Basic Principles of Toxicology: How Air Pollutants Move Around the Body and Cause Harm

Health Effects Workshop, Baltimore
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Nov. 6 & 7, 2008

With thanks to: David Brown, Sc.D.
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Focus on basic physiologic chemistry that controls toxic actions in the lung
Stages of Lung Toxic Responses

- **Stage #1**
  Exposure through inhalation

- **Stage #2**
  Action of agent on component of the cell starting with binding

- **Stage #3**
  Response of lung to loss of function

- **Stage #4**
  Transport of agents to other sites of action
Governing rules #1

- All toxic substances act by inhibiting processes in the body

Toxins bring nothing to the system they inhibit normal responses

Therefore start by understanding normal responses
Governing rules #2

- In order to act the agent must bind to a component of the system.
  
  Cellular concentration determines the amount of binding and the intensity of toxic response.

Therefore think about binding at the cellular level.
Governing rules #3

The amount of binding and the duration of the binding will determine the intensity of the action.

A toxic response is continuous moving from reversible to irreversible and from physiological changes to structural damage.

Therefore think about the amount of exposure and the duration of exposure.
Governing rules #4

- Toxic agents have more than one action.
  
  The higher the exposure the more actions are expressed and the more serious the damage.

Therefore think about the toxic responses in terms of amount and duration of exposure
e.g. headaches precede ataxia which precede irreversible brain damage
Governing rules # 5

- Repair and regeneration are fundamental characteristics of biological systems.

Repeated exposures increase the structural damage and ability to regenerate and repair systems.

Therefore think about the time between exposure and the assessment of the action. Expect evidence of structural damage with repeated low level effects. e.g. forgetfulness, frustration ataxia
National Air Quality Concerns

- Ozone
- Particulate Matter
- Nitrogen Dioxide
- Sulfur Dioxide
- Hazardous Air Pollutants (Toxins)
- Lead
- Carbon Monoxide
Direct Responses of the lung to inhaled toxics

• Asphyxia
• Functional changes: respiratory rate, respiratory depth. And clearance
• Allergic or immune based responses
• Development of tolerance
• Structural changes
• Cancer
Systemic responses to inhaled toxins

• Neurologically based
• Metabolically based
• Other target organs such as the skin
Direct Actions

Displacement of oxygen: asphyxicants such as carbon dioxide, or nitrogen simply displace oxygen and lower the amount of oxygen in the inhaled air available for oxygenation of the red cells.

The amount of oxygen carried by a red cell is directly related to the oxygen tension in the air.
Direct Actions

• Chemical inhibition of oxygen transport
  Binding of carbon monoxide to red cell hemoglobin which competes with oxygen for transport sites. These agents simply block transport so that oxygen cannot reach the cells.

• The differential affinity of the oxygen and carbon monoxide for the 4 binding sites on hemoglobin reduces transport. The action is slowly reversed in the presence of high oxygen tensions.
Functional parameters used to evaluate lung toxic effects

- Ability to take up a gas such as oxygen or carbon dioxide
- Ability to clear the lung of foreign matter such as particulate of bacteria
- Respiratory volumes per unit time, FEV 1 minute
- Respiratory rate measures
- Blood perfusion rates
- Blood gas levels
- Response of the lung to pharmacologic challenges
Direct irritation of the lung tissue

1. Agents such as ozone and acid gases act directly on the structure of the lungs producing chronic damage or neurological responses.

2. The majority of the upper airway responses act through neurological protective mechanisms.

Lower airway responses tend to act on the structural integrity of the alveoli and the bronchioles causing inflammation and edema.
Major take home lesson

- Lungs inhale about 1 cubic meter of air/hour irrespective of the atmospheric pressure or temperature. Under heavy activity that volume can increase by a factor of 3 to 5 and when sleeping it can decrease to 0.6 cubic meters.

All of the responses are dose related with respect to the dose in the lung.

- Concentration of a toxic substance in ambient air is a secondary indicator of dose to the lung.

- Reactions in the lung are on the order of minutes to hours thus basing health risk on 24 hour and annual averaging is hopeful at best.
For example, as part of the process to determine whether an area meets the EPA particulate matter standard, this 3-month long series of **hourly** observations would be collapsed to a single value… 9.2 ug/m³… **Totally obscuring any “structure” or other “content” within the data set** (Carmine Dibattista, CT DEP).
Synergistic interaction
The least understood and most important interaction in air pollution

How particles increase exposure of irritants to the deep lungs

- Diesel particle (PM 2.5 range)
- Irritant gas absorbed in water
- Water adsorbed
- Deep lung exposure to irritants

Irritant gases
Synergistic interactions

• In the 1970s Mary Amdur showed that the toxicity of reactive species in the lung acted at concentrations too low to produce direct “burning” of cells but instead acted by activating highly potent bioactive phospholipids.

• This observation is the basis for tolerance seen with repeated lung exposures to irritants.
Toxic conditions in the lungs

- Impaired lung development due to early childhood exposures. Asthmatic compounds
- Reduction of carrying capacity for oxygen and carbon dioxide due to inhibition of cell turnover.
Toxic conditions of the lungs

- Pneumoconiosis – a process of collagen growth that destroys elasticity and compliance caused by several particulate agents e.g. silica
- Lung Cancer – a process of tumor induction produced by accumulation of mineral dusts in the lung e.g. asbestosis
- Lung cancer – formation of tumors in the lung die to the action of carcinogenic gases and mixtures. E.g. tobacco smoke
Transfer to other organs

- Toxics move through the body via the blood or lymphatic systems.
- Highly water soluble materials or very active species never reach the deep lung or blood but are absorbed in the upper airways e.g. chlorine gases.
- Organics and small particles reach the deep lung and enter the blood system.
- Activation or inactivation reactions usually occur in the liver or kidney but not always.
Transfer to other organs

- Transport in the blood requires binding to either the red cells or plasma proteins.
- The binding is almost always competitive such that binding of a toxic substance can cause depleting of an essential nutrient.
- Binding and transport almost never requires use of cellular energy stores.
- Because saturation of binding sites and depleting of energy stores takes time the responses can be delayed.
- Agents not transported are either exhaled or they remain in the lung
Dose: The quantity of a pollutant taken in or absorbed

• Dose can be represented by:
  – Inhaled dose, or
  – Absorbed dose, or…

• Often Air Concentration is used as a surrogate.

• Assigning the proper averaging time may be critical.
Actual inhaled dose varies between day, time of day, activity and location for child.

Ug PM/day shown by 3 hr dose indoor and outdoor (based on ambient levels and normal activity)

- 24.00
- 21.00
- 18.00
- 15.00
- 12.00
- 9.00
- 6.00
- 3.00
Information on toxic responses

• Chamber studies with controlled exposures in humans or animals

• Personal monitors in workplaces with identification of workers activities
The relationships between sick populations and air pollution (The “tools”)

- Community surveys based on physician records and daily logs.
- Region wide epidemiology studies
- Risk assessment extrapolations to reference doses.
Reflection on Biology and Statistics

- Core concept is a biologically relevant dose measurement (BRDM). (a time and spatial question)

- Without BRDM one is left with Harvard Six Cities and NMMAPS studies that are too general to be applied to local populations

- The current challenge is to study local exposures in populations of 1000 or less.
The Epidemiological Range of Air Pollution Effects

- Death
- Hospital Admissions
- Doctor visits
- Asthma attacks, medication use, symptoms
- Lung function changes, immune cell responses, Heart rate or heart rate variability responses
Key Concepts of Epidemiology

• Cohort – A group of people with common experience followed over time

• Longitudinal – A group followed over time with representative measures and samples.

• Relative Risk – Comparison between two populations. Relative Risk of 1 means no difference between populations.

• Confounders – Variables not considered in the analysis, such as smoking, diet, co-pollutants, socioeconomic status

• Case series – Detailed assessment of a series of patients that permit study of the mixtures inhaled.
Summary

• Toxic actions are based on four factors:
  – Pattern of inhaled exposures
  – Ability of the agent to bind to cellular components
  – Capacity for cellular repair
  – Capacity to detoxify the agent and excrete from the body.

• It is essential to understand the interactions that occur between agents.