

# **An Improved Model of Human Response to Aerosol Chemical and Biological Agent Hazards**

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Technology Conference***

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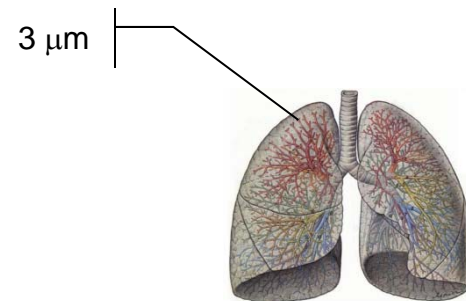
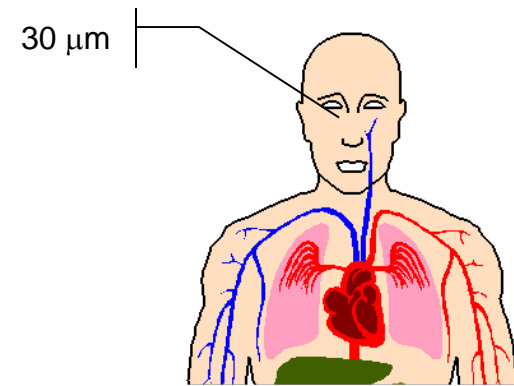
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# Project Objective

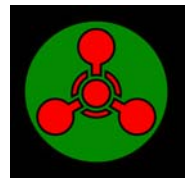
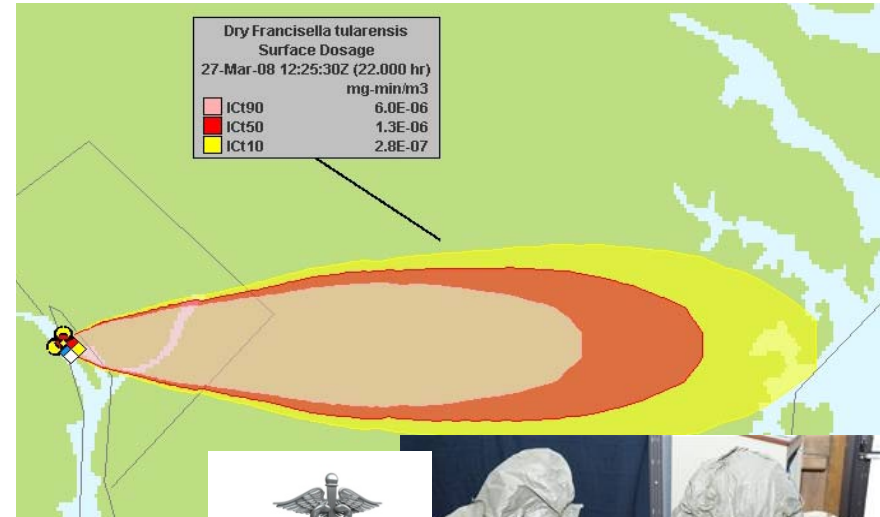
- Develop medical models for the influence of aerosol particle size on the health effects of inhaled CBRN hazards
- Improve casualty and patient modeling for DoD Consequence Assessment tools





# We Are Improving Current Approximations

- 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
  - 3-5 micron particles optimize lung deposition
- The actual situation is more complicated
  - Although 3-5 micron particles do optimize lung deposition, far less than 100% deposit
  - Large particles can cause illness elsewhere
  - Small (nanometer-scale) particles are retained





# The Respiratory Tract Has Three Anatomical-Functional Regions

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

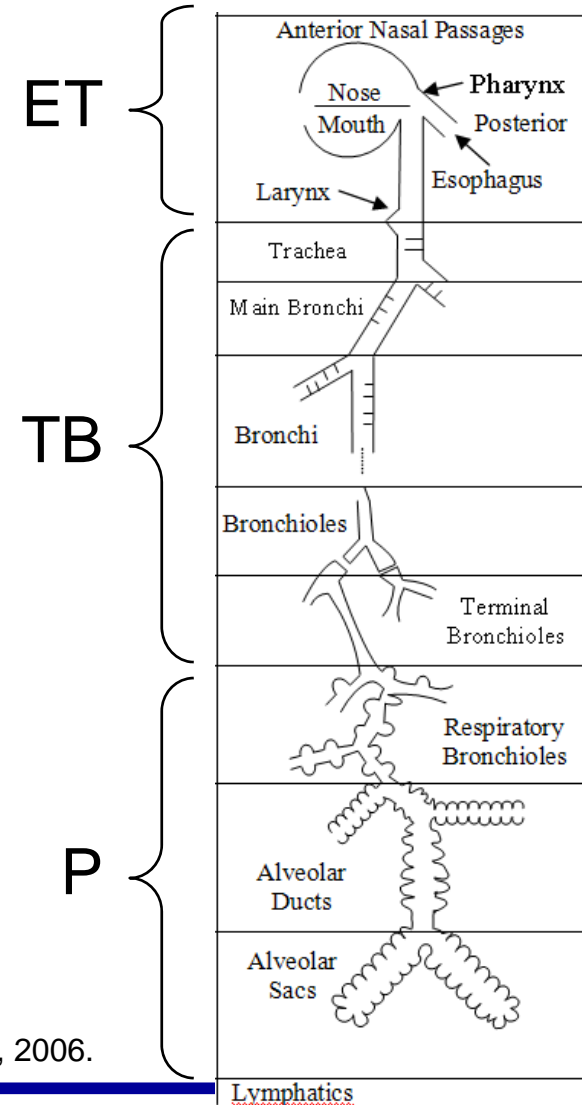


Illustration from Asgharian *et al.*, 2006.



# Physical Processes Govern Deposition

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

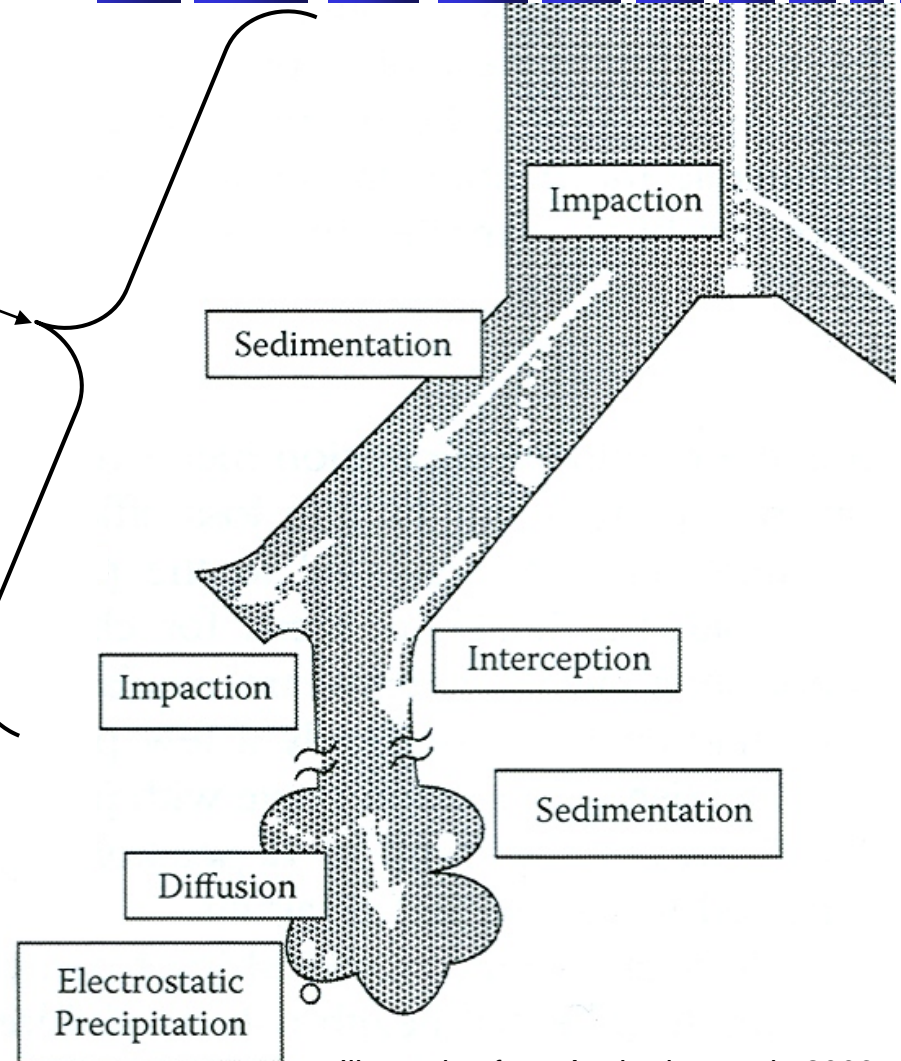


Illustration from Asgharian et al., 2006.



# We Use the Multiple Path Particle Dosimetry (MPPD) Model for Particle Deposition Calculations

- Includes multiple human lung-model geometries
  - Symmetric
  - Asymmetric – 5 lobe
  - Age-specific
  - Stochastic – 5 lobe
- Also includes a rat model
- Useful for basic calculations, but will also enable uncertainty analysis



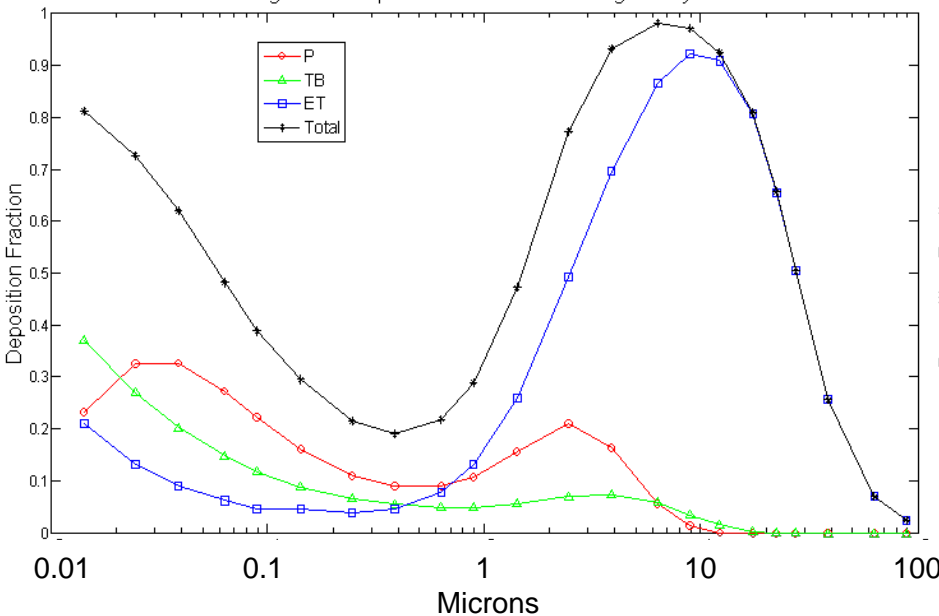
Developed and implemented modifications to MPPD to meet the needs of DARRT



# Breathing Mode Changes the Respiratory Deposition Pattern

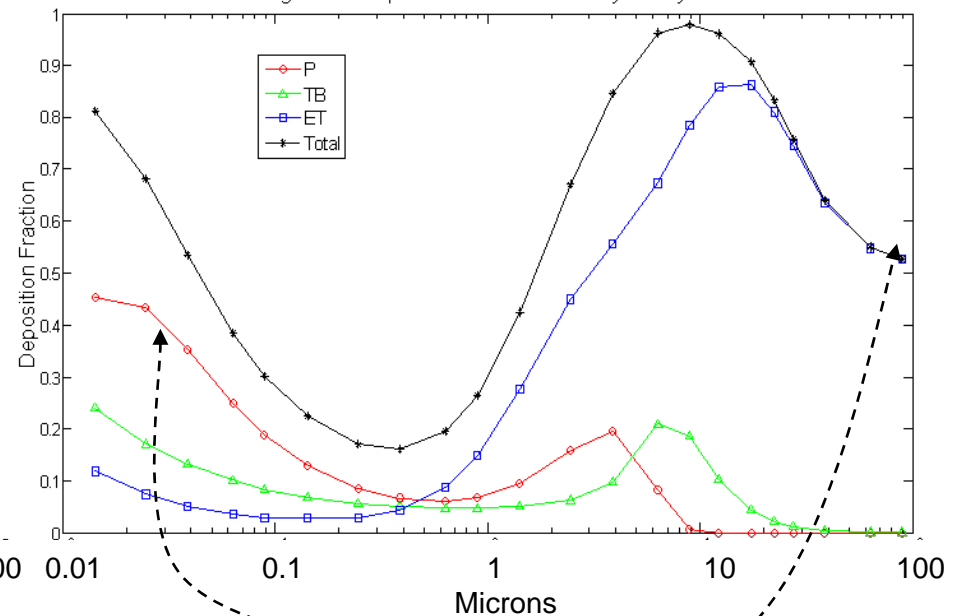
## Resting Activity in Still Air

Nasal Augmenter - Deposition Fractions for Resting Activity in Still Air



## Heavy Activity in Still Air

Nasal Augmenter - Deposition Fractions for Heavy Activity in Still Air



- Increased mouth breathing
  - More small particles deposit in the P region
  - More large particles deposit in the ET region



# Schematic for Model of Deposition and Response in the Respiratory Tract (DARRT)

## Data Input

- *JEM Material Files*
- *Mass of Agent by Particle Size*
- *User Set Parameters*

- Calculate the amount of material inhaled and deposited by region;
- Predict the probability of effects based on regional deposition

## Particle/Droplet Characteristics

- *Calculate Number of Particles*
- *Agent Containing Probability Calculation*
- *Liquid/Vapor Components*

## Respiratory Mechanics Calculations

- *Inhalability*
- *Respiratory Tract Deposition*

## Human Response Calculations

- *Probability of Infection/Effect*
- *Disease/Damage Site*
- *Probability of Mortality*



# Given Location of Particle Deposition and Probability of ACP, Predict Probability of Infection

- Limited human response data with particle size dependence
  - Operation White Coat studies (Saslaw, 1961)
- Many studies with particle size information were conducted with rhesus monkeys
  - Used in vaccine and other studies
  - Studies show distinctly different infection patterns depending on particle size (Day and Berendt, 1972)
    - Pulmonary
    - Extrathoracic
    - Ocular
  - The rhesus animal model is considered adequate because the respiratory structure and biological response are similar to humans (Hislop A, et al, 1983)



# We Know Particle Size Affects Deposition Location; Why Does it Matter?

*Macaca mulatta* (rhesus) monkeys exposed to *Pasteurella tularensis*<sup>1</sup>

Particle size:	2.1 and 7.5 $\mu\text{m}$	12.5 and 24.0 $\mu\text{m}$
# of animals exposed	48	45
% Infected	100%	84%
Primary infection site	Lower respiratory system, pneumonitis	Upper respiratory tract, nasal pharyngeal area, cervical and mandibular lymph nodes; eyes, also (15%)
Onset of illness	2-3 days	6-10 days
% fatal (of those ill)	69%	63%
Time to death	4-8 days	8-21 days
LD <sub>50</sub> (organisms)	14 and 378	872 and 4,447
LD <sub>50</sub> (agent-containing particles - ACPs)	14 and 28	11 and 8

“In conclusion, a change in the particle size distribution ... produced different clinical symptoms.”

<sup>1</sup>Day and Berendt., 1972.



# Tularemia Example Results: PSD 10 $\mu\text{m}$ median diameter, $\sigma_g = 2$

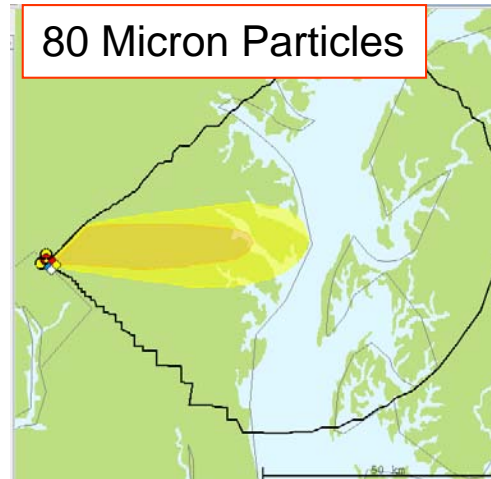
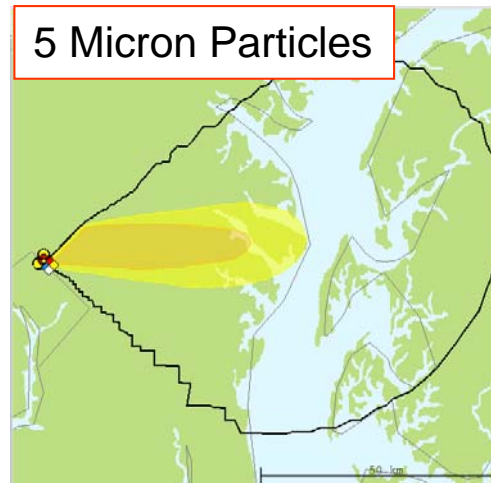
	Current Model	New DARRT Model		
	Probability of Infection	Probability of P Infection	Probability of ET Infection	Probability of Either ET or P Infection
Sampler Pt 1	93%	20%	75%	80%
Sampler Pt 2	60%	2%	38%	39%
Sampler Pt 3	18%	0.05%	11%	11%

ET and P infections manifest differently regarding onset time and patient presentation.



# Current Material Files Prevent Accurate Transport and Dispersion

- Incident modules allow definition of particle size distribution
- However, dry bioagents have only a single 5  $\mu\text{m}$  “bin” defined
- All material placed in this bin



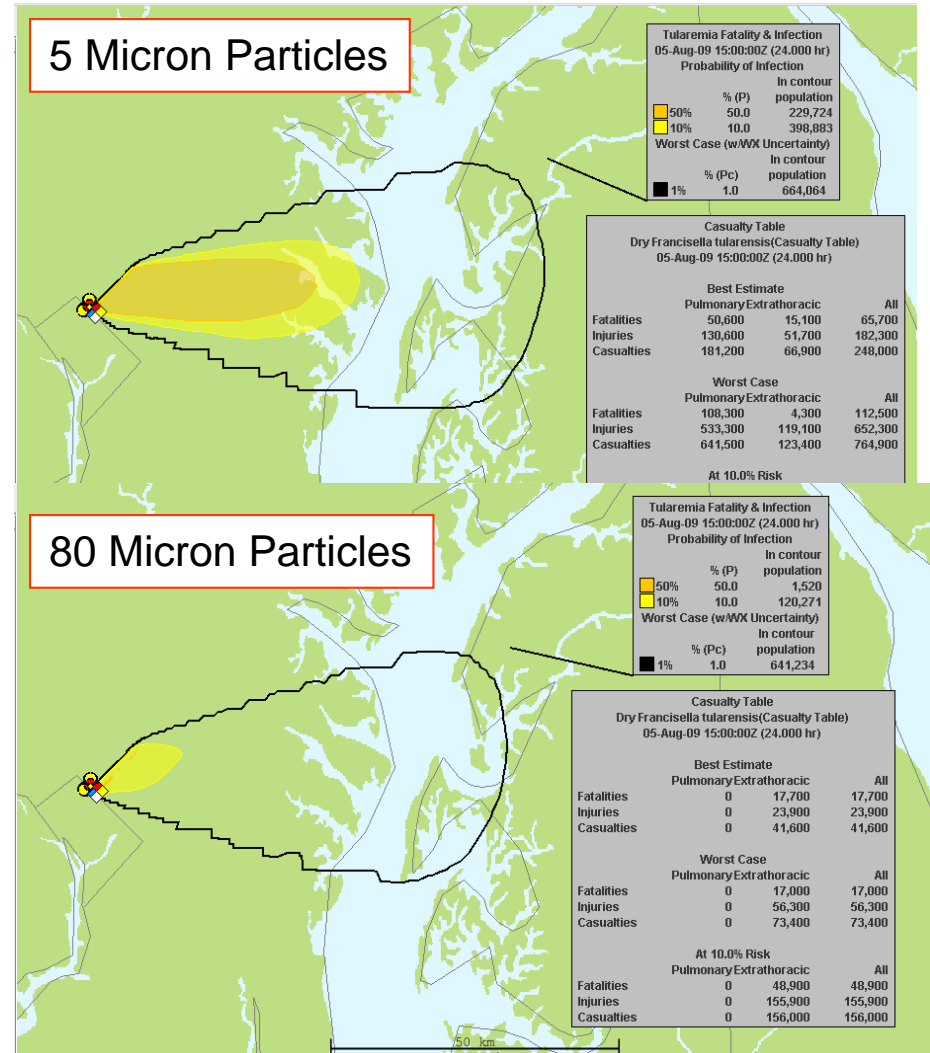
Casualty Table	
Dry Francisella tularensis(Casualty Table)	
05-Aug-09 15:00:00Z (24,000 hr)	
<b>Best Estimate</b>	
	No Protection
Fatalities	76,800
Injuries	131,500
Casualties	208,300
<b>Worst Case</b>	
	No Protection
Fatalities	251,800
Injuries	470,700
Casualties	722,500
<b>At 10.0% Risk</b>	
	No Protection
Fatalities	844,800
Injuries	911,400
Casualties	956,000

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# New Material File Bin Structures are Used for DARRT

- New material files for dry-particle agents include 22 bins
  - Smallest bin 0.01 – 0.02 microns
  - Largest bin is 80 – 100 microns
- Allows proper transport and dispersion
- Allows proper inhalation mechanics





# Number and Nature of Casualties Depends on Aerosol Particle Size

5 micron particles

Casualty Table			
Dry Francisella tularensis(Casualty Table)			
05-Aug-09 15:00:00Z (24.000 hr)			
Best Estimate			
	Pulmonary	Extrathoracic	All
Fatalities	50,600	15,100	65,700
Injuries	130,600	51,700	182,300
Casualties	181,200	66,900	248,000

80 micron particles

Casualty Table			
Dry Francisella tularensis(Casualty Table)			
05-Aug-09 15:00:00Z (24.000 hr)			
Best Estimate			
	Pulmonary	Extrathoracic	All
Fatalities	0	17,700	17,700
Injuries	0	23,900	23,900
Casualties	0	41,600	41,600

*(Pulmonary infections given precedence in casualty tables.)*



# Developed a Probability of Mortality Model for Inhaled Ricin

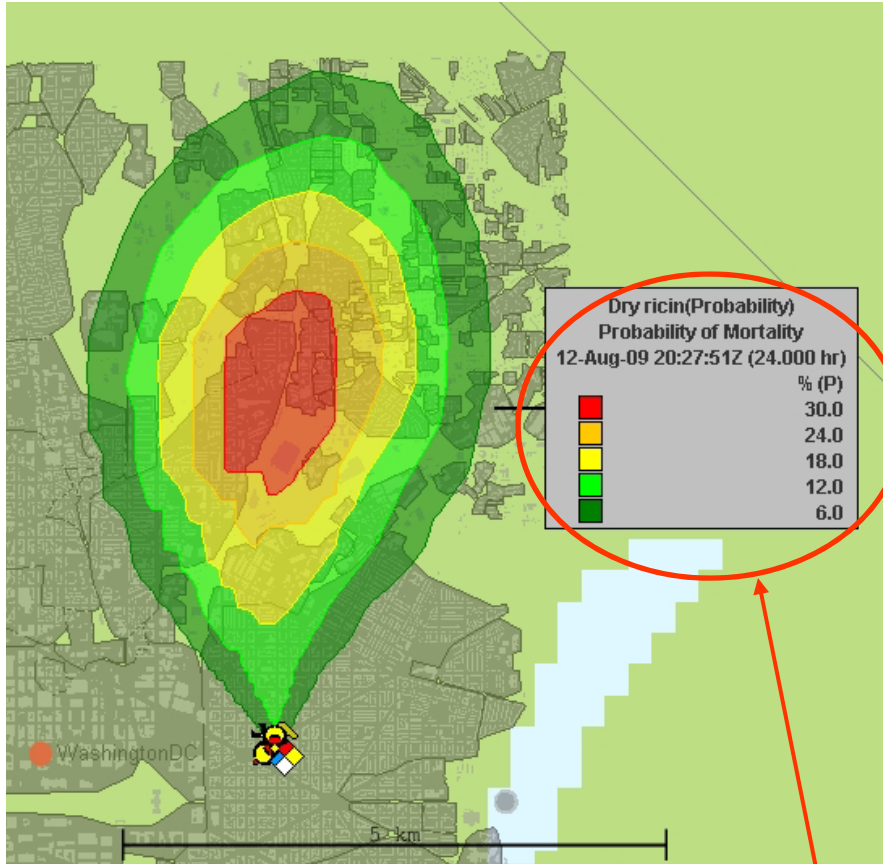
- Studies show that only pulmonary deposition poses a substantial inhalation risk for mortality\*
- Therefore, ricin dose deposited in the lung scaled by body mass ( $\mu\text{g}/\text{kg}$ ) is used for the probability of mortality calculation
- Compared data from mice and rats
  - $\text{LD}_{50}$  (in  $\mu\text{g}/\text{kg}$ ) values agree within a factor of 2
- Mouse model is most conservative
  - $\text{LD}_{50}$  is  $0.26 \mu\text{g}/\text{kg}$ ; probit slope of 42 ( $\log_{10}$ ) is quite steep

\* Griffith et al, 1993; Roy et al, 2002; Leffel et al, 2007

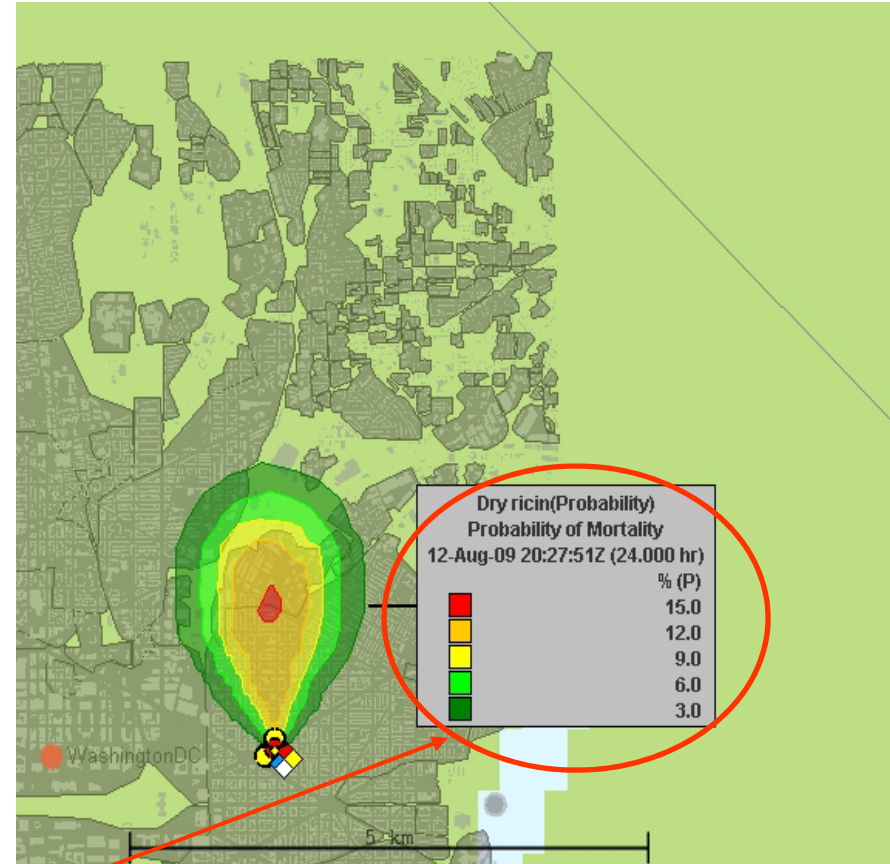


# The Probability of Mortality is Significantly Lower for Larger Particles\*

## • 5 Micron Particles



## • 10 Micron Particles



\*Note Differences in Scale

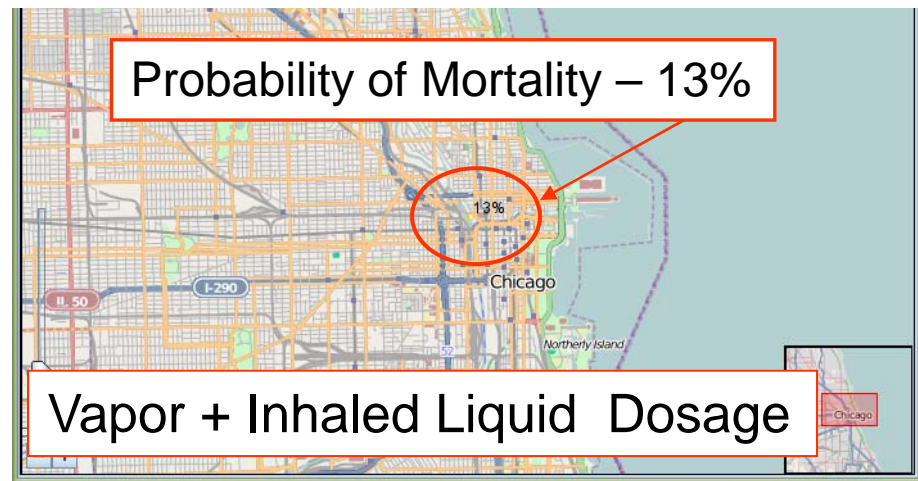
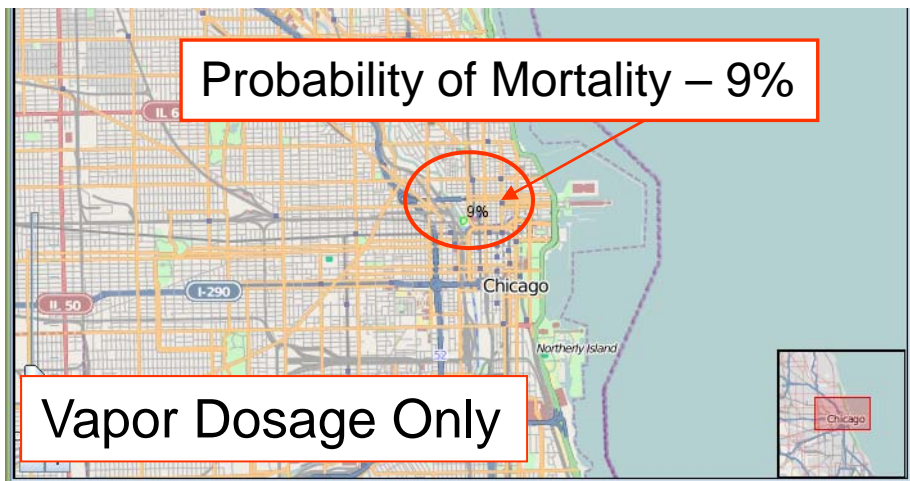
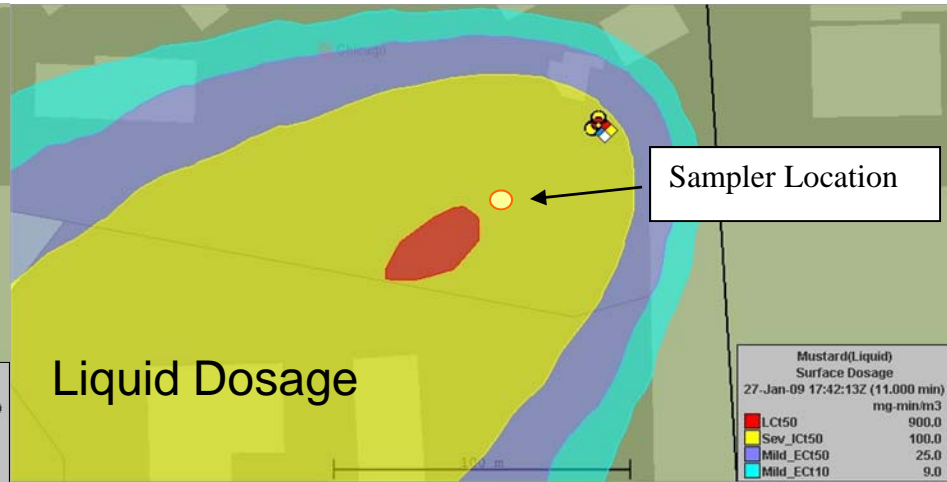
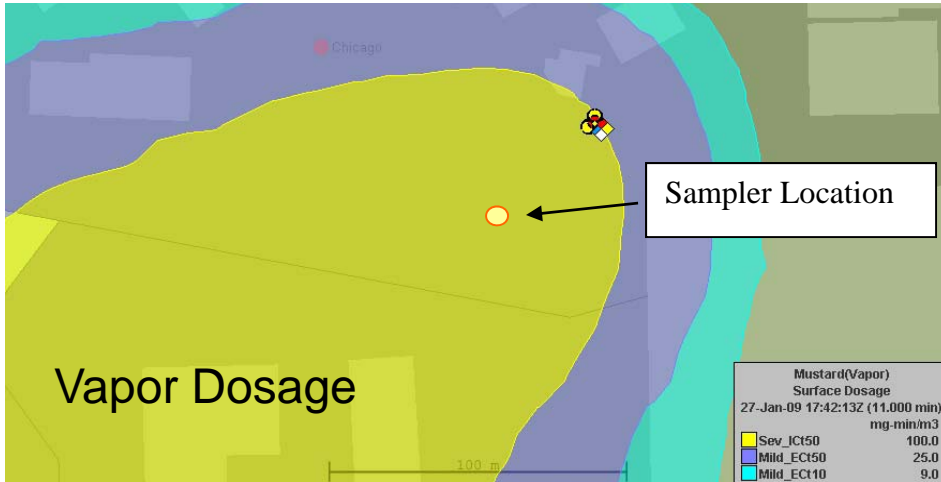


# DARRT Will Include Inhalation of Liquid Droplets for Volatile Chemical Agents

- Current chemical agent response model accounts for skin deposition, ocular deposition and vapor inhalation
- Not yet able to access size distribution for liquid droplets
- New prototype includes a simplified model to account for liquid droplet inhalation
- Assume deposited droplets create a mass-equivalent vapor inhalation source term



# Probability of Mortality Increases When Liquid Droplet Inhalation is Included





# Summary and Conclusions

- New DARRT model can significantly improve human response modeling for DoD consequence modeling tools
- Although “standard-sized” particles (3-5 $\mu\text{m}$ ) are most efficient as inhalation hazards, larger particles (10-25 $\mu\text{m}$ ) can be quite effective for some agents, but not for all
- Prototype model illustrates tularemia infectivity correlation with the number of agent containing particles deposited by region
- Liquid droplet chemical agent model and biological wet-agent models require architectural changes in JEM
- Although collecting adequate human response data is a challenge, particle size-dependent effects can and should be included in medical modeling and simulation



# References

- Anno, GH and Deverill AP (1997) Consequence Analytic Tools for NBC Operations Vol 1- Biological Agent Effects and Degraded Personnel Performance for Tularemia, Staphylococcal Enterotoxin B (SEB) and Q-Fever, DSWA-TR-97-61-VI, Defense Special Weapons Agency, Alexandria, VA.
- Asgharian, B., W. Hofmann, and F. J. Miller, (2006). Dosimetry of particles in humans: from children to adults. In Gardner, D.E., Toxicology of the Lung, 4th ed. Boca Raton: CRC Press, pp. 151-194.
- Asgharian, B., Hofmann, W., and Bergmann, R. (2001). Particle deposition in a multiple-path model of the human lung. *Aerosol Sci. Technol.* 34: 332-339.
- Blungell, GP. (1962). Response of Monkeys to *Pasturella tularensis*: Histopathology of Tularemia Induced with Aerosols of Different Particle Size. Army Tech Memo 20. Brown JS (2005) Particle inhalability at low wind speeds. *Inhalation Toxicology* 17:831-837.
- Day, WC, GW Pirsch, CW Beard et al. (1960b). Influence of Aerosol Particle Size on Respiratory Infectivity. II. Exposure of Rhesus Monkeys to Aerosols of *Pasturella tularensis*. BL Tech Memo 9-20.
- Day, WC. (1969). Aerosol Particle Size Research: A Critical Review. Army Tech Study 69.
- Day, W.C., and Berendt, R.F. (1972). Experimental tularemia in *Macaca mulatta*: relationship of aerosol particle size to the infectivity of airborne *Pasteurella tularensis*. *Infection and Immunity.* 77-82.
- Druett, H.A., et al. (1953). The influence of particle size on respiratory infection with anthrax spores. *J. Hyg. (Cambridge)* 51:359-371
- Druett, H.A., et al. (1956). Studies on respiratory infection: II. The influence of aerosol particle size on infection of the guinea pigs with *Pasteurella pestis*. *J. Hyg. (Cambridge)* 53:37-48



# References, Con't.

- Druett, H.A., et al. (1956). Studies on respiratory infection: III. Experiments with *Brucella suis*. *J. Hyg. (Cambridge)* 54(1):49-57
- Griffiths, G.D., Lindsay, C.D., Rice, P. and Upshall, D.G., (1993) The Toxicology of Ricin and Abrin Toxins – Studies on Immunisation Against Abrin Toxicity, *Proceedings of the Medical Defense Bioscience Review*, pp.: 1407 – 1416.
- ICRP. (1994) Human respiratory tract model for radiological protection. ICRP Publ 66. *Annals of ICRP*. 24: 23.
- Leffel, E.K., Hartings, J.M., Pitt, M.L.M, and Stevens, E. (2007) Comparison of Deposition Patterns for Small and Large Particle Aerosolized Toxins and Resulting Disease in Guinea Pigs and African Green Monkeys, In *Defence Against the Effects of Chemical Hazards: Toxicology Diagnosis and Medical Countermeasures, Meeting Proceedings RTO-MP-HFM-149*, pp. 11-1 – 11-12.
- Hislop A, et al (1983) Morphometric studies on the structural development of the lung in *Macaca fascicularis* during fetal and postnatal life, *J. Anat.*(1984), 138, 1:95-112.
- Millage, K., Bergman, J., Asgharian, B., McClellan, G., “A Review of Inhalability Fraction Models: Discussion and Recommendations”, *Inhalation Toxicology*, 2009 (In Press)
- Niinimaa V, et al (1981) Oronasal Distribution of Respiratory Airflow. *Respiratory Physiology* 43:69-75.
- Roy, C.J., Hale, M., Hartings, J.M., and Pitt, L. (2003). Impact of inhalation exposure modality and particle size on the respiratory deposition of *ricin* in *BALB/c* mice. *Inhalation Toxicology*. 15:619-638
- Saslaw, S, et al. 1961. Tularemia Vaccine Study: II – Respiratory Challenge. *Arch Ind Med* 107:134-146.
- Rep. Accession Number ADB254692, unclassified (DoD distribution only)