Medical Modeling of Particle Size Effects for Inhalation Hazards

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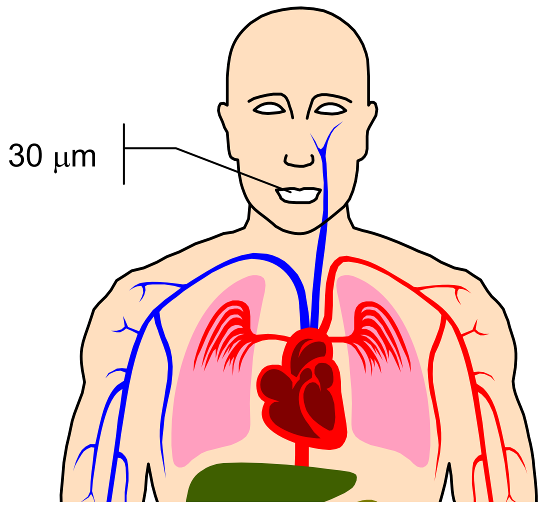
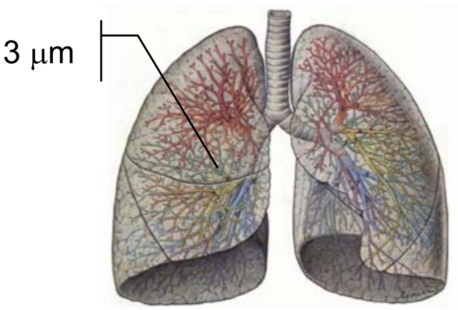
Topic Outline

- Objective
- Background
- Why should we care
- Inhalation mechanics
- Dispersion by particle size
- Anatomy and biokinetics
- Conclusion

Objective

- Develop medical models for the influence of aerosol particle size on the health effects of inhaled CBRN hazards to improve hazard assessment, particularly in urban environments.





Background – Aerosol Inhalation

- Techniques well developed for radionuclides and atmospheric particulates
  - Inhalation mechanics well established
  - Human response well studied
- Particle size modeling is incomplete for chem-bio agents
  - Inhalation mechanics is applicable
  - Critical new piece is variation in human response

Modeling of Particle Size Effects in CBRN Consequence Assessment Is Incomplete

- Used in atmospheric transport
  - Nuclear fallout directly dependent on settling
  - CBWPN in HPAC allows User to specify a lognormal particle size distribution
- Radionuclide dose conversion factors for inhalation account for particle size
- Inhalation model for CB agents is crude
  - Typically assume 5 μ particles, 100% inhaled
  - Or use a size cut-off like 10 μ
  - Neglected for liquid agents

Why Should We Care?

- Often-expressed beliefs
  - Can neglect large particles
    - They settle out too quickly
    - Don't penetrate deeply into the lung
  - Can neglect small particles
    - Not retained in lungs

- These are arguments for efficacy of 3 - 5 μ range
  - Valid, but…
  - Arguments do not support the converse!

Particle Size-Dependent Tularemia

Macaca mulatta (rhesus) monkeys[1]

Particle size	2.1 and 7.5 μm	12.5 and 24.0 μm
Exposed	48	45
% Infected	100%	84%
Onset Time	2-3 Days	6-10 Days
Primary infection site	Lower respiratory system, pneumonitis	Upper respiratory tract, nasal pharyngeal area, cervical and mandibular lymph nodes; eyes (15%)
% fatal	69%	53%
Time to death	4-8 Days	8-21 Days
LD_{50} (organisms)	14 and 378	872 and 4,447
LD_{50} (particles)	14 and 28	11 and 8

[1]Data from Day and Berendt., 1972.

Particle Size-Dependent Ricin Intoxication

BALB/c mice[1]

Particle size	1.0 μm	5.0 and 12.0 μm
Exposed mice	48	48
Dose delivered (fixed)	~4.5 times the LD_{50}	~3.7 times the LD_{50}
Regional deposition (1-hr post-exposure)	60% lungs 20% trachea 10% nares 10% stomach	20% lungs 80% trachea
% affected	Ricin binds to almost all mammalian cells, allowing for effects on most cell types	
% fatal	100%	0%
Time to death	Within 72 hours	--

[1]Roy et al., 2003.

- The large particles lack regional deposition into pulmonary portion of lung
  - -Do not affect cell types necessary to induce a lethality

The Respiratory Tract Has Three Anatomical-Functional Regions

- Head (or extra-thoracic, ET) airways
  - Nose and mouth to the larnyx
  - Nasal airways and the oral cavity
- Tracheobronchial (TB) region
  - Larnyx to the terminal bronchioles
  - Ciliated epithelium, mucous-secreting
- Pulmonary (P) region
  - Respiratory bronchioles to the terminal alveoli
  - Gas-exchange epithelium, non-ciliated

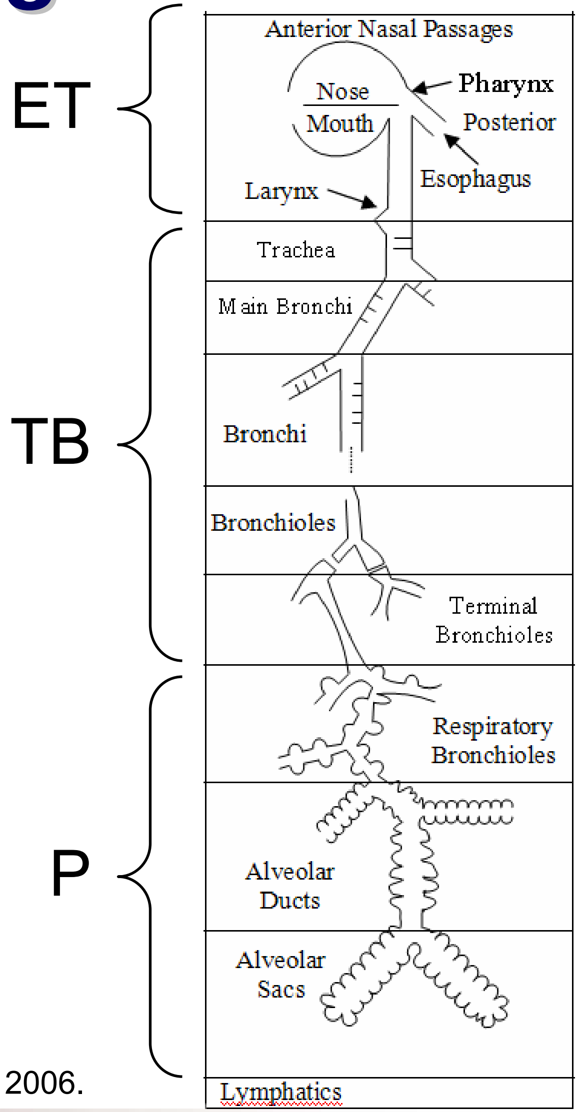


Illustration from Asgharian et al., 2006.

Deposition vs. Size Is Complex

Humans.
Nasal breathing.
Fraction of inhaled particles.

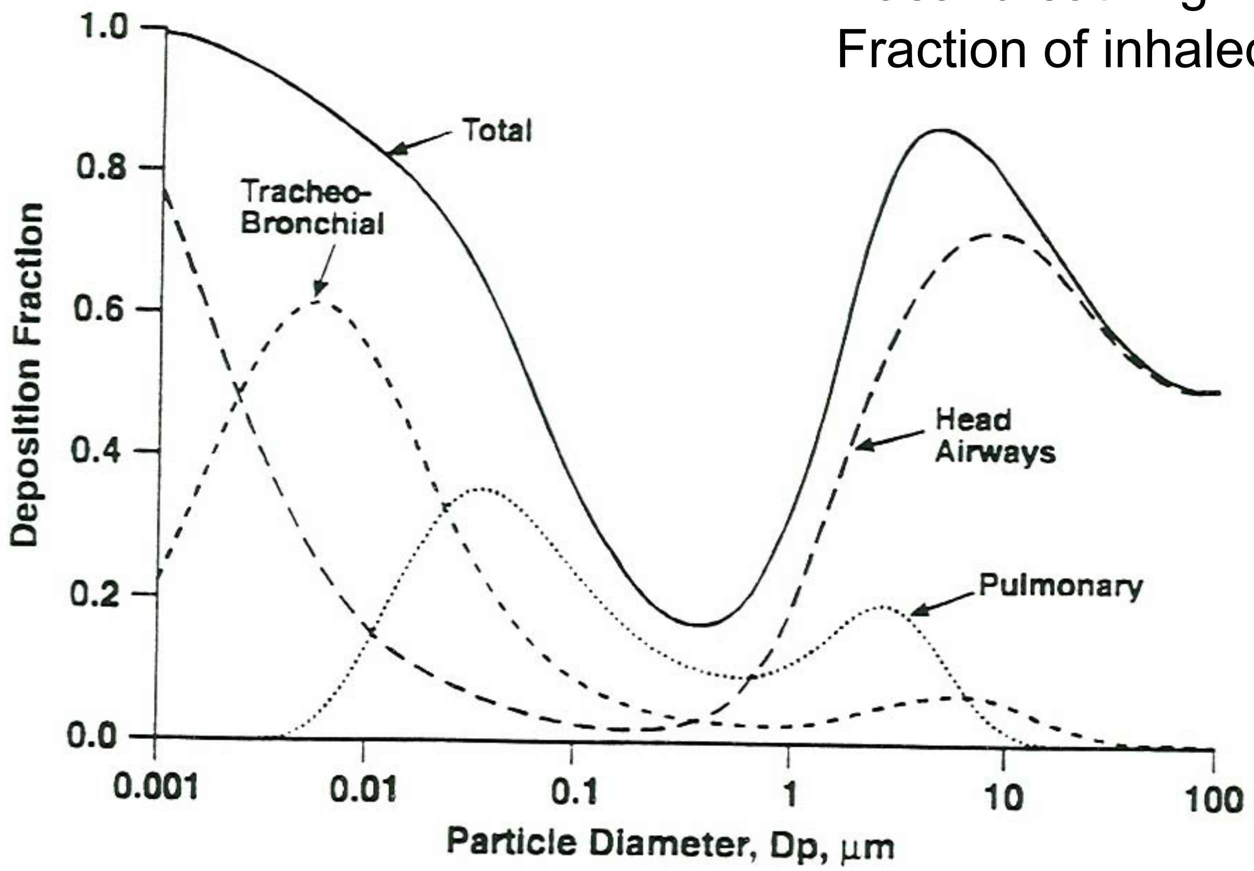
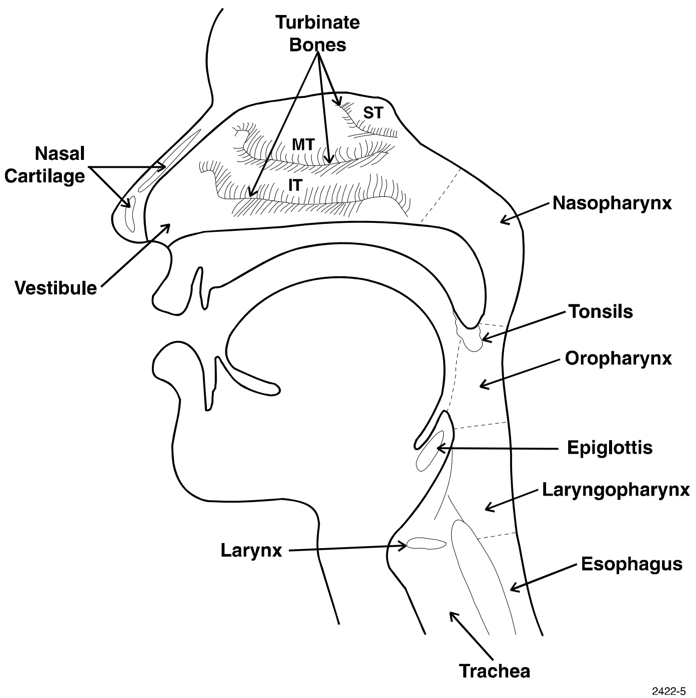


Illustration from Snipes, 1994.

Inhalability Factor Is Important for Particles Larger Than 3 - 5 μm

- Inhalability $I(d_{ae})$ measures likelihood of particle inspiration
- Nasal breathing only,
  - I approaches 0 for particles larger than 100 μm[1]
- Oronasal breathing,
  - I remains 0.5, even for particles 100-150 μm[2]

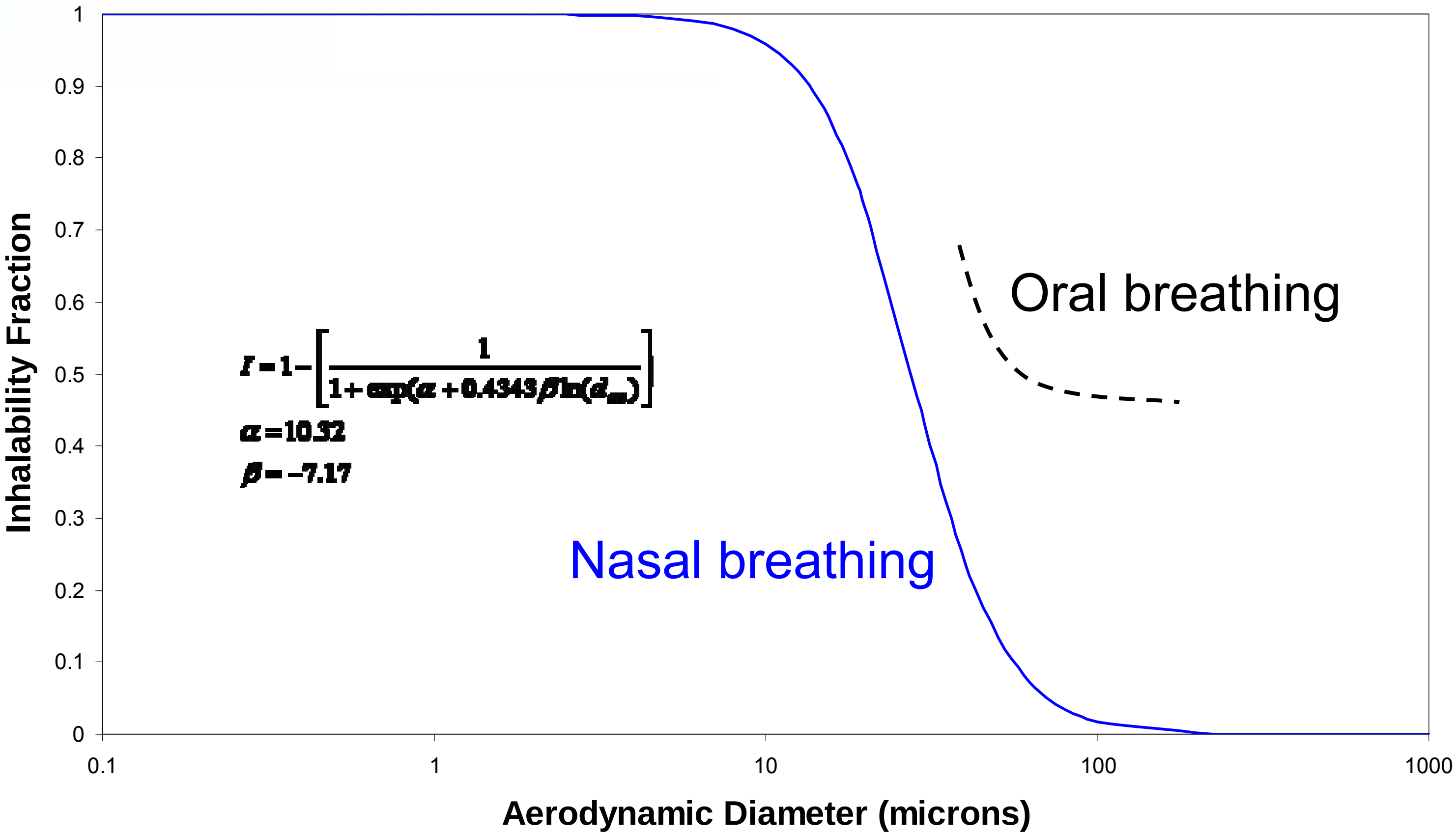
$$I(d_{ae}) = \frac{C_{inspired}(d_{ae})}{C_{ambient}(d_{ae})}$$



[1] Menache et al., 1995

[2] ICRP66, 1994

Inhalability Ratio Can Be Modeled[1]



$$I = 1 - \left[\frac{1}{1 + \exp(\alpha + 0.4343 \beta \ln(d_{ae}))} \right]$$

$\alpha = 10.32$

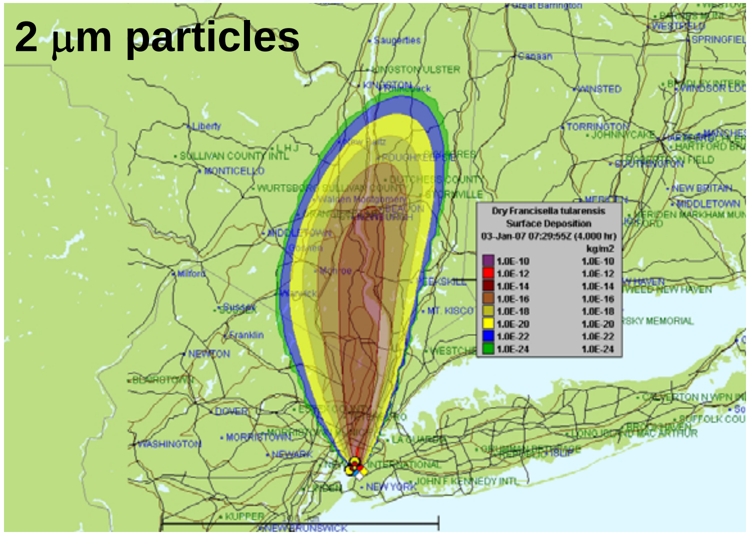
$\beta = -7.17$

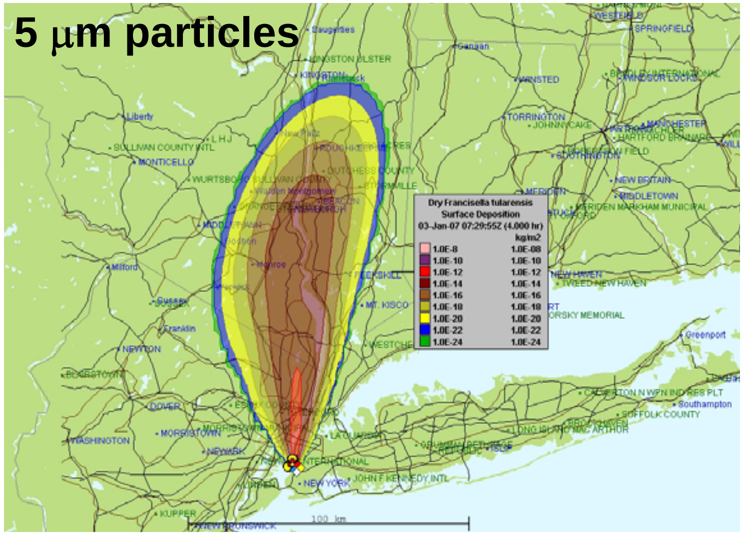
[1] Menache et al., 1995

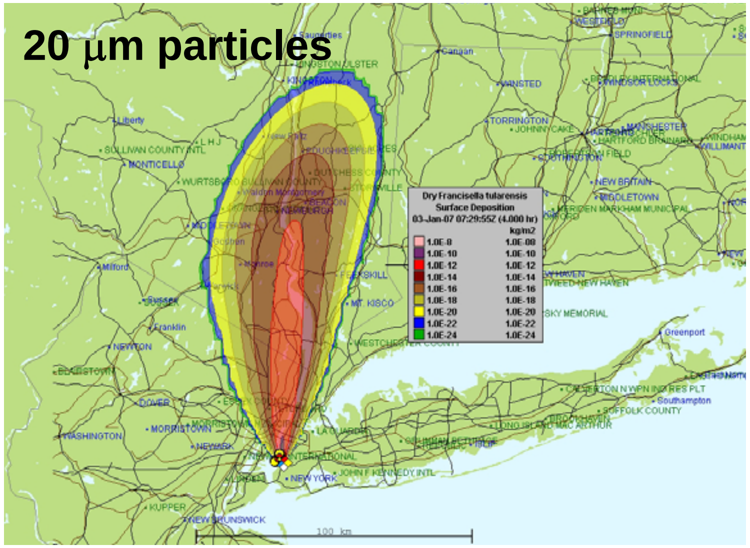
Particle Settling - HPAC Test Cases

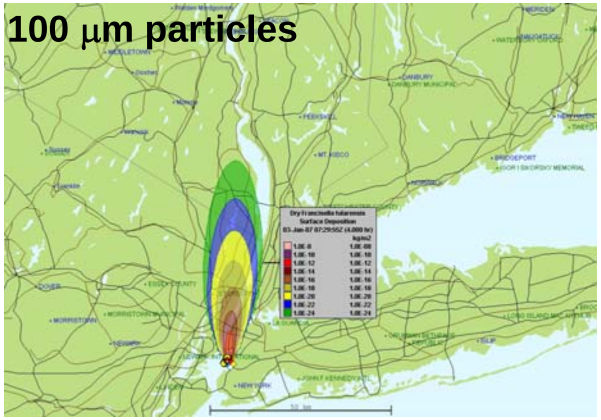
- *F. tularensis*, dry agent
- Missile with sub-munitions, close spread (10 m) to simulate single point release
- Particle sizes from 2, 5, 20, and100 microns
- Release mass fixed (1.6 kg dispersed)
- All releases at same location and time
- Historic winds

Surface Deposition @ 4hr

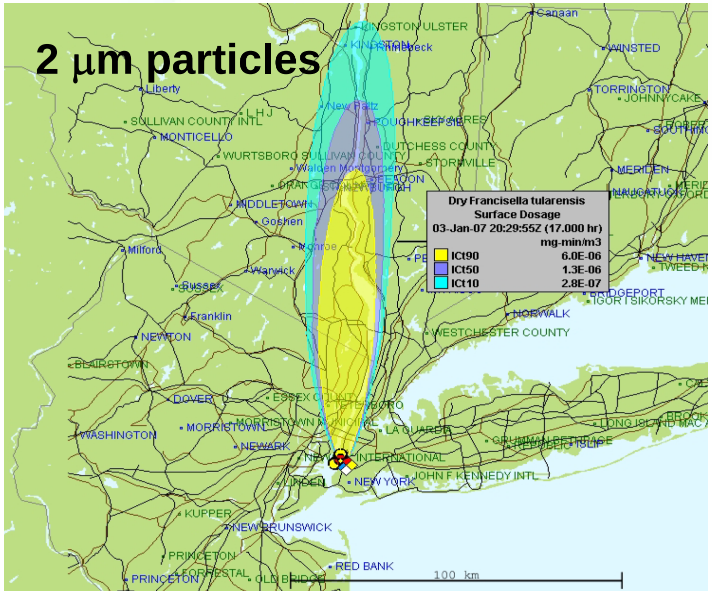


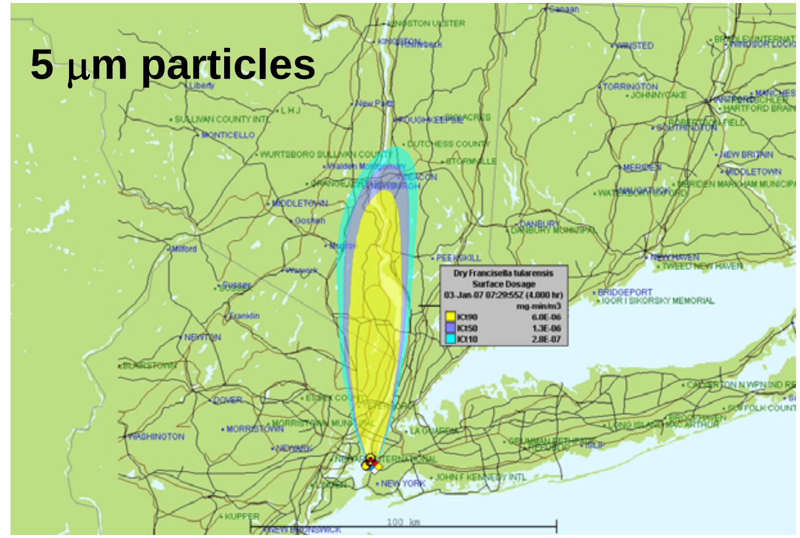


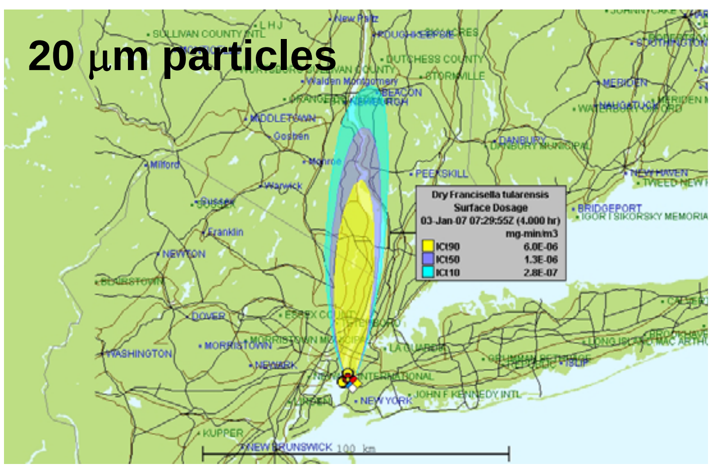


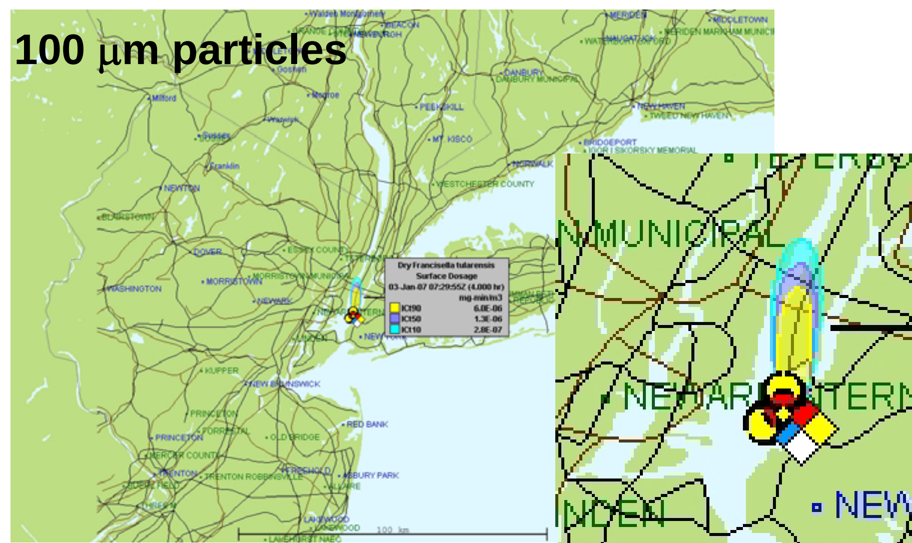


Surface Dosage @ 4 Hours









Inhalation and Biokinetics of Aerosols

- Deposition
  - Physical processes
  - Anatomy
  - Breathing mode
- Dissolution-absorption-colony formation
- Clearance

Physical Characteristics of Particles Affect Deposition Processes

- Deposition processes

- Physical characteristics
  - Aerodynamic size
  - Particle shape
  - Hygroscopicity
  - Electrical charge

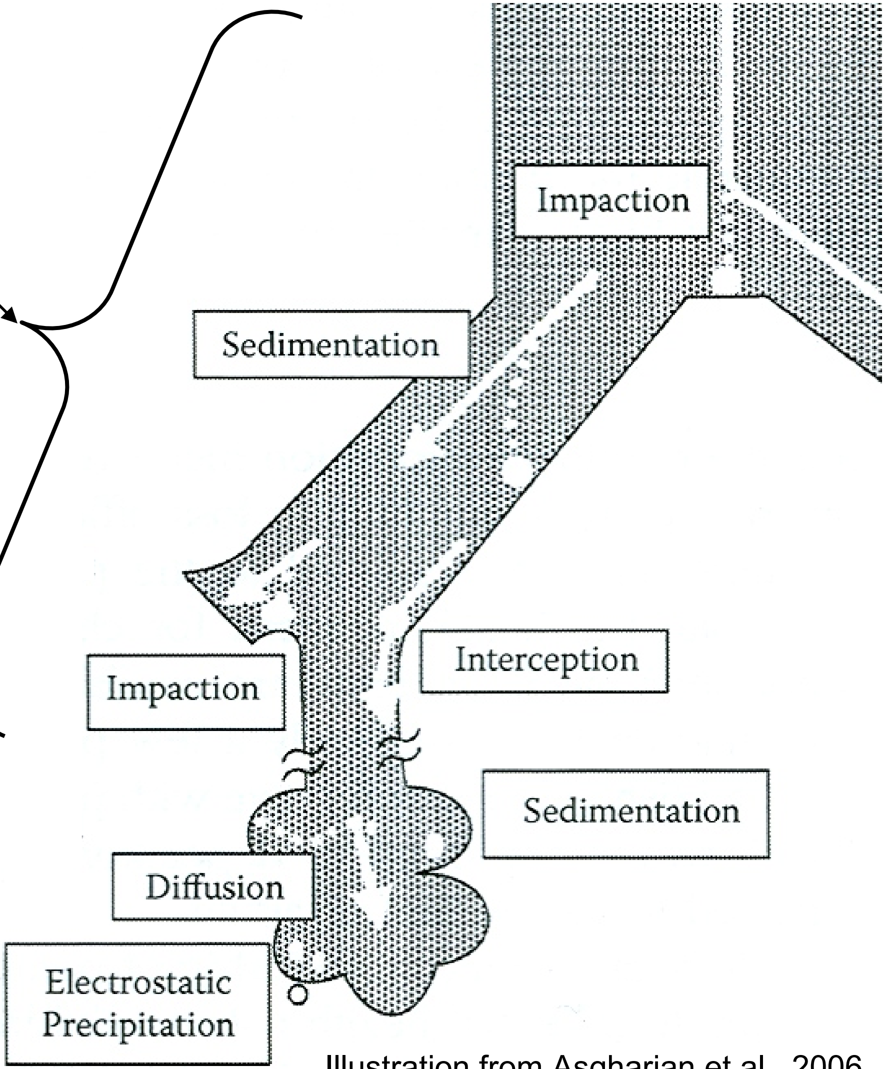


Illustration from Asgharian et al., 2006.

Respiratory Tract Anatomy and Geometry Influence Deposition

- Physical structure
  - Airway diameters
  - Branching patterns
  - Path length to alveoli
  - Structural dynamics
  - Response to biological or chemical stimuli
  - Inflammatory response
- Intersubject variability
- Breathing mode
  - Nasal
  - Oral

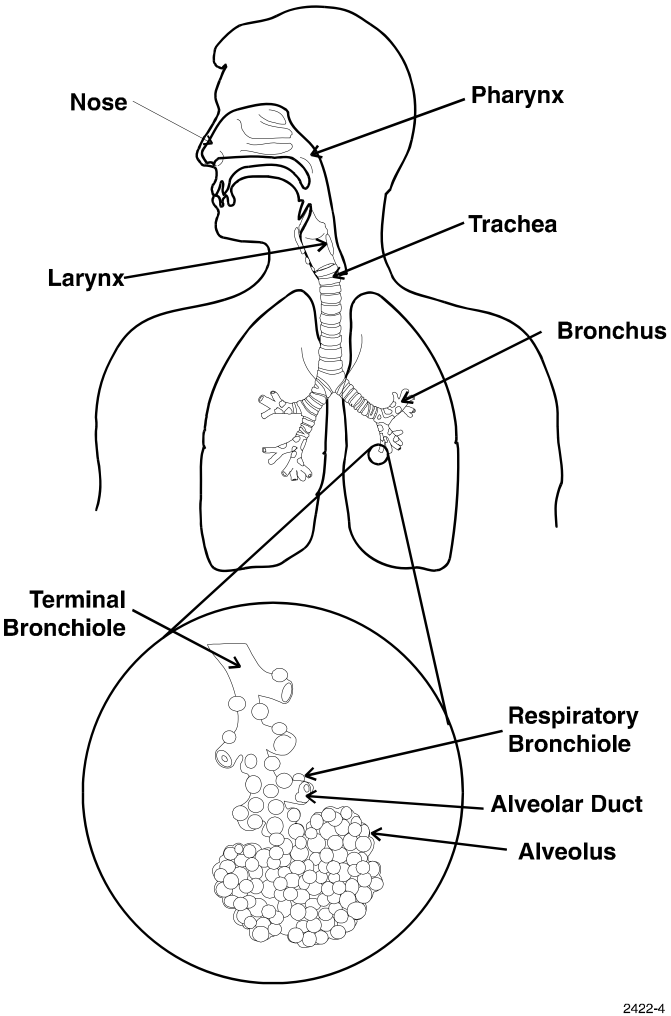


Illustration from ????.

Breathing Mode Has Major Impact on Particle Deposition Pattern

- Nasal breathing
  - Convoluted airways
  - Filter large and small
- Oral breathing
  - Increases TB and P exposure
  - Raises inhalability of larger particles
- Oronasal breathing
  - Linear combination
  - Varies with exertion

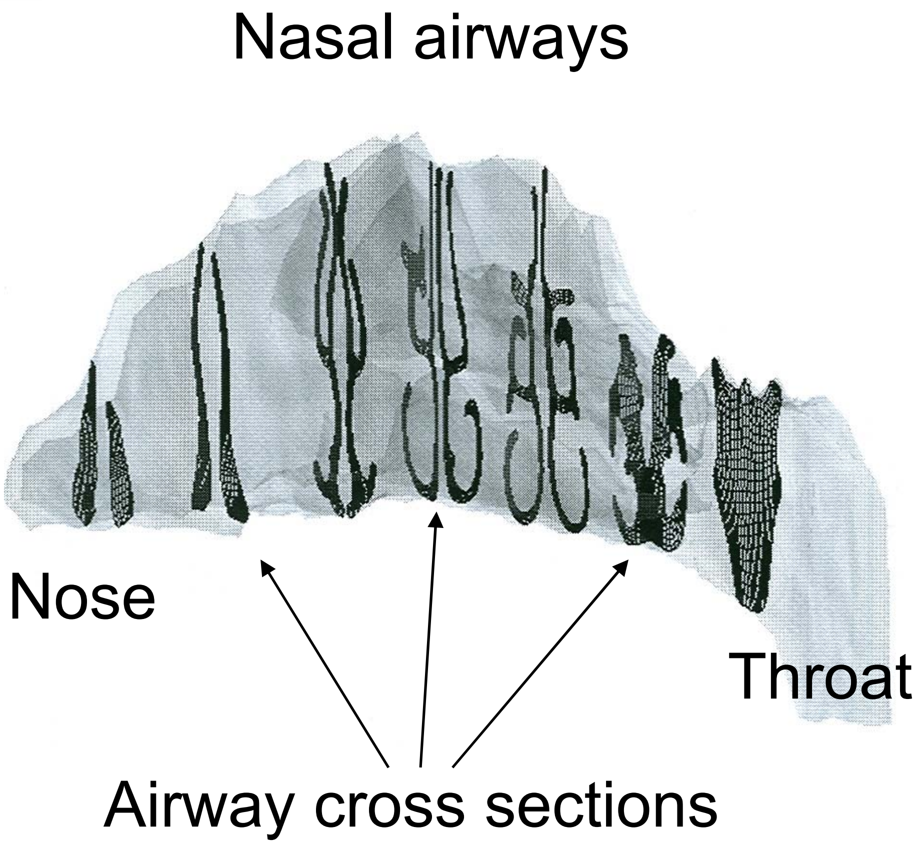
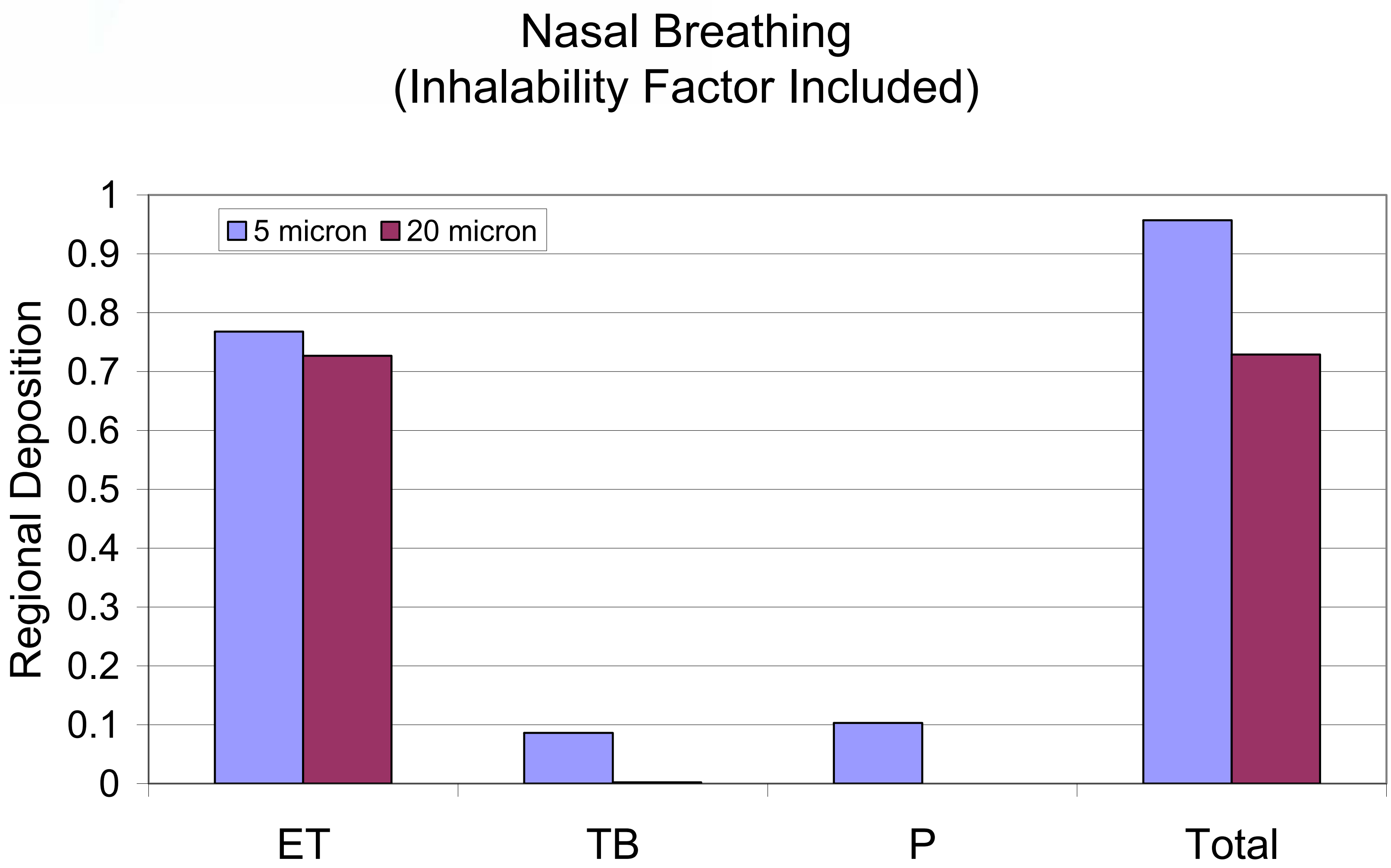


Illustration from Asgharian et al., 2006.

Clearance After Depostion

- Physical clearance
  - ET
    - Mostly swallowed
    - Some by blowing nose
  - TB
    - Mucociliary “elevator” → swallowed
    - 24 – 48 h clearance time
  - Pulmonary
    - Collection by macrophages
    - Slow clearance; months…
- Dissolution-absorption
  - Dependent on physical and chemical properties

Calculated Deposition for Humans Correlates With The Tularemia Data for Monkeys



Deposition calculated with MPPD (Asgharian et al., 2001).

Conclusion

- "Standard-sized" particles (3-5m) are most efficient as inhalation hazards
- Larger particles (10-25m) are quite effective for some agents, but not for all
- Medical outcome depends on particle size
  - Data shown for tularemia, ricin
  - Data exist for plague, anthrax, SEB, Q fever, brucellosis, and botulism
- Particle size-dependent effects can and should be included in medical modeling and simulation

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