

Aerosol Dosimetry and Extrapolation between Species

International Aerosol Conference
Bioaerosols II - Research Challenges
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Michael J. Oldham



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Outline

- In Vitro
 - Submerged Cultures
 - Air-Liquid Interface (ALI)
- In Vivo
 - Anatomical Considerations
 - Clearance Considerations
 - Biomarkers
- Conclusions



Goal – In vitro

- Know the intracellular dose that results in the observed in-vitro/ex-vivo response?
- Know the cell surface dose that results in the observed in-vitro/ex-vivo response?
- Know the cell exposure concentration that results in the in-vitro/ex-vivo observed response?
- Know the intended exposure concentration that results in the in-vitro/ex-vivo observed response?



Submerged Cultures - Dosimetry

- ISDD: (In-vitro Sedimentation, Diffusion Dosimetry) model by Hinderliter et al., 2010 & ISD³ Thomas et al., 2018

R = gas constant

T = temperature

Na = Avogadro's #

μ = media viscosity

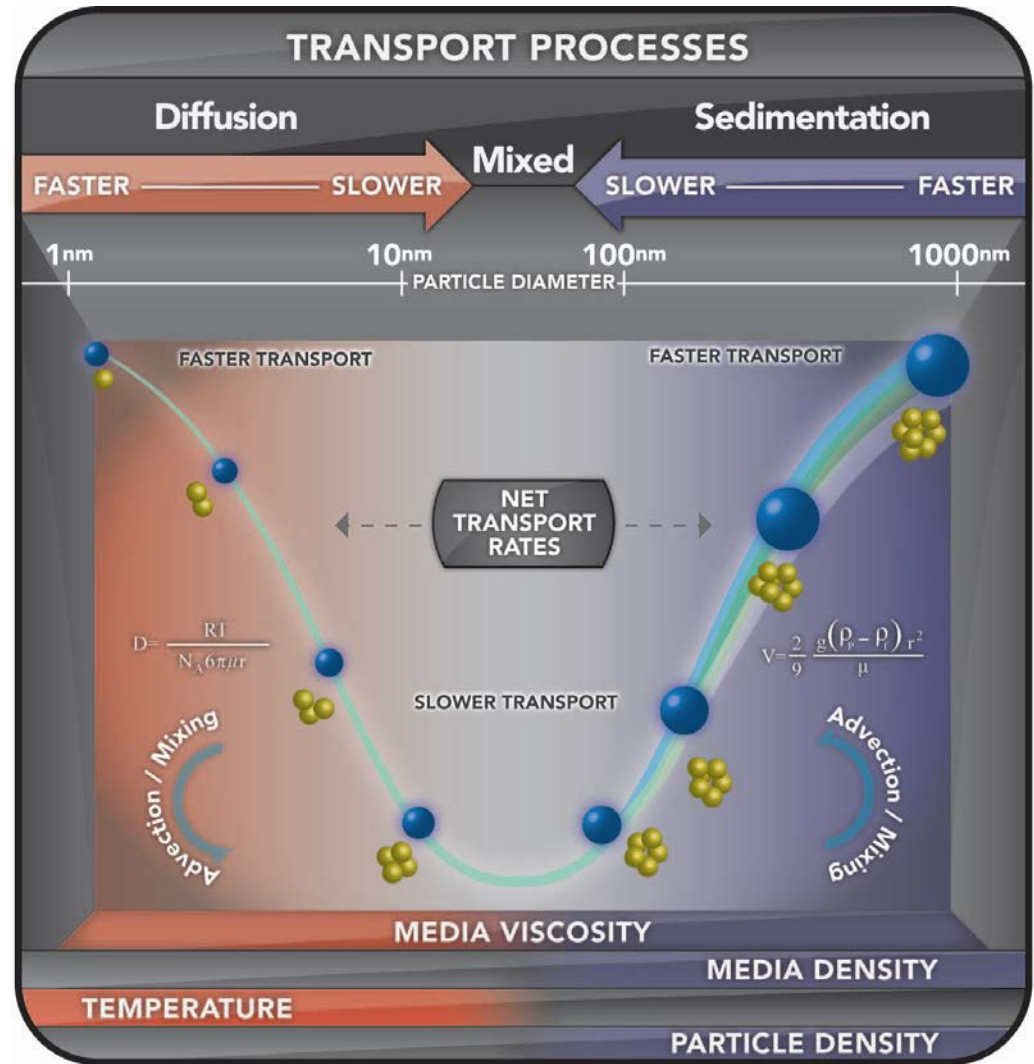
r = particle radius

g = gravitational acceleration

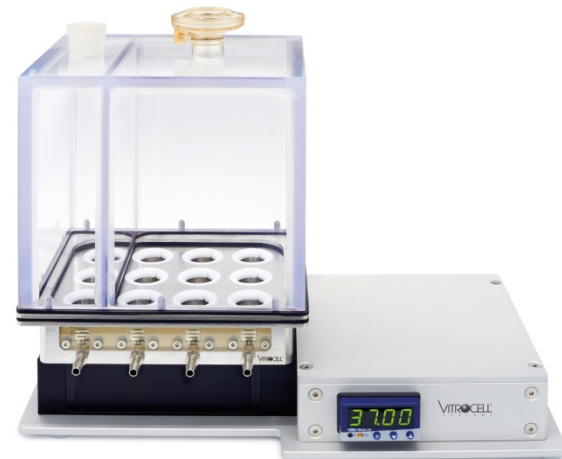
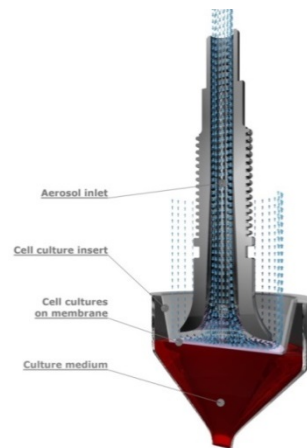
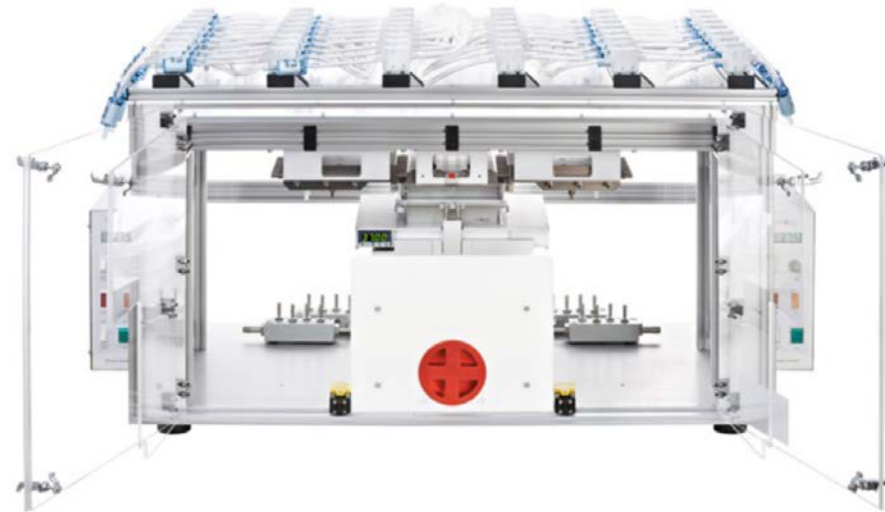
ρ_p = particle density

ρ_f = fluid density

L = total media height



Air Liquid Interface - Dosimetry



Pictures and Diagrams Courtesy of Vitrocell Systems GmbH



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Goal – In vivo

- Know the target cell(s) dose ($\mu\text{g}/\text{mm}^2$ per unit time) within the respiratory tract that results in the observed in-vivo response?



- Know the regional respiratory target surface dose ($\mu\text{g}/\text{mm}^2$ per unit time) that results in the observed in-vivo response?



- Know the total respiratory tract dose ($\mu\text{g}/\text{unit time}$) from an exposure concentration ($\mu\text{g}/\text{m}^3$) that results in the in-vivo observed response?

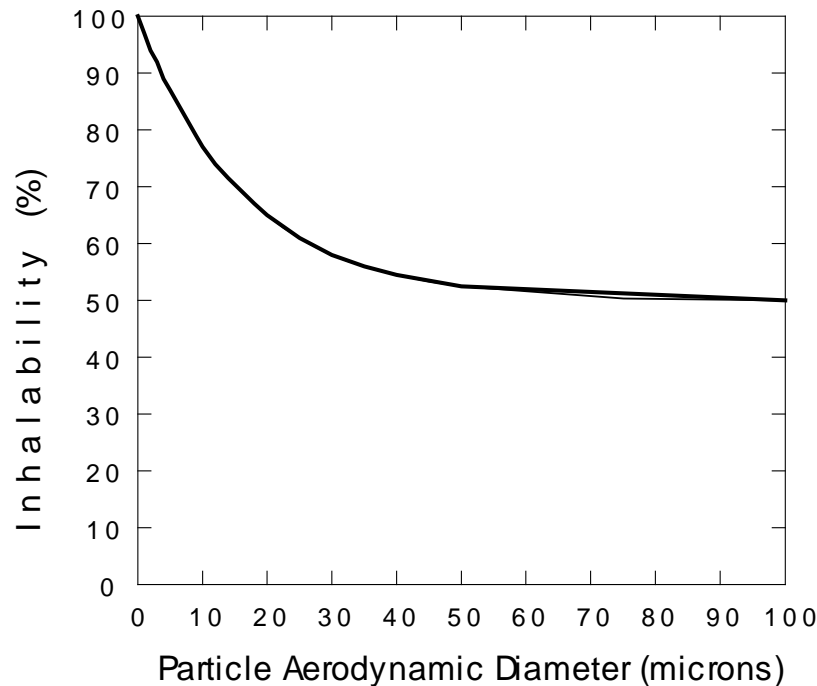


- Know the intended exposure concentration ($\mu\text{g}/\text{m}^3$) that results in the in-vivo observed response?

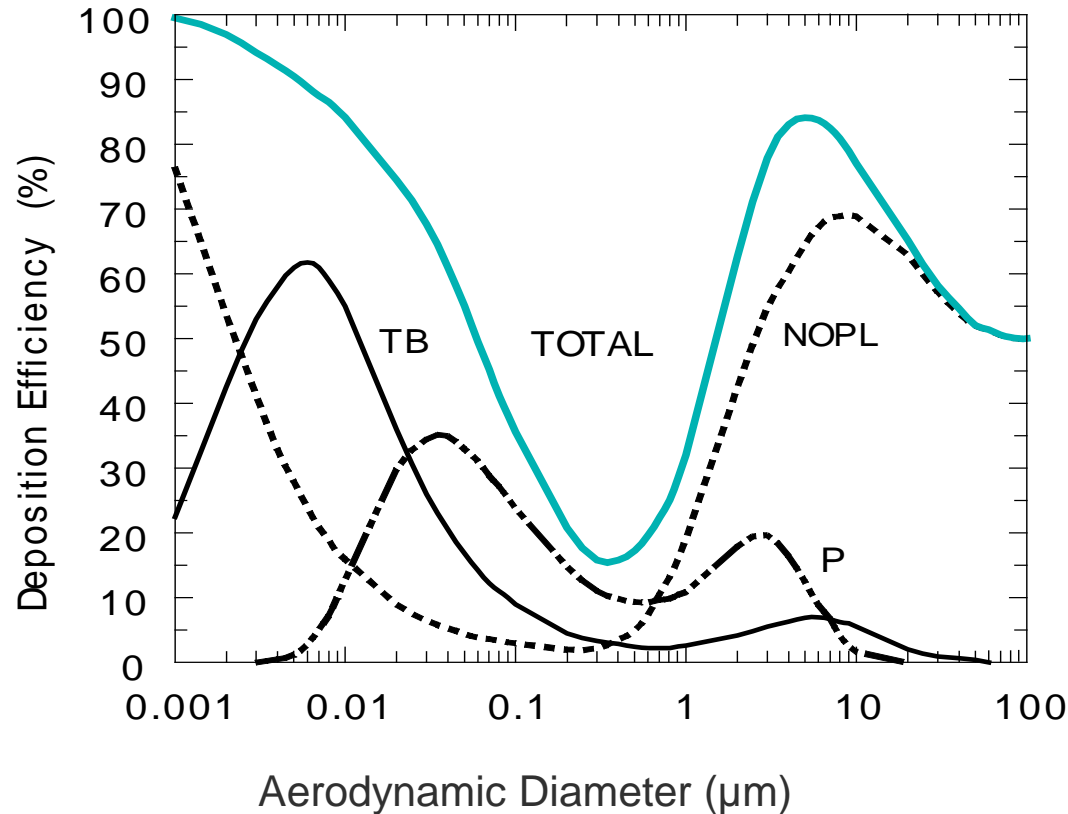


In-vivo Anatomical Considerations

- Inhalability – particle sampling efficiency of the entrance airways (nose and mouth)
 - Human – averaged over all wind angles (0-360°) and low wind speeds (ACGIH®, 2001)



In-vivo Anatomical Considerations



NOPL = nasal-oral-pharyngeal-laryngeal; TB= tracheobronchial; and P=pulmonary

Predicted Particle Deposition in Regions of the Human Respiratory Tract during Normal Respiration (NCRP, 1997; adapted from Phalen 2002)



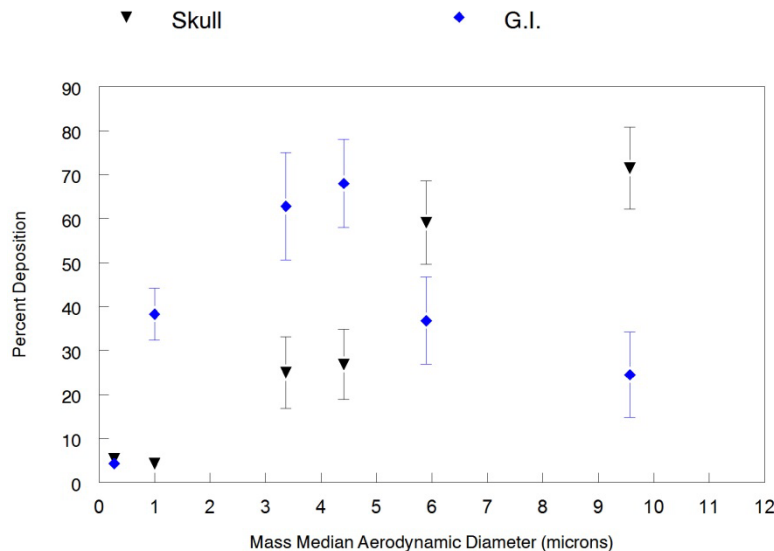
In-vivo Anatomical Considerations

■ Inhalability

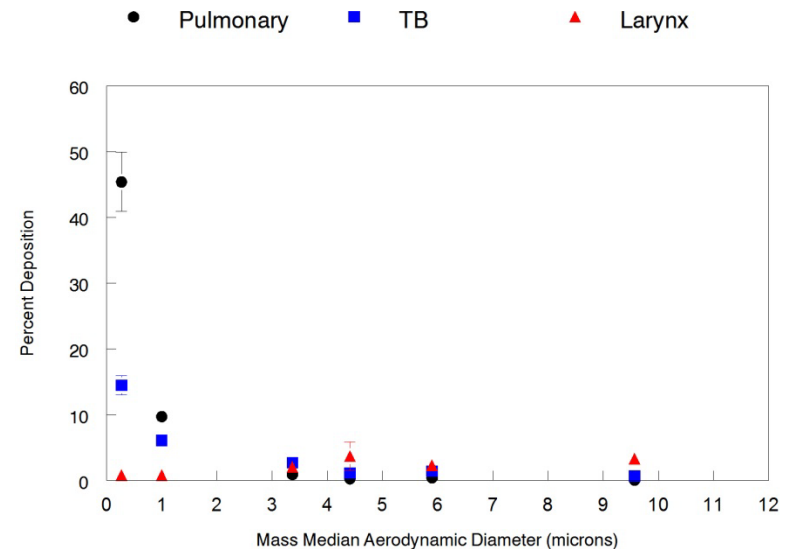
- Animal

- Determined experimentally in exposure systems
- CFD predictions based extrathoracic μ CT scans

Mean % Deposition of Inhaled Monodisperse Radiolabeled Aerosol
CF₁ Mouse (Raabe et al. 1988)

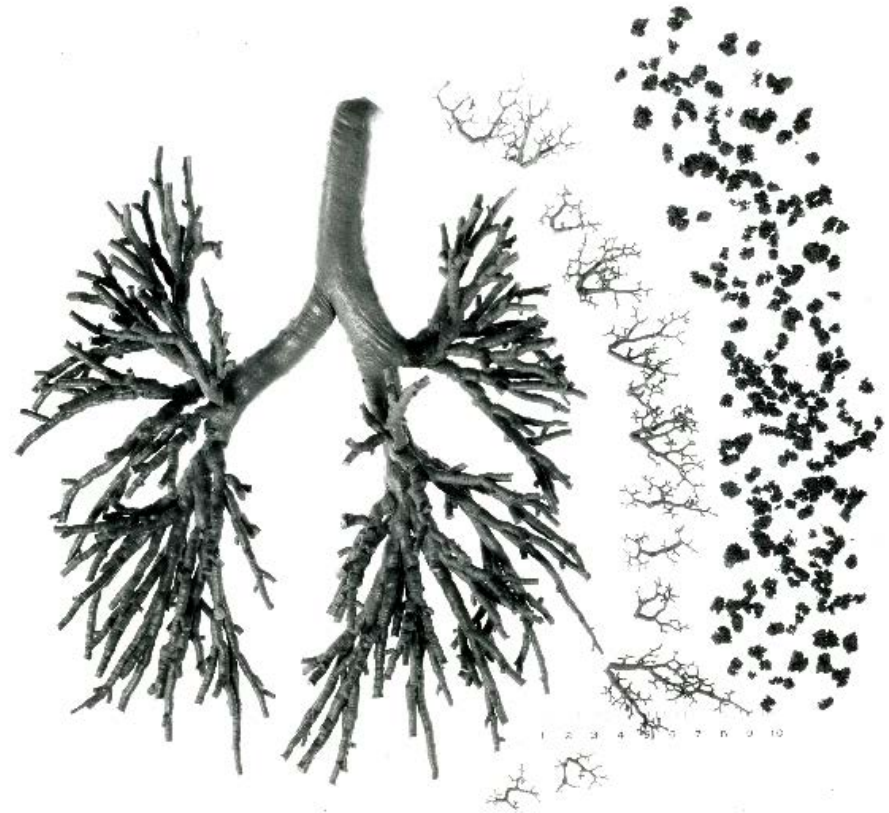
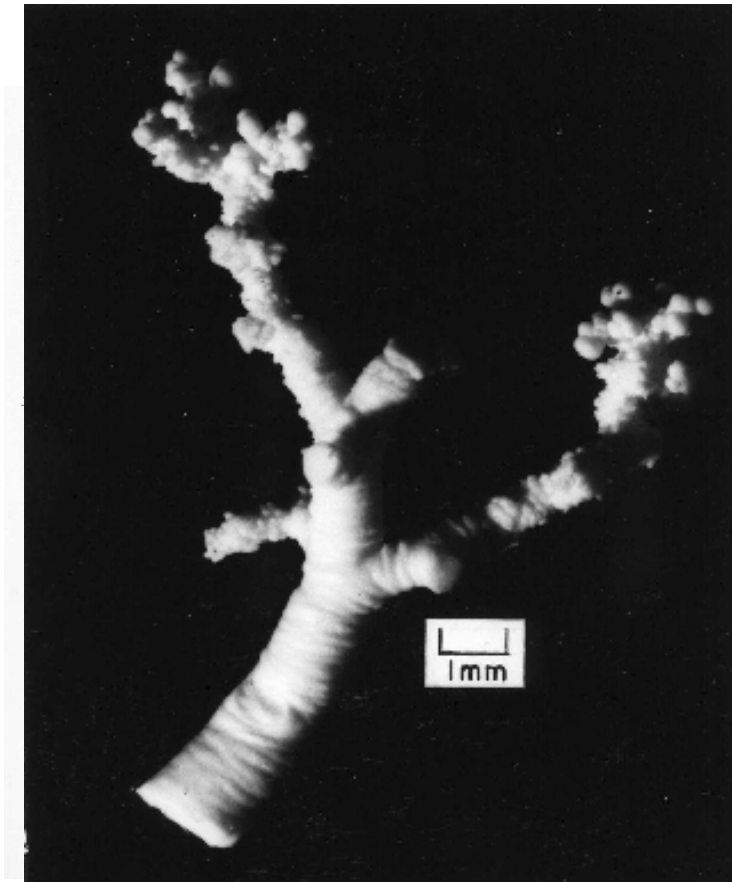


Mean % Deposition of Inhaled Monodisperse Radiolabeled Aerosol
CF₁ Mouse (Raabe et al. 1988)



In-vivo Anatomical Considerations

Adult human lung in-situ lung cast

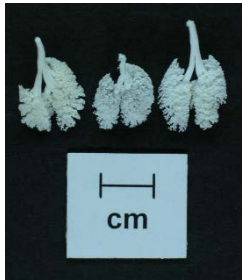


Courtesy of Dr. R. Phalen, Air Pollution Health Effects Laboratory, University of California, Irvine



In-vivo Anatomical Considerations

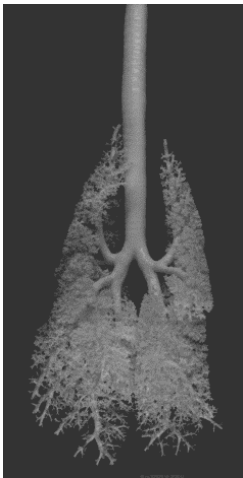
B6C3F₁, Balb/c & AJ Mice



Brown
Norway
Rat



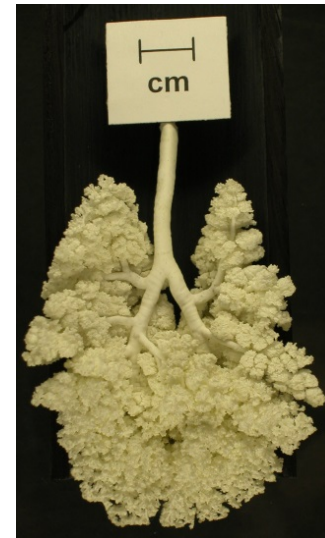
Ferret



Sprague
Dawley
Rat



Rhesus
Monkey

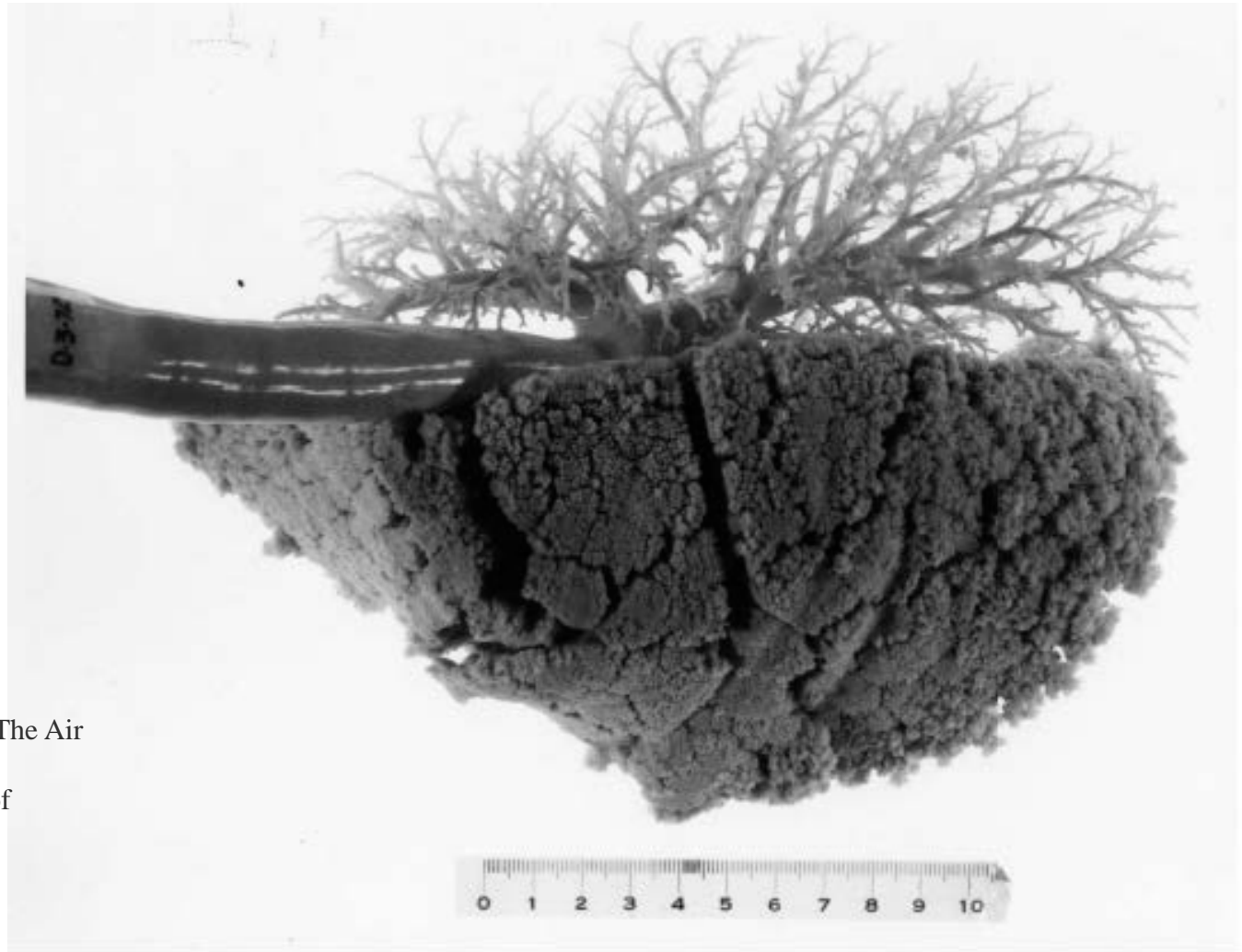


Photographs courtesy of The Air Pollution
Health Effects Laboratory, University of
California, Irvine



In-vivo Anatomical Considerations

Beagle
Dog

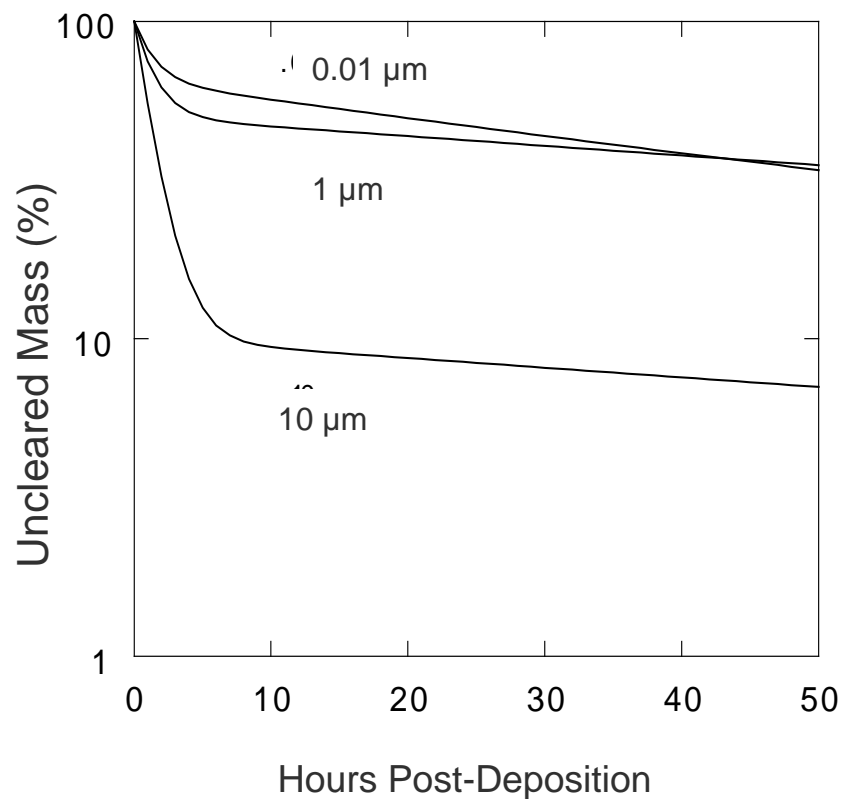


Photograph courtesy of The Air
Pollution Health Effects
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California, Irvine



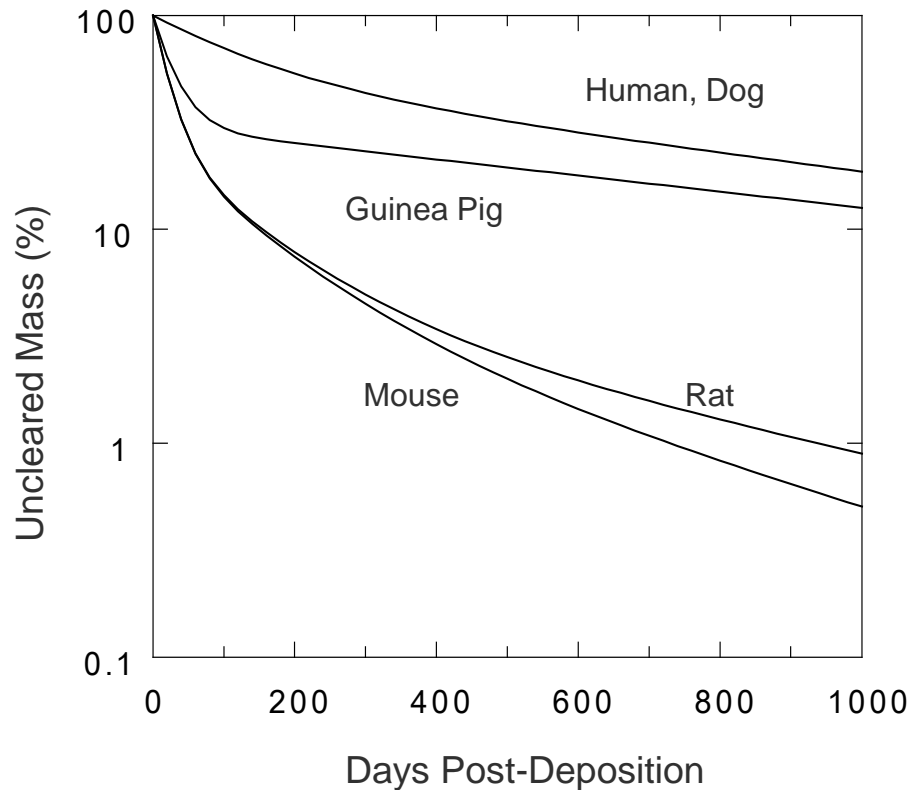
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In-vivo Clearance Considerations



Insoluble particle clearance curves for humans
(Wolff, 1996; ICRP, 1994; adapted from Phalen, 2002)

In-vivo Clearance Considerations



Insoluble particle clearance curves for 1 to 3 μm diameter particles in humans, dogs, guinea pigs, rats and mice (Wolff, 1996; ICRP, 1994; adapted from Phalen, 2002)



Biomarkers

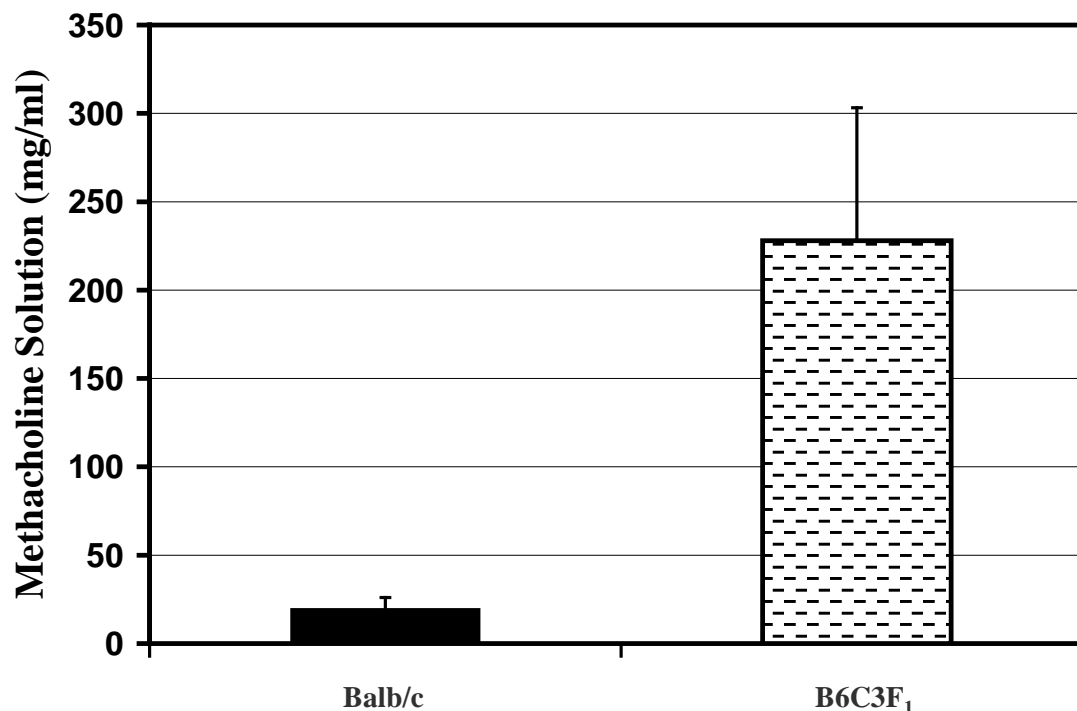
- Definition - “A constituent or metabolite that is measured in a biological fluid or tissue that has the potential to interact with a biological macromolecule; sometimes considered a measure of internal dose” US National Academy of Sciences – Institute of Medicine 2001.
- Ideal Biomarker of Exposure (US National Academy of Sciences – Institute of Medicine 2001)
 - Specific to the source compound
 - Correlated with exposure
 - Easy to obtain
 - Able to be measured accurately
- Body fluid – saliva, sputum, blood, urine or feces

Biomarkers - Examples

Constituent/Metabolite	Biomarker Examples	Body Fluid
1,3-butadiene	Mono & di hydroxybutenylmercapturic acid	Urine
B. anthracis	Infection/infectivity	Blood
Benzo[a]pyrene	3-Hydroxybenzo[a]pyrene	Urine
Carbon monoxide	carboxyhemoglobin	Blood
Naphthalene	1& 2-hydroxynaphthalene	Urine
Ochratoxin A	Ochratoxin A	Serum
Permethrin	3-phenoxybenzoic acid	Urine
Tobacco Smoke	Nicotine, cotinine & metabolites	Serum, urine
E-vapor aerosol*	Nicotine, cotinine & metabolites	Serum, urine

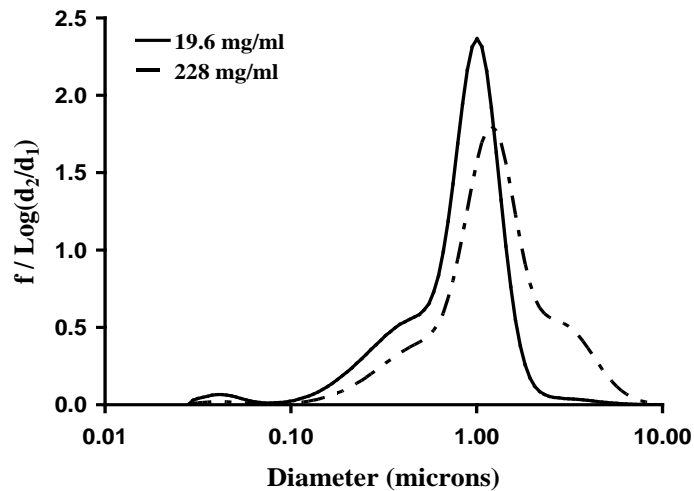
* Products containing nicotine

In-vivo – Mouse Strain Differences

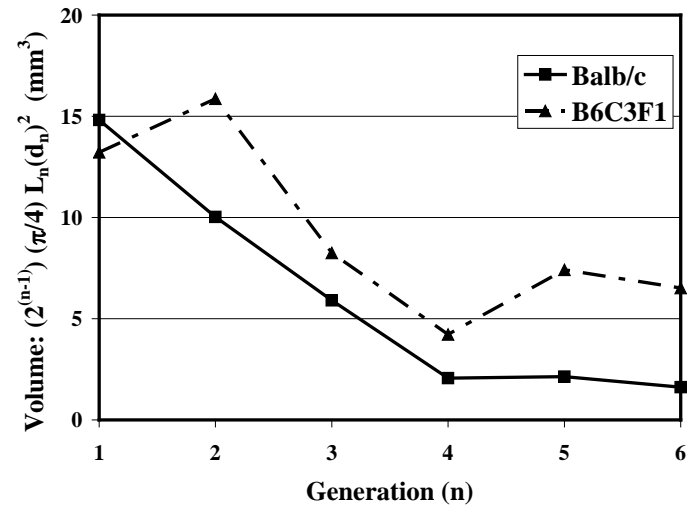


Methacholine challenge in Balb/c & B6C3F₁ mice; concentration of methacholine in the solution nebulized to produce a 200% increase in resistance to breathing

In-vivo – Mouse Strain Differences



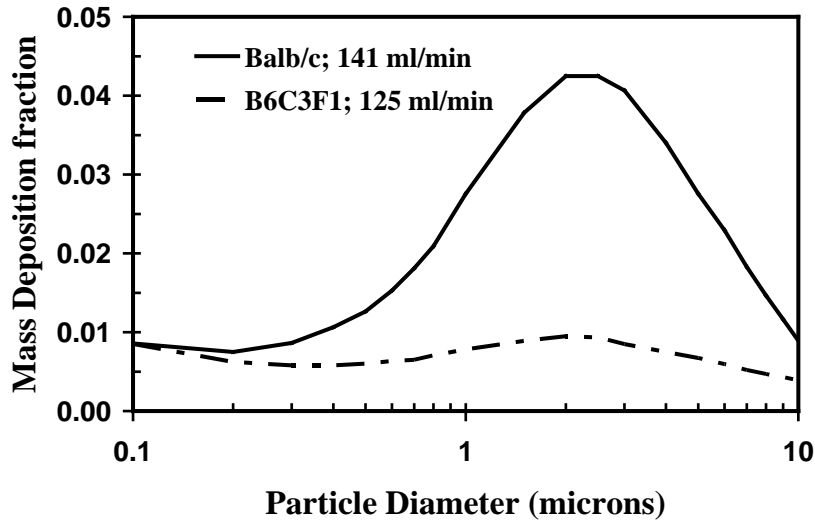
Size distribution of methacholine aerosol measured in breathing zone of Balb/c (solid line) & B6C3F₁ (dashed line).



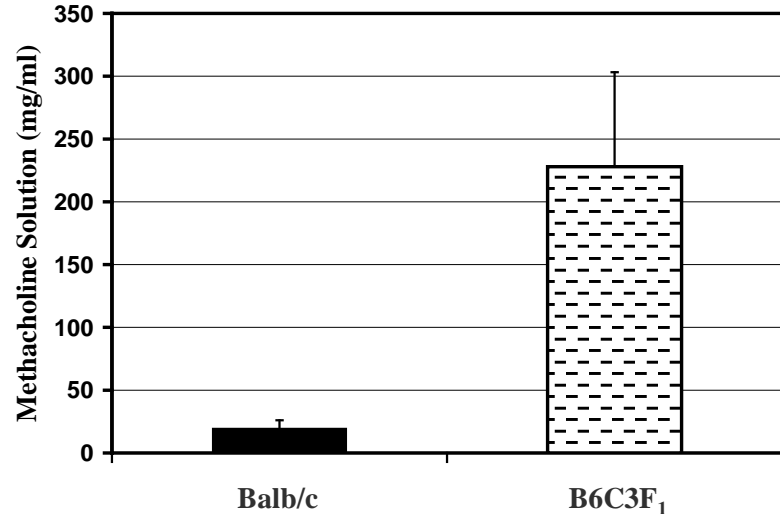
Airway volume of Balb/c & B6C3F₁ mice; Trachea = generation 1



In-vivo – Mouse Strain Differences



Without considering Inhalability, influence of airway size & minute ventilation on particle deposition.



50% of the difference in concentration of methacholine is attributable to dosimetry and 50% is attributable to inherent biochemical sensitivity



In-vivo Considerations - Summary

■ Humans

- Small olfactory epithelium region
- Near-symmetric bronchial branching
- Prolonged post-birth alveolar development
- Multi-generations of respiratory bronchioles
- Slow alveolar clearance
- Long lifespan

■ Rodents

- Large olfactory epithelium region – sensitivity to odors
- Monopodial bronchial branching
- Missing/scant respiratory bronchioles
- Decreased cardiopulmonary function when stressed
- Nocturnal activity

In-vivo Considerations - Summary

- Dogs, ferrets*, rabbits, goats, & golden hamsters
 - Monopodial airway branching (*least monopodial)
 - 2-6 orders of respiratory bronchioles
 - Relatively easy to handle
- Non-human primates
 - More-human like anatomy and physiology
 - Uncooperative
 - Increasingly difficult to obtain
- Equines
 - Human-like sub-gross anatomy and pulmonary pathophysiology
 - Variable temperament
 - Require freedom of head movement



Literature Cited

ACGIH®, 2001 TLVs® and BEIs®, American Conference of Governmental Industrial Hygienists', Cincinnati, OH, 2001.

Green, H.L. and Lane, W.R, Particulate clouds: Dusts, smokes and mists. 2nd ed., E.&F.N. Spon Ltd., London 1964.

Hinderliter, P.M., Minard, K.R., Orr, G., Chrisler, W.B., Thrall, B.D., Pounds, J.G., Teeguarden, J.G. ISDD: A computational model of particle sedimentation, diffusion and target cell dosimetry for in vitro toxicity studies, Particle and Fibre Toxicology, 7:36, 2011.

ICRP, (International commission on radiation Protection, task group of Committee 2), *Human Respiratory Tract Model for Radiological Protection*, Publication 66, Pergamon Press, New York, New York, 1994.

NCRP, Deposition retention and dosimetry of inhaled radioactive substances, NCRP SC 57-2 Report, National Council on radiation Protection and Measurements, Bethesda, MD, 1997.

Phalen, R.F., *The particulate air Pollution Controversy: A case study and lessons learned*, Kluwer Academic Publishers, 2002.

Raabe, O.G., Al-Bayati, M.A., Teague, S.V., Rasolt, A. (1988). Regional deposition of inhaled monodisperse coarse and fine aerosol particles in small laboratory animals. In *Inhaled Particles VI*, eds. J. Dodgson, R.I. McCallum, M.R. Bailey and D.R. Fisher, pp. 53-63. Pergamon Press, Oxford U.K.

Thomas, D.G., Smith, J.N., Thrall, B.D., Baer, D.R., Jolley, H., Munusamy, P., Kodali, V., Demokritou, P., Cohen, J., Teeguarden, J.G. ISD3: a particokinetic model for predicting the combined effects of particle sedimentation, diffusion and dissolution on cellular dosimetry for in vitro systems, Particle and Fiber Toxicology, 15:6, 2018. doi: 10.1186/s12989-018-0243-7

Wolff, R.K., Experimental investigation of deposition and fate of particles: animal models and interspecies differences, in *Aerosol Inhalation: Recent Research Frontiers*, ed by Marijnissen, J.C.M., and Gradon, L., Kluwer Academic Publishers, Norwell, MA, pp. 247-263, 1996.

Literature of Interest

Crapo, J.D., et al. (1989), Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases, Academic Press.

Gardner, D.E., Crapo, J.D., and McClellan, R.O. (1999), Toxicology of the Lung, 3rd Edn., Taylor & Francis.

Gardner, D.E. (2006), Toxicology of the Lung, 4th Edn., CRC Press.

Gehr, P. and Heyder, J. (2000), Particle-Lung Interactions, Marcel Dekker.

Harding, R. Pinkerton, K.E. and Plopper, C.E. (2004), The Lung: Development, Aging and the Environment, Elsevier

Marijnissen, J.C.M. and Gradon, L. (1996), Aerosol Inhalation: Recent Research Frontiers, Kluwer Academic.

McClellan, R.O. and Henderson, R.F. (1995), Concepts in Inhalation Toxicology, 2nd Edn, Taylor & Francis.

Parent, R.A. (1991 & 2015) Comparative Biology of the Normal Lung, CRC Press.

Thank you

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