Considerations for Inhalation Safety Assessment: Approaches and Application

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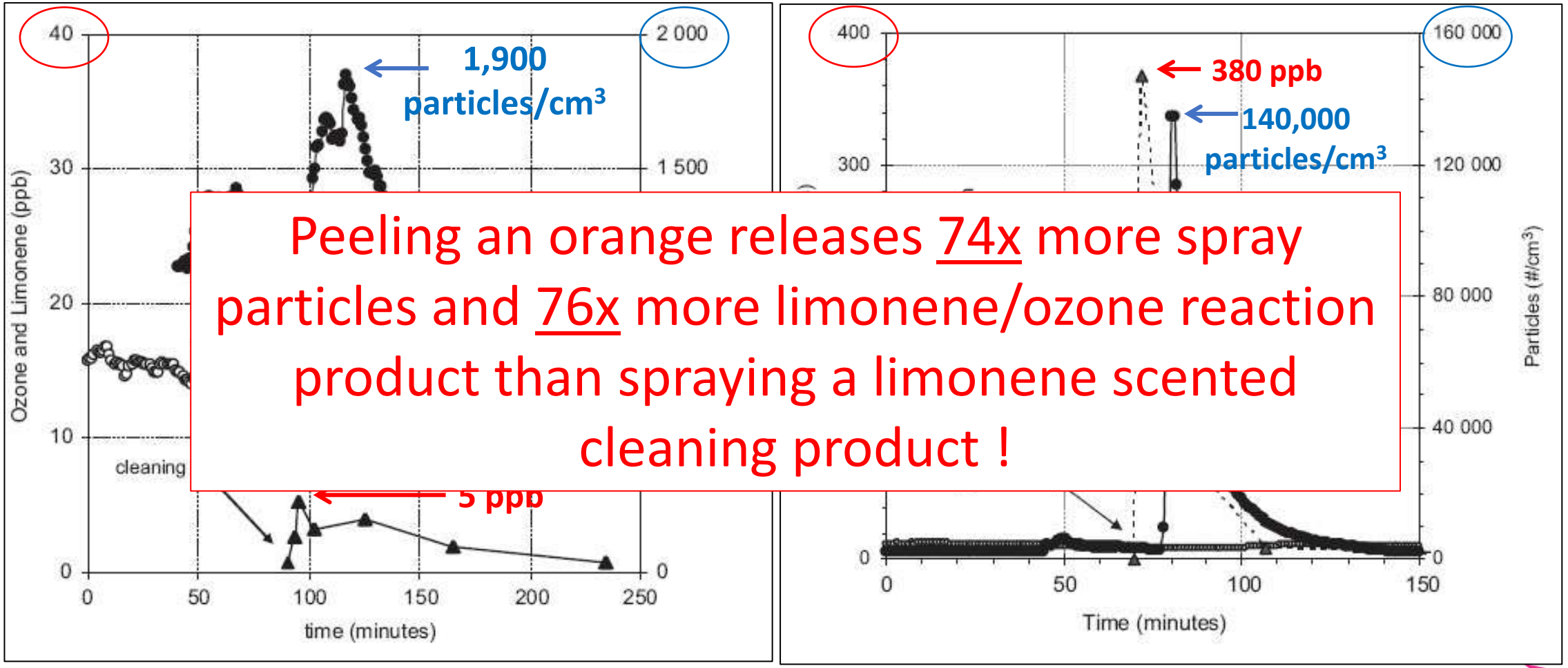
Objectives

- Inhalation exposure assessment paradigm
- Gases, vapors, and droplets/particles
- Particle specifications
- Air exposure versus deposition and bioavailability
  - 2-Box Air Dispersion Model
  - Multiple Path Particle Deposition Model
- Translating air concentration to systemic dose
  - Local effects versus systemic toxicity
- Data assessment and evaluation of exposure margin of safety

Exposure, Air Concentration and Context

Lemon Cleaning Product

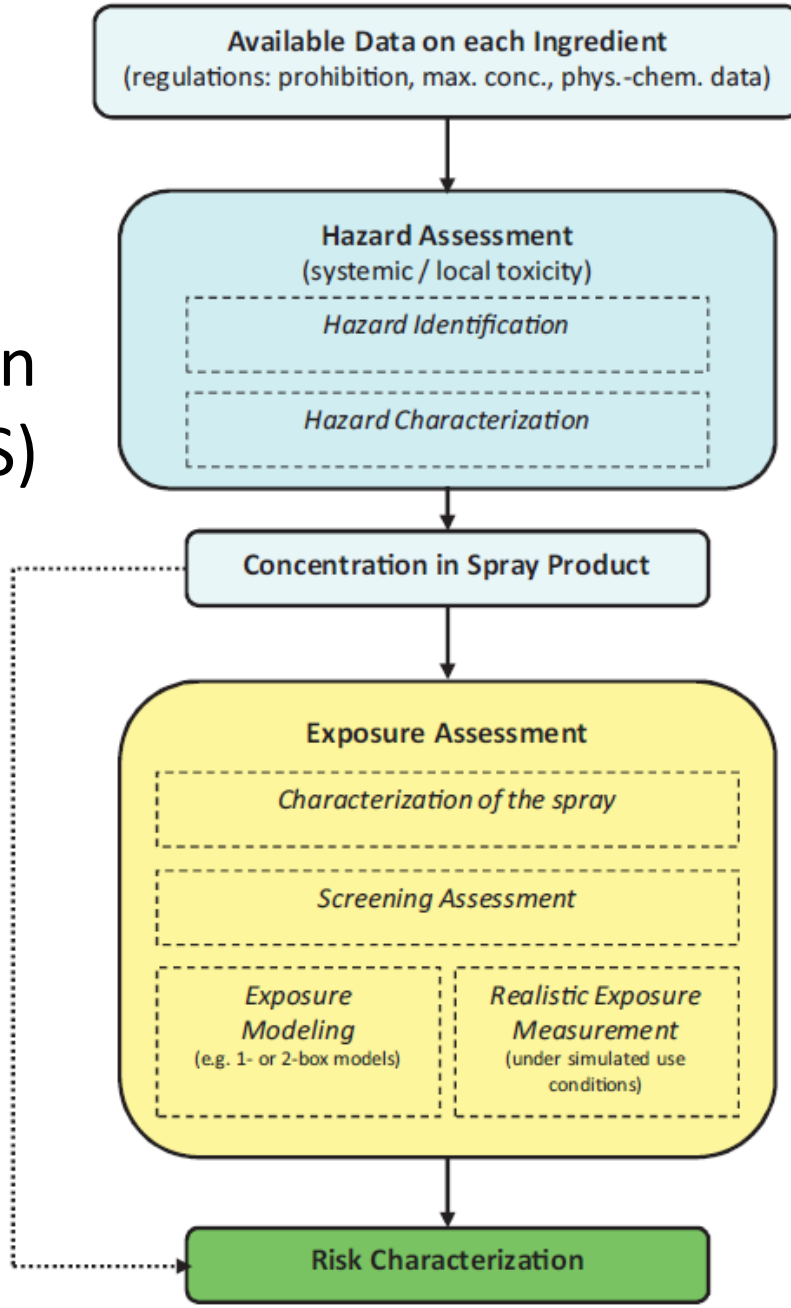
Whole Fruit Orange



Peeling an orange releases 74x more spray particles and 76x more limonene/ozone reaction product than spraying a limonene scented cleaning product !

Langer, et al., Atmospheric Environment, 2008

Inhalation Safety Assessment per EU Scientific Committee on Consumer Safety (SCCS)



SCCS, 2012

Based on existing data or generation of empirical data

Understanding of formulation and device operation/output

Application of parameters for formulation and device using *in silico* prediction methods

Comparison to existing data or toxicological threshold of concern (in absence of data)

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Defining Inhalation Assessment Parameters

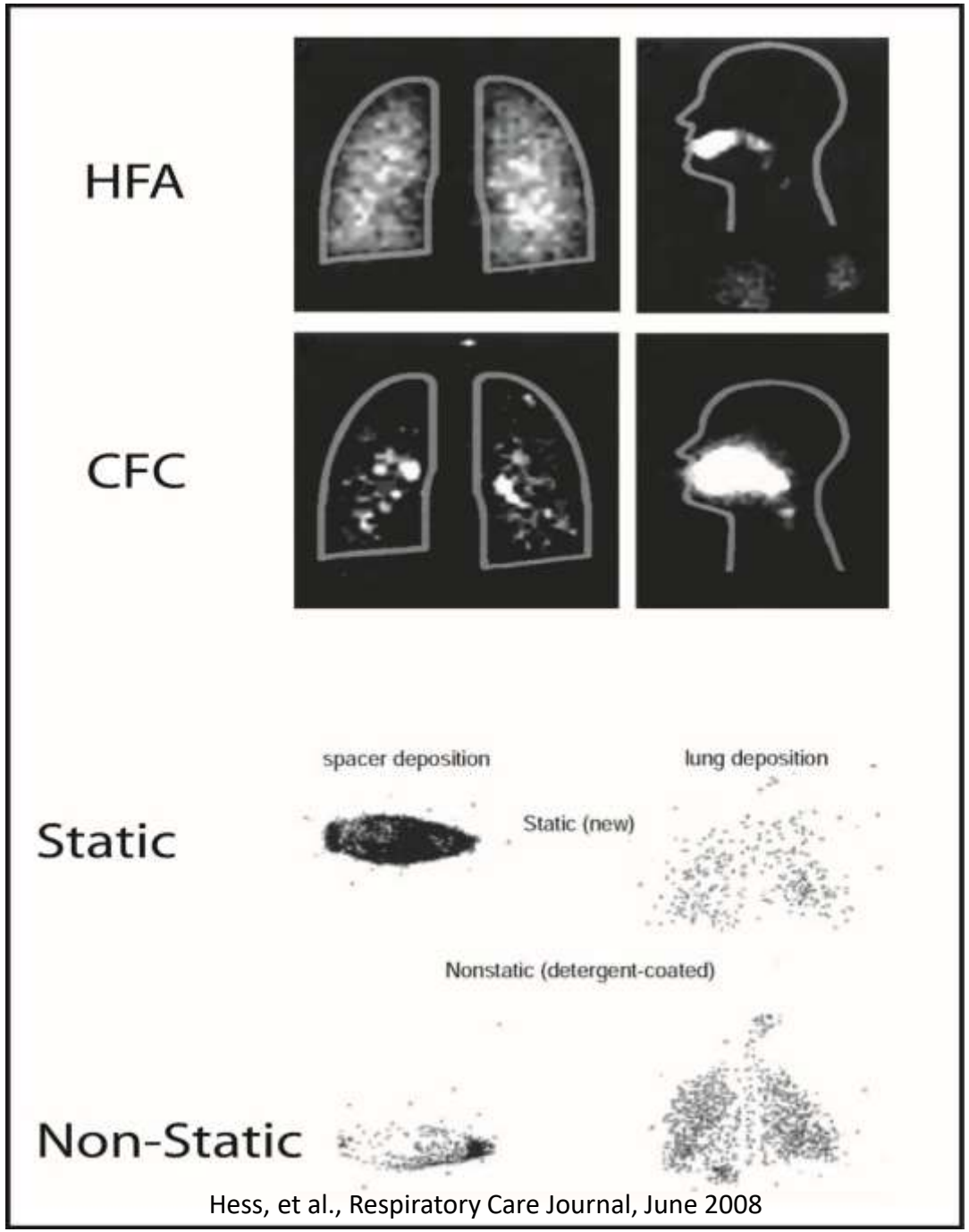
- Airborne concentration (mg/m^3)
- Air Exchange Rate (ACH)
  - N = (60*Q)/Vol
    - Where:
      - N = number of air changes per hour
      - Q = Volumetric flow rate of air
      - Vol = Space volume L × W × H
- Particle/Droplet size distribution (MMAD and GSD)
- Respiratory rate and tidal volume
  - Based on age, activity and health
- Duration of exposure
- Chemical, physical or biological properties of the hazardous

What's in the Air? - Distinct Characteristics

- Gases, vapors, and particles/droplets
  - Low vapor pressure compounds (droplet phase and solid particles)
  - Medium vapor pressure compounds (mixture of vapor and particle phases)
  - High vapor pressure compounds (vapor phase)
    - Nanosize droplets/particles are modeled by MPPD as the vapor component emulates nanosized droplets/particle behavior
    - Nanoscale is defined as a dimension between 1-100 nm (ISO, 2008)
      - Nanoparticle – having a mean mass aerodynamic diameter of 1-100 nm
      - Nanomaterial – an aerosol dispersion containing >50% droplets/particles characterized as nanoscale

Particle/Droplet Specifications

- Mean mass aerodynamic diameter and geometric standard deviation
  - Size dictates depth of deposition
  - Cells affected will determine impact of exposure
- Biochemical reactivity
  - Interaction with phospholipid bilayer of the cell membrane
  - Potential for paracellular transport and interaction with internal cellular processes
  - Activation of oxidant-mediated systems
- Structure and solubility
  - Mass per surface area
- Surface charges



Hess, et al., Respiratory Care Journal, June 2008

Evaluation of deposition efficiency and impact of propellant

HFA = hydrofluoroalkane
CFC = chlorofluorocarbon

Evaluation of deposition efficiency and impact of surface static charge

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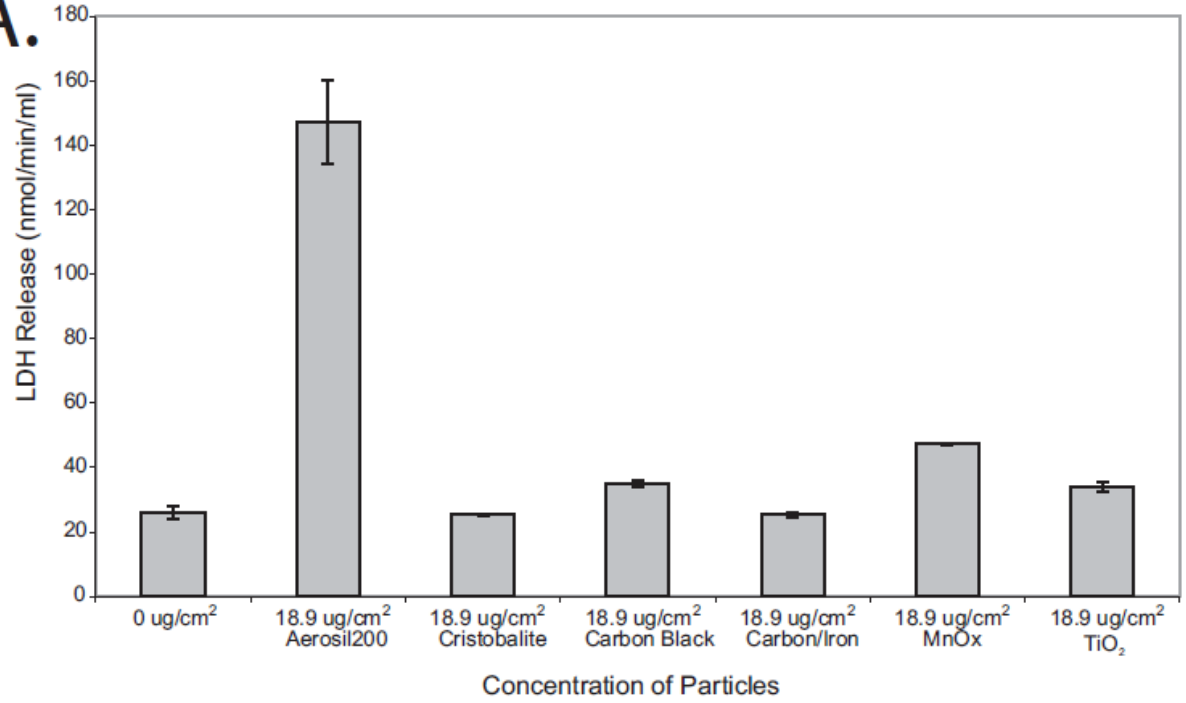
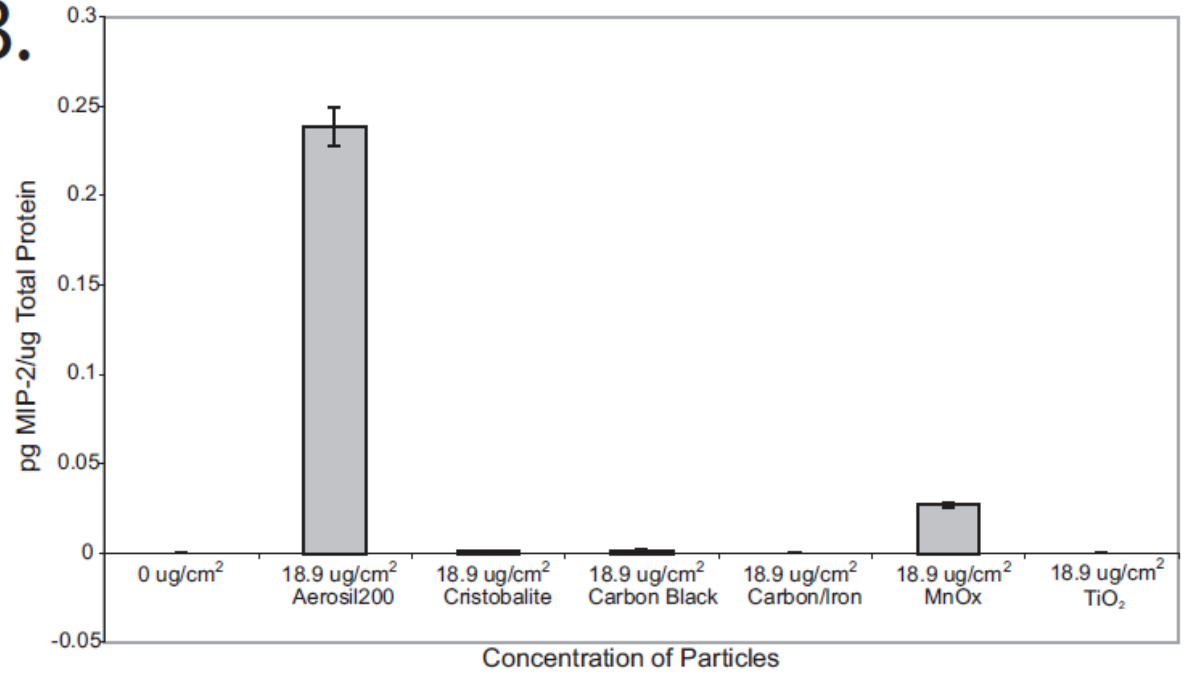
A.



Evaluation of cytotoxicity induced by exposure to solid particles of differing structure and/or charge status

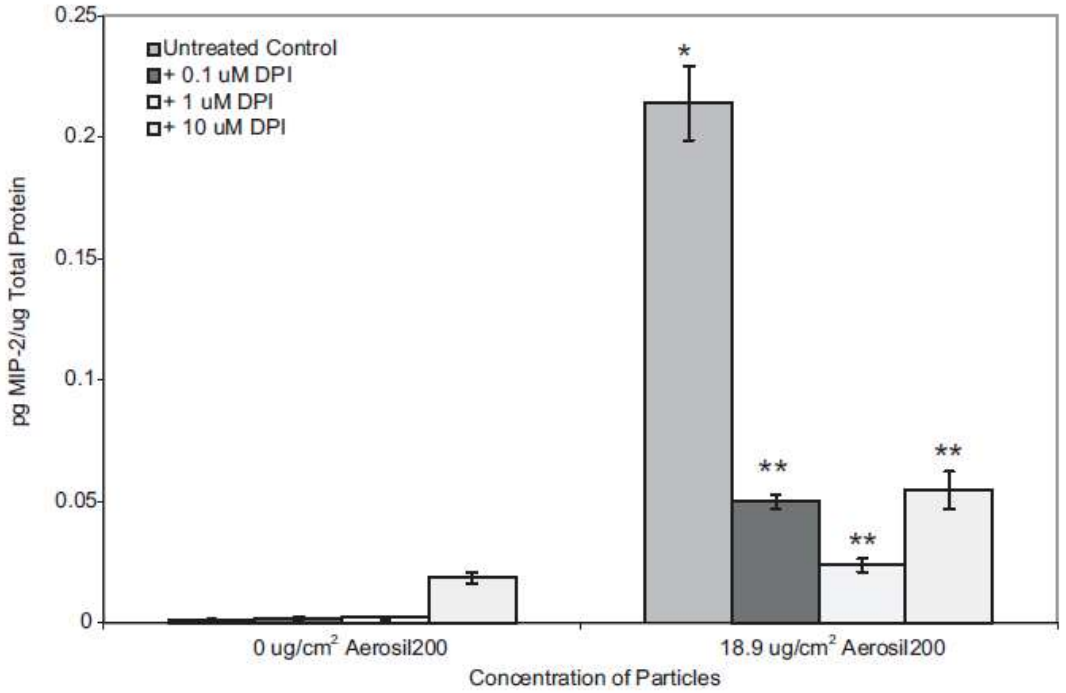
B.



Quantification of inflammatory mediator response following exposure to solid particles of differing structure and/or charge status

Singal, M., Doctoral Dissertation, University of Rochester, 2005

A.



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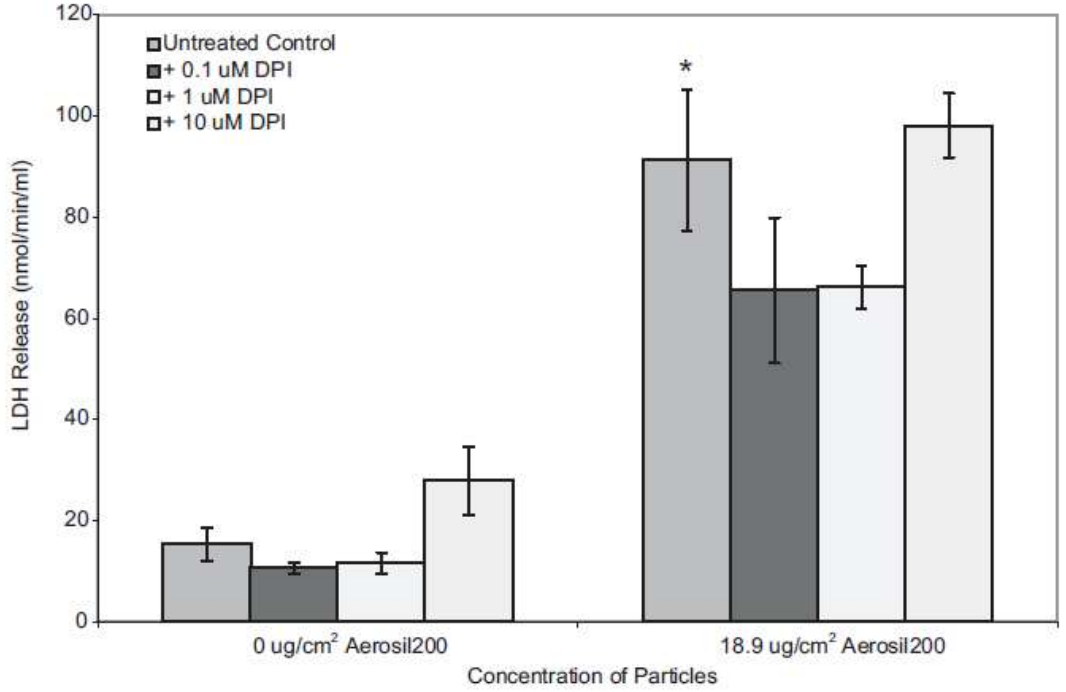

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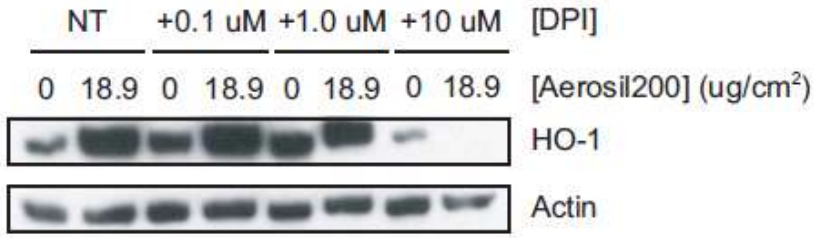

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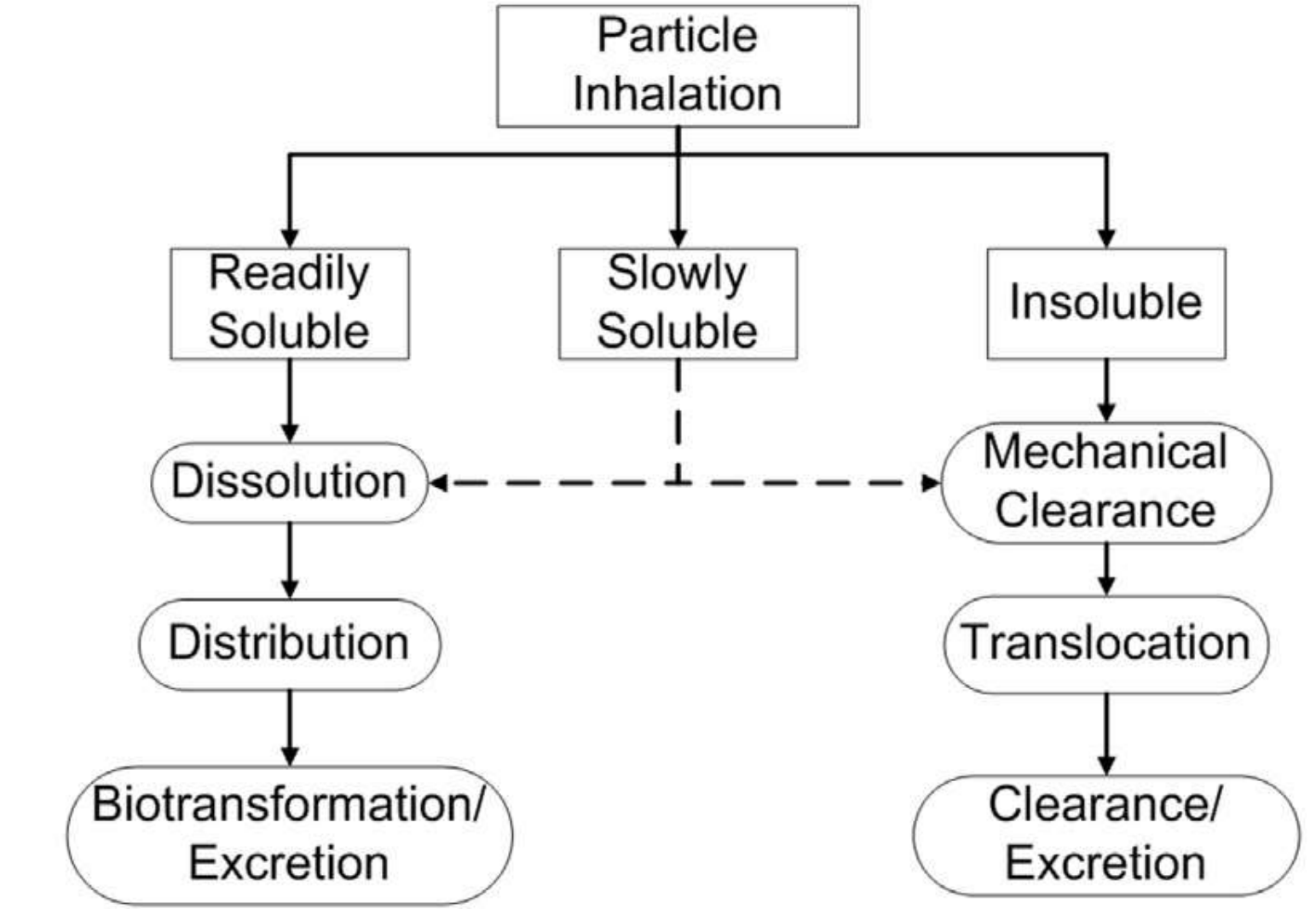
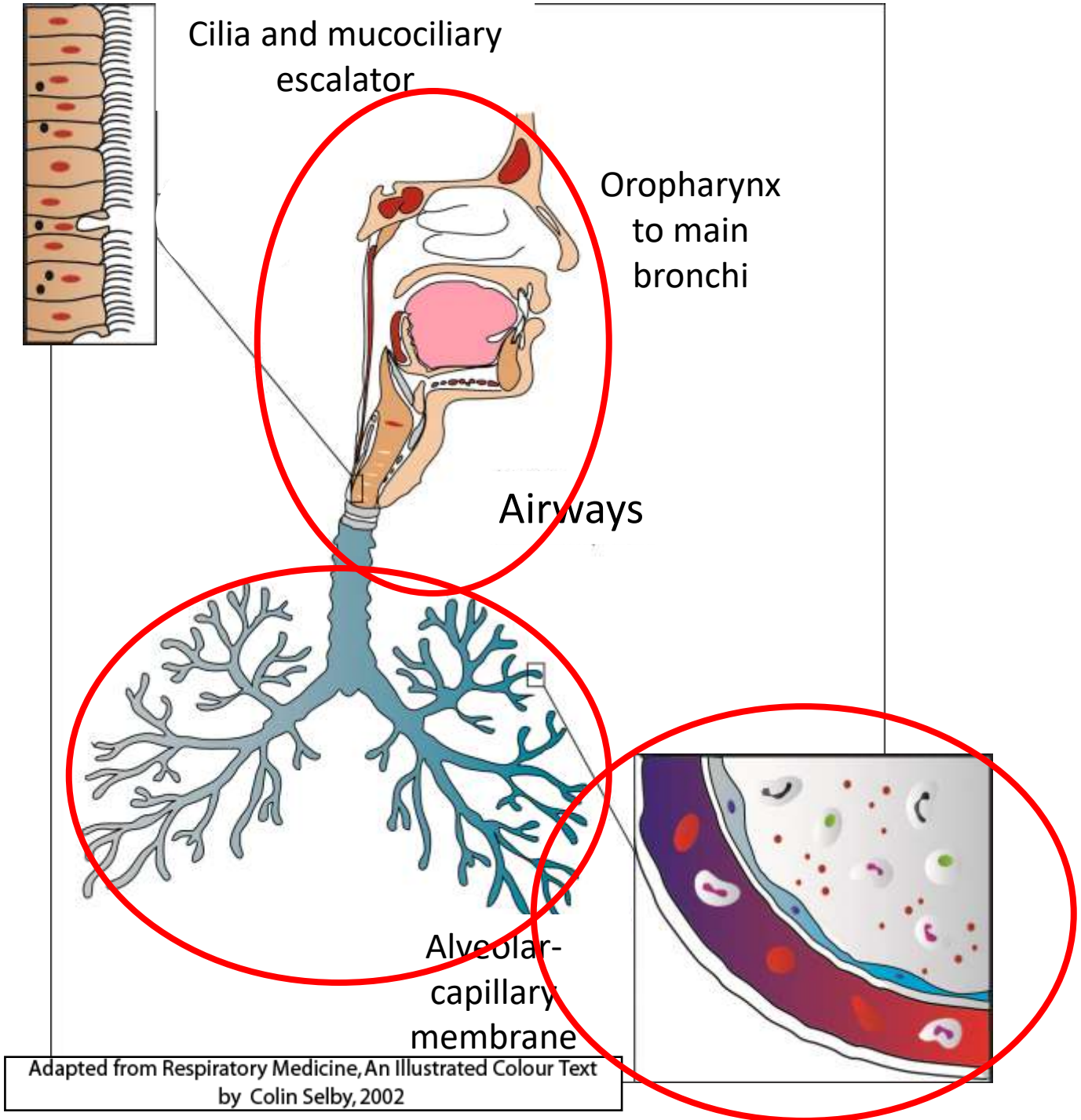
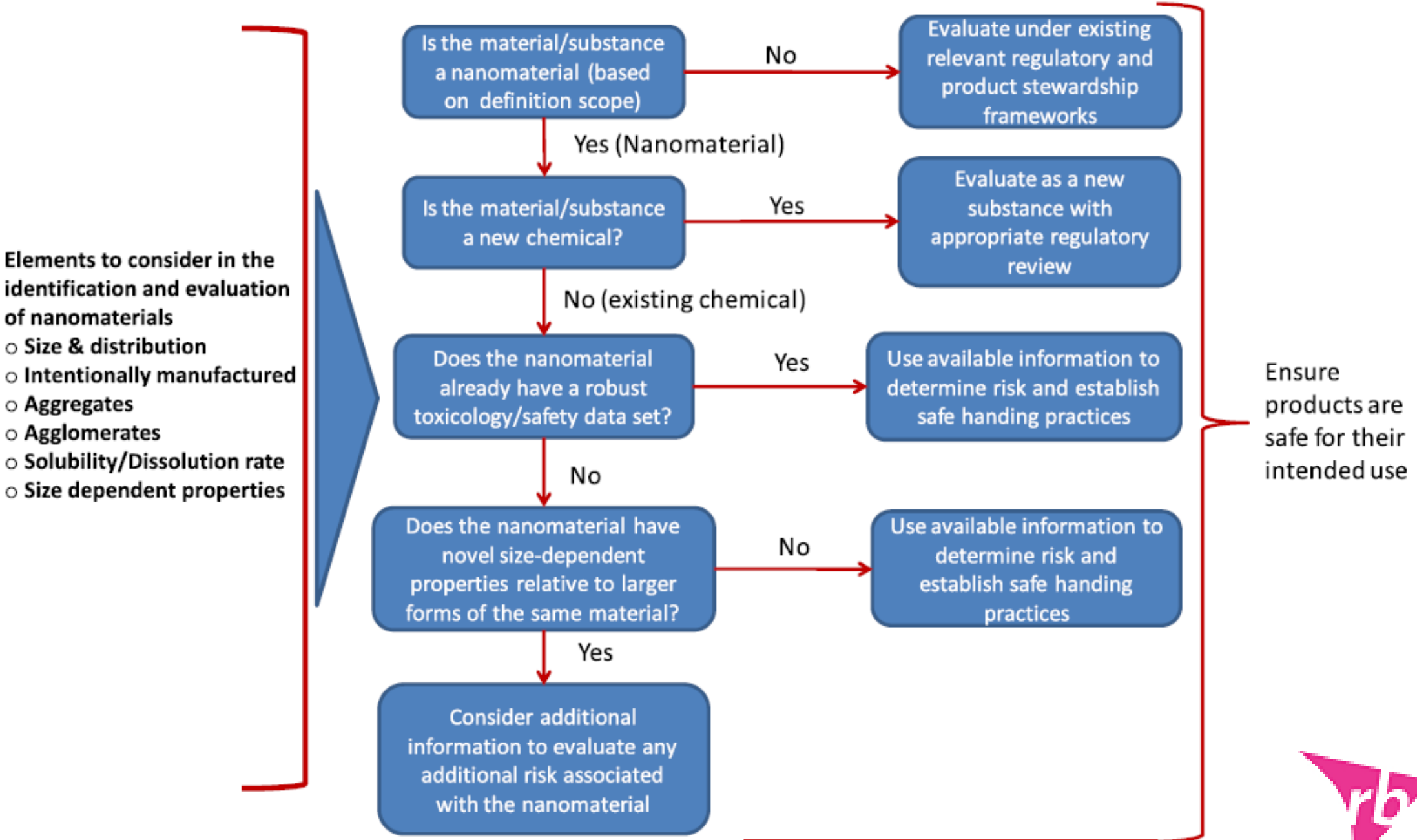


Boverhof, D. et al., Regulatory Toxicology and Pharmacology 73 (2015) 137-150



Adapted from Respiratory Medicine, An Illustrated Colour Text by Colin Selby, 2002

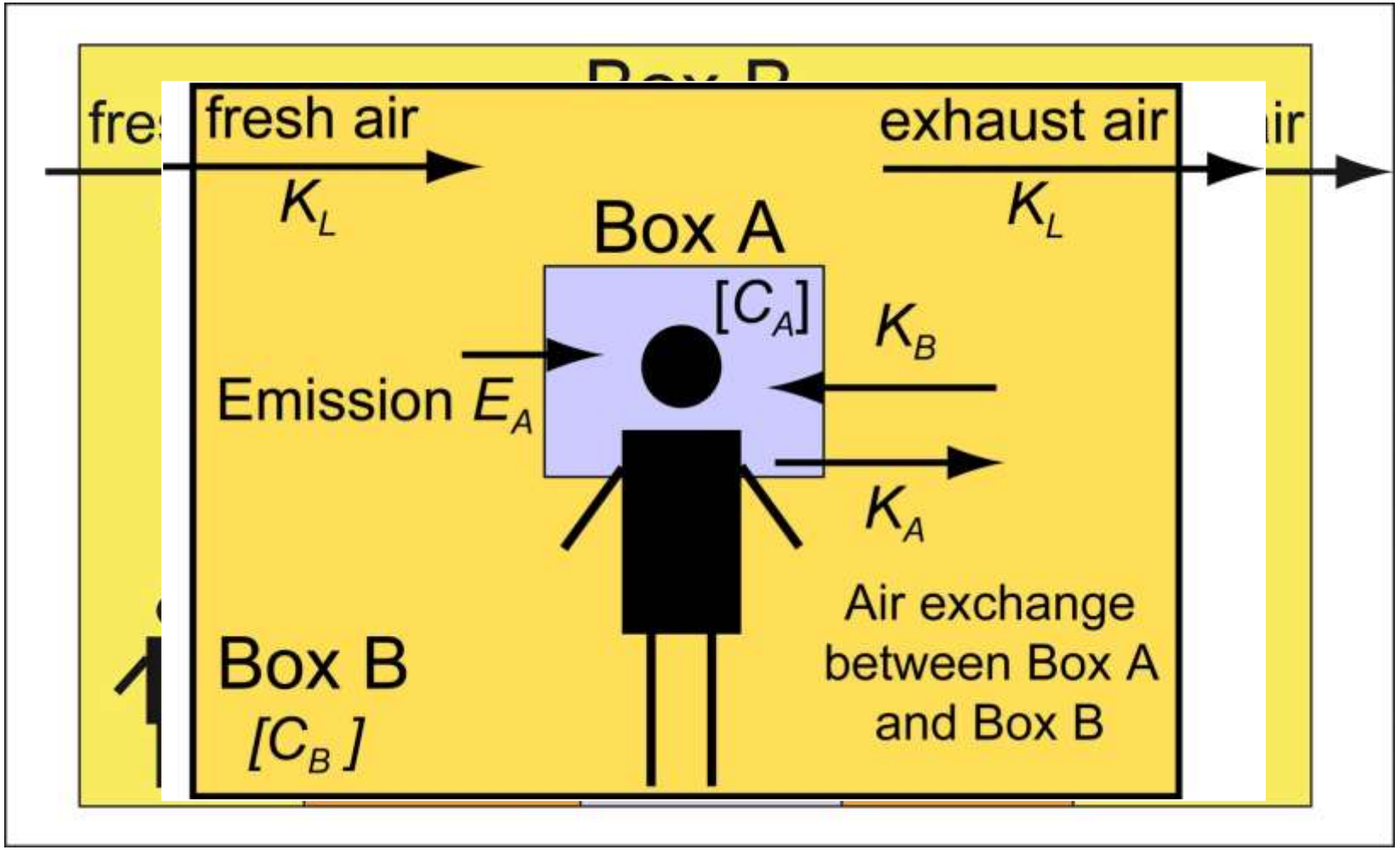


Boverhof, D. et al., Regulatory Toxicology and Pharmacology 73 (2015) 137-150

Air Exposure vs. Deposition and Bioavailability

- 2-Box Air Dispersion Model, ConsExpo, IKW, BAMA, MCCEM
  - All evaluate possible exposure under defined conservative consumer and/or occupational scenarios
  - Basic assumptions include:
    - Homogeneous distribution of emitted concentration
    - 100% potential for inhalation of airborne concentration
- Multiple Path Particle Deposition Model
  - Allows refinement of the exposure assessment by evaluation of regional deposition in the respiratory tract
  - Models include ages 3 months old to adult
  - Pulmonary condition can be modeled to emulate disease (asthma, COPD)
  - Tissue disposition can also be evaluated

2-Box Air Dispersion Model - Near field Analysis



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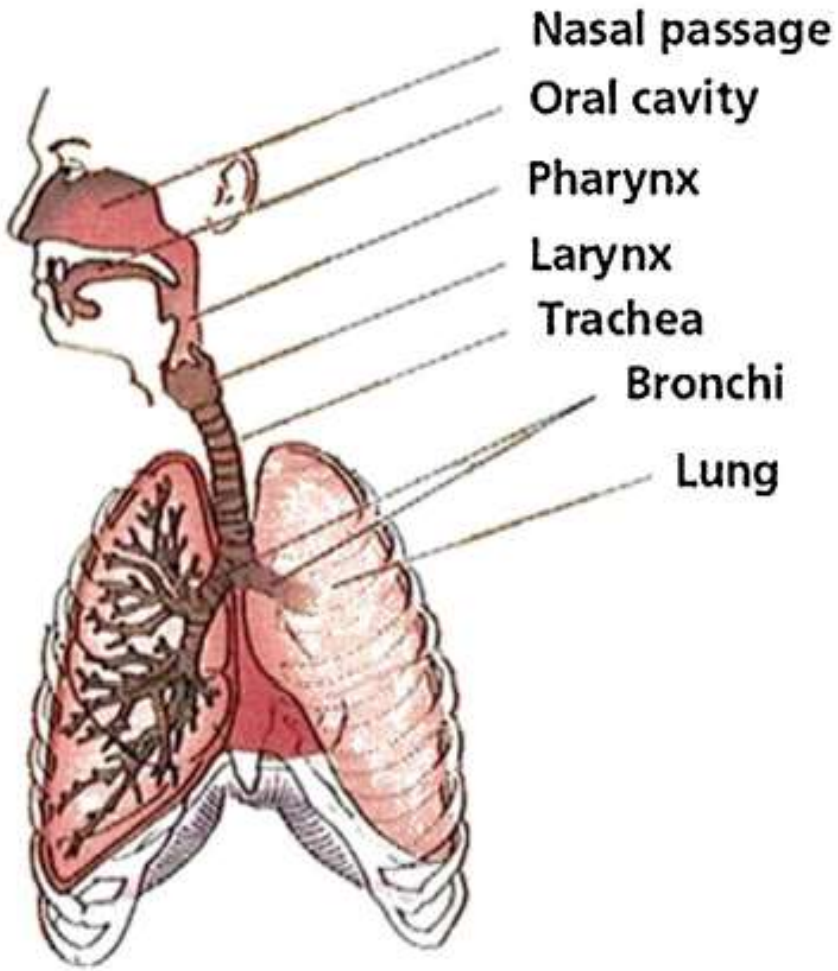
Regional Deposition



Nasopharyngeal region

Deposition:	impaction, diffusion
Clearance:	mucociliary, sneezing/blowing
Targeted by:	>30 µm particles highly reactive, water soluble gas, "**inhalable fraction**"

Tracheobronchial region

Deposition:	impaction, sedimentation, diffusion
Clearance:	mucociliary, coughing
Targeted by:	10-30 µm particles, 200 µm fibres, "**thoracic fraction**"

Pulmonary region (parenchyma)

Deposition:	sedimentation, diffusion
Clearance:	phagocytosis, solubilisation,
interstitial	
Targeted by:	<10 µm particles, 10-12 µm fibres less reactive/water soluble gas, "**respirable fraction**"

W. Steiling et al., Toxicology Letters 227 (2014) 41–49

Predictive Power of Dosimetry Modeling

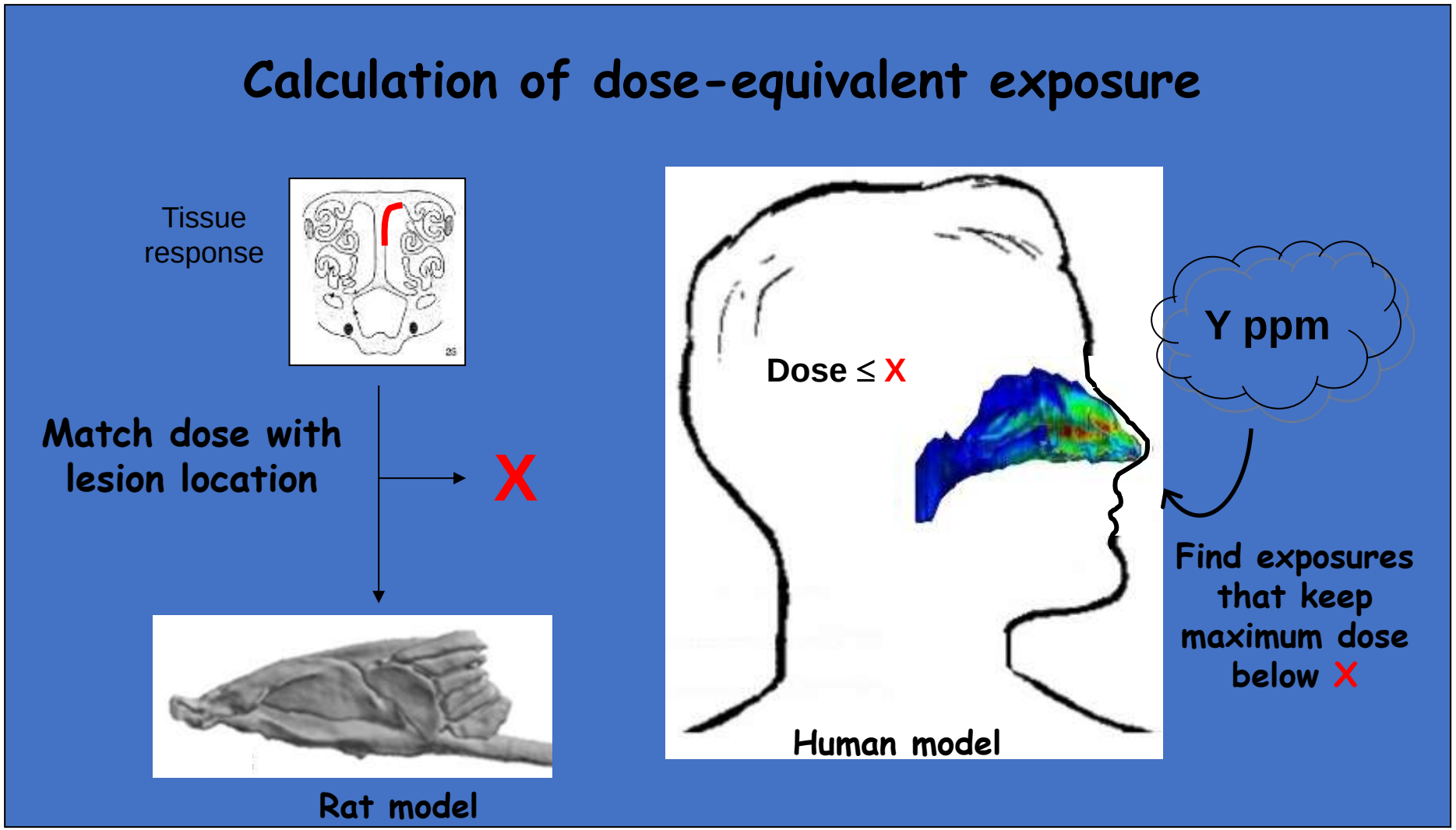
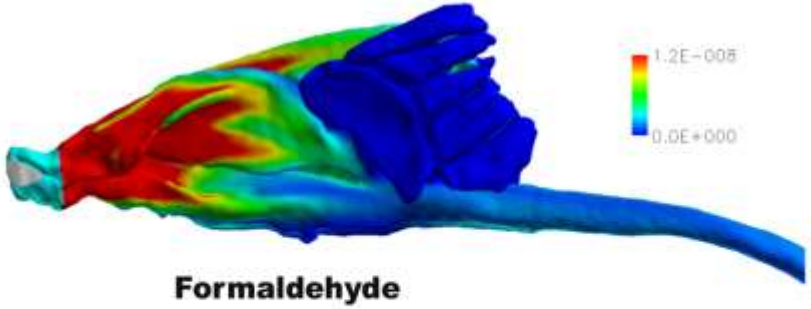
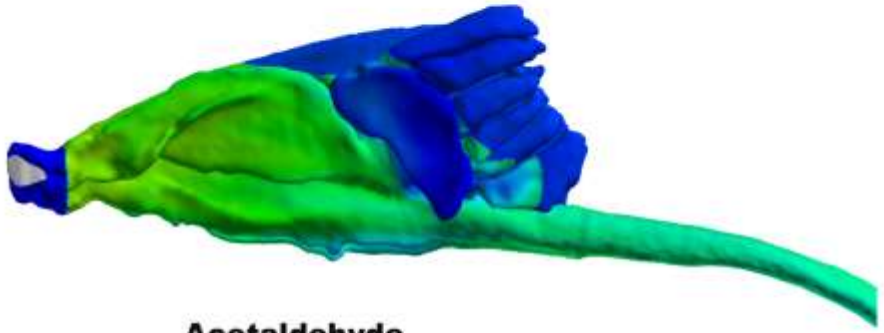


Image courtesy of Dr. Jeffry Schroeter, Applied Research Associates

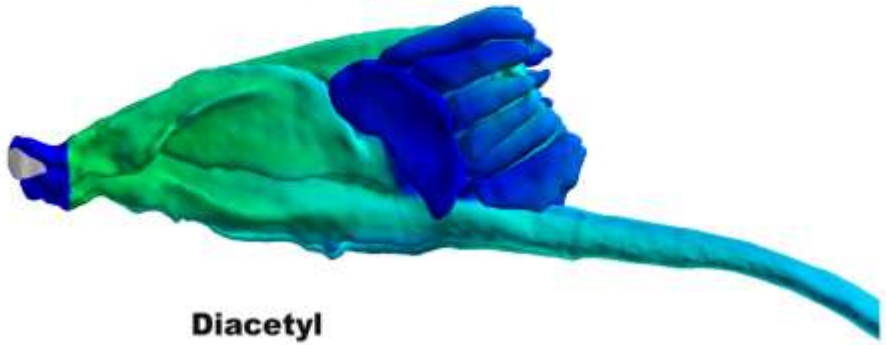


Formaldehyde

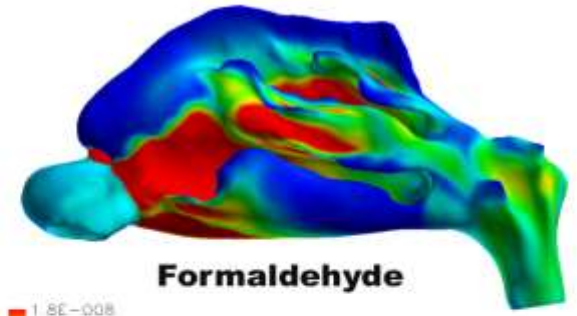
Acrolein



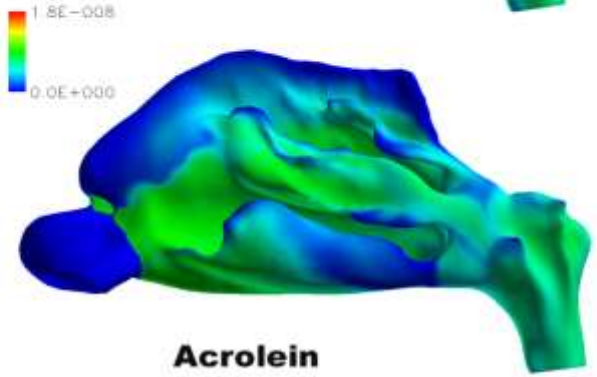
Acetaldehyde



Diacetyl



Formaldehyde



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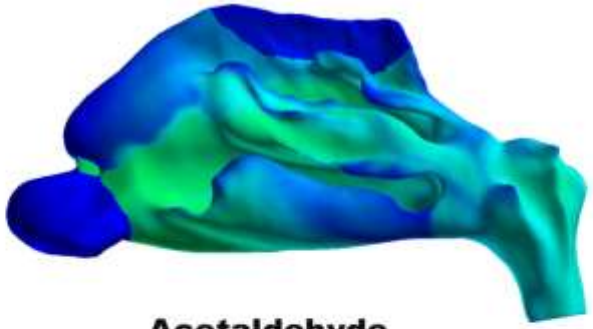

Acetaldehyde

Diacetyl

Image courtesy of Dr. Jeffry Schroeter, Applied Research Associates

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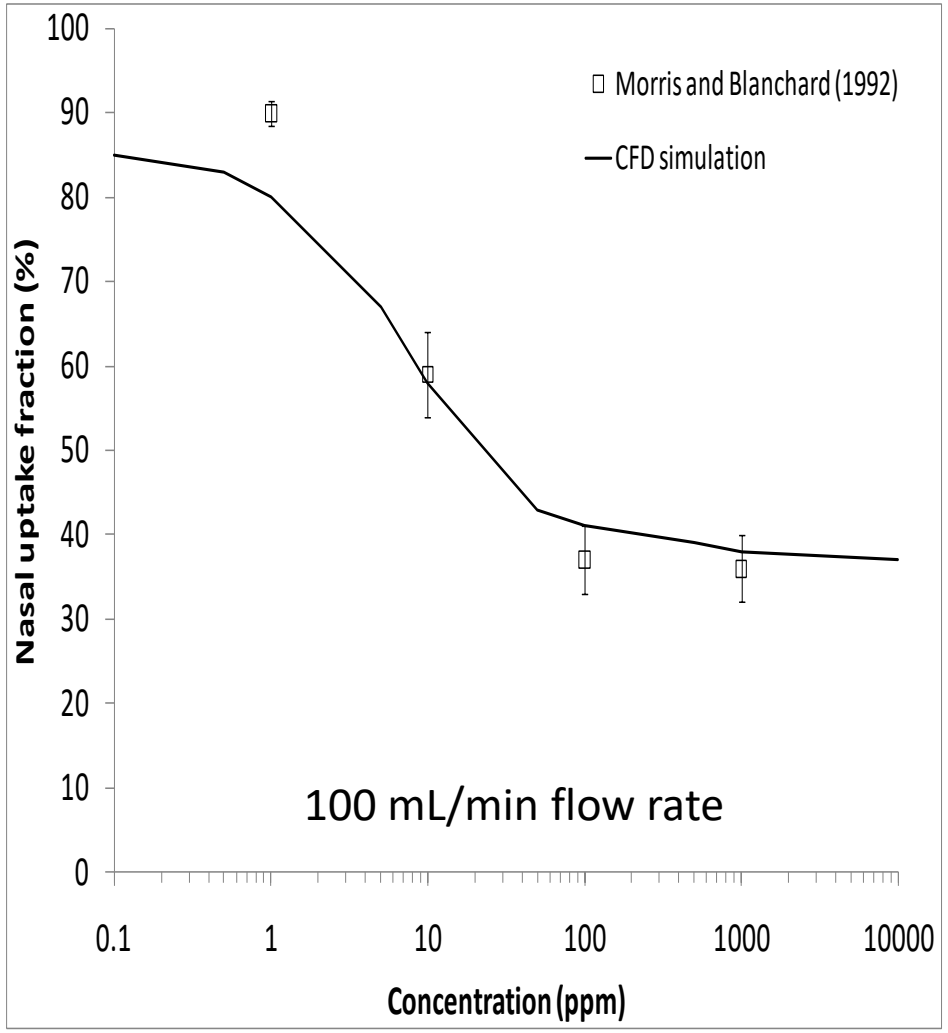
Acetaldehyde Model Predictions Match Published Experimental Data



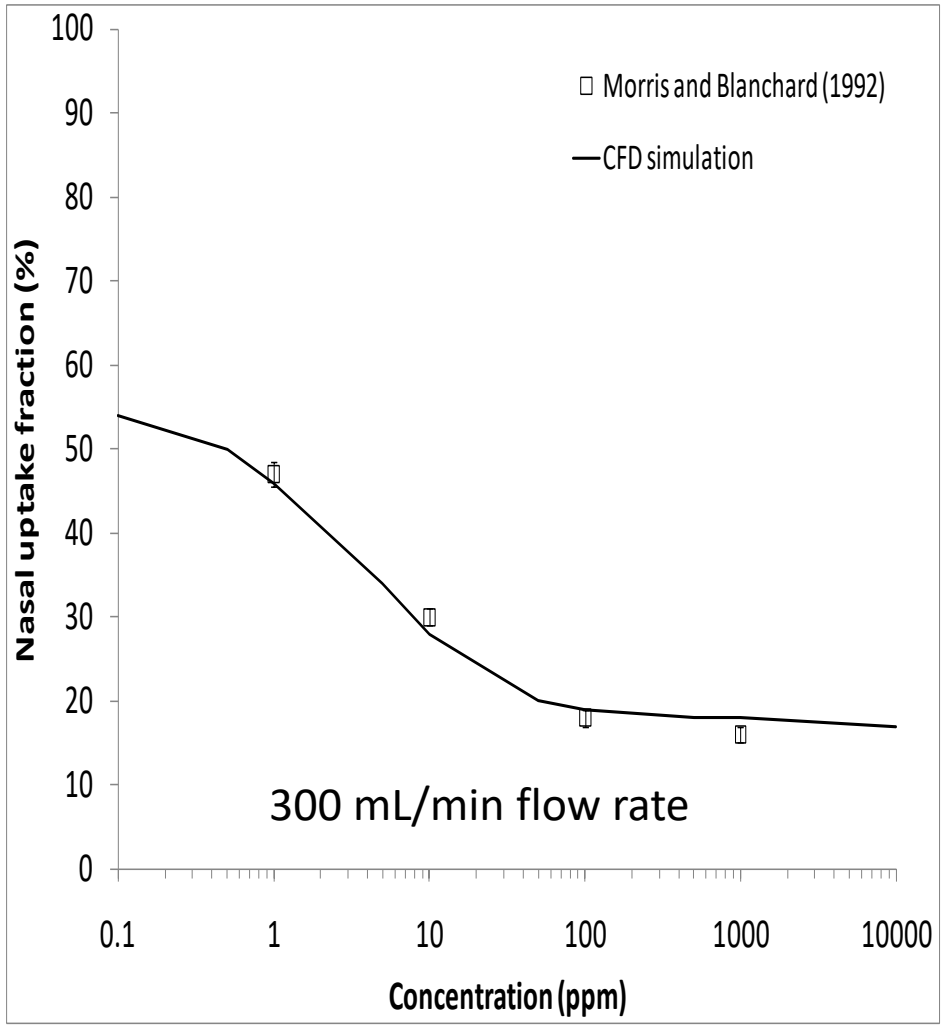
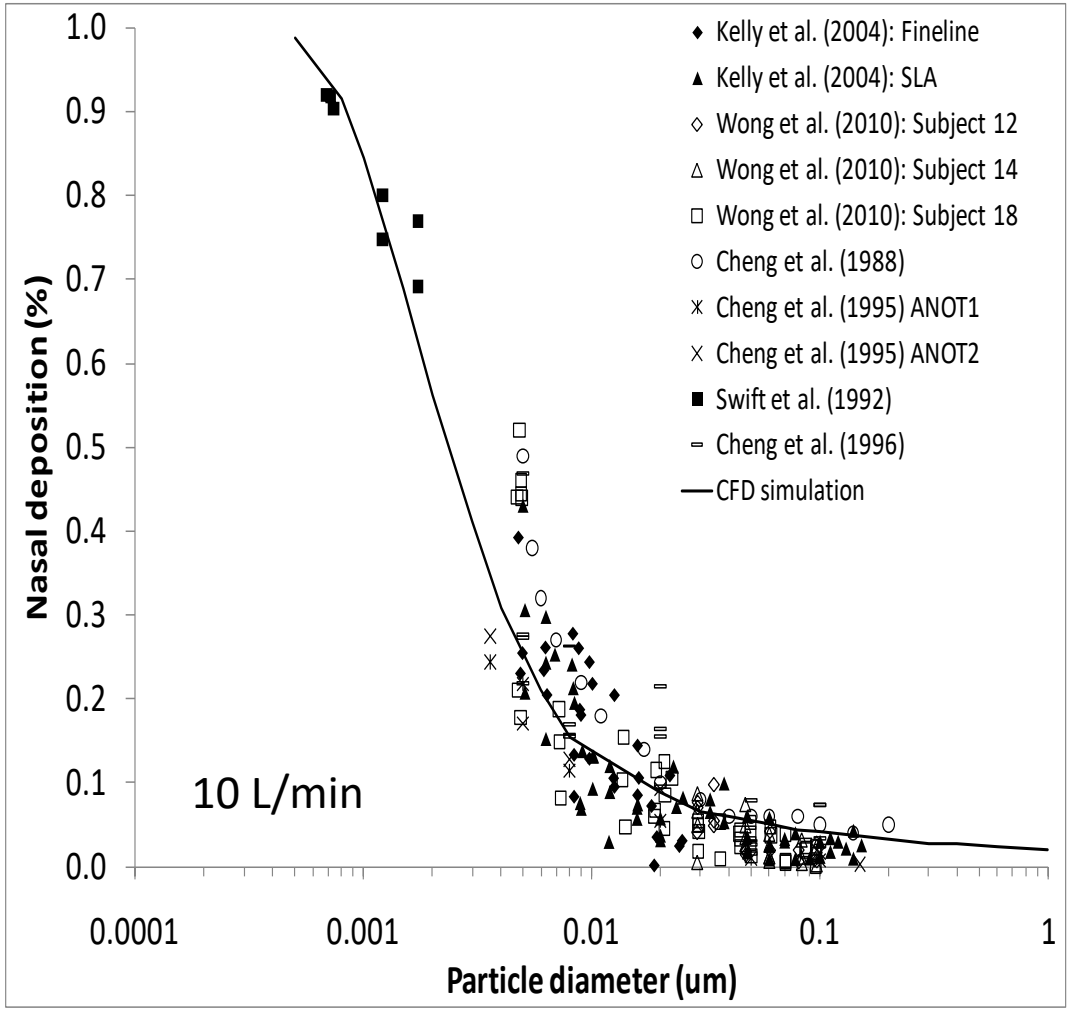


Image courtesy of Dr. Bahman Asgharian, Applied Research Associates

Human Nasal Deposition Patterns



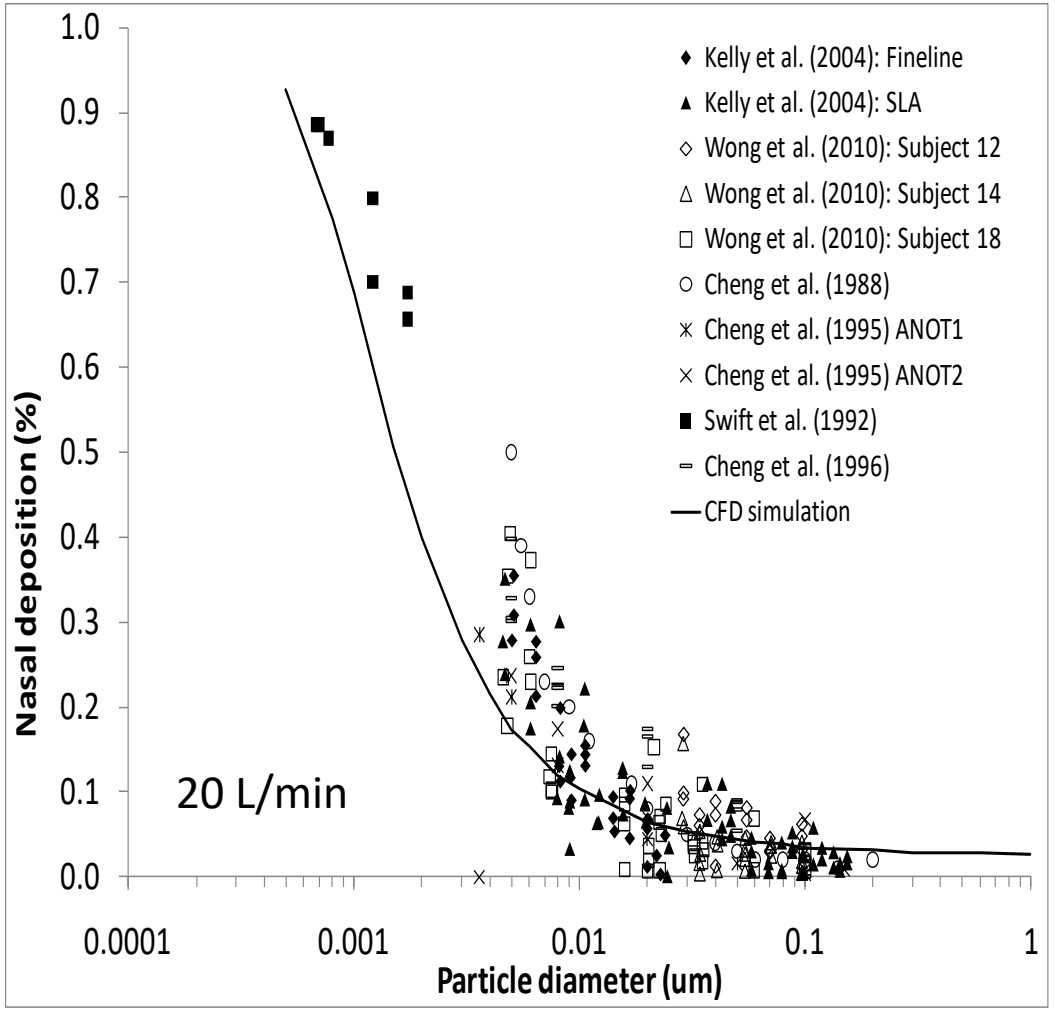
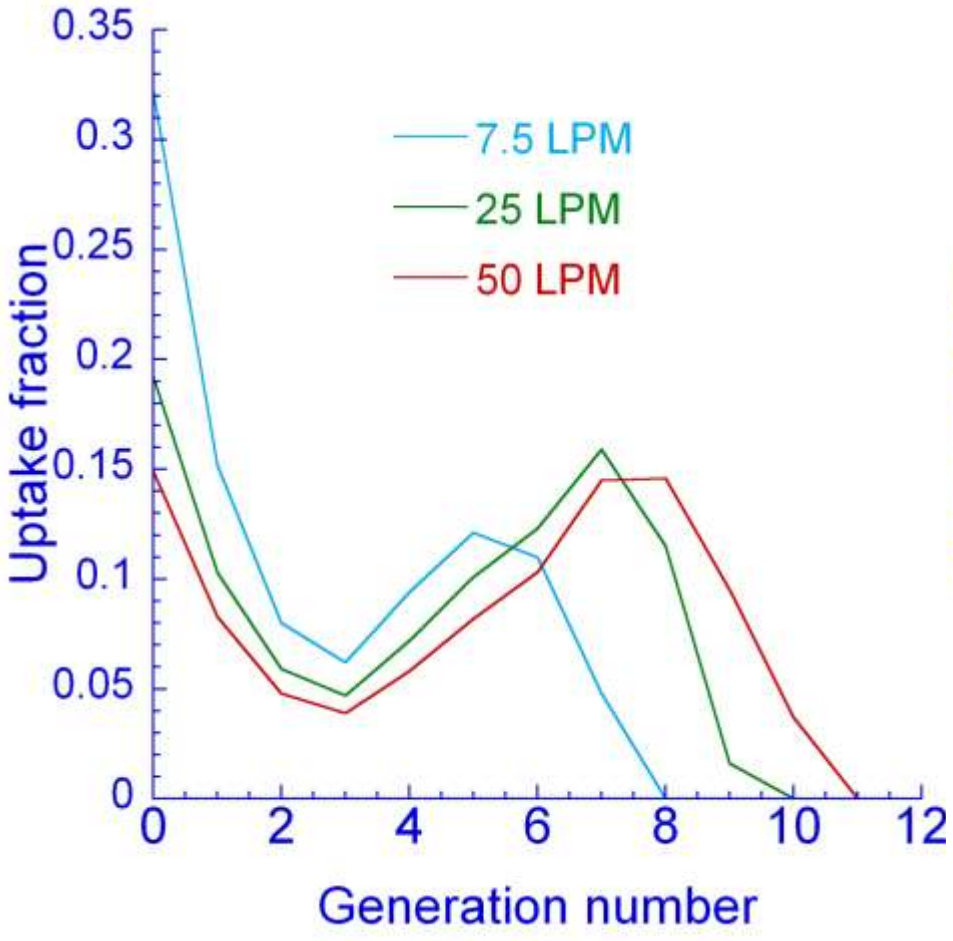


Image courtesy of Dr. Jeffry Schroeter, Applied Research Associates

Percent of Vapor Uptake in the Lower Airway

FORMALDEHYDE



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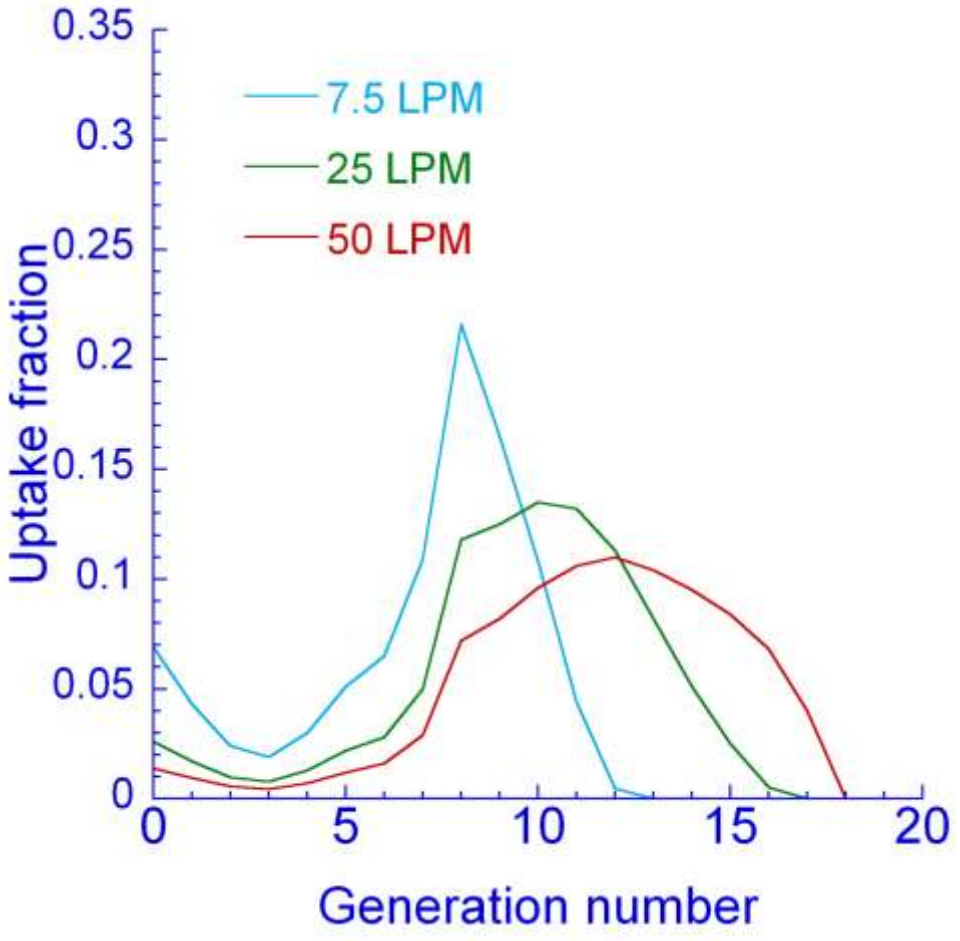

Image courtesy of Dr. Bahman Asgharian, Applied Research Associates

Absorption in the Lower Airway

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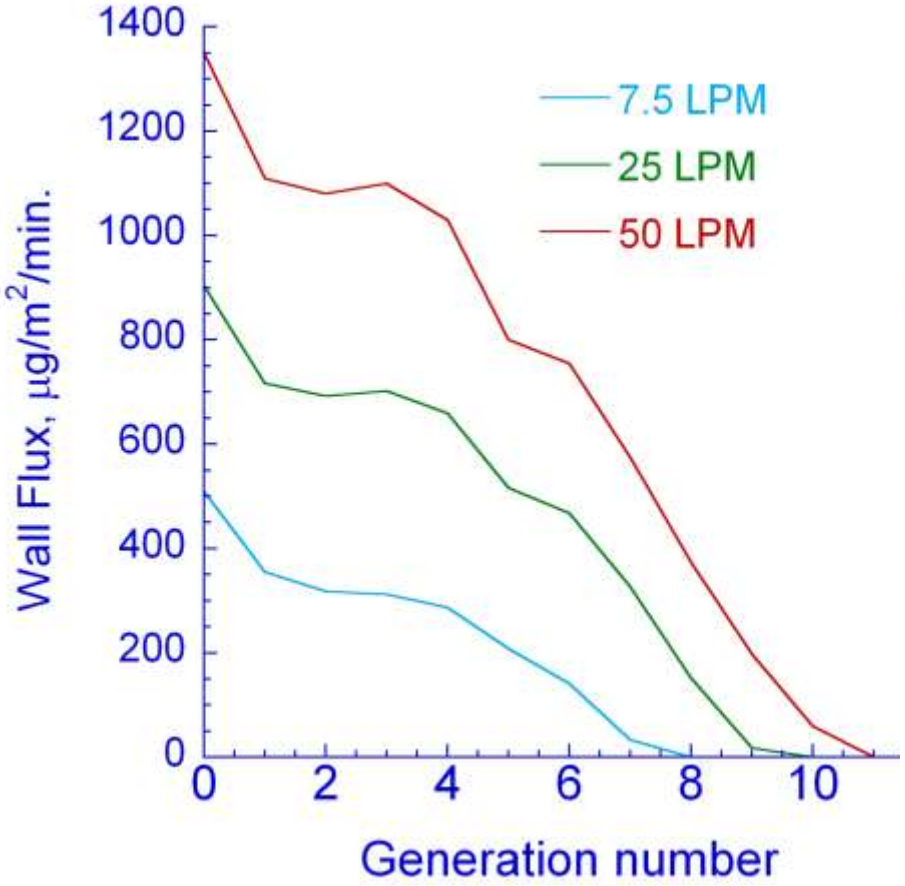

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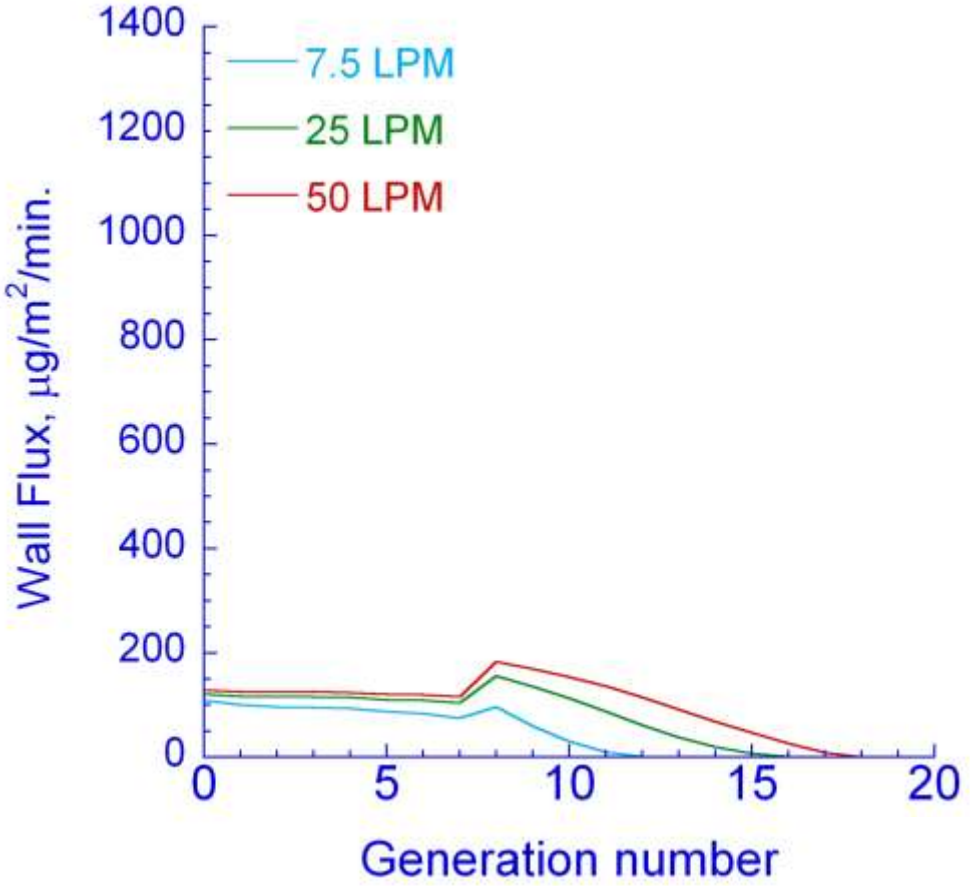
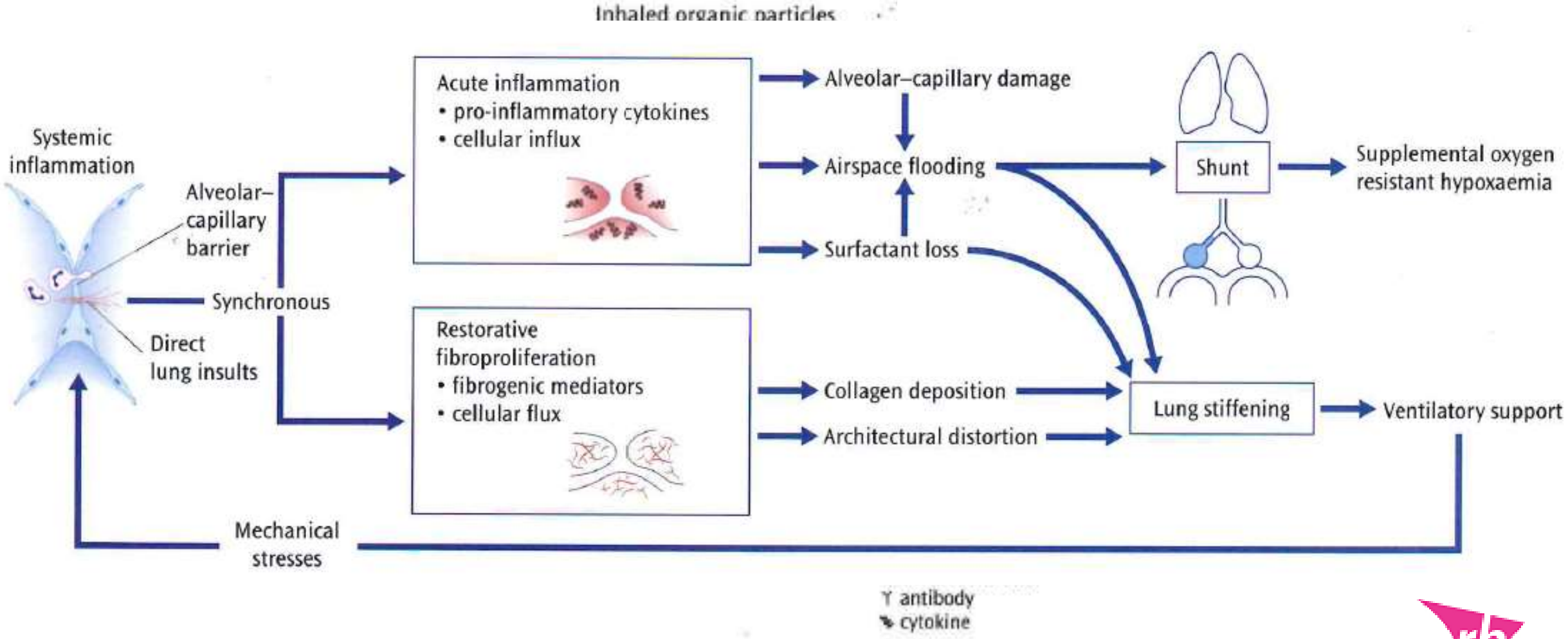


Image courtesy of Dr. Bahman Asgharian, Applied Research Associates

Acute Inhalation vs. Long-term Inhalation Toxicity



Respiratory Medicine, An Illustrated Colour Text by Colin Selby, 2002

Translating Air Concentration to Systemic Dose

- The output from an exposure-only model is applied as the anticipated human systemic dose (mg/kg/day)

$$\text{mg/kg/day} = \frac{(\text{mg/L/day})(A)(D)(MV)}{BW}$$

- A conservative, route non-specific approach for MOE calculation:

$$MOE = \frac{\text{NOAEL (mg/kg/day)}}{\text{Anticipated Human Exposure (mg/kg/day)}}$$

Inhalation Toxicology, 2nd Edition, 2006

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$$MOE = \frac{(NOAEL)(DAF)(D_A)}{(\text{Human exposure})(D_H)\left[\frac{(\text{Human } MV_{actual})}{(\text{Human } MV_{rest})}\right]}$$

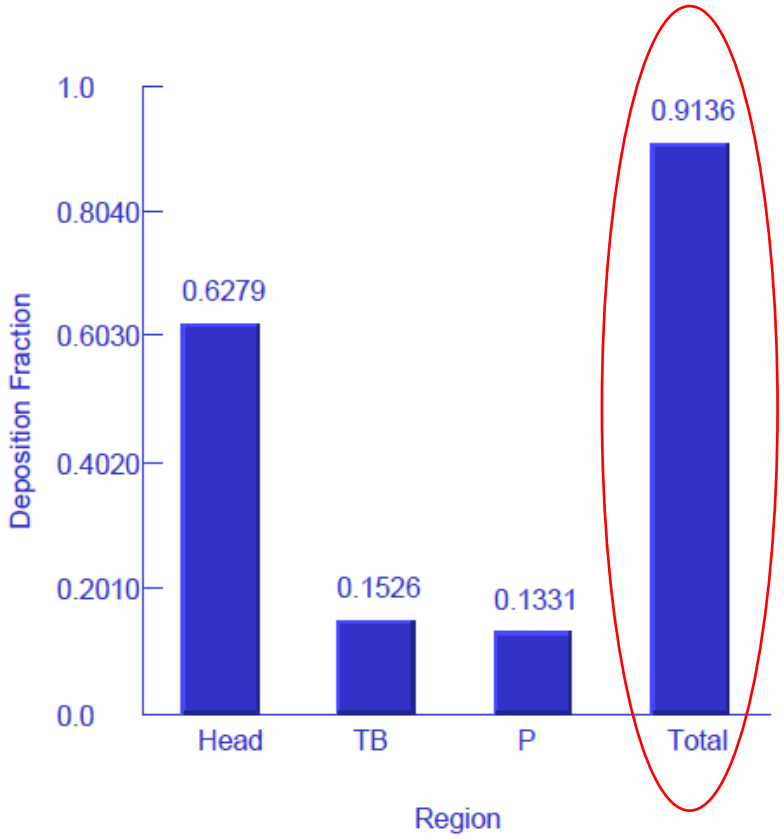
- NOAEL – No observed adverse effect level from an animal inhalation toxicology study in units of air concentration (mg/L/day, mg/m^3/day, ppm/day)
- Human exposure – measured or surrogate in the same concentration units as the animal NOAEL
- D_A – Duration of animal exposure (minutes/day)
- D_H – Duration of human exposure (minutes/day
- DAF – Dosimetric adjustment factor for respiratory tract region (regional deposited dose ratio (RDDR) for aerosol droplets/particles or a regional gas dose ratio (RGDR) for gases and vapors)
- MV_{actual} – Human minute ventilation (L/min) at actual level of activity
- MV_{rest} – Human minute ventilation (L/min) at rest

Inhalation Toxicology, 2nd Edition, 2006

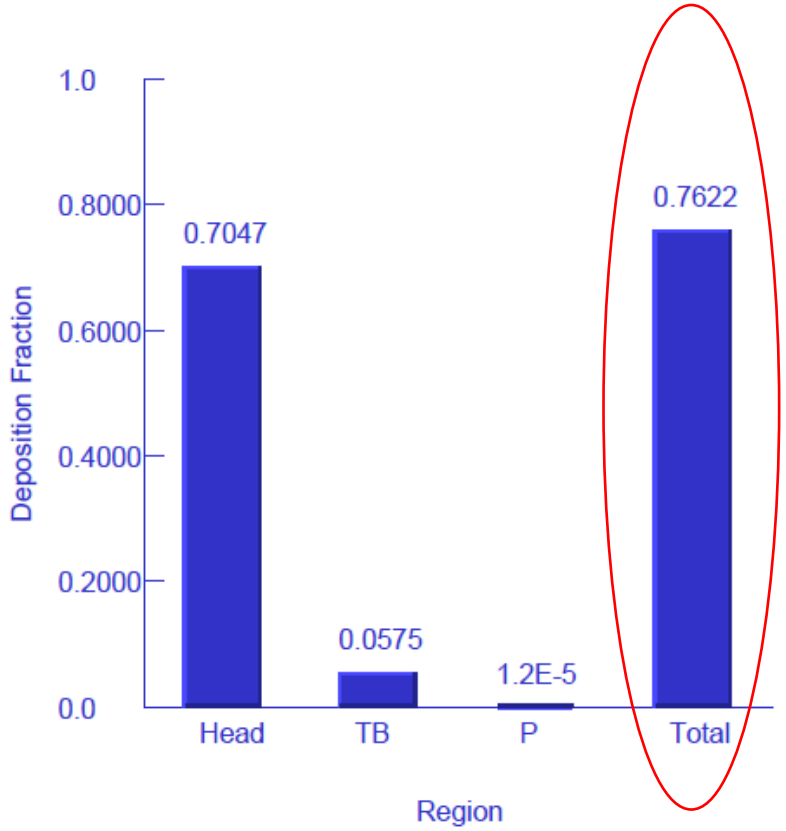
Data Assessment and Evaluation

		Endpoints														
Solvent	Cramer Class	% Solvent	Droplet Size Distribution MMAD (µm)	GSD (µm)	Total Product Amount Release (g/s)	Typical Usage (Sprays per Day)	Length of Time per Spray (s)	Total Spray Time (s)	Cumulative Air Concentration of Solvent Present (mg/day)	Cumulative Inhalation Concentration per Day (mg/m³)** based on 9 L/min	Pass/Fail TTC (Class III <0.47 mg/m³ and Class 1 <1.4 mg/m³)	NOAEL	MOS	Pass/Fail MOS (>100)	Fraction total deposition (adult)	Adjusted Cumulative Inhalation Concentration per Day (mg/m³)** based on 9 L/min	Pass/Fail TTC (Class III <0.47 mg/m³ and Class 1 <1.4 mg/m³)
Ethanol	I	40	6	1	0.005	48	6	288	7.43	0.573302469	PASS	2000	16150.7	PASS			
Isopar	III	86	6	1	0.005	48	6	288	15.98	1.233024691	FAIL	86.4	324.406	PASS	0.9136	1.126491358	FAIL
DPnP	III	20	6	1	0.005	48	6	288	3.72	0.287037037	PASS	21	338.71	PASS			
Acetone	I	40	6	1	0.005	48	6	288	7.43	0.573302469	PASS	171	1380.89	PASS			
Solvent	Cramer Class	% Solvent	Droplet Size Distribution MMAD (µm)	GSD (µm)	Total Product Amount Release (g/s)	Typical Usage (Sprays per Day)	Length of Time per Spray (s)	Total Spray Time (s)	Cumulative Air Concentration of Solvent Present (mg/day)	Cumulative Inhalation Concentration per Day (mg/m³)** based on 9 L/min	Pass/Fail TTC (Class III <0.47 mg/m³ and Class 1 <1.4 mg/m³)	NOAEL	MOS	Pass/Fail MOS (>100)	Fraction total deposition (adult)	Adjusted Cumulative Inhalation Concentration per Day (mg/m³)** based on 9 L/min	Pass/Fail TTC (Class III <0.47 mg/m³ and Class 1 <1.4 mg/m³)
Ethanol	I	40	64	3.17	0.15	10	1	10	7.74	0.597222222	PASS	2000	15503.9	PASS			
Isopar	III	86	64	3.17	0.15	10	1	10	16.65	1.284722222	FAIL	86.4	311.351	PASS	0.3269	0.419975694	PASS
DPnP	III	20	64	3.17	0.15	10	1	10	3.87	0.298611111	PASS	21	325.581	PASS			
Acetone	I	40	64	3.17	0.15	10	1	10	7.74	0.597222222	PASS	171	1325.58	PASS			

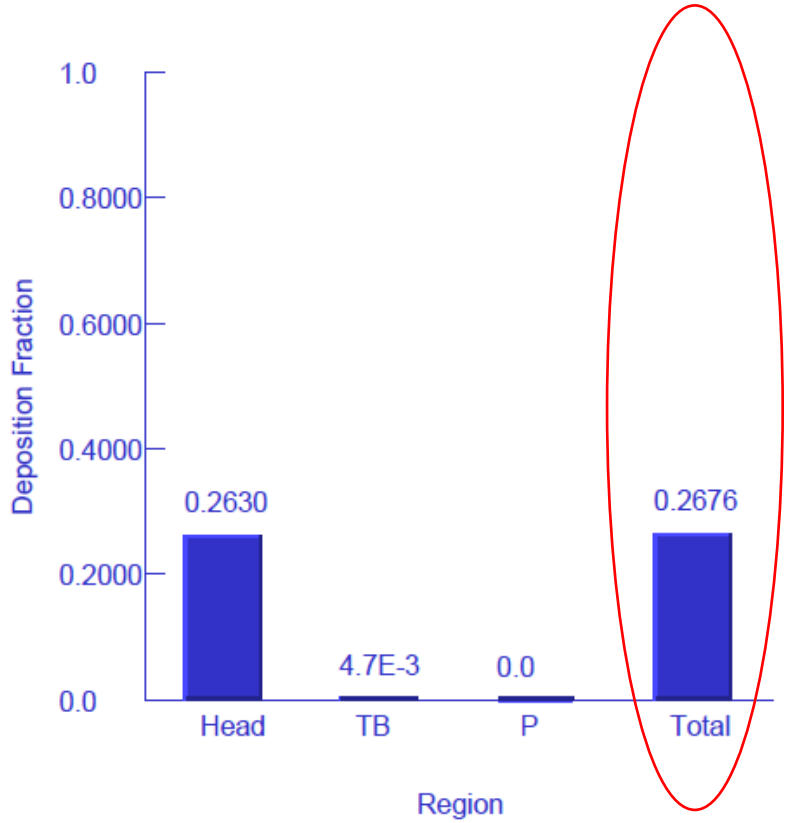
Oronasal Regional Deposition Profile



6 µm droplets



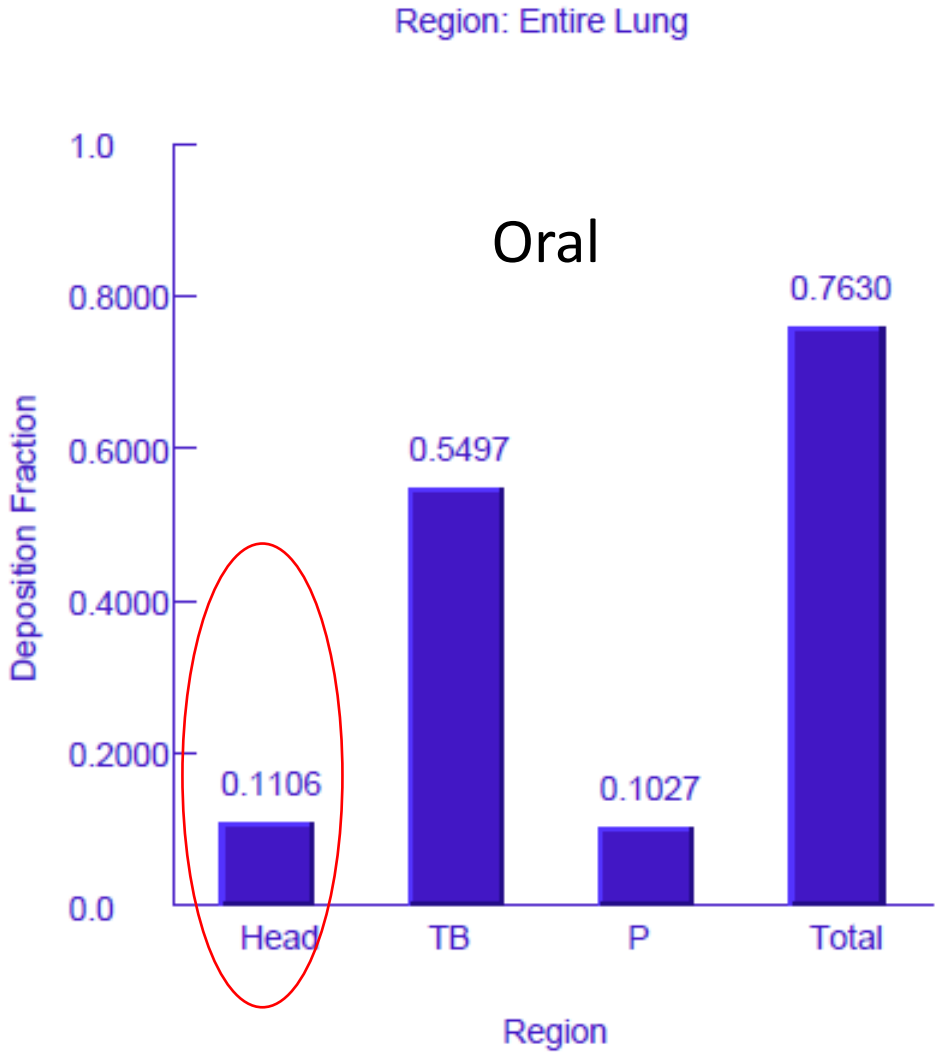
20 µm droplets

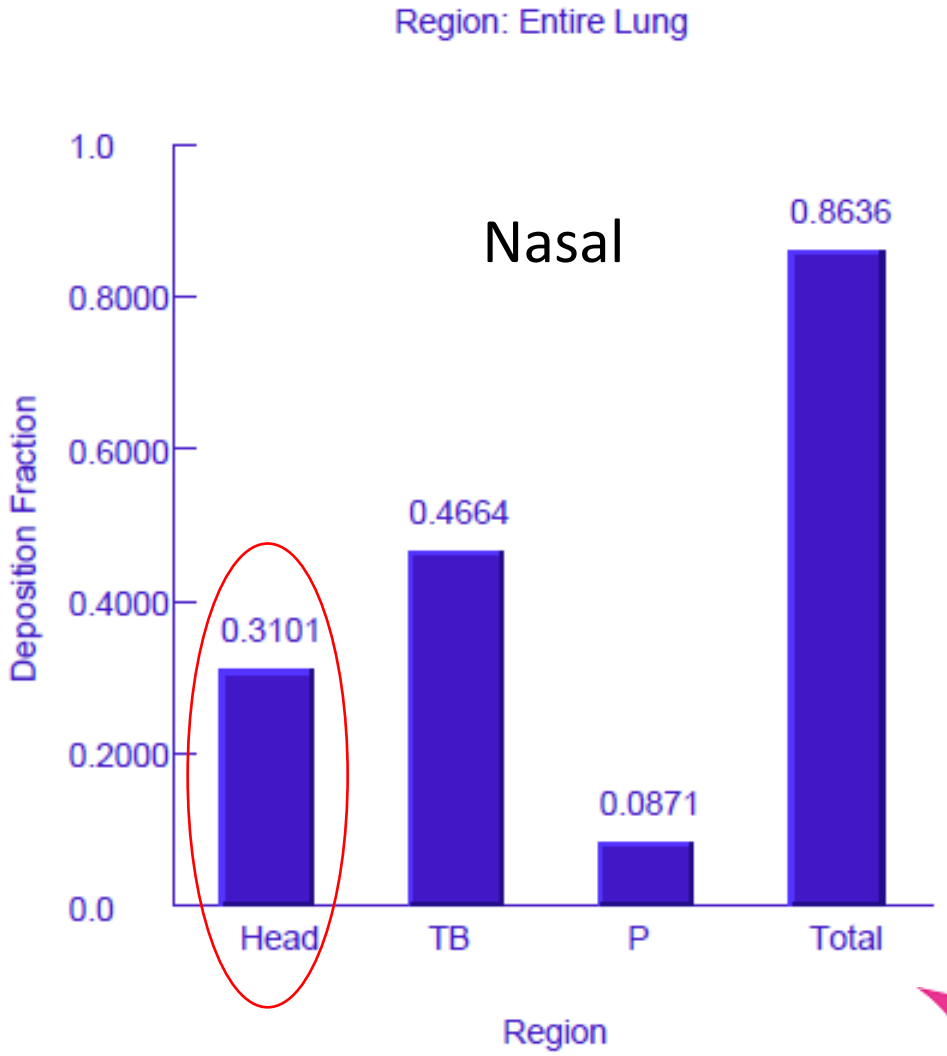


50 µm droplets

6 µm Oral vs. Nasal Deposition Profile*

*in 3 Month Old Child





Acknowledgements

- 2-Box Air Dispersion Model
  - Applied Research Associates
    - Owen Price
- Respiratory In Silico Deposition Model (MPPD)
  - The Hamner Institutes for Health Sciences, Applied Research Associates, and University of North Carolina
    - Bahman Asgharian
    - Jeffry Schroeter
    - Julie Kimball
    - Owen Price