is a nasal, upper respiratory, and eye irritant
    - It has an odor threshold of approximately 0.5 ppm and is intolerable to most exposed individuals at exposures greater than 4 ppm.
    - It is used in both industrial and consumer products
      - Exposure is difficult to avoid
  - Acrolein is both more reactive and irritating than formaldehyde, and the damage inflicted by exposure can be irreversible.

Exposures to Air Pollutants:

**Particulates**

- Particulate matter (PM) is another important pollutant associated with increased asthma severity
  - Examples
    - Diesel exhaust particles increase nonspecific airway reactivity in asthmatic individuals
    - Endotoxin is commonly found in the PM of many grains and produces increased airway symptoms in agricultural workers
      - It is capable of producing inflammation in both nonasthmatic and nonallergic individuals and can result in nonspecific airway reactivity in those individuals with asthma.
Defense Strategies

• Clearance mechanisms
  – The processes involved in the active removal of foreign matter in contact with the stratum corneum interface.
  – In the respiratory system, clearance mechanisms are a nonspecific means of particulate and dissolved chemical removal; they vary with the site of deposition.
  – The two clearance mechanisms are:
    • Mucociliary transport (mucus excretion) in the airways
    • Alveolar WBCs in the gas exchange regions

Defense Strategies(2)

• For aerosols, particle size, shape, and physicochemical properties of the particulate are important for determining deposition.
• Deposition mechanisms include:
  – Impaction
  – Interception
  – Sedimentation
  – Diffusion
• Clearance of relatively insoluble inhaled toxicants occurs in the
  – Nasal cavity by filtering mechanisms that trap and eliminate larger particles (>10 μm).
  – Sneezing and coughing
  – Conducting airways through the process of mucociliary transport
  – Alveoli by the action of alveolar macrophages

Other Pulmonary Defense Mechanisms

• Bronchoconstriction can be induced by a variety of means in response to respired particulate matter or chemicals.
  – Bronchoconstriction is considered protective because it reduces air flow to the lungs, thereby limiting pulmonary exposure to inhaled toxicants.
• Airway epithelial cells are capable of producing inflammatory mediators that alter vascular permeability.
  – This recruits inflammatory cells to the injury site.
Types of Injury

- **Acute**
  - An irritant gas such as sulfur dioxide may trigger an immediate reflex, producing bronchoconstriction

- **Delayed**
  - Often trigger an acute inflammatory response, leading to edema, reduced airflow, and bronchitis (typically ~12hr delay)
  - Examples
    - NO₂, herbicides, siphoning gasoline (aspiration)

Types of Injury (2)

- **Chronic**
  - The chronic condition, emphysema, is responsible for about 3% of deaths in the United States.
  - Cigarette smoke leads to the loss of gas exchange surface, inflammation, and fibrosis.

Asthma

- A critical feature of asthma is nonspecific airway hyperresponsiveness
- changes to the airways seen in both occupational and nonoccupational environmental bronchial asthma include:
  - Infiltration of inflammatory cells
  - Evidence of bronchial epithelial damage
  - Airway smooth muscle hyperreactivity
  - Thickening of subepithelial collagen are examples of some.
Asthma

- In asthmatics, environmental exposures may trigger a number of responses:
  - Immediate (within minutes)
  - Late (several hours post-exposure)
    - Appears to be directly associated with airway mucosal inflammation.
    - Appears similar to occupational asthma
  - Dual
    - Combining both an immediate and late response.
- It is not known why specific chemical exposures lead to sensitization whereas others have little to no lasting effect.

Asbestosis

- Chronic inflammation and fibrosis of lung tissue due to inhalation of asbestos fibers
  - The size and shape of the fibers influence whether the disease may progress to cancer.
  - Fibers that reach the deep lung are usually <2 µm in diameter and <100 µm in length.
  - All forms of asbestos are fibrous silicates composed of silicon dioxide with various substituted elements.
- Two types of cancer associated with asbestosis are:
  - Bronchiocarcinoma
  - Malignant mesothelioma.
- Malignant mesothelioma is a cancer of the lungs' outer lining
  - Exposures are mostly occupational, but also some environmental
  - Process: Macrophages only partially digest long fibers before they die, which releases the fibers to start process anew with other macrophages
  - Low incidence (IR = 1 per 1,000,000 annually)
  - Notables:
    - Steve McQueen, Merlin Olsen
- Bronchiocarcinoma
  - Neoplastic material grows in small masses among alveoli
Homework

- Brief cardiotoxicology investigations
  - Select two (2) cardiac health effects (not listed on previous slide) that are linked to chemical exposures
  - For each effect provide:
    • Exposure route
    • Symptoms
    • Treatment
    • Outcome
    • Anything else of interest

Homework

- Brief respiratory system toxicology investigations
  - Select two (2) respiratory system health effects (not discussed today) that are linked to chemical exposures
  - For each effect provide:
    • Exposure route
    • Symptoms
    • Treatment
    • Outcome
    • Anything else of interest