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THE UNIVERSITY OF TOKYO

Fate and Effects of Inhaled Nanomaterials: What are the Perceived and Real Risks?

Günter Oberdörster
University of Rochester

April 4, 2014

UNIVERSITY of ROCHESTER MEDICAL CENTER

ALASKA
SCALE 1:5,000,000
Albers equal area projection, standard parallels 55°N and 65°N, central meridian 154°W
ALEUTIAN ISLANDS
RAT ISLANDS
ANDREANOF ISLANDS
FOX ISLANDS
PACIFIC OCEAN
CANADA
BRITISH COLUMBIA
ALBERTA
SASKATCHEWAN
MANITOBA
ONTARIO
QUEBEC
NEW BRUNSWICK
WASHINGTON
OREGON
CALIFORNIA
NEVADA
IDAHO
MONTANA
WYOMING
UTAH
ARIZONA
COLORADO
NEW MEXICO
NORTH DAKOTA
SOUTH DAKOTA
NEBRASKA
KANSAS
OKLAHOMA
TEXAS
MINNESOTA
IOWA
MISSOURI
ARKANSAS
LOUISIANA
WISCONSIN
ILLINOIS
INDIANA
OHIO
PENNSYLVANIA
WEST VIRGINIA
VIRGINIA
KENTUCKY
MISSISSIPPI
ALABAMA
GEORGIA
FLORIDA
MAINE
ROCKY MOUNTAINS
GREAT PLAINS
LLANO ESTACADO
EDWARDS PLATEAU
Lake Superior
Lake Huron
Lake Erie
Lake Ontario
ATLANTIC OCEAN
GULF OF MEXICO
Gulf of California
MEXICO
BAJA CALIFORNIA
SONORA
CHIHUAHUA
COAHUILA
NUEVO LEON
DURANGO
ZACATECAS
TAMAULIPAS
CUBA
Seattle
San Francisco
Los Angeles
San Diego
Phoenix
El Paso
Ciudad Juárez
Dallas
Houston
San Antonio
Chicago
Detroit
Toronto
New York
Boston
Washington
Jacksonville
Winnipeg
Calgary
Montreal
Monterrey
STANDARD TIME ZONES
POPULATED PLACES
1,000,000 and over
500,000 – 999,999
100,000 – 499,999
25,000 – 99,999
24,999 and less
National capital
State or provincial capital
Urban areas
Chicago
Seattle
Omaha
Washington
Albany
TRANSPORTATION
Interstate; limited access highway
Other principal highway
Ferry
Railroad
PHYSICAL FEATURES
Streams: perennial; intermittent
Lakes: perennial; intermittent
Bathymetry (meters)
Highest elevation in state (feet)
Other elevations (feet)
Forest cover
SCALE 1:5,000,000
Albers equal area projection, standard parallels 29°30'N and 45°30'N, central meridian 96°W
Compiled by U.S. Geological Survey
2001
Principal Islands of HAWAII
Puerto Rico and the Virgin Islands


ALASKA
ALEUTIAN ISLANDS
CANADA
MONTANA
NORTH DAKOTA
SOUTH DAKOTA
MINNESOTA
WISCONSIN
WYOMING
IDAHO
OREGON
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POPULATED PLACES
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Maps & Directions NEW YORK STATE
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NYS THRUWAY
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FINGER LAKES
Syracuse
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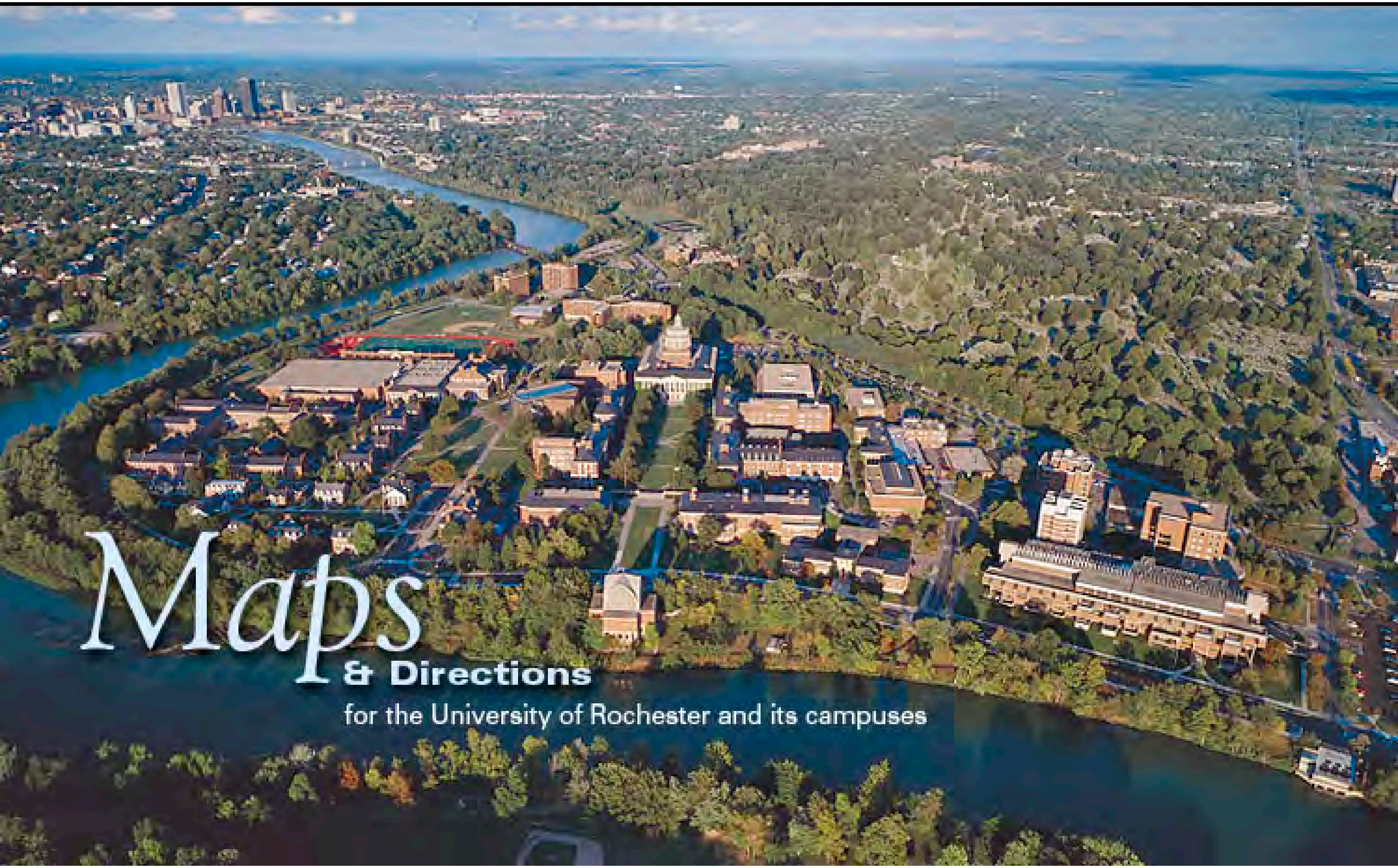


Maps & Directions

for the University of Rochester and its campuses

UNIVERSITY of ROCHESTER MEDICAL CENTER

OUTLINE

Nanotoxicology, some Basics

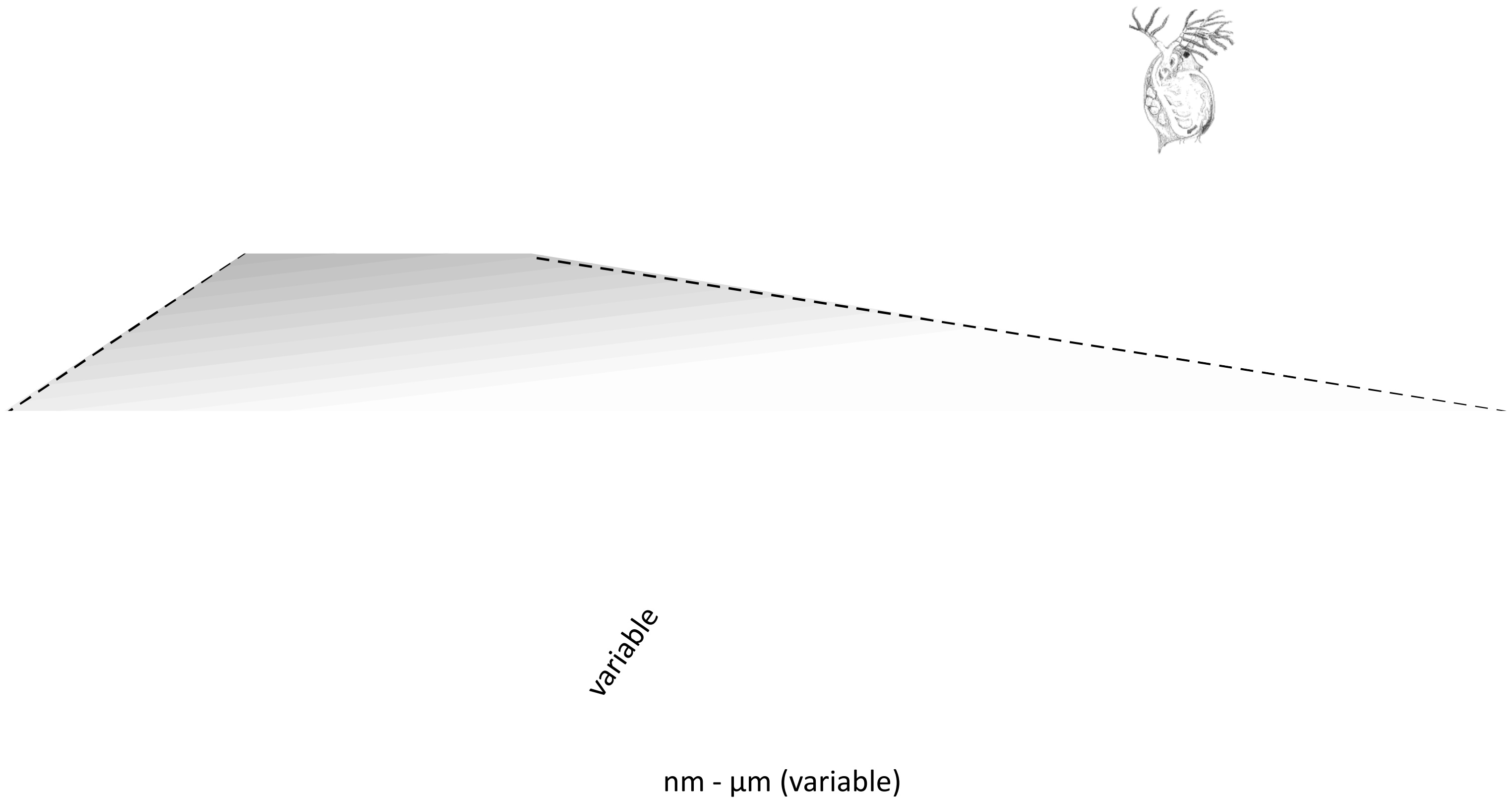
Dosing the respiratory tract

Nanoparticle biokinetics

Hazard/Risk characterization

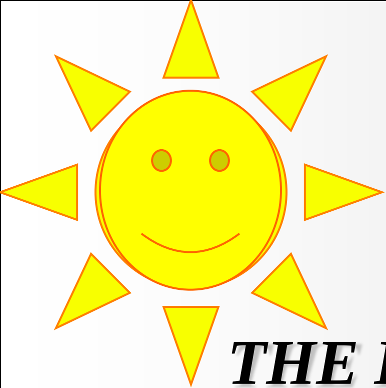
Environmental ultrafine particles

Nanoscale Materials



Length scales for natural and synthetic structures (above)
and some examples of engineered nanomaterials of varying size and shape (below)

From: Casarett & Doull's Toxicology, in press, 2012



NANOTECHNOLOGY

THE BRIGHT! *and* *THE DARK?*

Multiple Applications/Benefits

- **Structural Engineering**
- **Electronics, Optics**
- **Food and Feed Industry**
- **Consumer Products**
- **Energy Technology**
- **Soil/Water Remediation**
- **Nanomedicine:**
  - ***therapeutic***
  - ***diagnostic***
  - ***drug delivery***
  - ***cancer***
  - ***nanosensors***
  - ***nanorobotics***

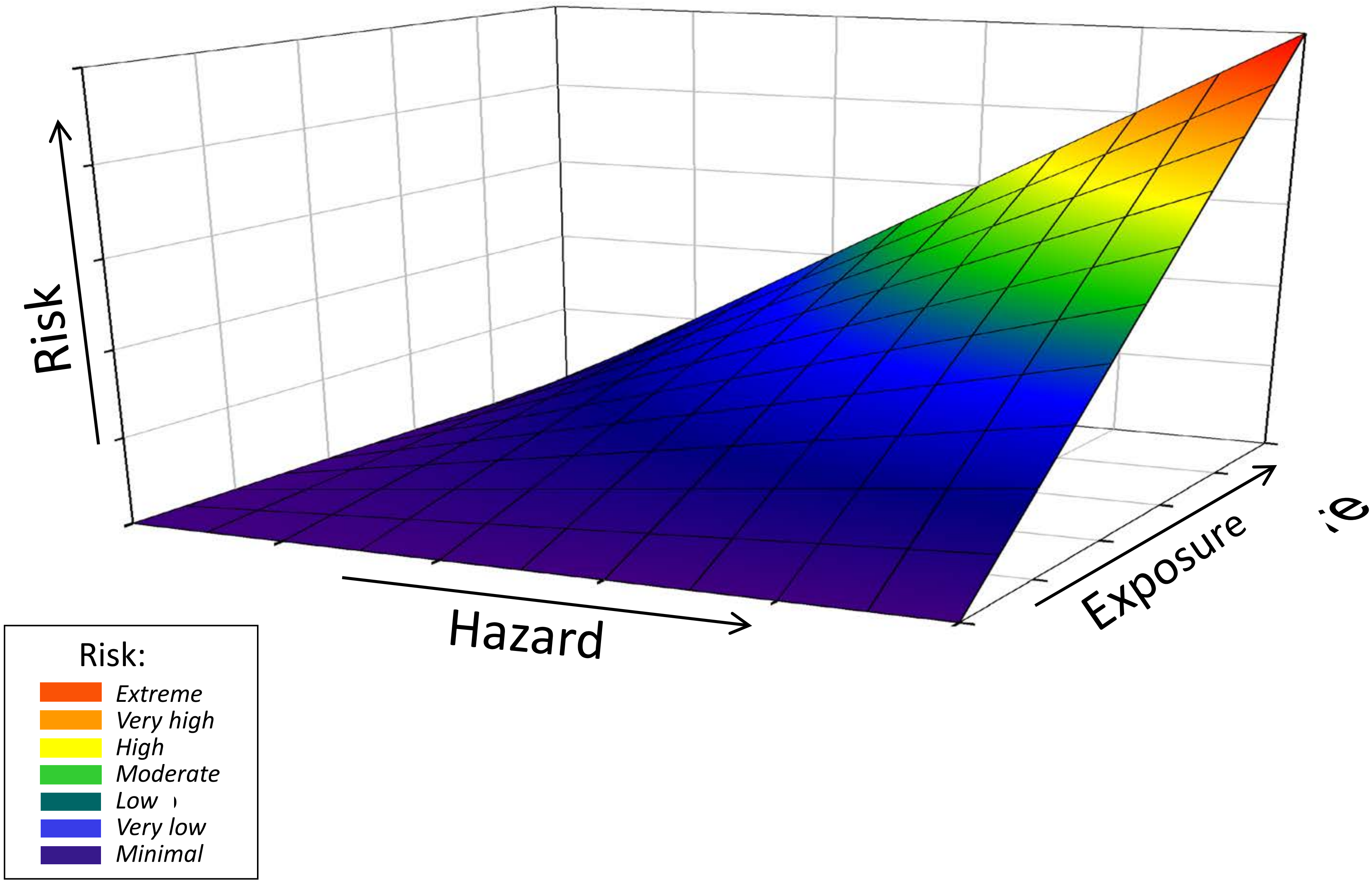
Consumer Fears/Perceived Risks

- **Safety: Potential adverse effects**
- **Environmental Contamination**
- **Inadvertent Exposure**
  (inhalation, dermal, ingestion)
- **Susceptible Subpopulation**
- **Societal Implications**

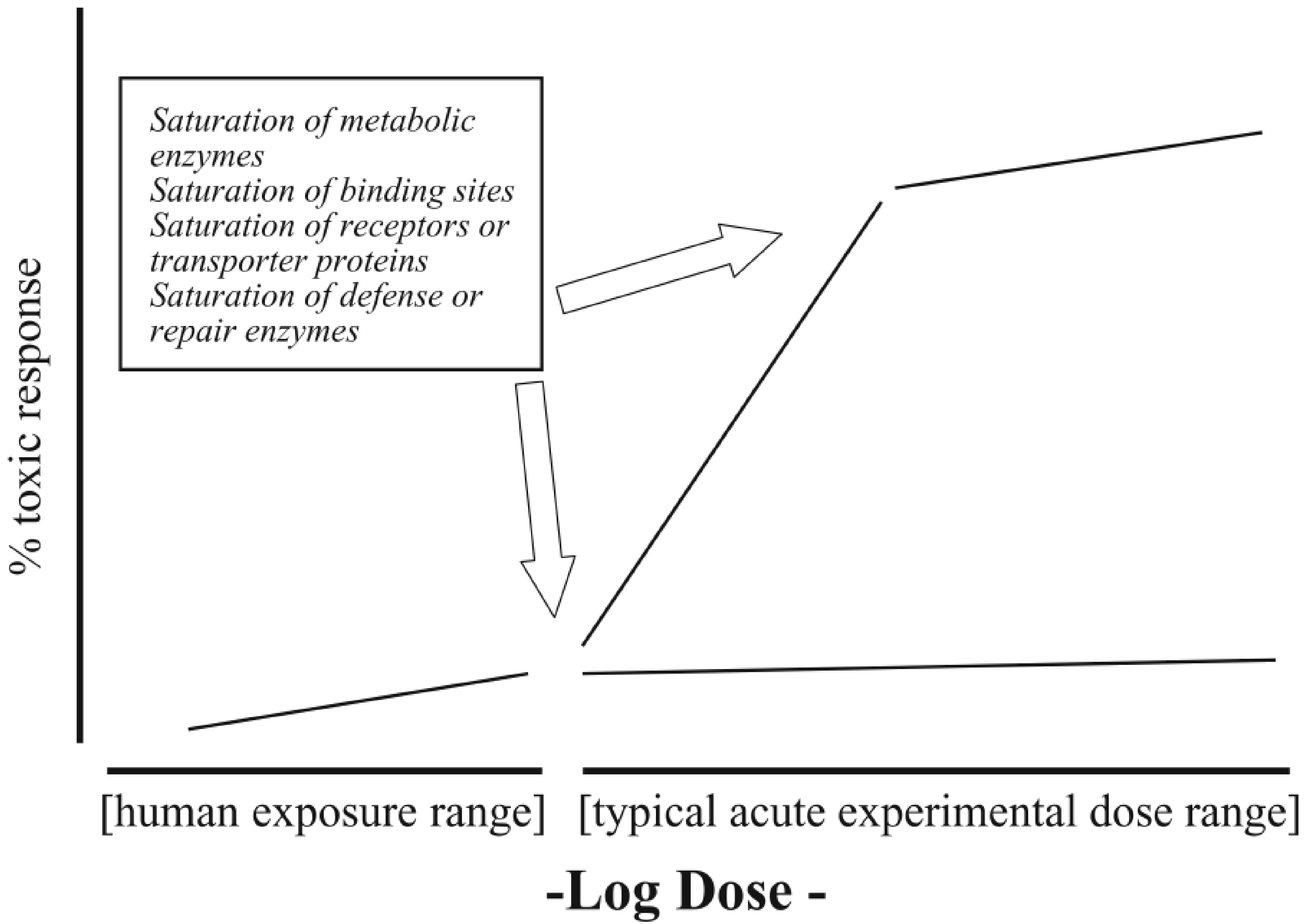
- **Nanotoxicology:**

  Safety/Risk Assessment of engineered Nanomaterials and of Nanotechnology enabled Applications

Risk = f (hazard; exposure)



Conceptual Depiction of Factors for Considering Dose-dependent Transitions in Determinants of Toxicity



From: Slikker Jr., et al. 2004

All things are poison,
and nothing is without poison;
only the dose permits something
not to be poisonous

The Dose makes the poison

Paracelsus, 1493 - 1541

Toxicology 254 (2008) 82–90

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Time-dependent translocation and potential impairment on central nervous system by intranasally instilled TiO_2 nanoparticles

Jiangxue Wang[a,b], Ying Liu[a,b], Fang Jiao[a,b], Fang Lao[a,b], Wei Li[a,b], Yiqun Gu[c], Yufeng Li[a,b], Cuicui Ge[a,b], Guoqiang Zhou[a,b], Bai Li[a,b], Yuliang Zhao[a,b,*], Zhifang Chai[a,b], Chunying Chen[a,b,**]

[a] *Laboratory for Bio-Environmental Effects of Nanomaterials and Nanosafety and Key Lab of Nuclear Analytical Techniques, Institute of High Energy Physics, Chinese Academy of Sciences, Beijing 100049, PR China*
[b] *National Center for Nanoscience and Technology, Beijing 100190, PR China*
[c] *Maternity Hospital of Haidian District, Beijing 100080, China*

Nanoparticles can be administered via nasal, oral, intraocular, intratracheal (pulmonary toxicity), tail vein and other routes. Here, we focus on the time-dependent translocation and potential damage of TiO_2 nanoparticles on central nervous system (CNS) through intranasal instillation. Size and structural properties are important to assess biological effects of TiO_2 nanoparticles. In present study, female mice were intranasally instilled with two types of well-characterized TiO_2 nanoparticles (i.e. 80 nm, rutile and 155 nm, anatase; purity > 99%) every other day. Pure water instilled mice were served as controls. The brain tissues were collected and evaluated for accumulation and distribution of TiO_2, histopathology, oxidative stress, and inflammatory markers at post-instillation time points of 2, 10, 20 and 30 days. The titanium contents in the sub-brain regions including olfactory bulb, cerebral cortex, hippocampus, and cerebellum were determined by inductively coupled plasma mass spectrometry (ICP-MS). Results indicated that the instilled TiO_2 directly entered the brain through olfactory bulb in the whole exposure period, especially deposited in the hippocampus region. After exposure for 30 days, the pathological changes were observed in the hippocampus and olfactory bulb using Nissl staining and transmission electron microscope. The oxidative damage expressed as lipid peroxidation increased significantly, in particular in the exposed group of anatase TiO_2 particles at 30 days postexposure. Exposure to anatase TiO_2 particles also produced higher inflammation responses, in association with the significantly increased tumor necrosis factor alpha (TNF-α) and interleukin (IL-1β) levels. We conclude that subtle differences in responses to anatase TiO_2 …

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Nano TiO_2 repeated bolus instillation into mouse:

7.5 mg into mouse = 17.5 grams into human nose!

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17.5 g TiO_2 (P25)

Some Headlines in the Popular Press:

Nanoparticles (NPs)

kill workers

cause cancer

damage DNA

soften your brain

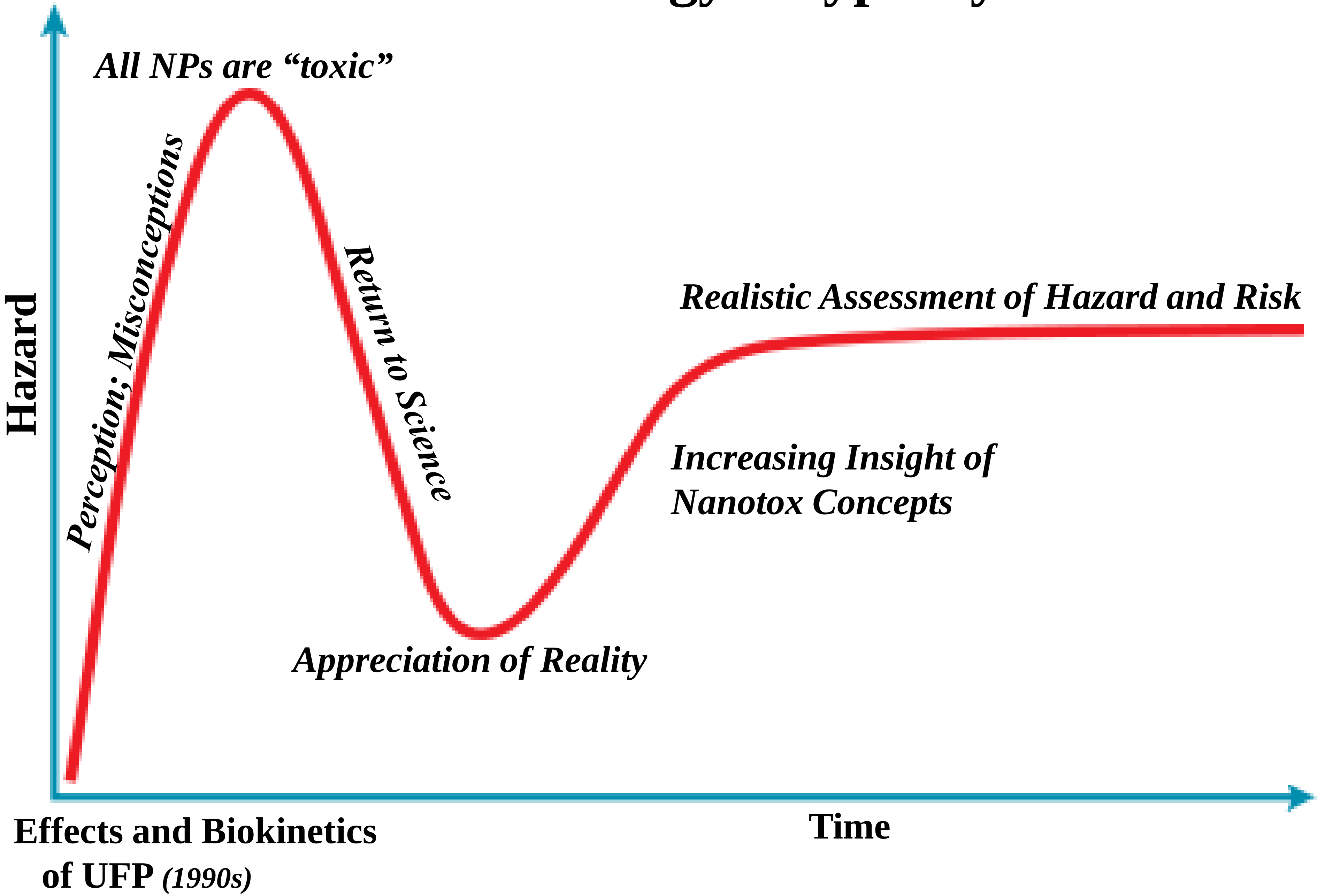
cause lung damage

cause genetic damage

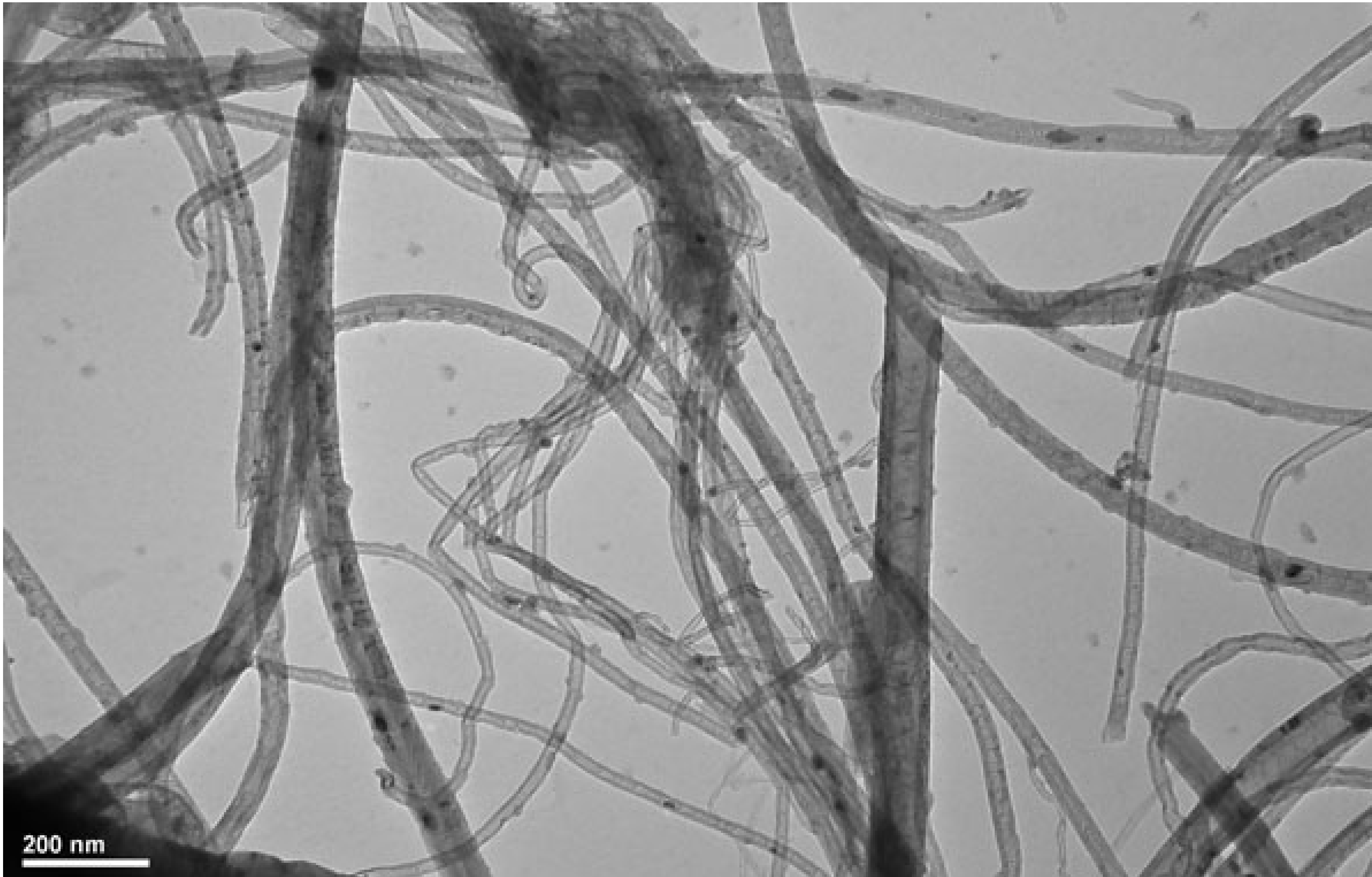
in sunscreen cause Alzheimer’s?

are carbon nanotubes the next asbestos?

Nanotoxicology - Hype Cycle



DPPC/Alb-Dispersed Mitsui Multiwalled Carbon Nanotubes (MWCNTs)

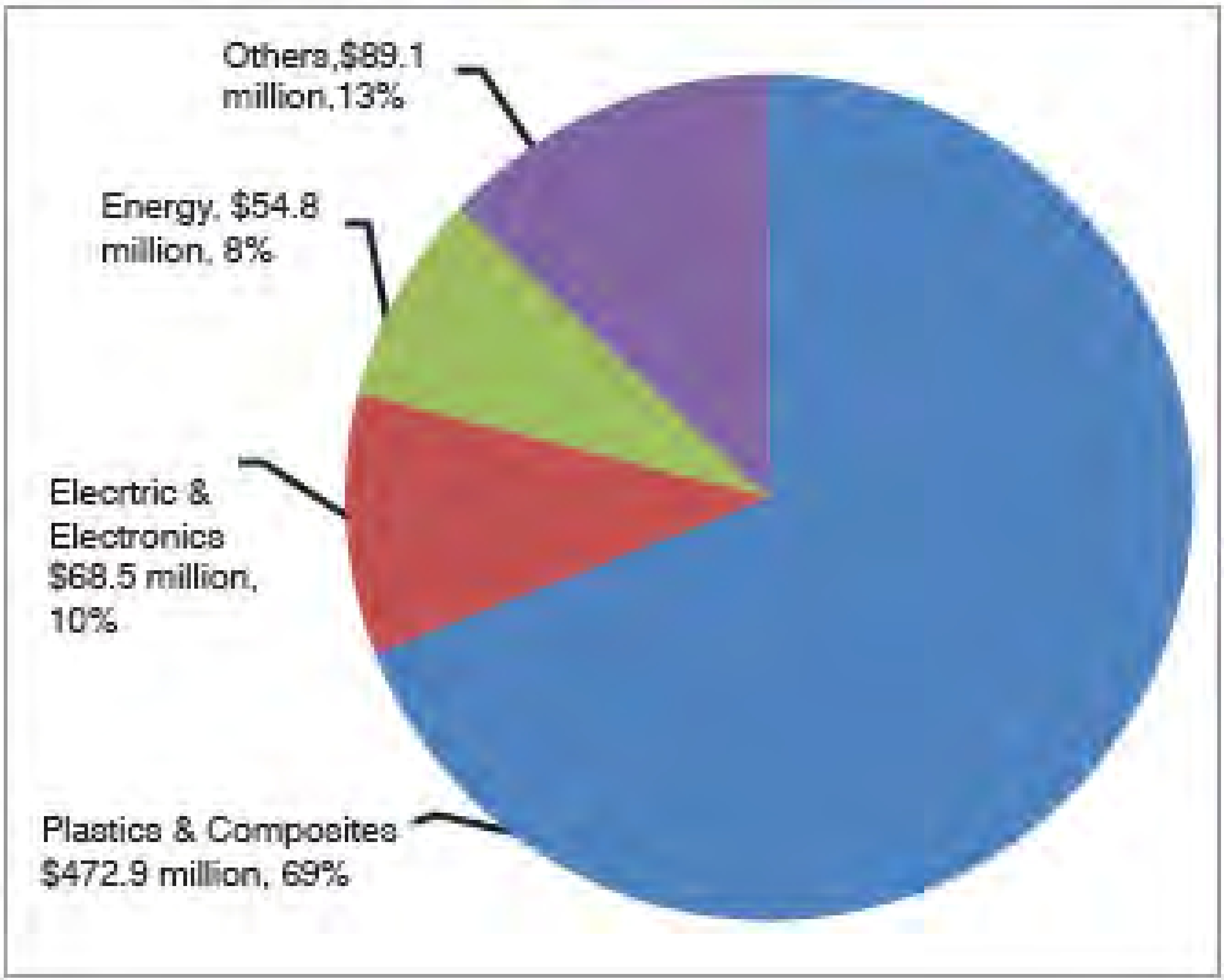


Next five years forecast (2011-2016) for global CNTs market

(compounded annual growth rate)

http://www.nanowerk.com/spotlight

Global CNTs market by industry (2010)



http://www.nanowerk.com/spotlight

Induction of mesothelioma in p53+/- mouse by intraperitoneal application of multi-wall carbon nanotube

Takagi et al., J. Toxicol. Sci. 33 (No. 1): 105-116, 2008

Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study

CRAIG A. POLAND, RODGER DUFFIN, IAN KINLOCH, ANDREW MAYNARD, WILLIAM A. H. WALLACE, ANTHONY SEATON, VICKI STONE, SIMON BROWN WILLIAM MACNEE, AND KEN DONALDSON

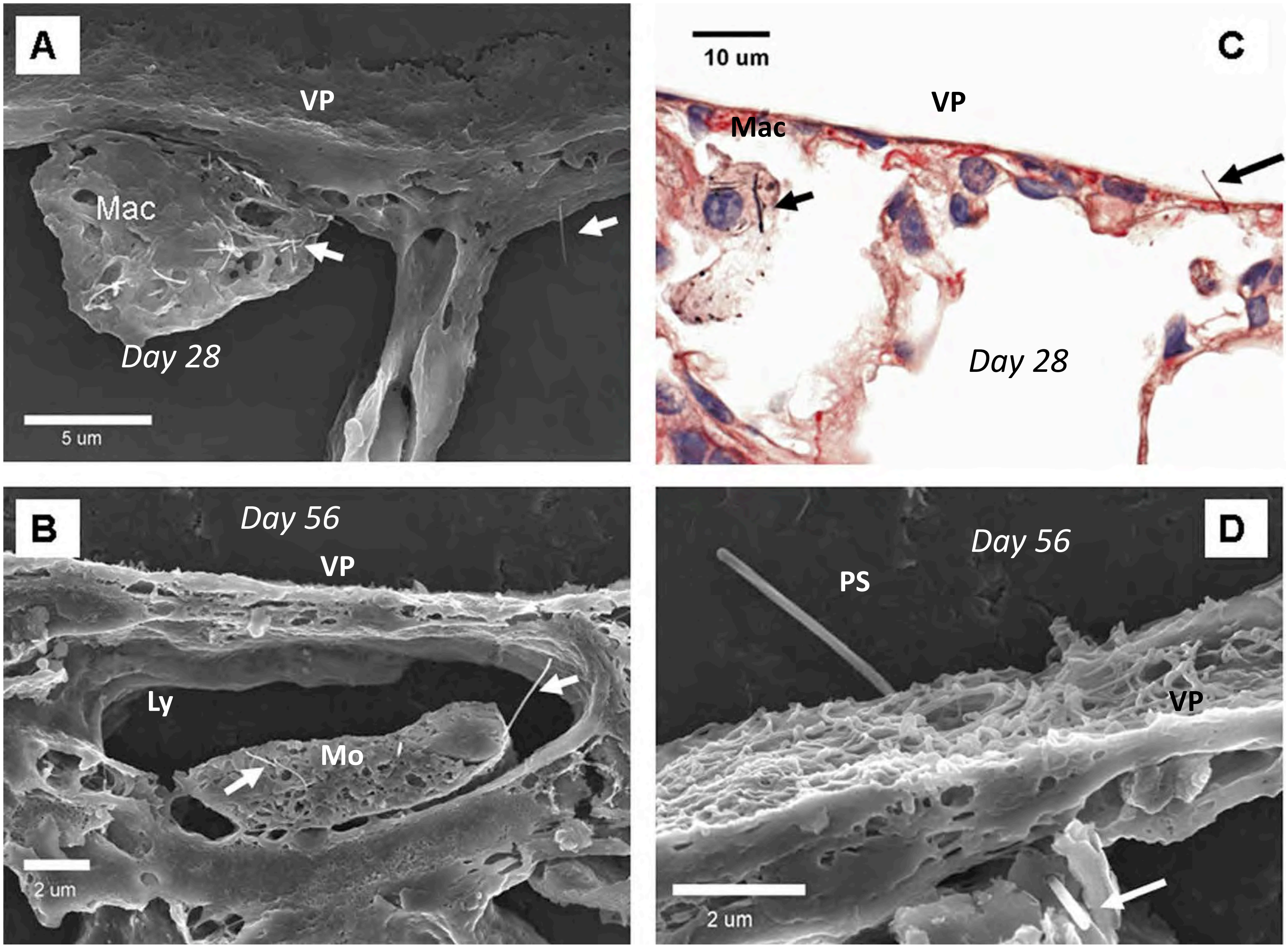
Nature Nanotechnology/Vol. 3/July 2008

Induction of mesothelioma by a single intrascrotal administration of multi-wall carbon nanotube in intact male Fischer 344 rats

Sakamoto et al, J.Tox. Sci., 34, 65-76, 2009

MWCNT in Subpleural Tissues, Visceral Pleura and Pleural Space of Mice Following Oro-Pharyngeal Aspiration (80 µg)

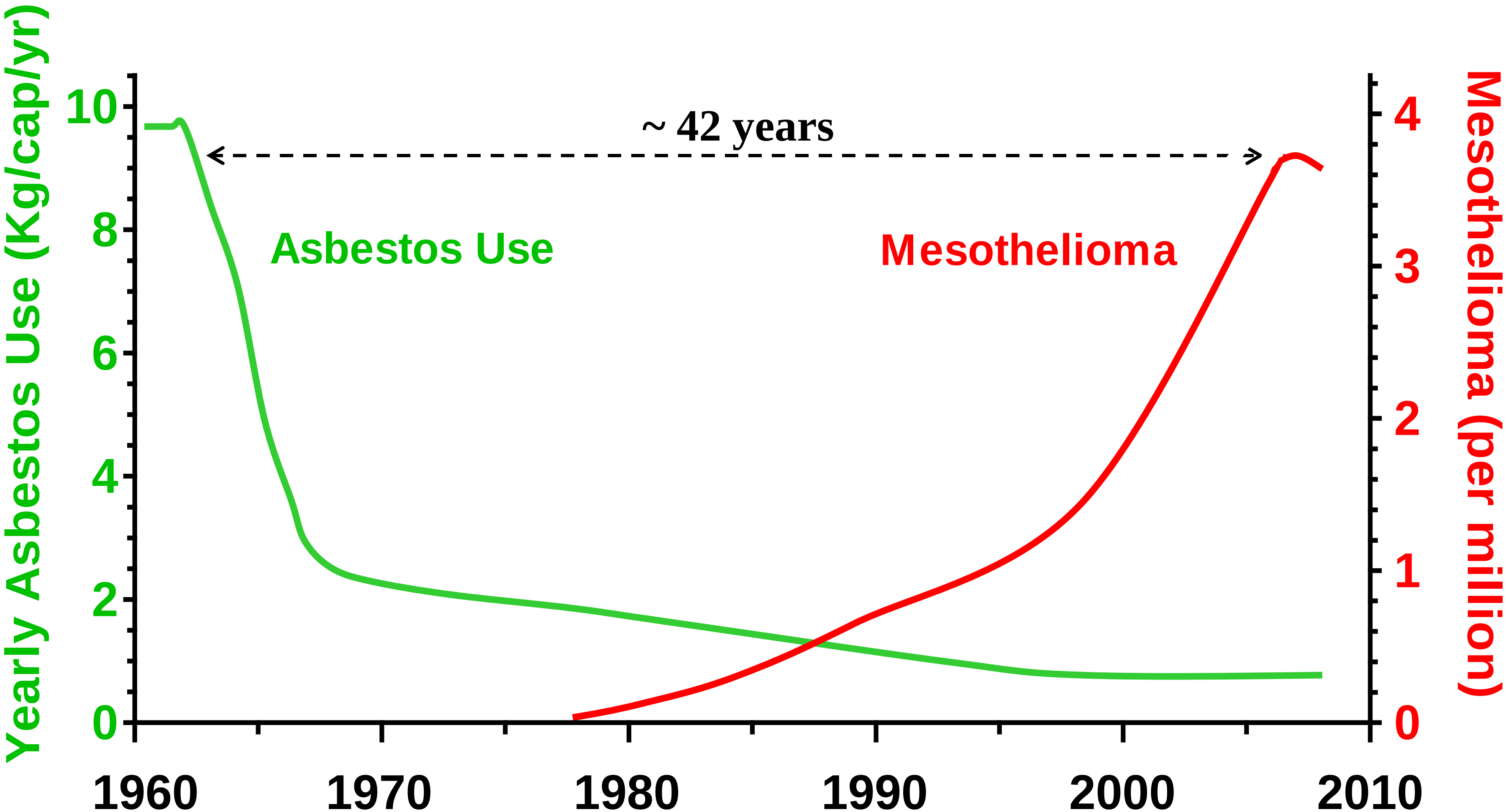
From: Mercer et al., 2010



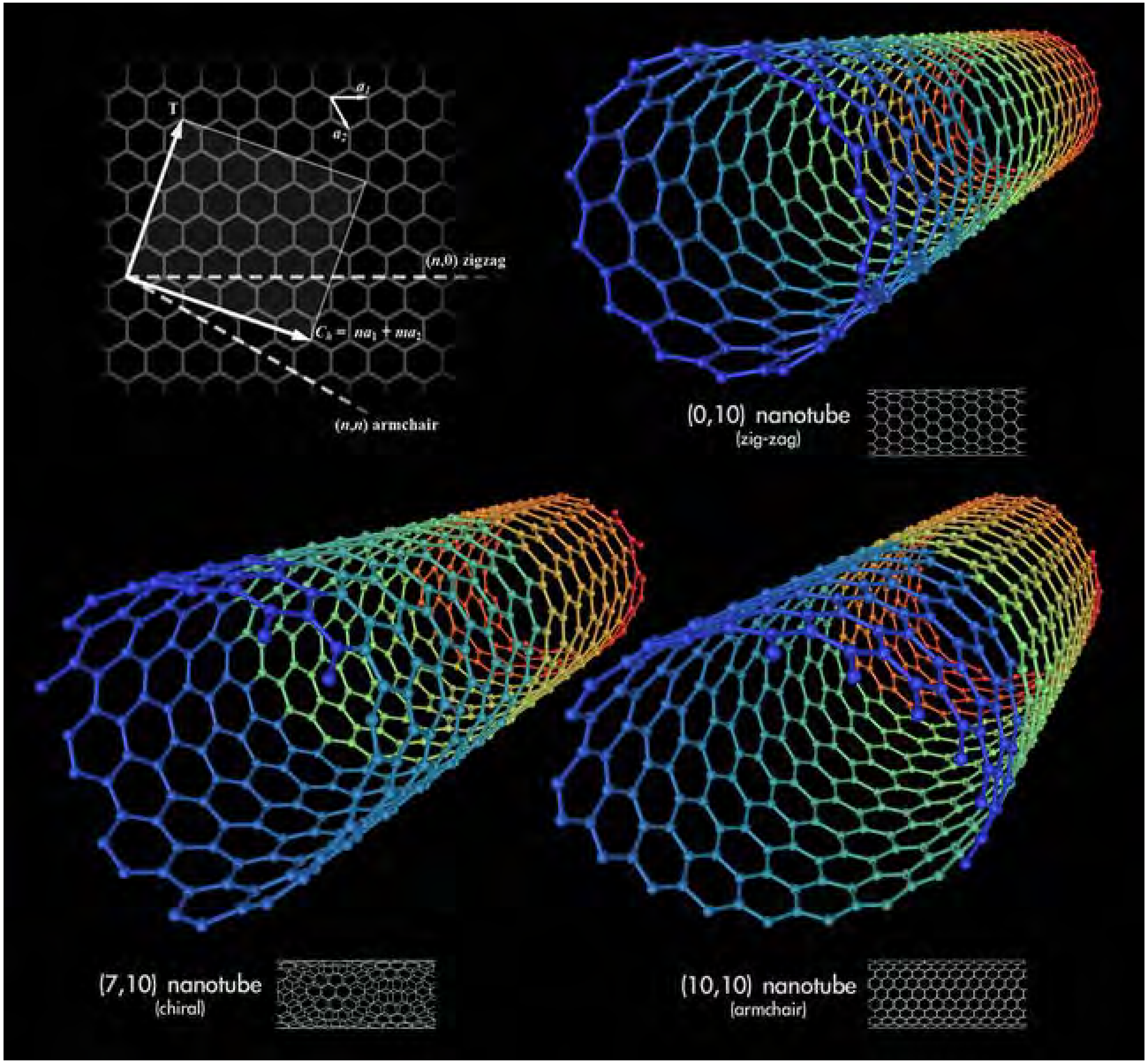
VP: visceral pleura; Mac: alveolar macrophage; Mo: monocyte; Ly: lymph vessel; PS: pleural space

Asbestos Use and Age Standardized Mesothelioma Incidence Rates in Hong Kong

Tse et al EHP, 2010

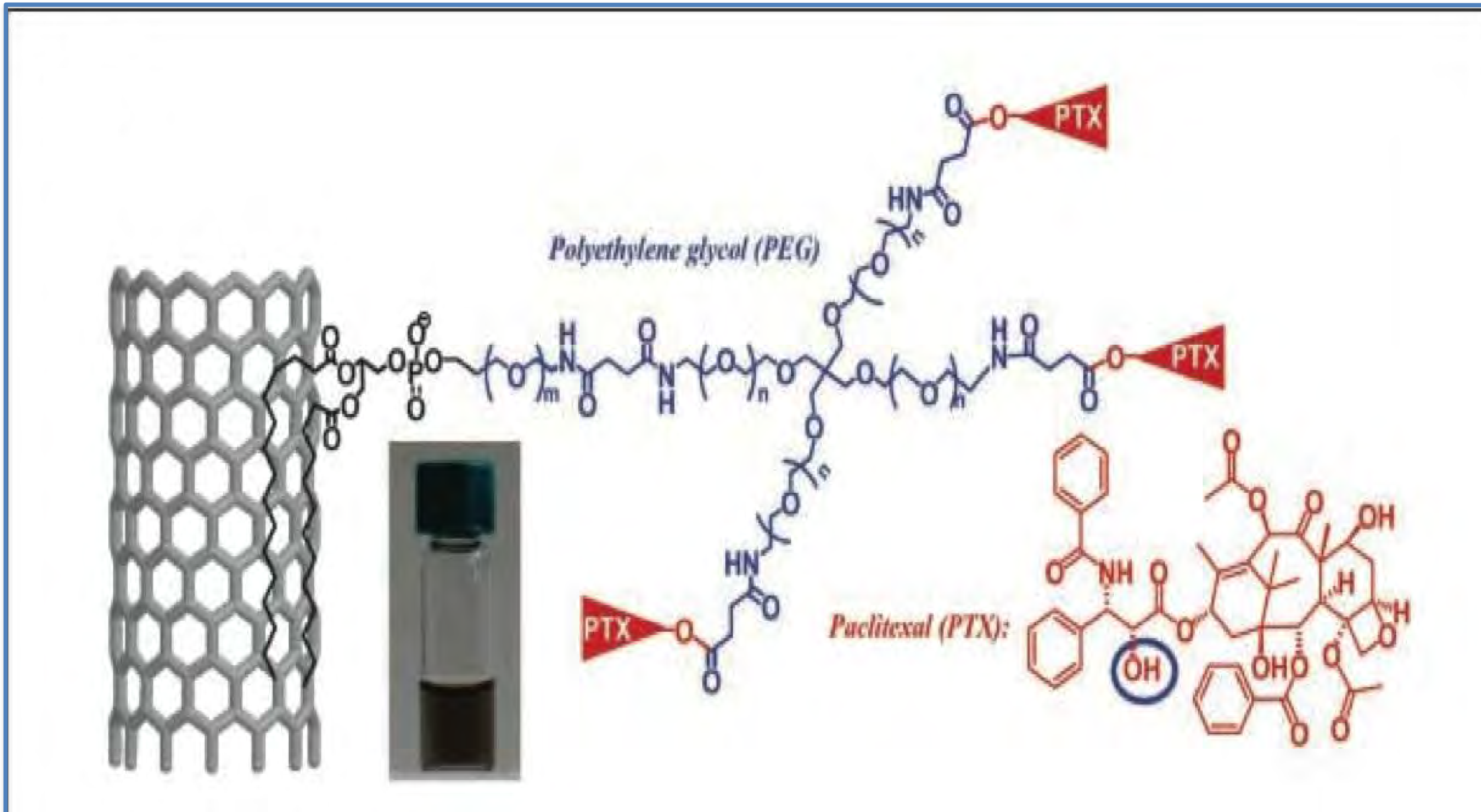


Single Walled Carbon Nanotubes (SWCNTs)



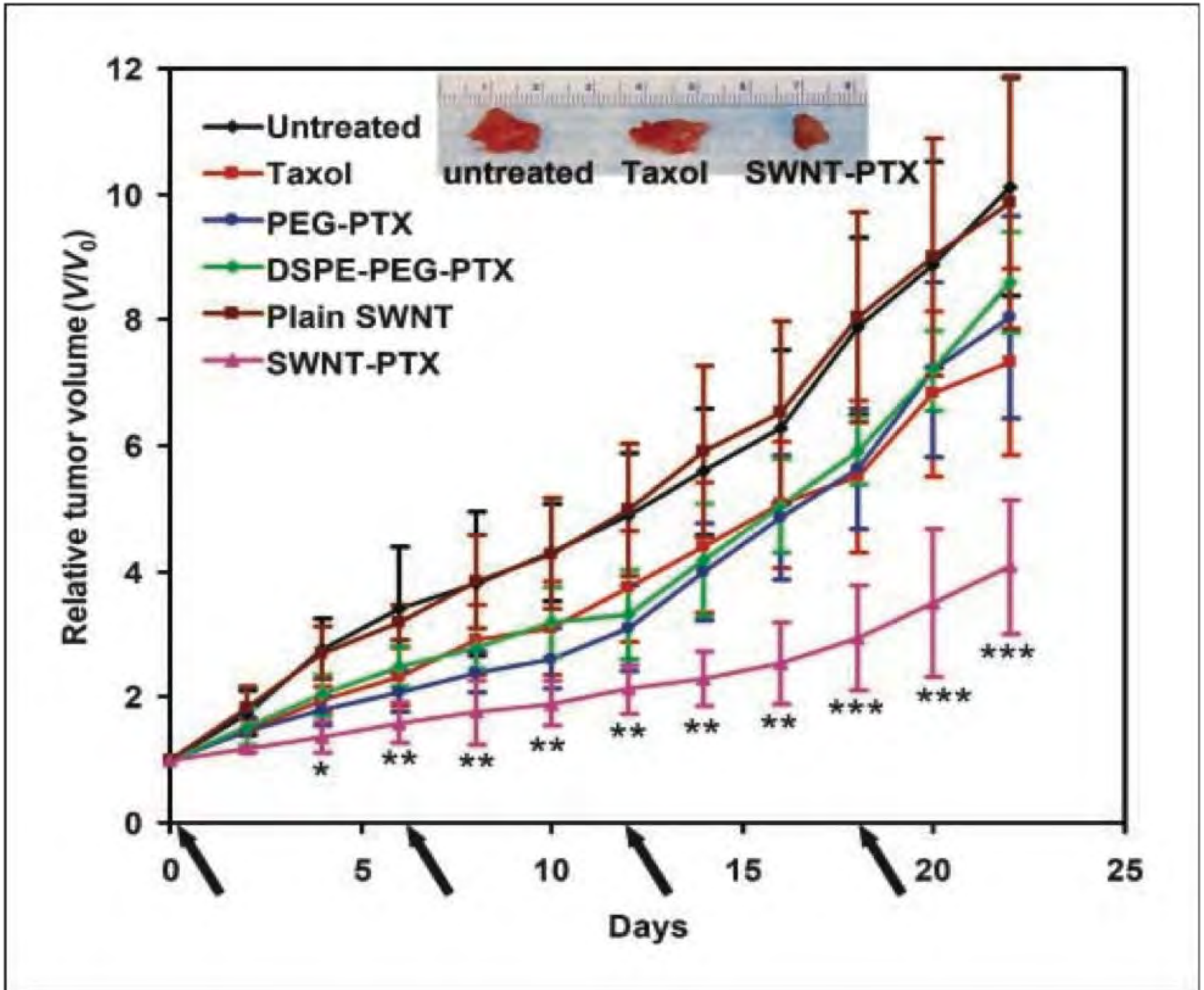
http://en.wikipedia.org/wiki/Carbon_nanotube

Carbon nanotube for PTX delivery



From Liu et al., 2008

Nanotube PTX delivery suppresses tumor growth of 4T1 breast cancer mice model



From Liu et al., 2008

Physico-chemical NP Properties of Relevance for Toxicology

Size *(aerodynamic, hydrodynamic)*

Size distribution

Shape

Agglomeration/aggregation

Density (material, bulk)

Surface properties:
- area *(porosity)*
- charge
- reactivity
- chemistry *(coatings, contaminants)*
- defects

Solubility/Sol-Rate (*lipid, aqueous, in vivo*)

Crystallinity

Biol. contaminants (e.g. endotoxin)

Properties can change

-with: method of production
preparation process
storage

-when introduced into
physiol. media, organism

Key parameter: Dose!

Particle Number and Particle Surface Area per 10 pg/cm^3 Airborne Particles

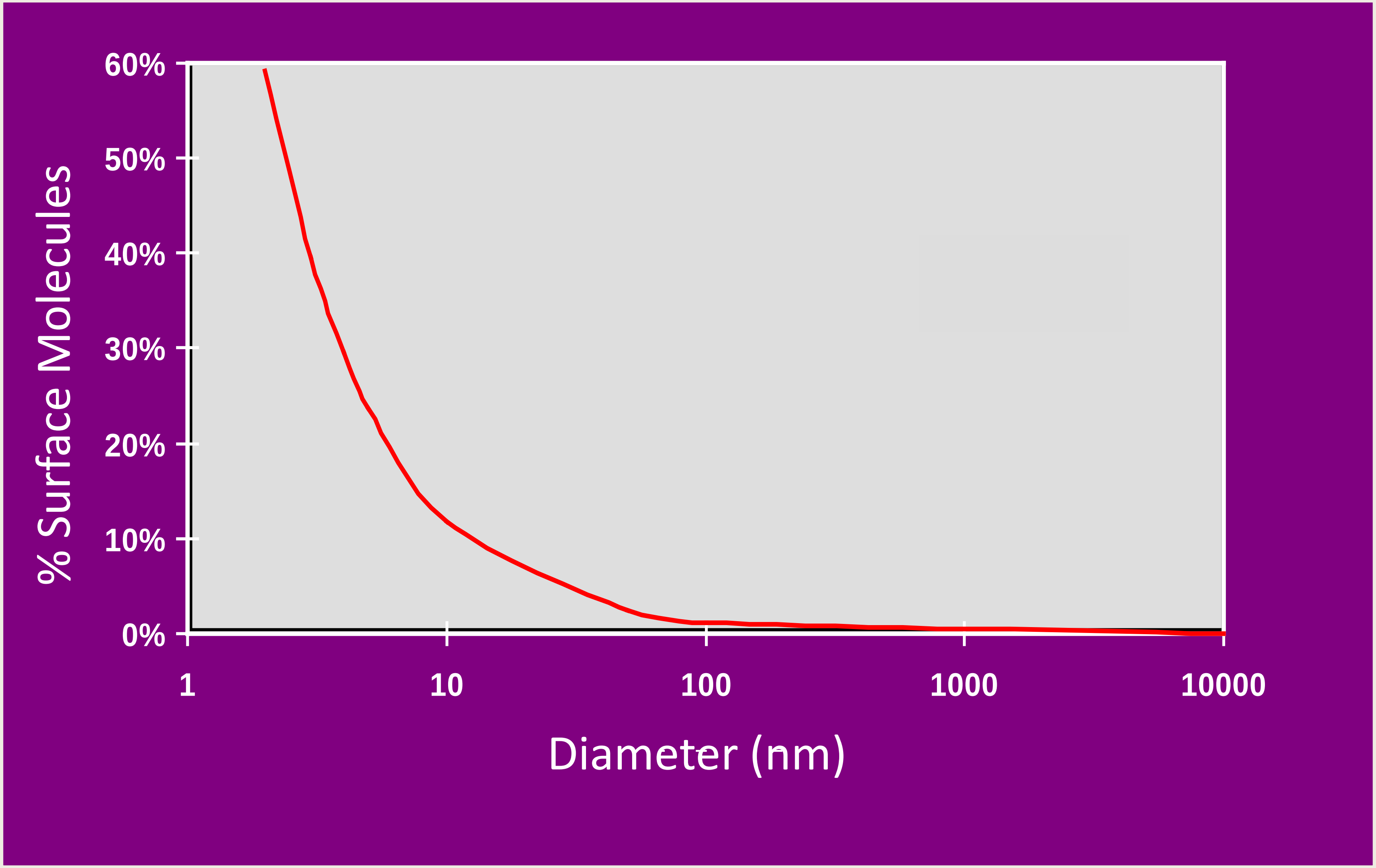
(Unit density particles)

Particle Diameter nm	**Particle Number N/cm^3**	**Particle Surface Area μm^2/cm^3**
5	**153,000,000**	**12,000**
20	**2,400,00**	**3,016**
250	**1,200**	**240**
5,000	**0.15**	**12**

Small size, high number per mass, and surface chemistry confer both desirable and undesirable properties.

Detailed Physico-chemical characterization of NP is essential.

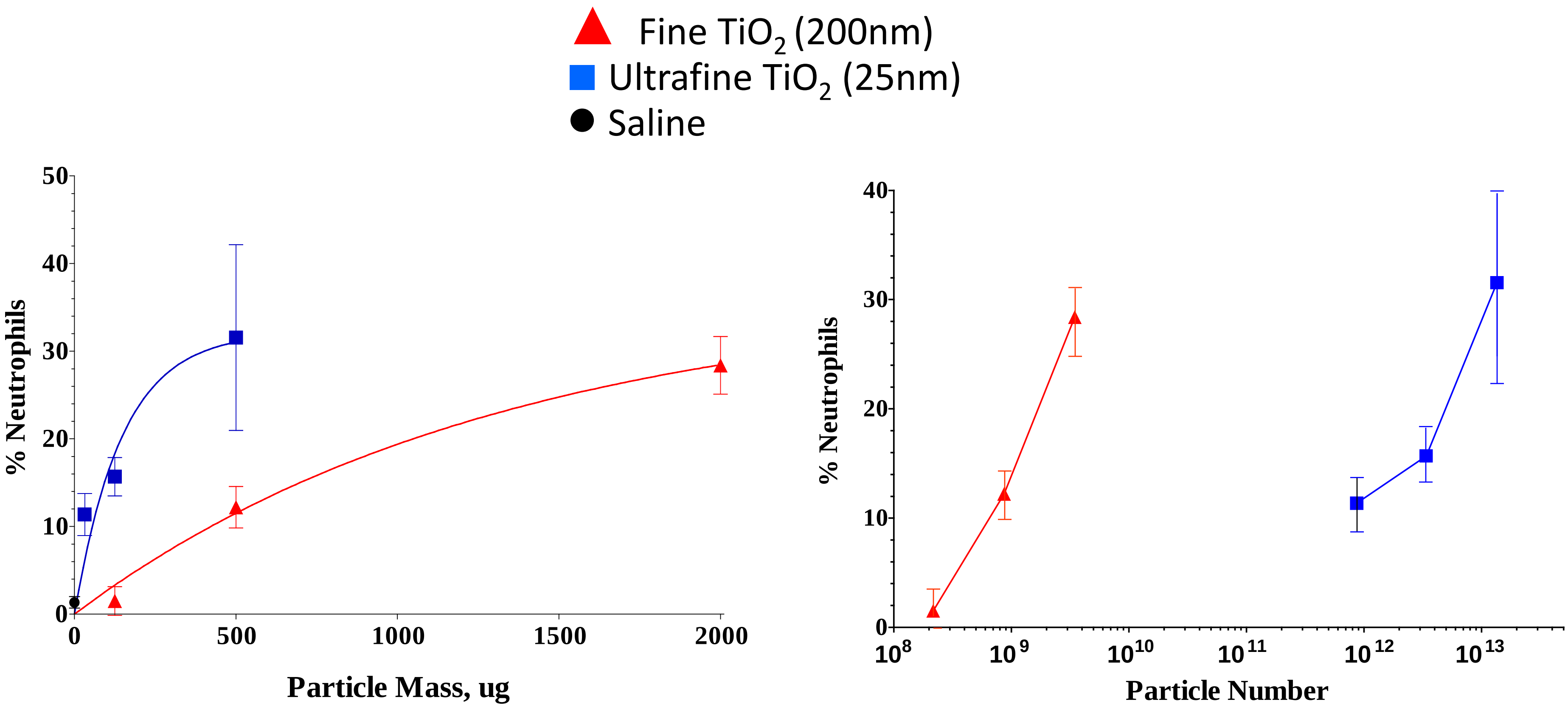
Surface Molecules as Function of Particle Size



From Fissan, 2003

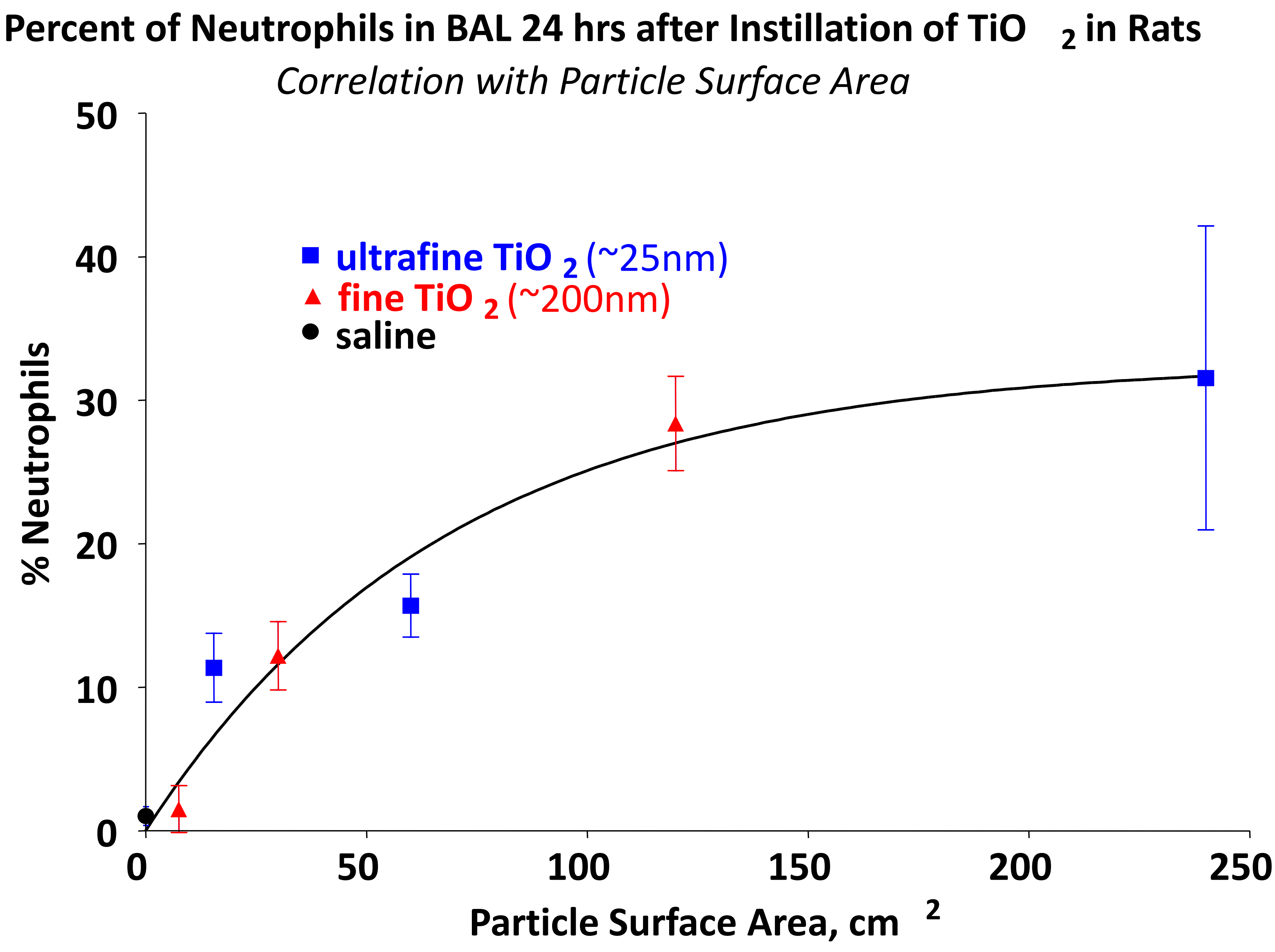
Which Dose-Metric?

Percent of Neutrophils in Lung Lavage 24 hrs after Intratrachael Dosing of Ultrafine and Fine TiO_2 in Rats



Particle Mass ***vs*** ***Particle Number***

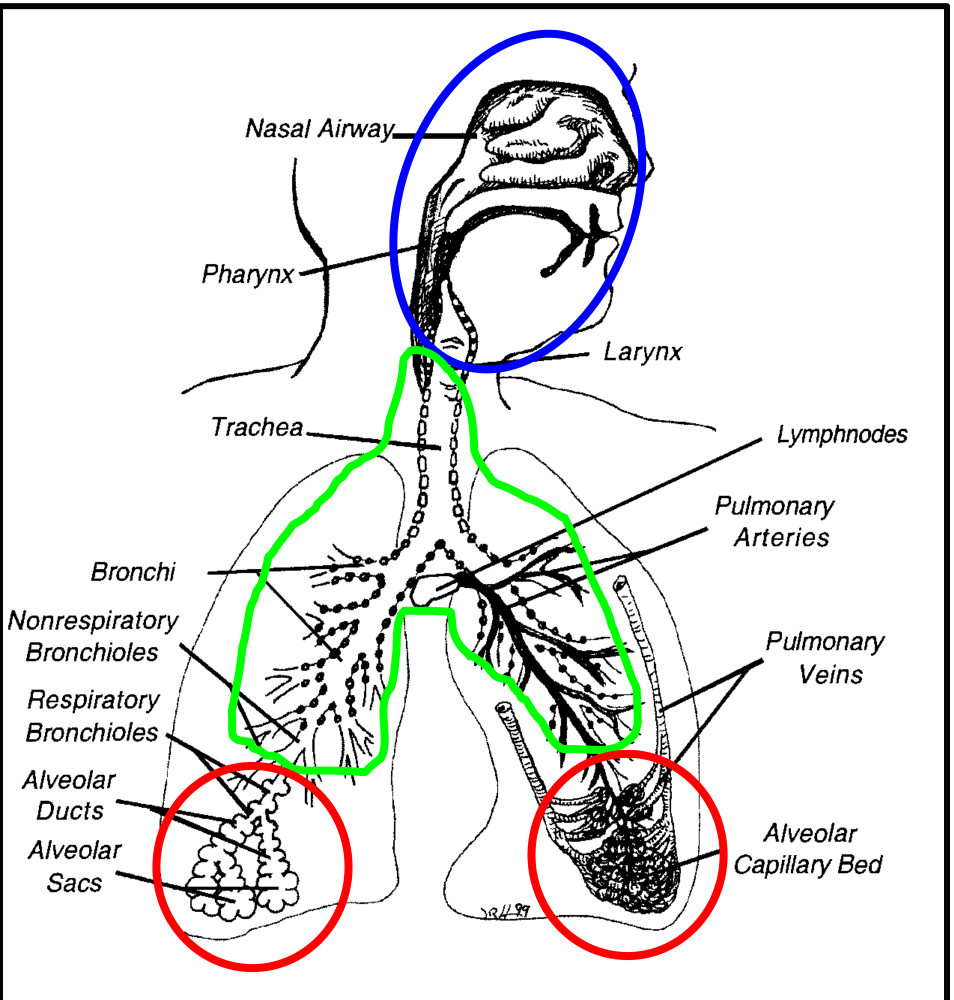
Which Dose-Metric?



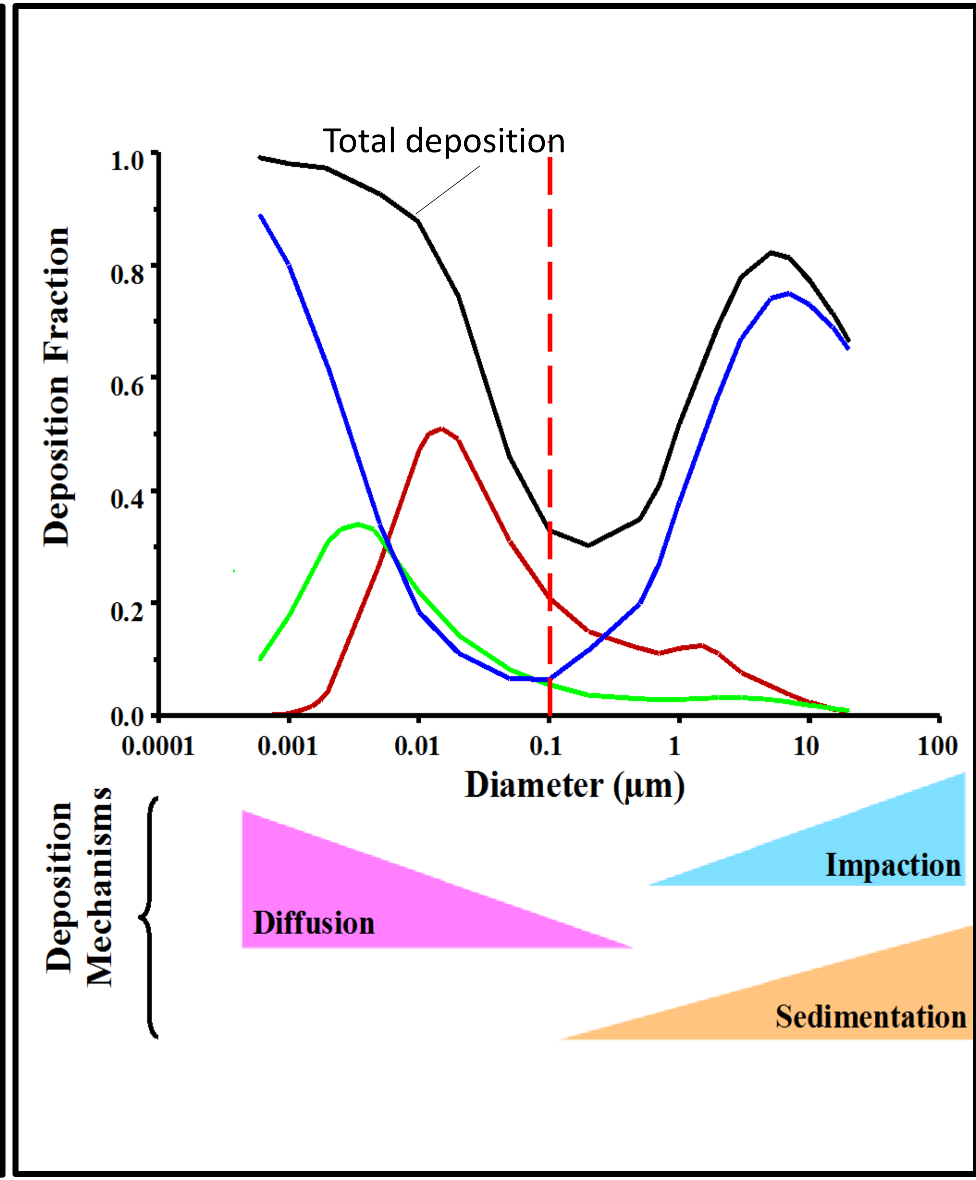
Dosing the Respiratory Tract
Impact of Dose-Rate

Fractional Deposition of Inhaled Particles in the Human Respiratory Tract

(ICRP Model, 1994; Nose-breathing)



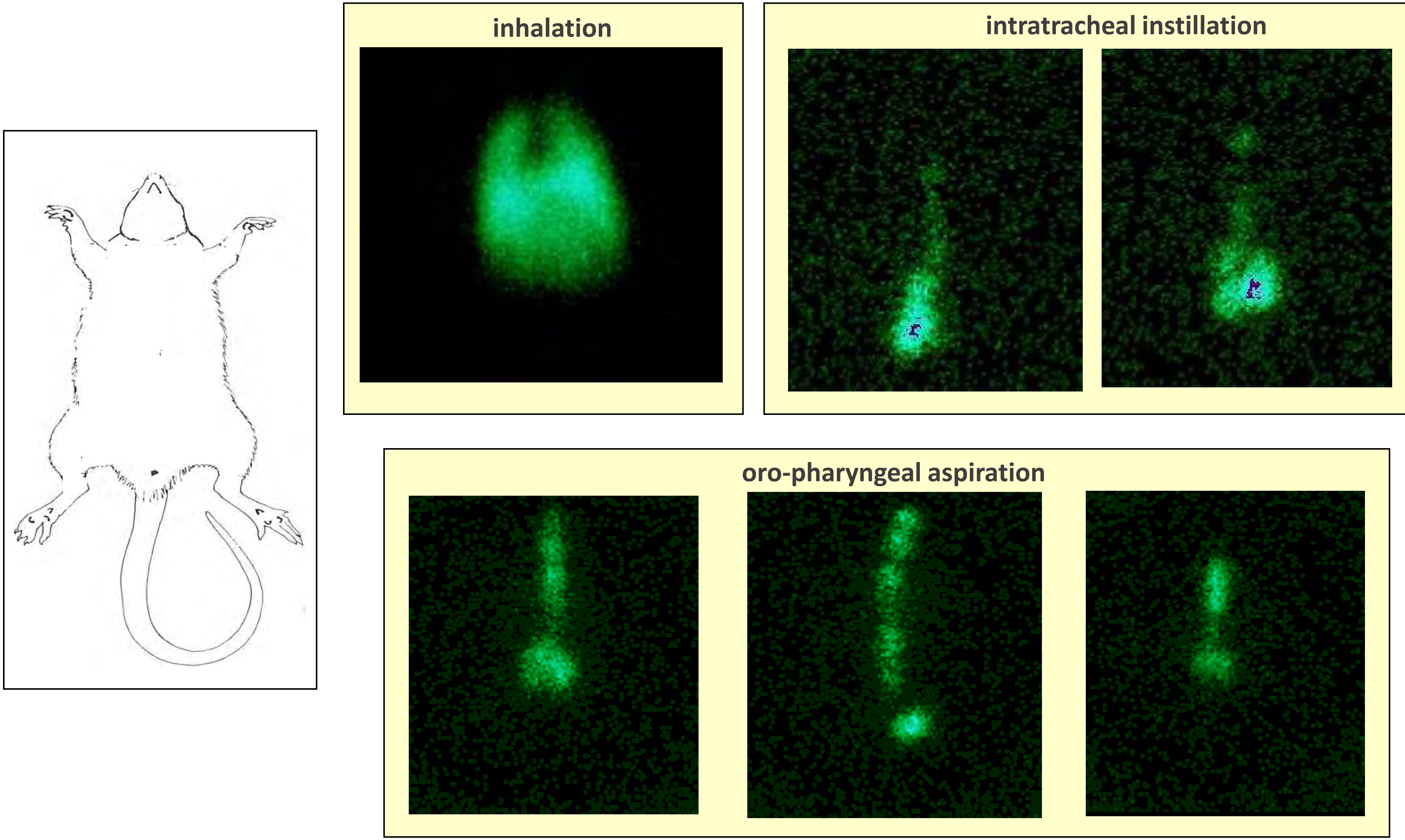
Inhalable	**Thoracic**	**Respirable**
< 100um	*< 30um*	*< 10um*



Rat: Inhalation vs. Intratracheal Instillation vs. Oro-pharyngeal Aspiration of Nanoparticles

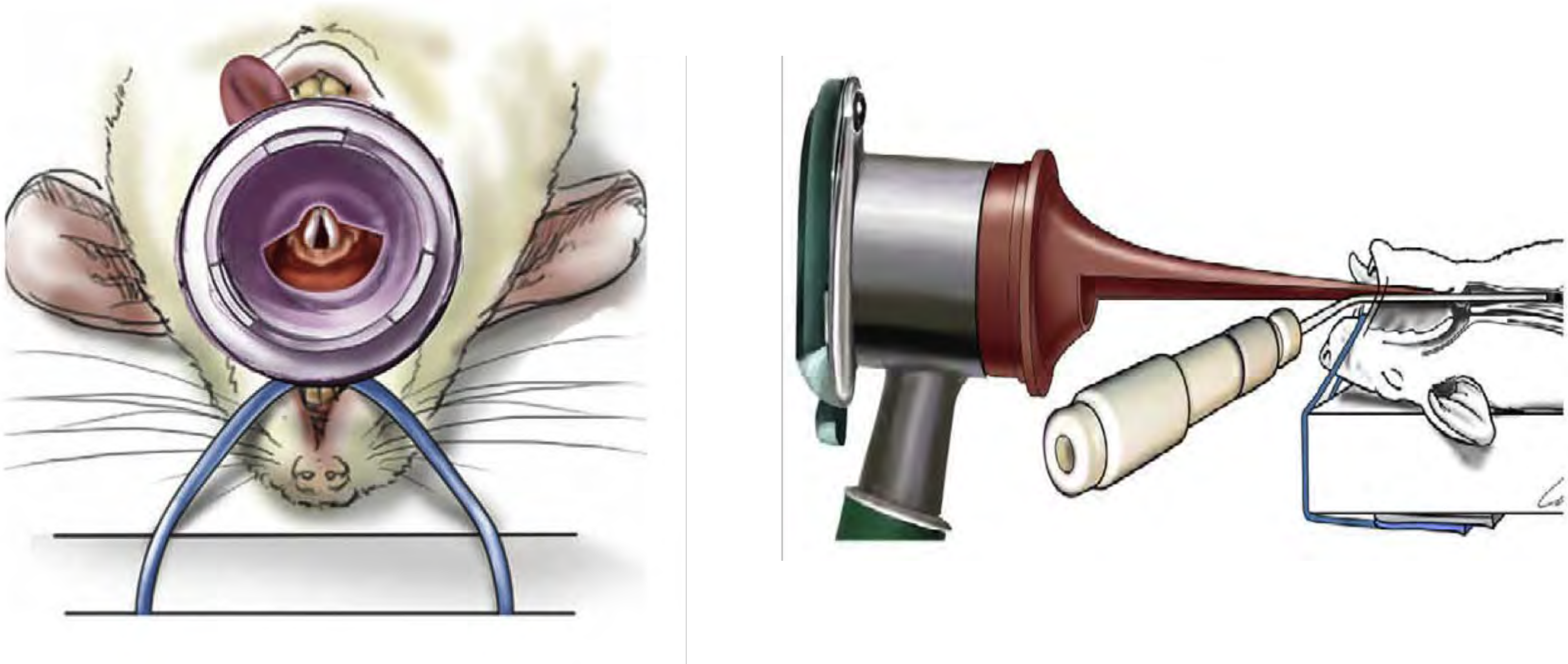
(Inhalation: ^{192}Ir NP, 20 nm; Instillation + Aspiration: 18 nm ^{198}Au NP)

Deposition in Lower Respiratory Tract immediately Post-Exposure, *(γ-Camera Pin-Hole Images)*



Courtesy: W. Kreyling and M. Semmler-Behnke

Intratracheal Administration of Particles in Rodents



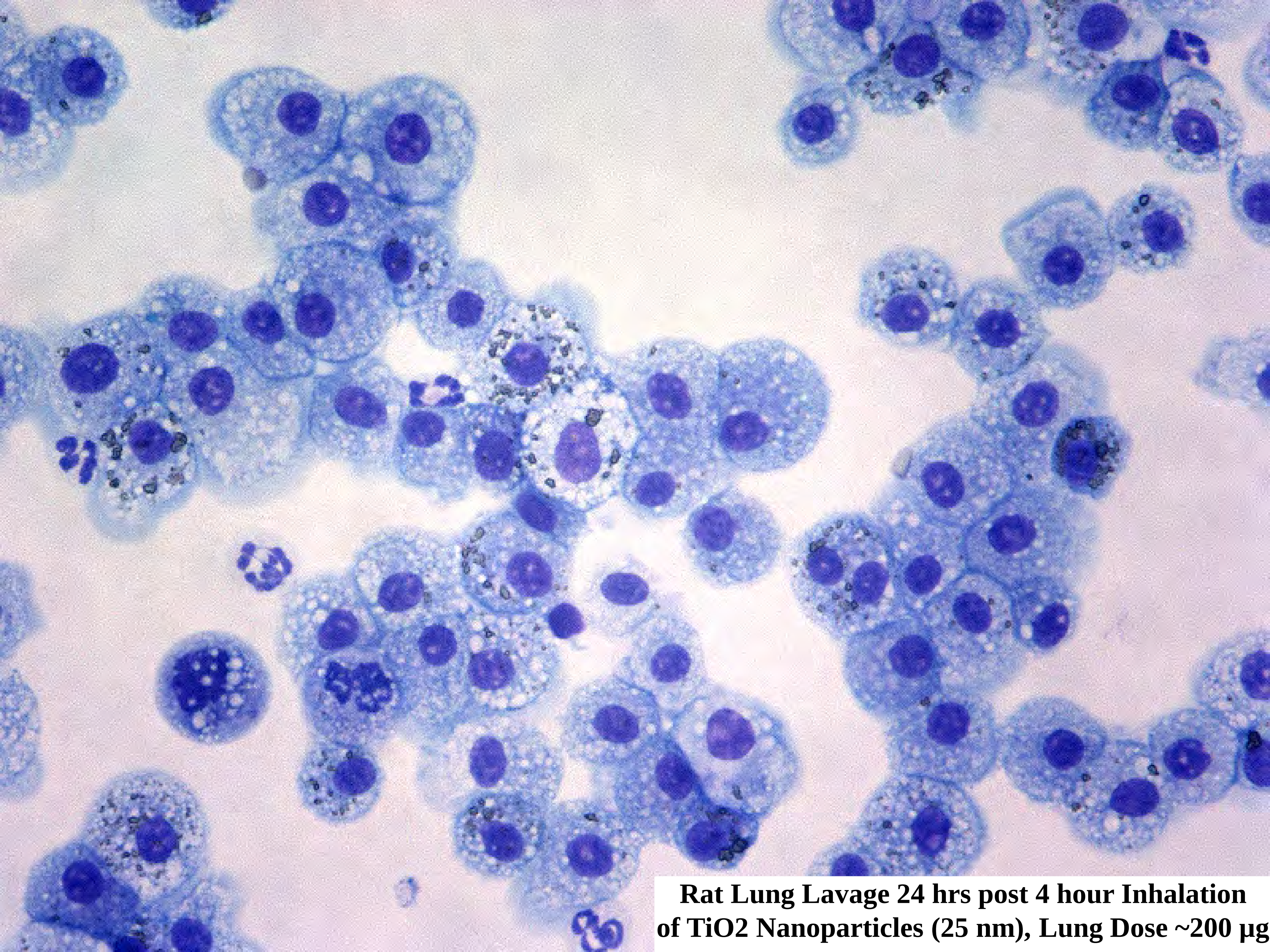
From: Morello et al., 2009

Comparing Responses in the Lung of Rats

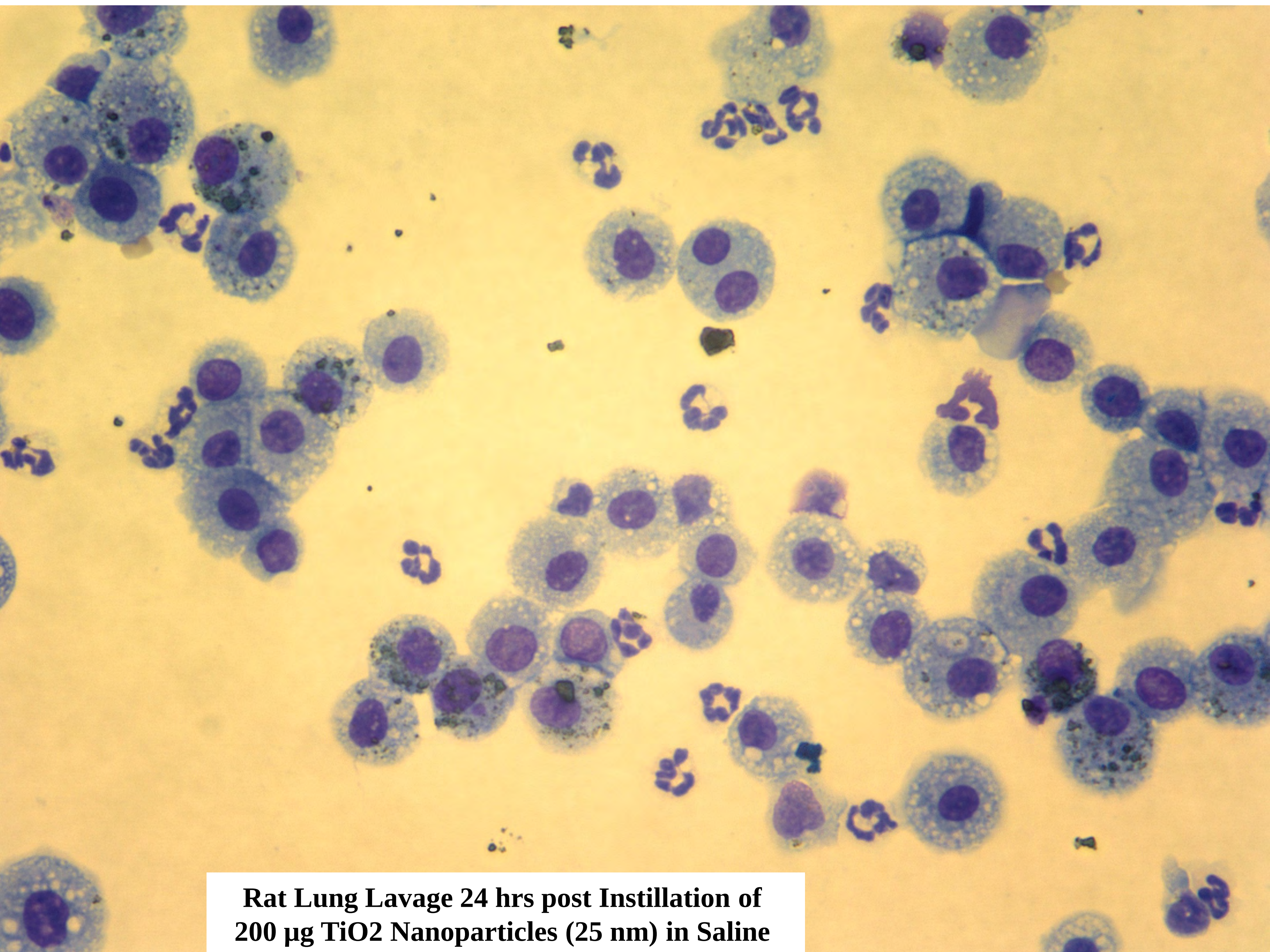
when the same Lung Dose of 200 µg TiO_2 Nanoparticles

is administered by 4 hour Inhalation

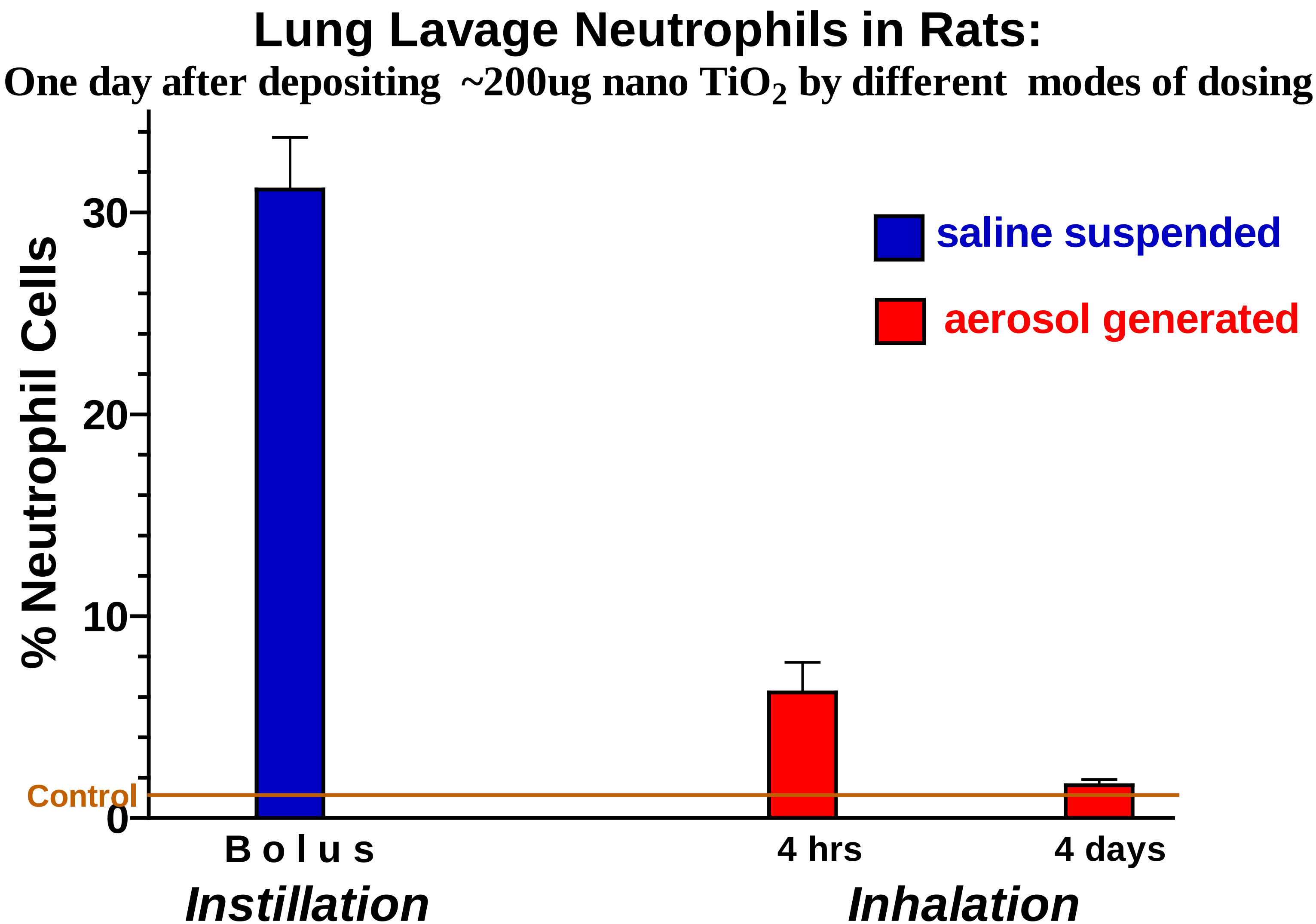
or by 0.5 second intratracheal Instillation



Rat Lung Lavage 24 hrs post 4 hour Inhalation of TiO_2 Nanoparticles (25 nm), Lung Dose ~200 µg



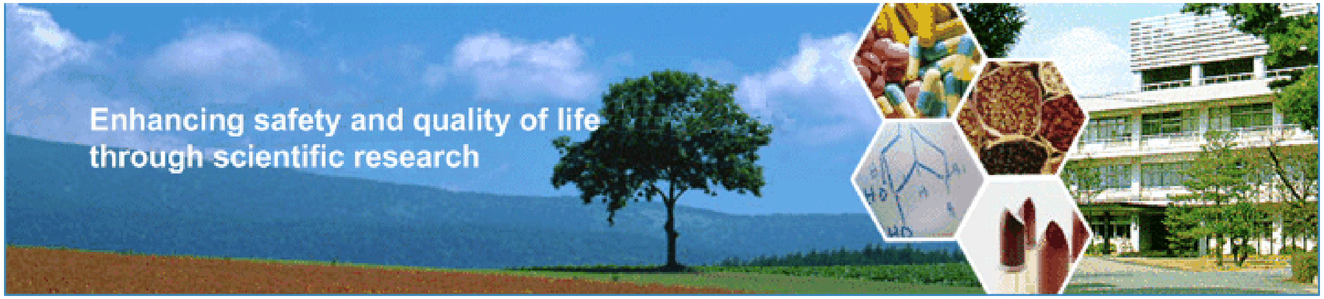
Rat Lung Lavage 24 hrs post Instillation of 200 µg TiO2 Nanoparticles (25 nm) in Saline


Lung Lavage Neutrophils in Rats:
One day after depositing ~200ug nano TiO_2 by different modes of dosing
% Neutrophil Cells
30
20
10
0
Control
saline suspended
aerosol generated
B o l u s
4 hrs
4 days
Instillation
Inhalation

Dose and Dose-Rate Determine Toxicity

Biokinetics andTranslocation of Inhaled Nanoparticles

National Institute of Health Sciences
国立医薬品食品衛生研究所



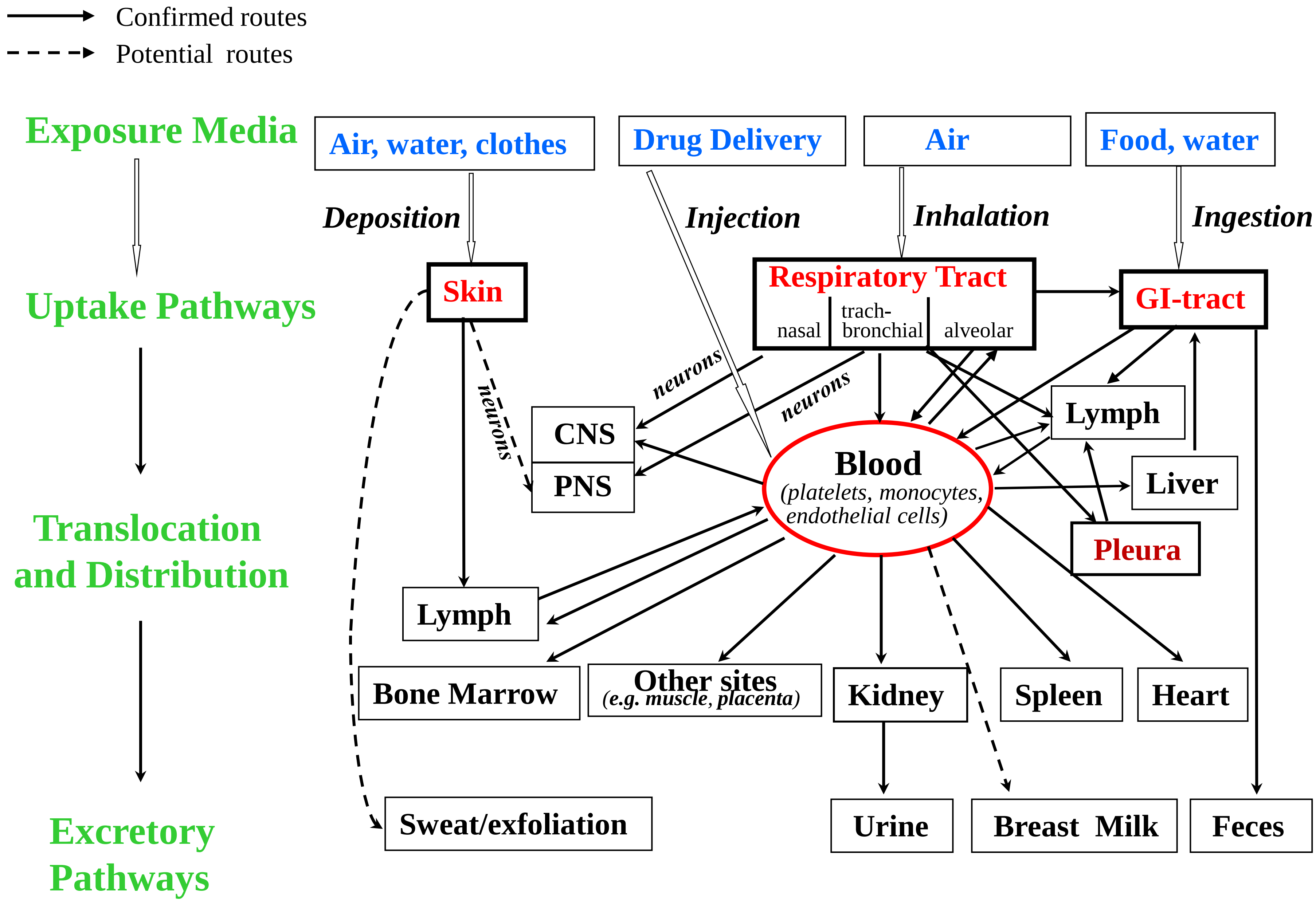
From Exposure-Dose-Response Data to Hazard and Risk Characterization of Inhaled Nanomaterials

Günter Oberdörster
University of Rochester

April 3, 2014

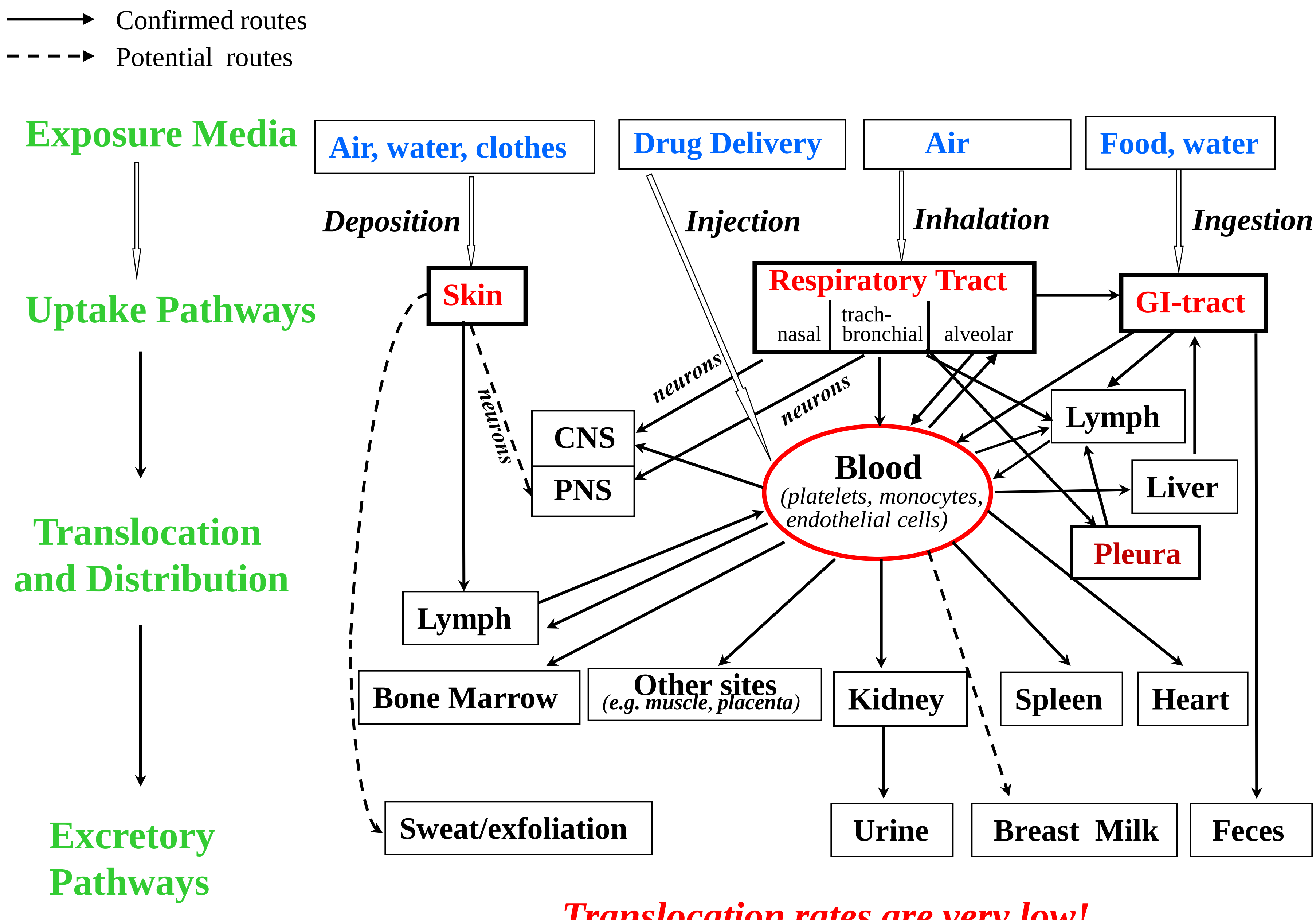
UNIVERSITY of ROCHESTER MEDICAL CENTER

Exposure and Biokinetics of Nanoparticles



(Modified from Oberdörster et al., 2005)

Exposure and Biokinetics of Nanoparticles



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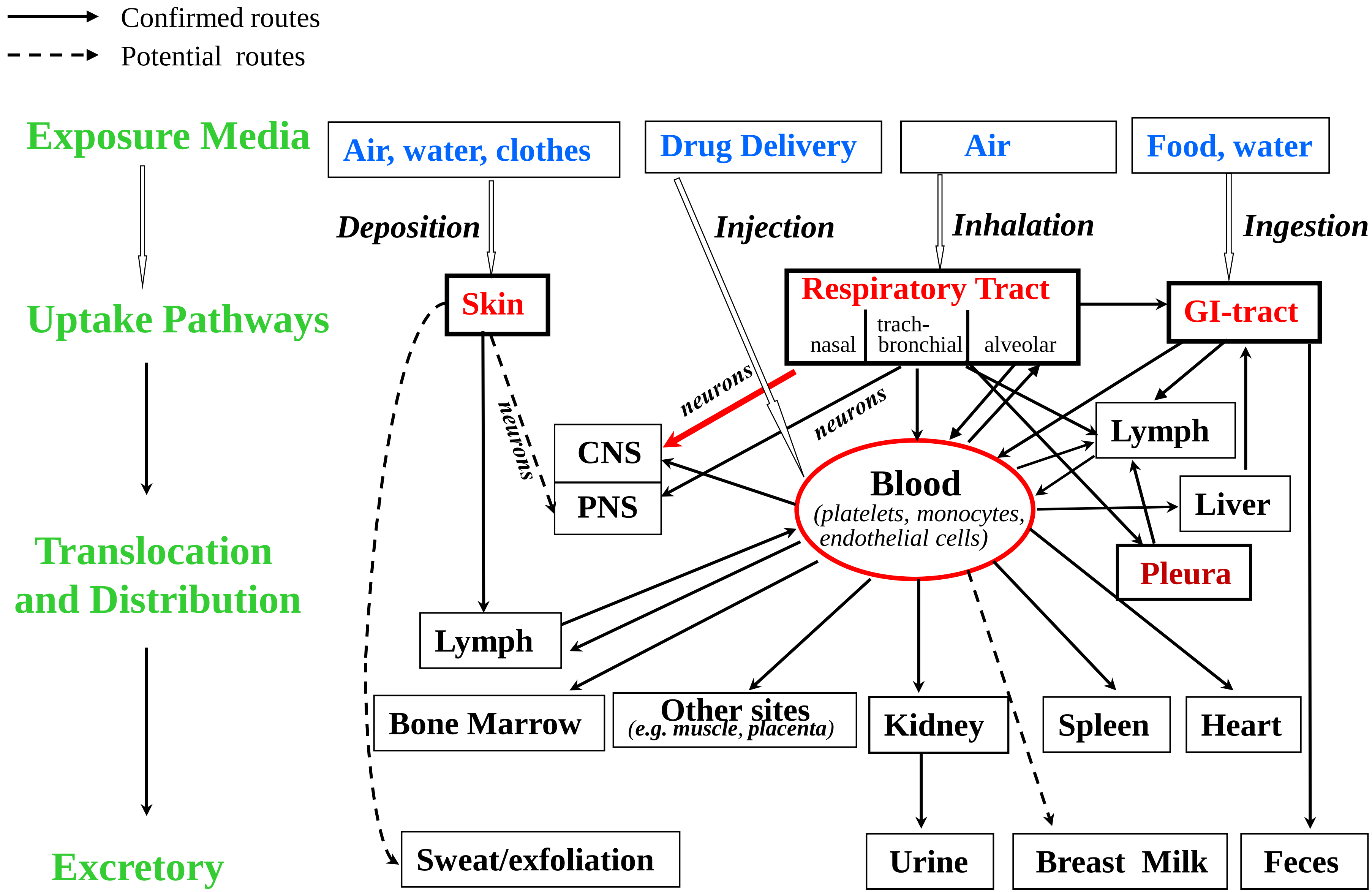
Exposure and Biokinetics of Nanoparticles



Translocation rates are very low!

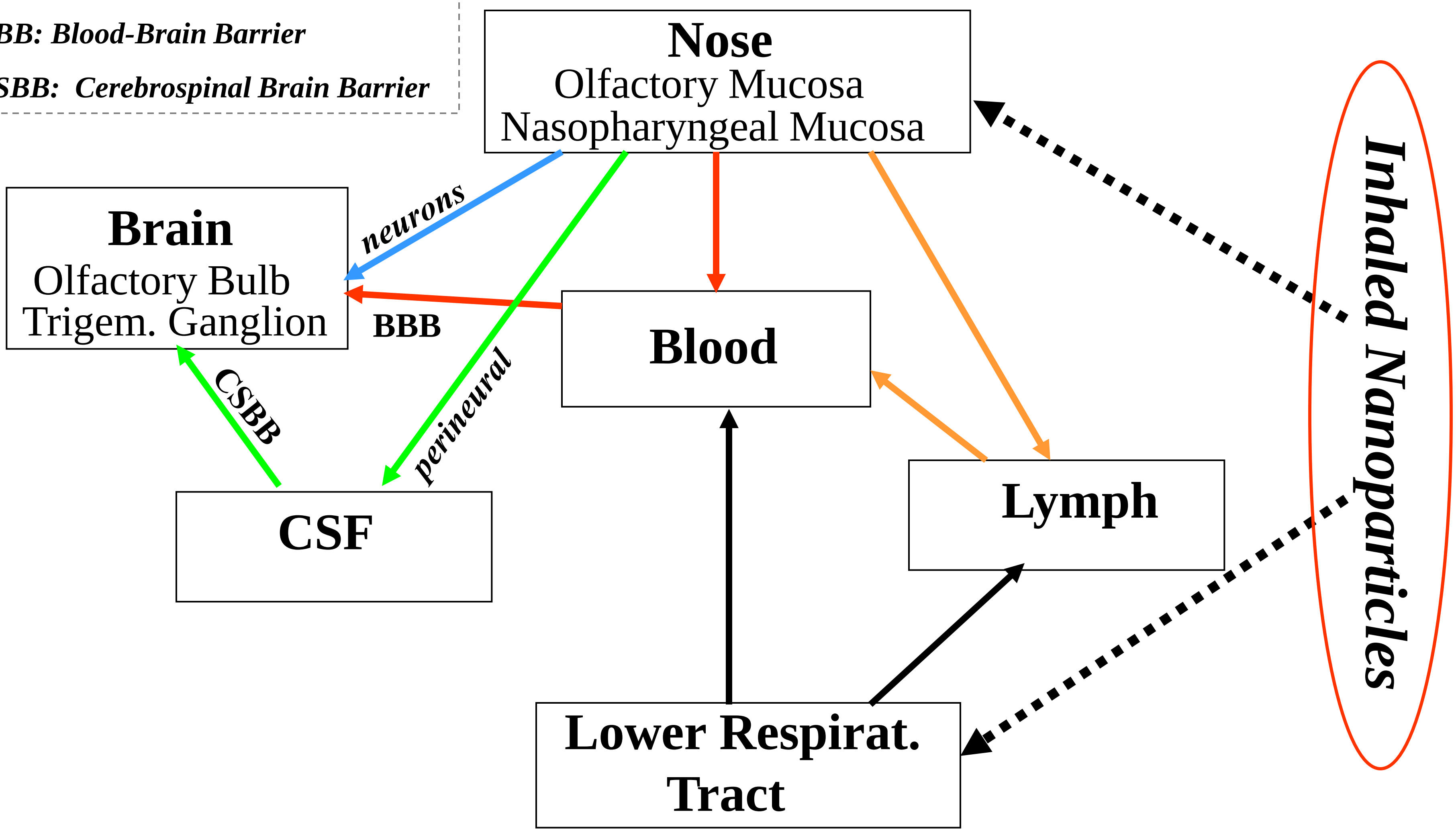
(Modified from Oberdörster et al., 2005)

FROM RESPIRATORY TRACT TO BRAIN:
POTENTIAL TRANSLOCATION PATHWAYS OF NANOPARTICLES

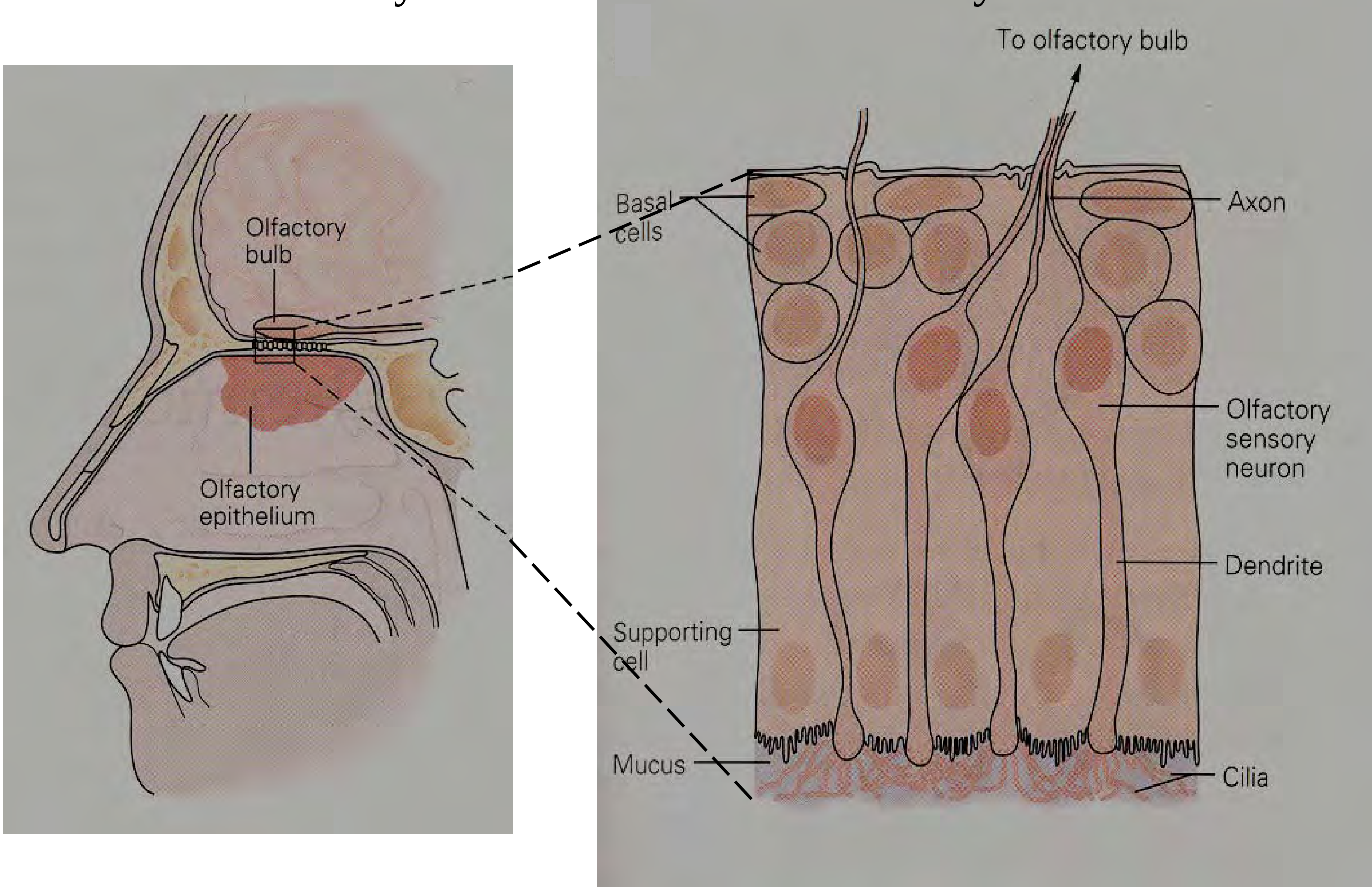
CSF: Cerebrospinal Fluid

BBB: Blood-Brain Barrier

CSBB: Cerebrospinal Brain Barrier



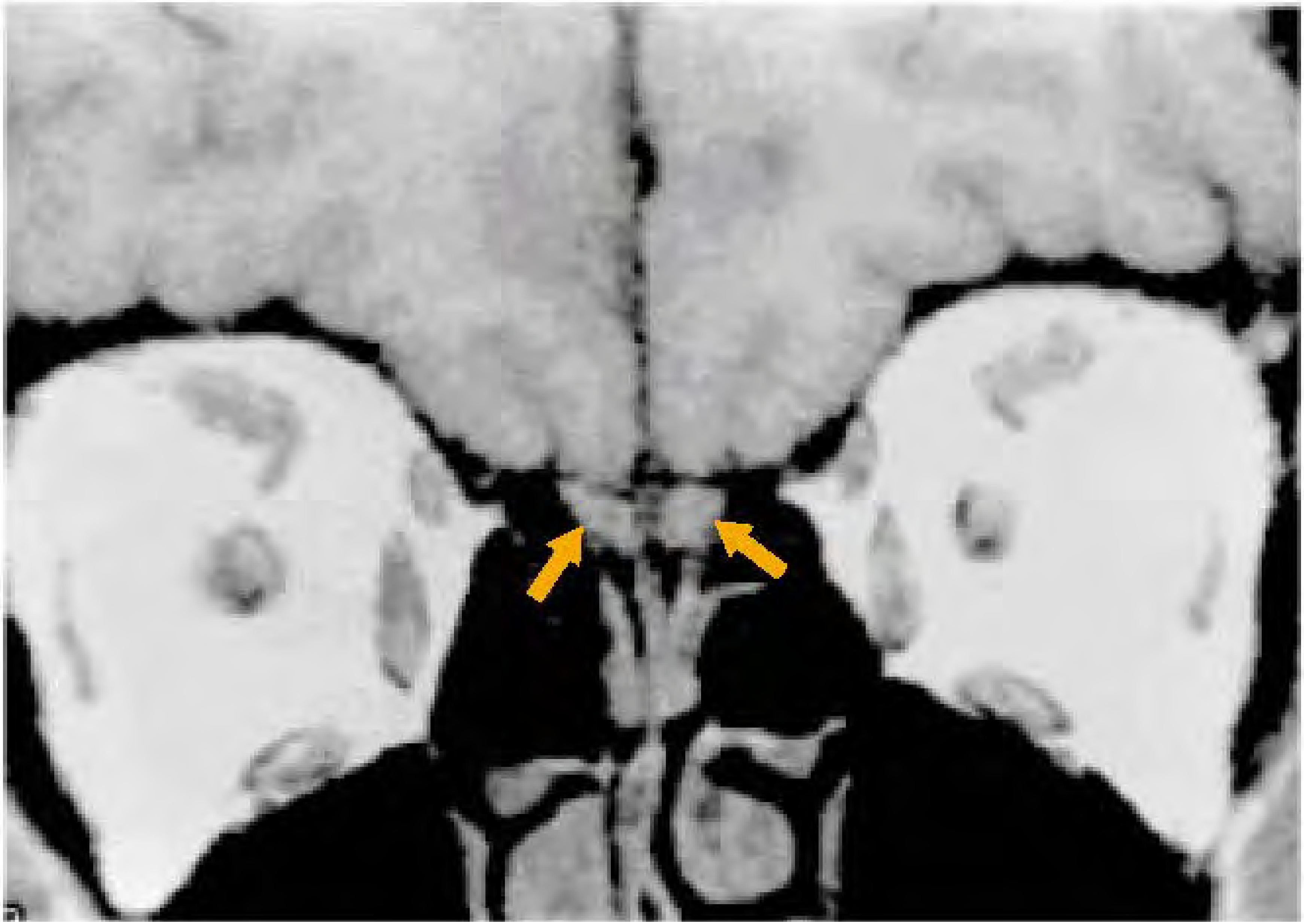
Olfactory Nerve Translocation Pathway



From: *Kandel, Schwartz and Jessel: Principles of Neural Science, 2000*

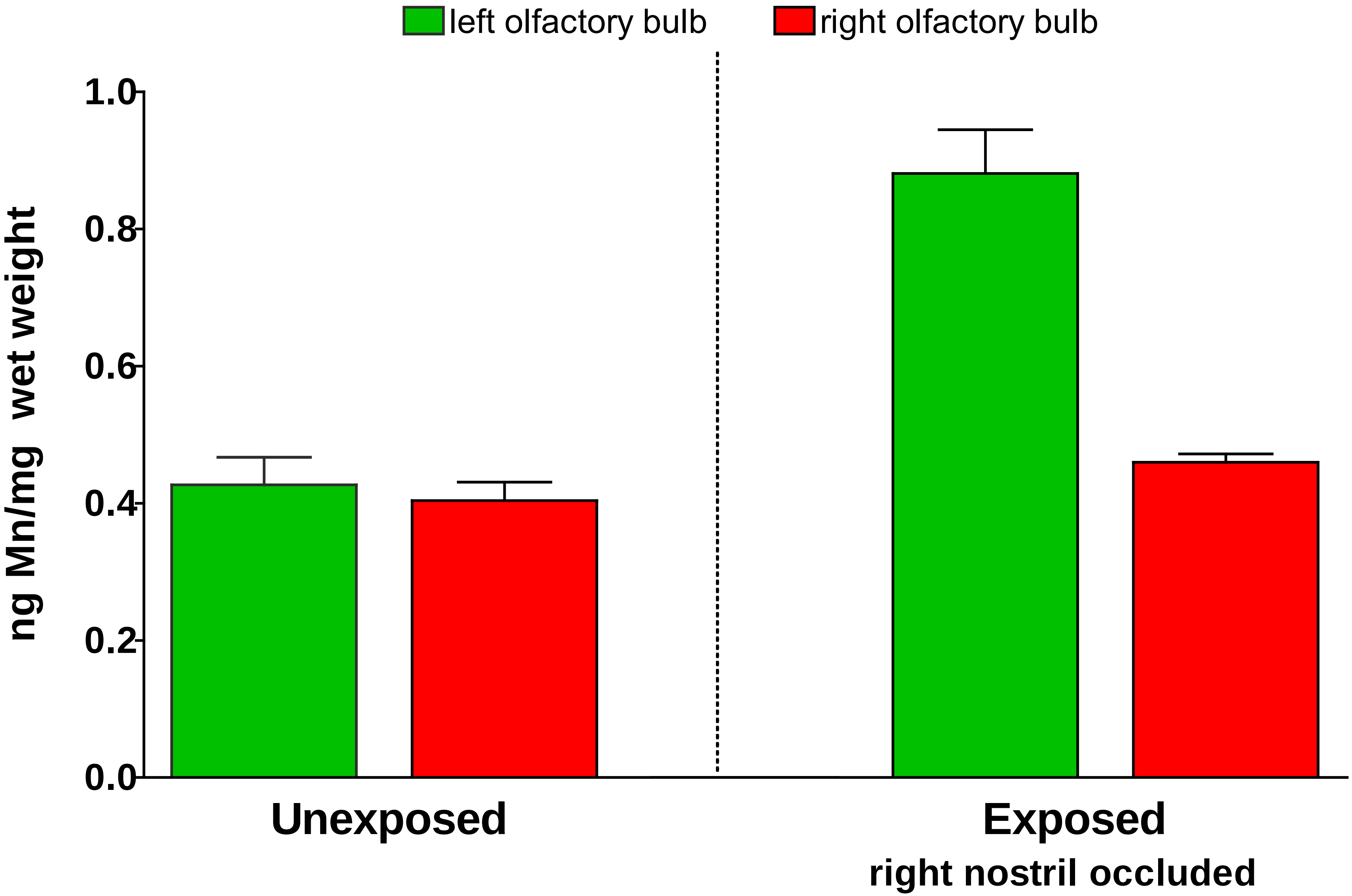
MRI Scan of Olfactory Bulbs

(from Turetsky et al., 2003)



Rat, Right Nostril Occlusion Model:

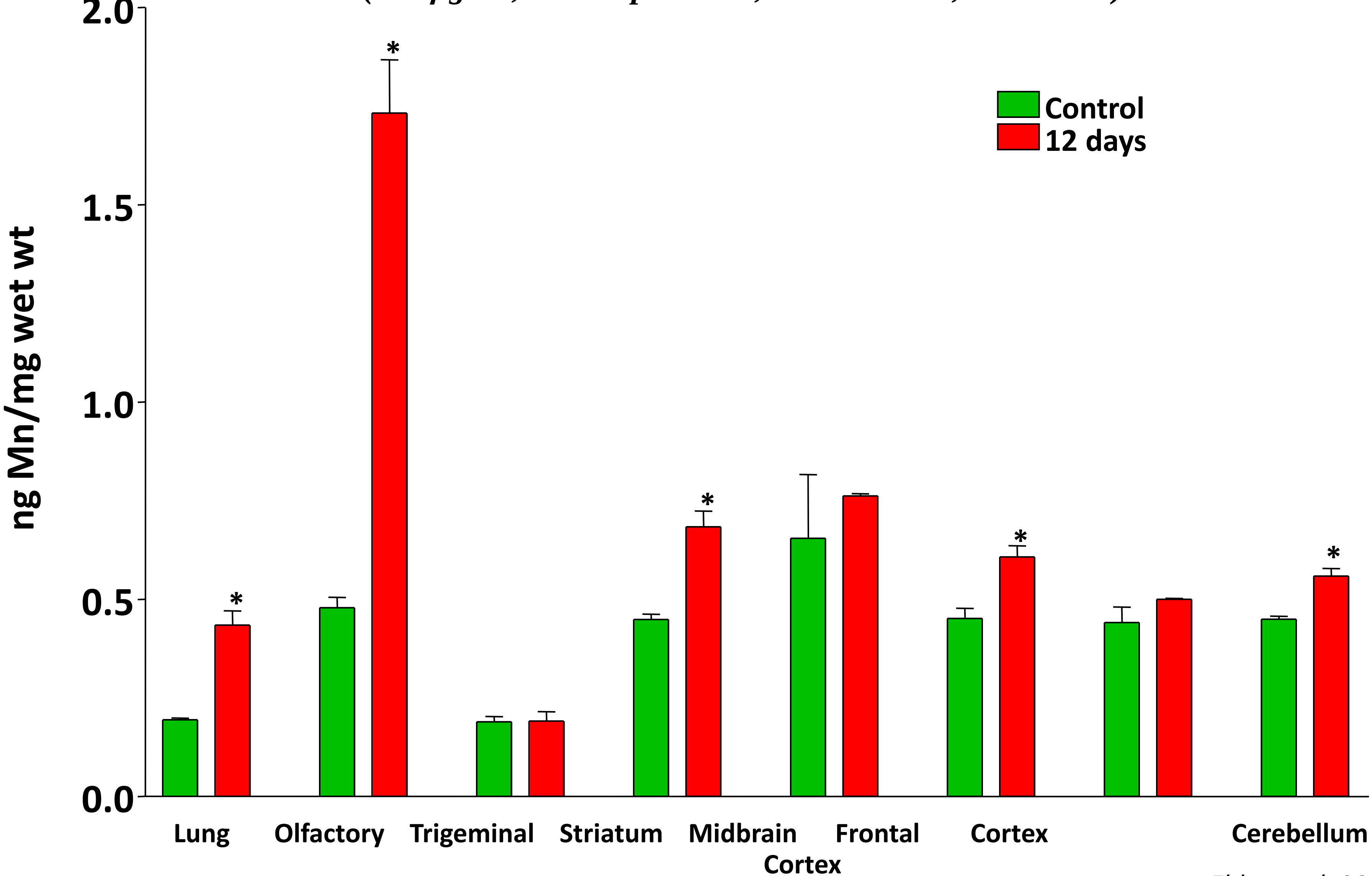
***Accumulation of Mn in Right and left Olfactory Bulb 24 Hours after Exposure to Ultrafine** (~30nm) **Mn Oxide Particles** (n=3-5, mean+/-SD)*



Elder et al, 2006

Mn concentration in lung and brain regions of rats following 12 days ultrafine Mn-oxide exposure *(mean +/- SD)*

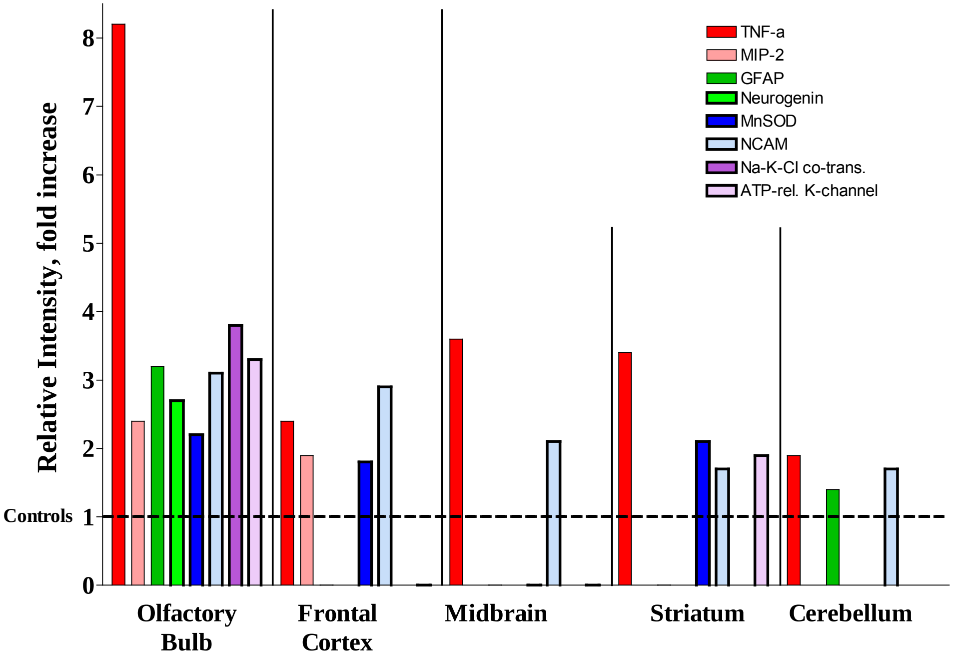
(465 µg/m³; 17x10⁶ part./cm³; CMD: 31 nm; GSD: 1.77)



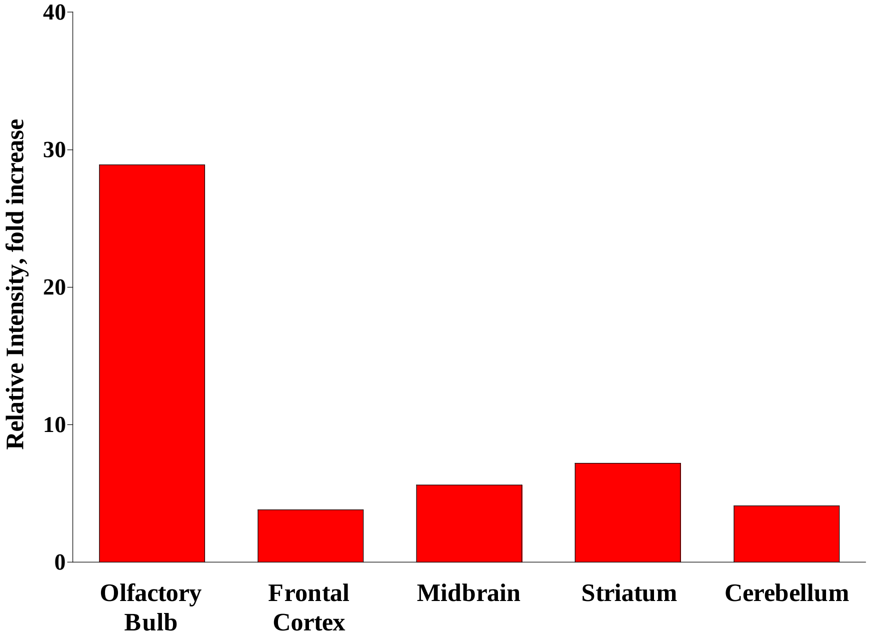
Elder et al, 2006

Inflammation in the Brain Regions where Mn Signal was Found

mRNA Levels

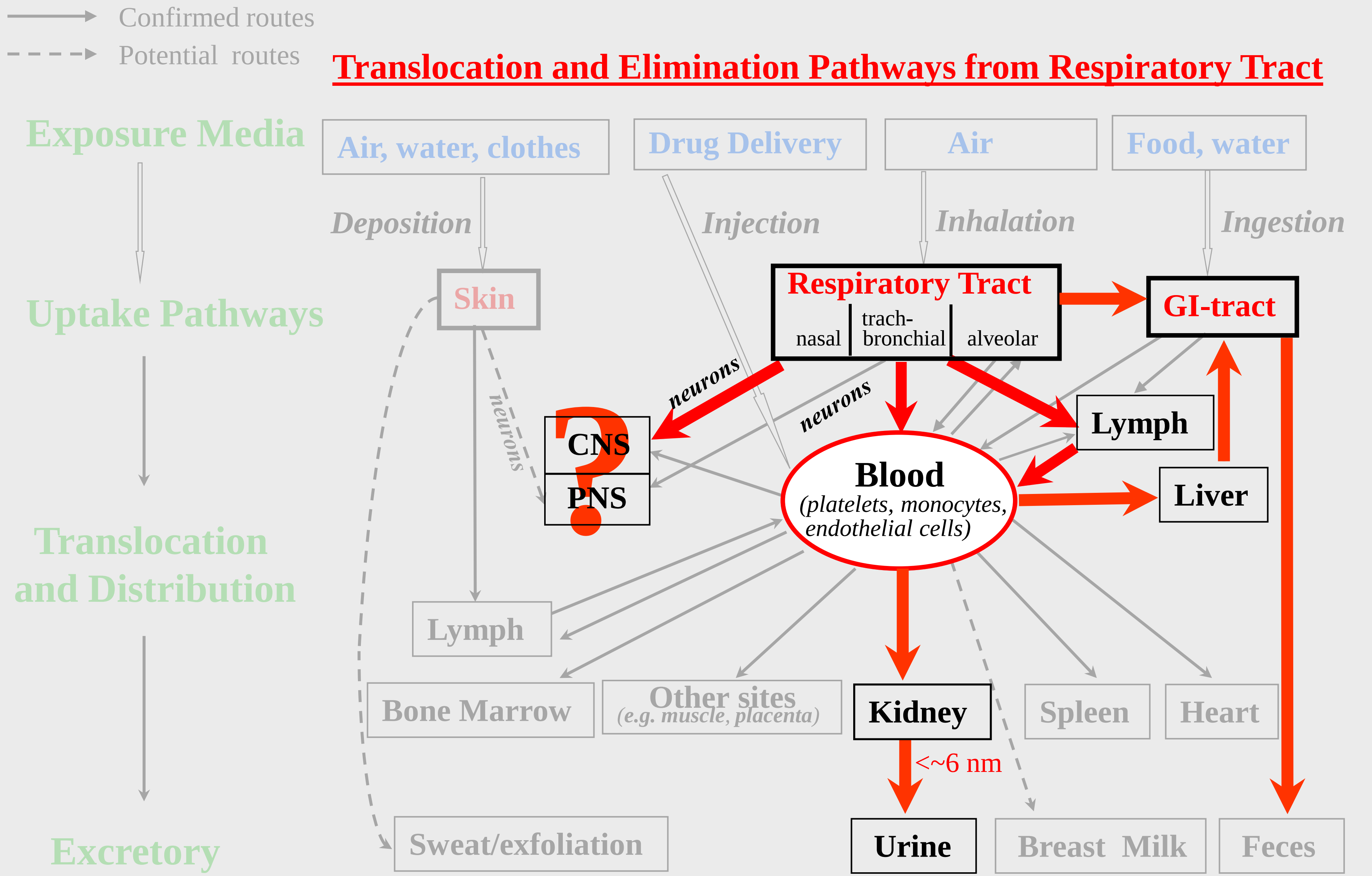


TNF-□Protein



Elder et al, 2006

Exposure and Biokinetics of Nanoparticles

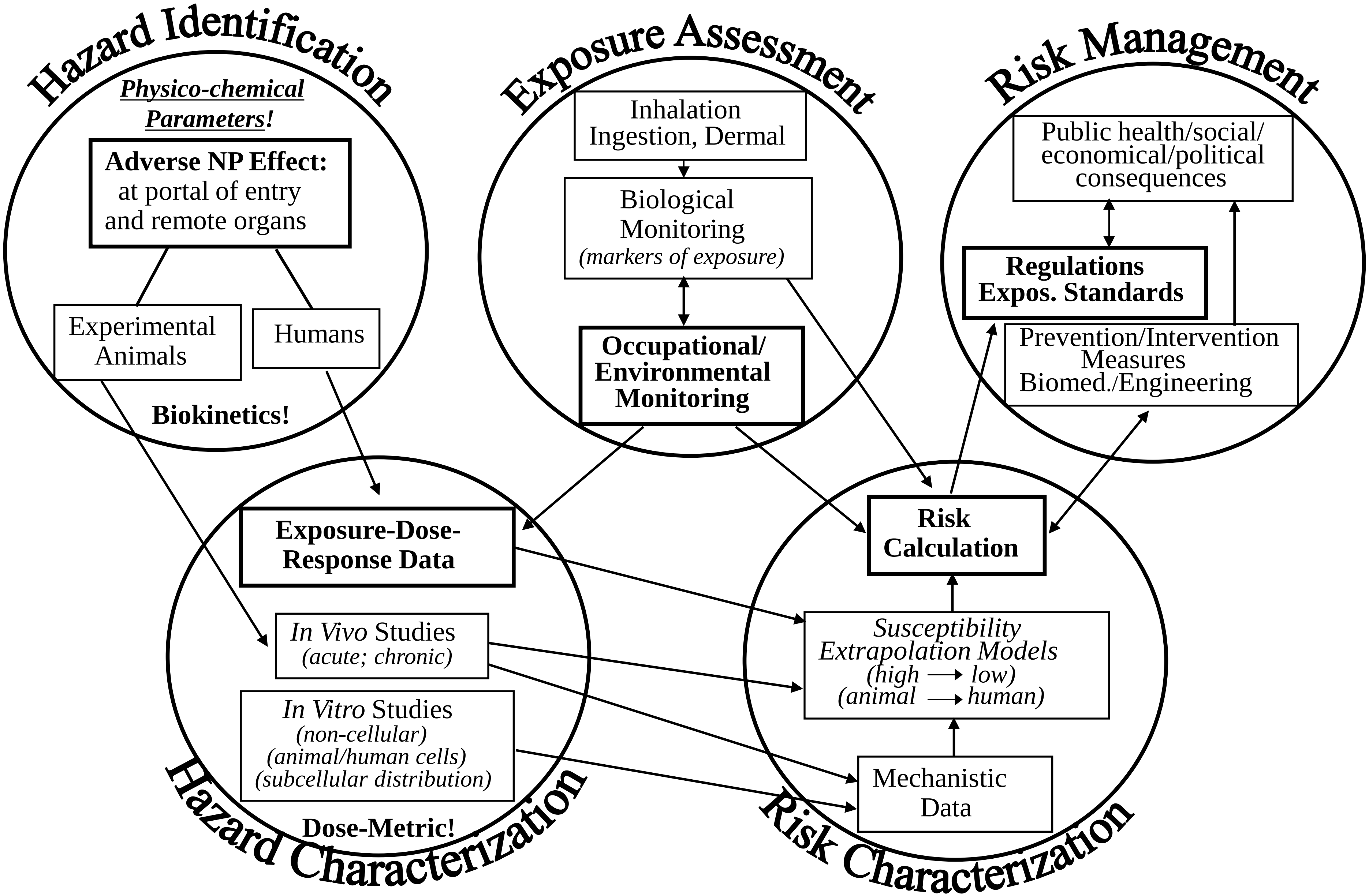


GI-tract and kidney as major excretory organs

(Modified from Oberdörster et al., 2005)

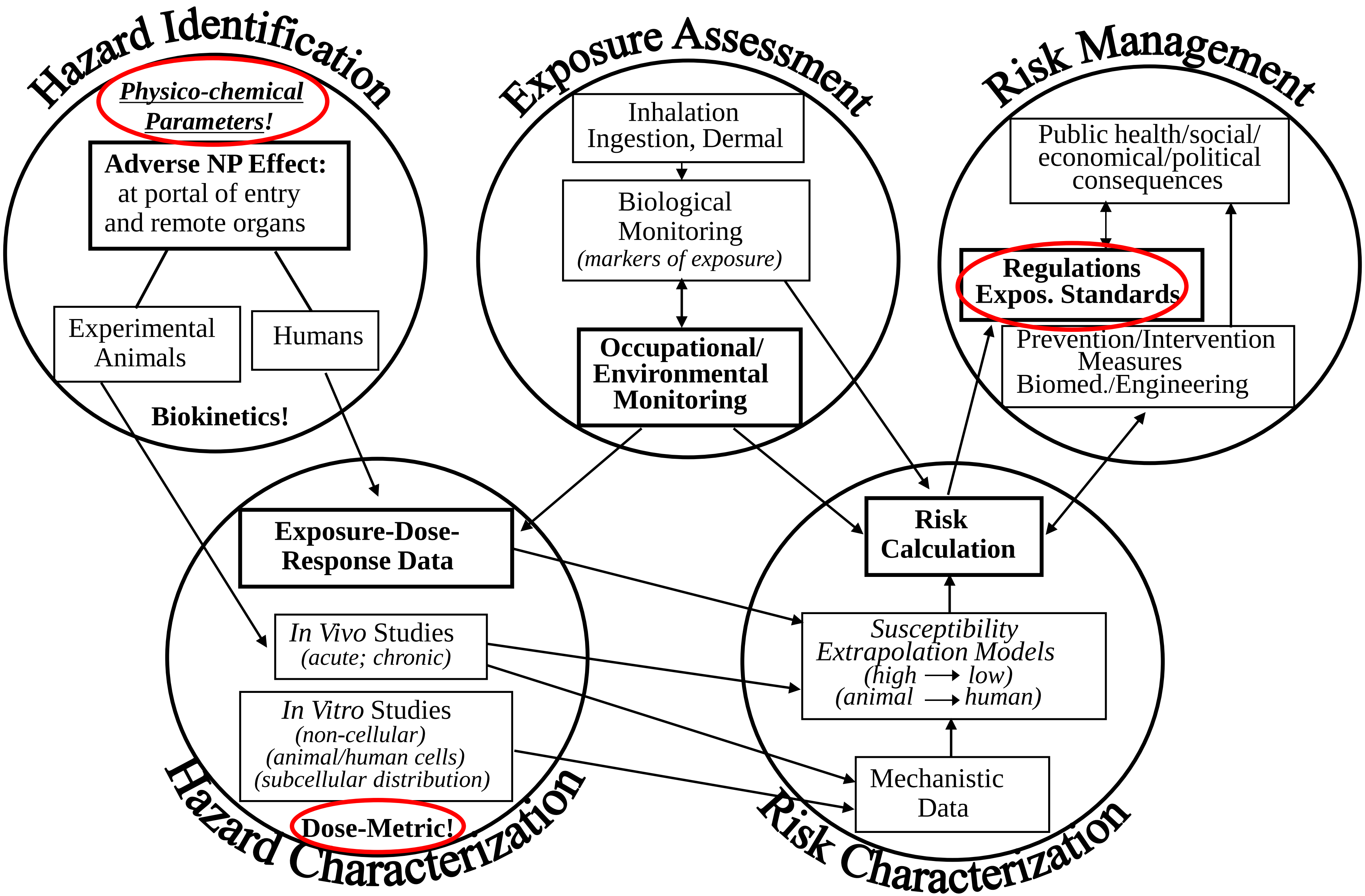
Hazard and Risk Characterization

Risk Assessment and Risk Management Paradigm For Engineered Nanoparticles (NPs)



Modified from Oberdörster et al., 2005

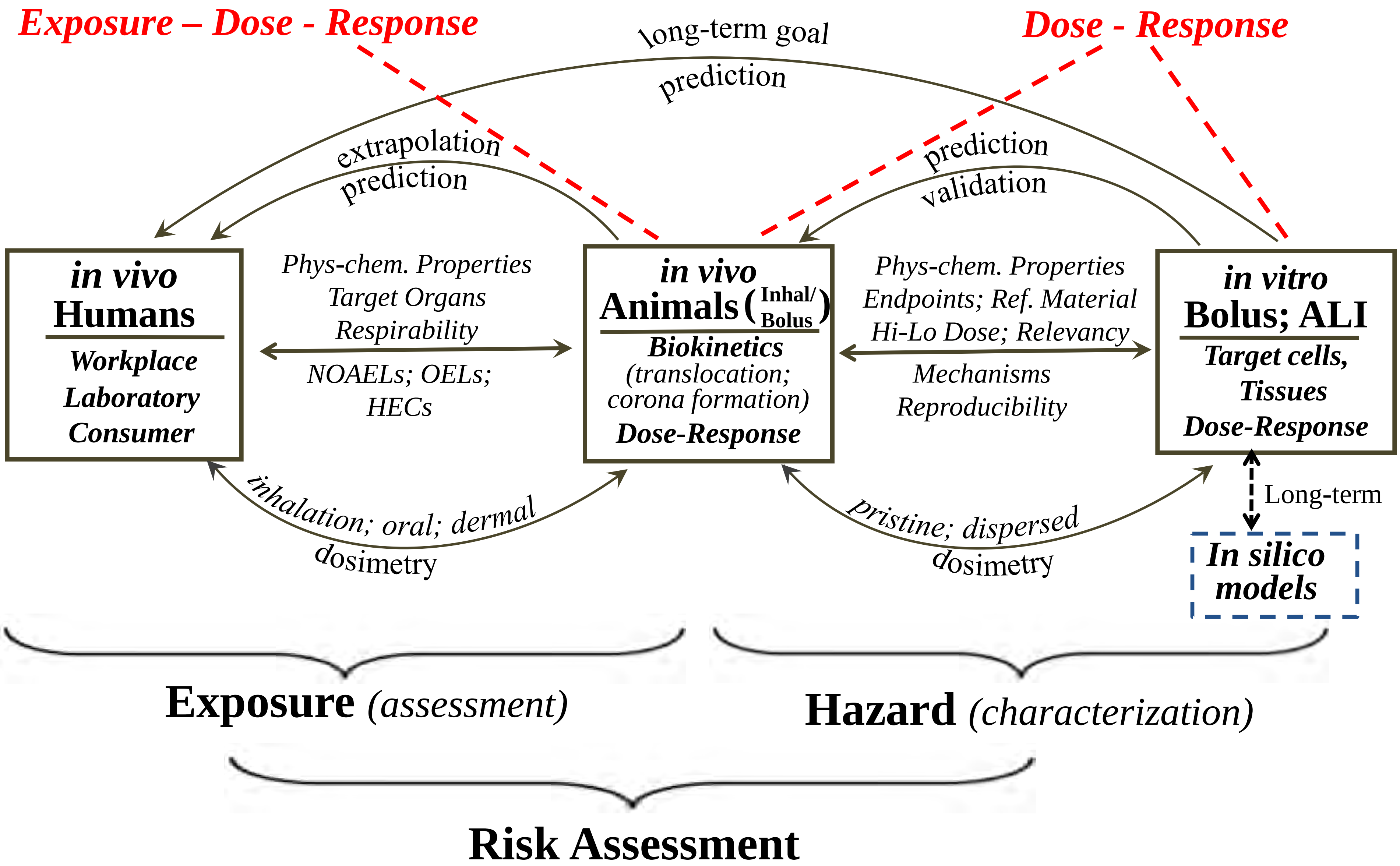
Risk Assessment and Risk Management Paradigm For Engineered Nanoparticles (NPs)



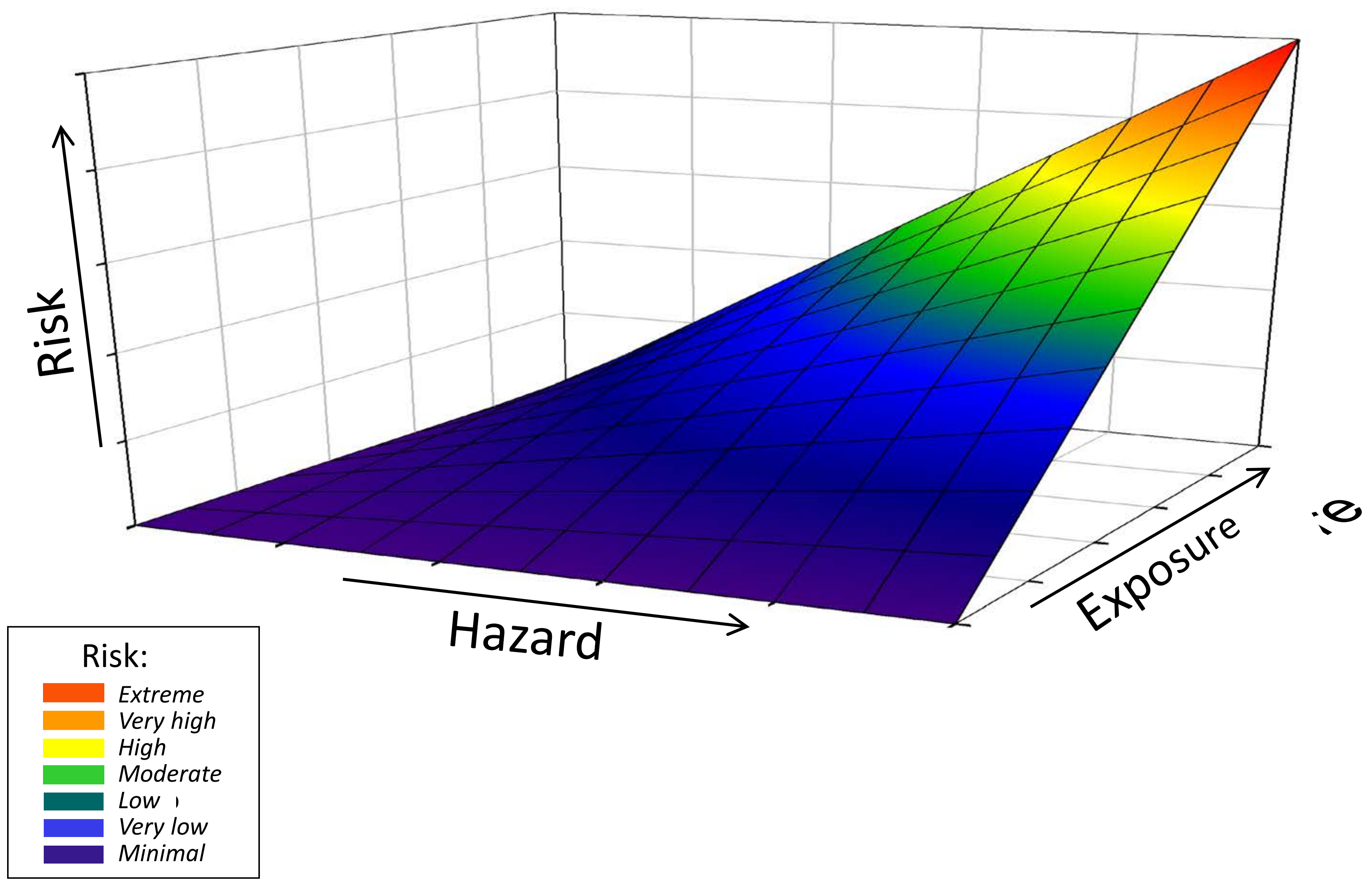
Modified from Oberdörster et al., 2005

Concepts of Nanomaterial Toxicity Testing:

Considering Exposure and Hazard for Risk Assessment



Risk = f (hazard; exposure)



Subchronic Carbon Nanotube/Nanofiber Inhalation Studies in Rats

Inhalation Toxicity of Multiwall Carbon Nanotubes in Rats Exposed for 3 Months

Lan Ma-Hock,* Silke Treumann,* Volker Strauss,* Sandra Brill,* Frederic Luizi,† Michael Mertler,‡ Karin Wiench,* Armin O. Gamer,* Bennard van Ravenzwaay,*[,1] and Robert Landsiedel*

**Product Safety, BASF SE, 67056 Ludwigshafen, Germany; †Nanocyl S. A., 5060 Sambreville, Belgium; and ‡Process Engineering, BASF SE, 67056 Ludwigshafen, Germany*

TOXICOLOGICAL SCIENCES **112(2)**, 468–481 (2009)

Subchronic 13-Week Inhalation Exposure of Rats to Multiwalled Carbon Nanotubes: Toxic Effects Are Determined by Density of Agglomerate Structures, Not Fibrillar Structures

Jürgen Pauluhn[1]

Department of Inhalation Toxicology, Institute of Toxicology, Bayer Schering Pharma, Building Number 514, 42096 Wuppertal, Germany

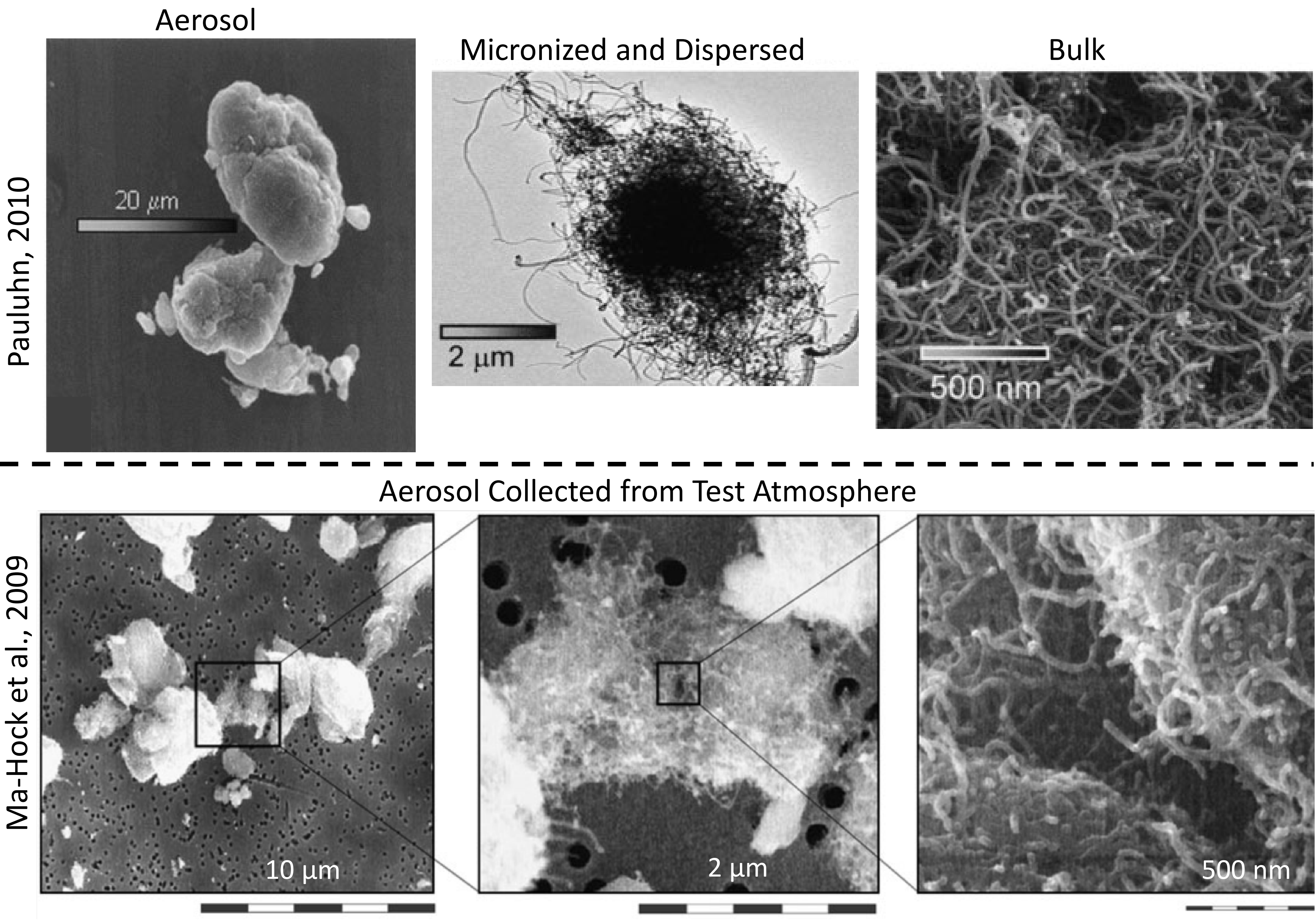
TOXICOLOGICAL SCIENCES **113(1)**, 226–242 (2010)

Ninety-Day Inhalation Toxicity Study With A Vapor Grown Carbon Nanofiber in Rats

Michael P. DeLorme,* Yukihiro Muro,† Toshihiro Arai,† Deborah A. Banas,‡ Steven R. Frame,* Kenneth L. Reed,* and David B. Warheit*[,1]

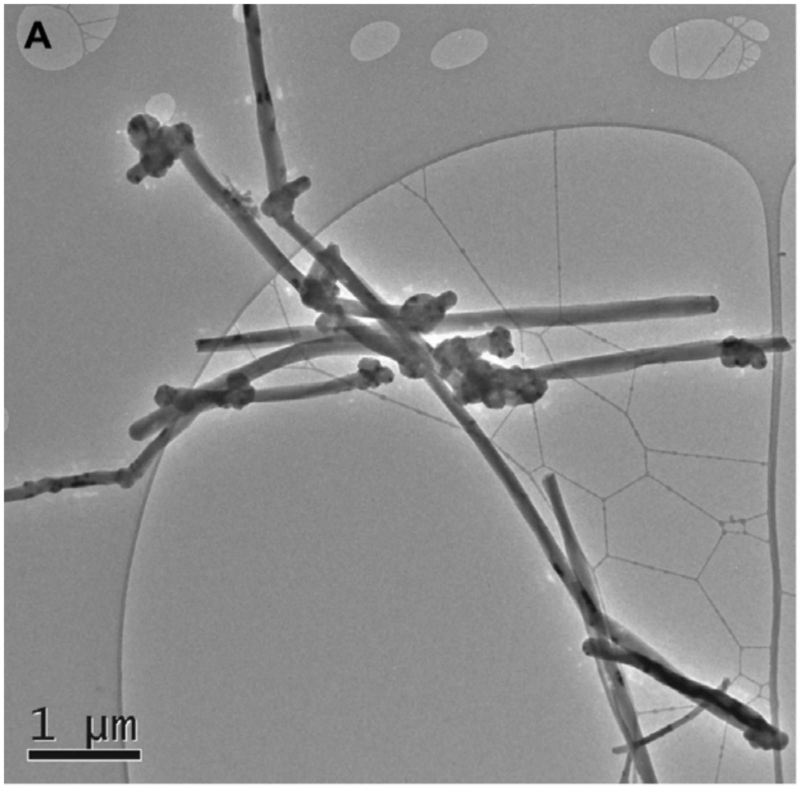
TOXICOLOGICAL SCIENCES **128(2)**, 449-460 (2012)

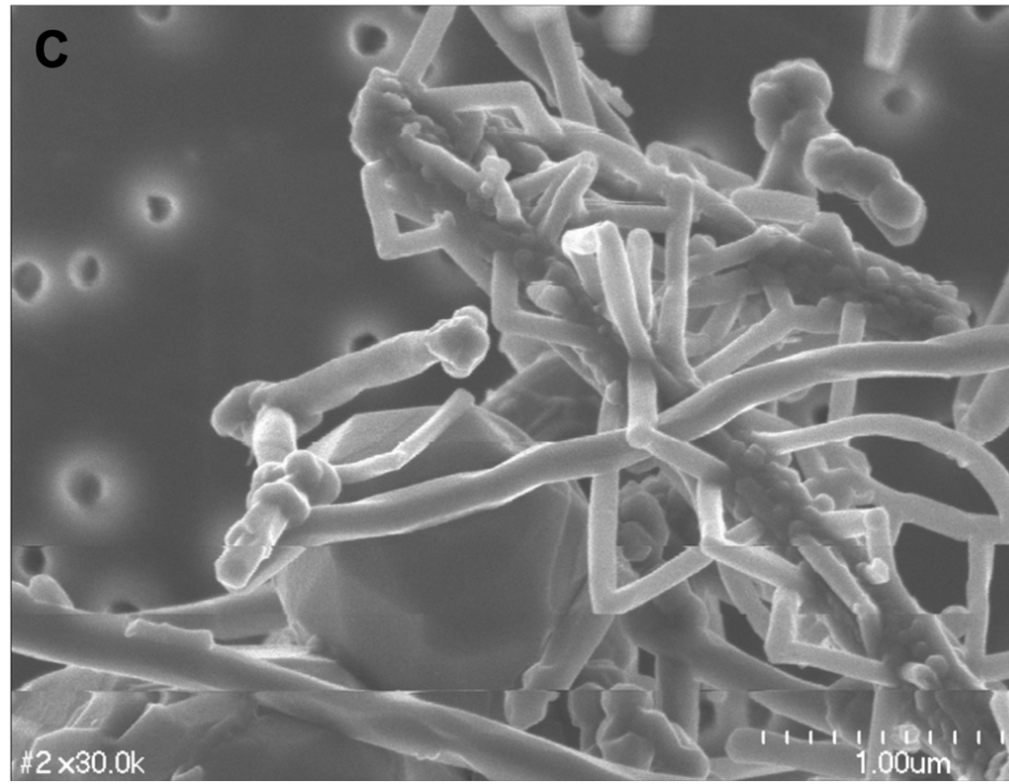
SEM Images: MWCNT Used in Pauluhn (2010) and Ma-Hock et al. (2009) Inhalation Studies



Carbon Nanofiber (CNF) Aerosol of 90-Day Rat Inhalation Study,

DeLorme et al., 2012





90-Day Rat Inhalation Studies with MWCNT and CNF, Exposure-Dose-Response Comparison

	Ma-Hock et al. (2009)	Pauluhn (2010)	DeLorme et al. (2012)
Material	MWCNT (Nanacyl NC7000)	MWCNT (Baytubes)	CNF (VGCF-H)
Characterization			
Length/diameter, nm	100-10,000 /5-15 nm	200-1000/10 nm	1000-14000/40 -350 nm
Impurities	9.6% Al; <0.2% Co	~0.5% Co	0.003% Fe
BET surf area, m^2/g	250 – 300	255	13.8
Packing dens, g/cm^3	0.043	0.11 – 0.31	0.077
Exposure			
Conctr, mg/m^3	0; 0.1; 0.5; 2.5	0, 0.1; 0.4; 1.5; 6	0.54; 2.5; 25
Ret. Lung Burden	No	Yes	No
Response			
Lung weight *(90 days)*	+ 1%; + 23%; + 81% (males)	+0; + 12; +27; +61% (males)	-2; +8; +22 (males)
BAL–PMN *(90 days)*	Not reported	~0.5; 3.8; 13; 19%	1.4; 2.7; 11%
Evaluation			
NOAEL	No	100 $\mu g/m^3$	540 $\mu g/m^3$
LOAEL	100 $\mu g/m^3$	400 $\mu g/m^3$	2500 $\mu g/m^3$

Approach for Risk Assessment
Based on Subchronic (3 months) Rodent Inhalation Studies

- subchronic multi-concentration inhalation studies with CNT and CNF in rats and results of **“positive” and “negative” reference materials** as benchmarks

- select sensitive endpoints of response *(quantitative, functional preferable)*

- establish **Exposure – Dose - Response** relationships by different dosemetrics *(particle-mass, -surface area, -volume, -number)*

- establish: ***hazard* ranking** *against pos. and neg. control, by different dosemetrics*
  risk: subchronic *“safe” level for rat: BMD analysis using NOAEL; LOAEL*

- estimate **chronic** “safe” effect level for rat *(based on accumulated lung burden)*

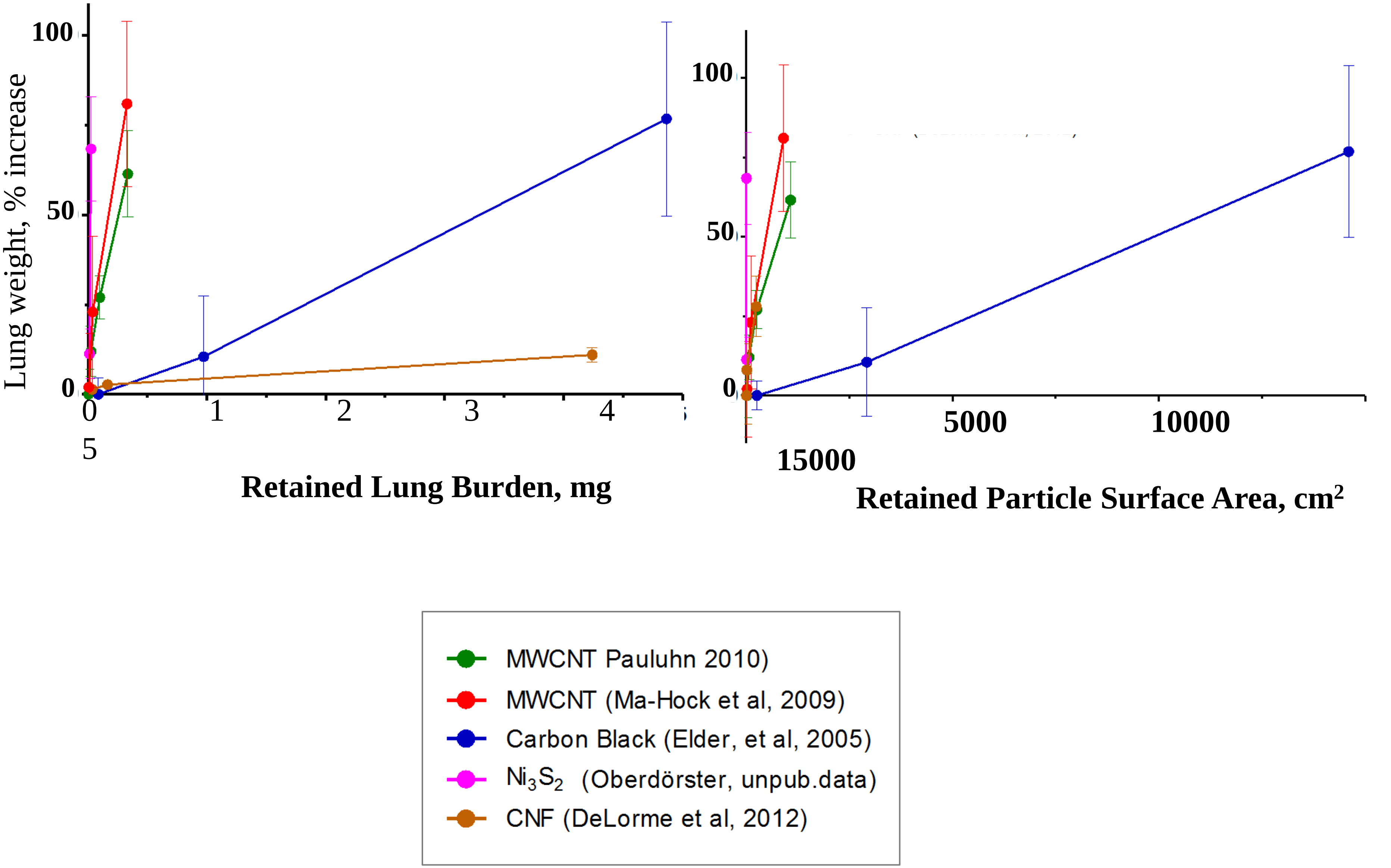
- use dosimetric extrapolation to estimate **HEC** *(Human Equivalent Concentration)*

<u>Comparing MWCNTand CNF results with two other subchronic rat inhalation studies:</u>

ultrafine carbon black		*negative*
		Benchmark materials
nickel subsulfide		*positive*

Dose-Response relationships of 3-month inhalation studies in rats with MWCNT, CNF and CB

– Lung weight dose-responses based on retained lung burden expressed as mass, surface area and volume –



Hazard Ranking of Different (Nano)-Materials Based on Different Metrics and Steepest Slope of Exposure-Dose-Response Relationships from Subchronic Rat Inhalation Studies (endpoint: lungweight increase)

Metric	Ranking
Exposure Conc. **:**	**CNF** = **CB** < **MWCNT**-P = **MWCNT**-MH < Ni_3S_2

Retained Lung Burden:

Mass:	**CNF** < **CB** < **MWCNT**-P = **MWCNT**-MH < Ni_3S_2
Surface area:	**CB** < **CNF** = **MWCNT**-P = **MWCNT**-MH < Ni_3S_2
Volume (bulk dens)**:**	**CB** < **CNF** < **MWCNT**-MH = **MWCNT**-P < Ni_3S_2
Volume (mat. dens)**:**	**CNF** = **CB** < **MWCNT**-P = **MWCNT**-MH < Ni_3S_2

Hazard Ranking of Different (Nano)-Materials Based on Different Metrics and Steepest Slope of Exposure-Dose-Response Relationships from Subchronic Rat Inhalation Studies (endpoint: lungweight increase)

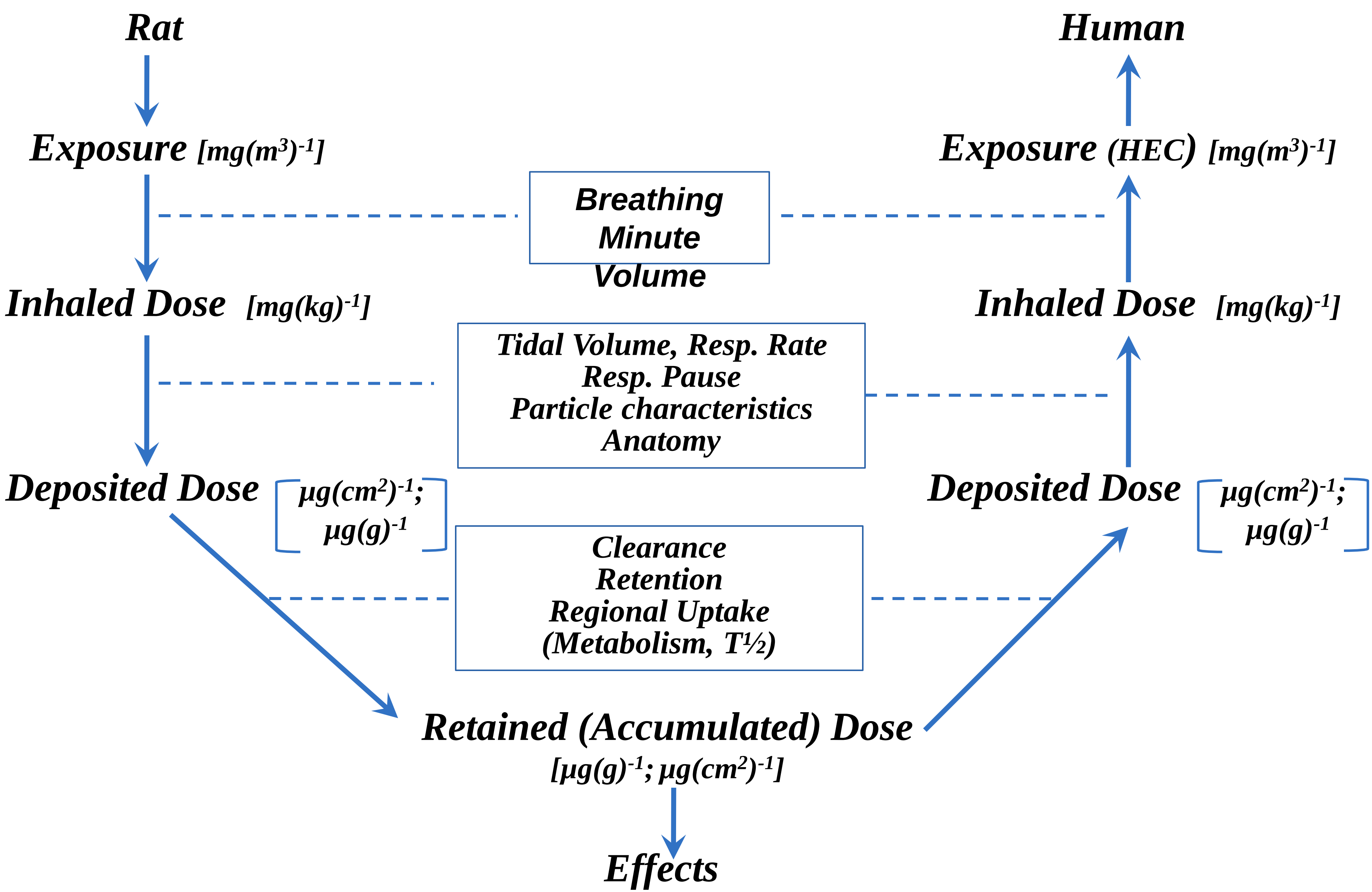
Three Hazard Groupings:

Low: ***CB; TiO_2*** ⟶ ***< 0.3 % lungwt. incr./cm^2***

Medium: ***MWCNT*** ⟶ ***0.3 – 1 % lungwt. incr./cm^2***

High: ***SiO_2; Ni_3S_2*** ⟶ ***>1 % lungwt. incr./cm^2***

Dosimetric Extrapolation of Inhaled Particles from Rats to Humans



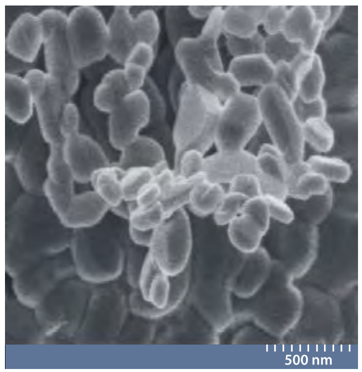
Assumption: If retained dose is the same as in rats and humans, then effects will be the same

Human Health Risk of MWCNT/CNF OEL Estimates Based on Subchronic Rodent Inhalation

Reference	Basis	Endpoint	Extrapolation Method	OEL µg/m^3	Author Comments
NIOSH, 2013	Pauluhn, 2010 Ma-Hock, 2009 DeLorme, 2012	Histopath. Inflammation; fibrosis; septal thickening	BMD analysis, dosimetric adjustment (MPPD), deposited, retained dose; HEC based on alveolar surface area; assessment factors: 20 - 60	**2** (P) **1** (MH) **1** (DL)	Limit of quantitation: 7 µg/m^3
Aschberger, *et al.*, 2010	Pauluhn, 2010 Ma-Hock, 2009	NOAEL (P) LOAEL (MH)	REACH Guidance; no correction for species differences in deposition and retention; assessment factors for LOAEC and inter-species extrapolation	**2** (P) **1** (MH)	No definite conclusion; need for exposure data
Pauluhn, 2010	Baytubes® Pauluhn, 2010a,b	Volumetric overloading of AM clearance	MPP dosimetric extrapolation, avoiding volume overload; T½ human 1 year; normalization to bodyweight; no assessment factors	**50**	Consistent with MAK approach of ½ subchronic rat NOAEL; Baytubes® behave similar to PSP (carbon black)
This analysis (*preliminary*)	Pauluhn, 2010 Ma-Hock, 2009 DeLorme, 2012	Increase in lung weight	BMD analysis; dosimetric extrapolation (MPPD) to BMCL; HEC based on Gregoratto et al. particle lung retention model using mass/ lung weight metric; extrapolat. to chronic exposure; assessment factors: 12 - 16	**4** (P) **1** (MH) **2** (DL)	MPPD estimation of deposited and retained lung burden for Ma-Hock *et al.* and DeLorme et al.

CURRENT INTELLIGENCE BULLETIN 63

2011



CDC Workplace Safety and Health

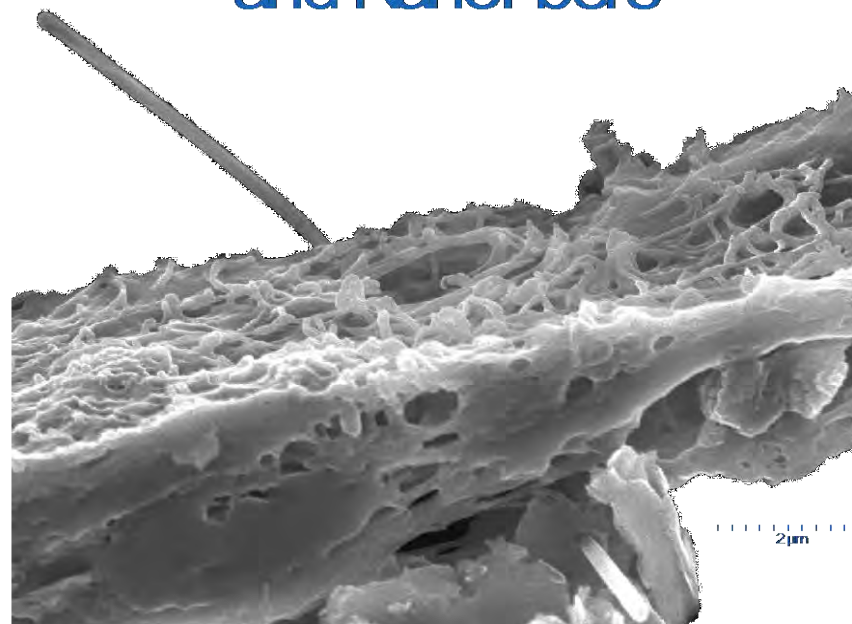
REL: Fine: 2.5 mg/m^3

Nano: 300 µg/m

CURRENT INTELLIGENCE BULLETIN 65

2013

Occupational Exposure to Carbon Nanotubes and Nanof bers



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

CDC Workplace Safety and Health NIOSH

REL: 1 µg/m^3

<u>CHALLENGES FOR ESTABLISHING OEL FOR CNT/CNF</u>:

***Workplace monitoring*: 1 μg/m^3; distinguishable from background?**

***One generic OEL for all*: Are all CNTs and CNFs toxicologically of equal potency?**

Surface modification or functionalization,
level of impurities, surface defects are known
to alter toxicity

<u>But</u>: Unless there are convincing data to the contrary,
it is prudent to treat airborne CNTs/CNFs as highly hazardous

<u>CHALLENGES FOR ESTABLISHING OEL FOR CNT/CNF</u>:

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level of impurities, surface defects are known
to alter toxicity***

**<u>But</u>: Unless there are convincing data to the contrary,
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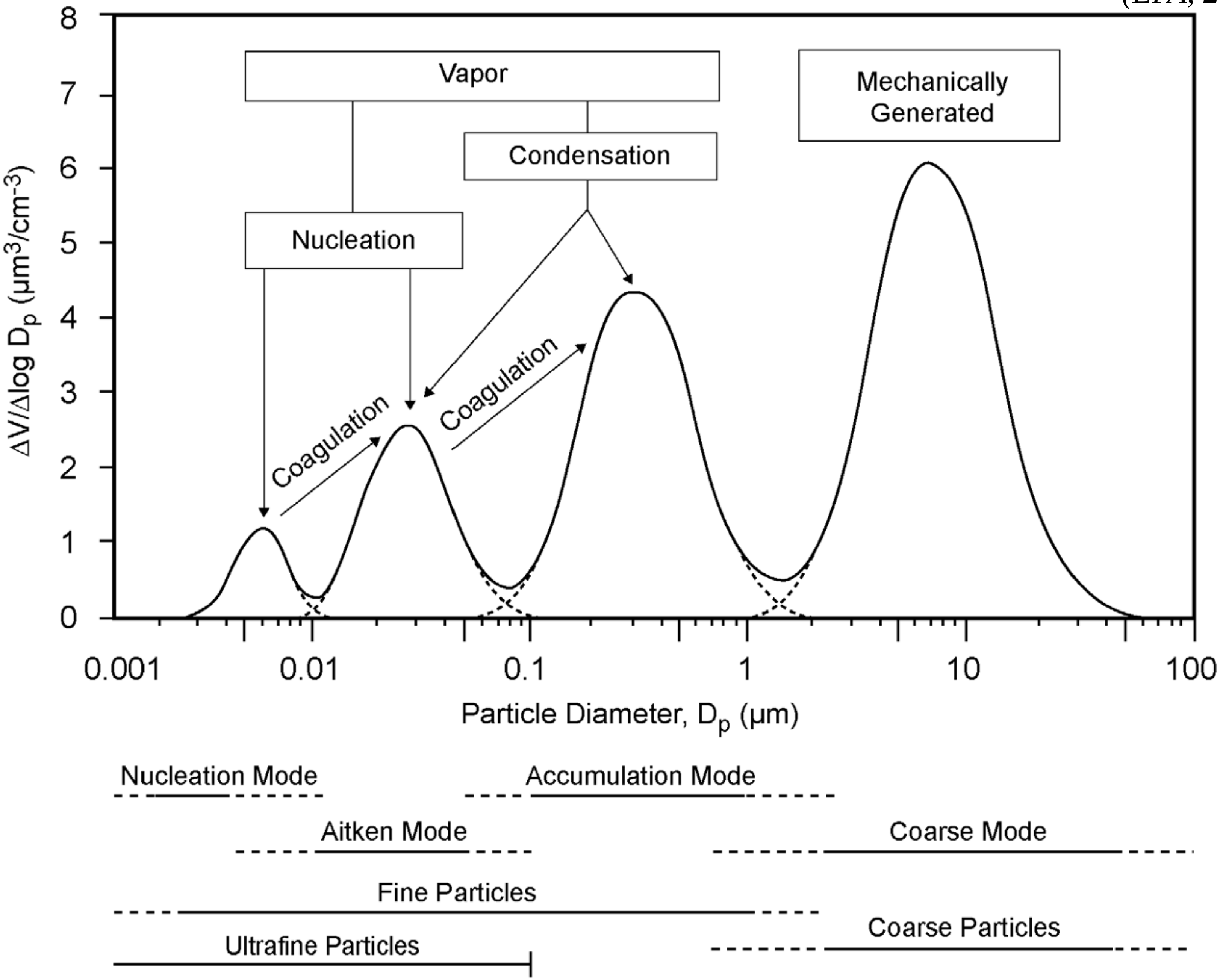
Desirable: Results of chronic inhalation study

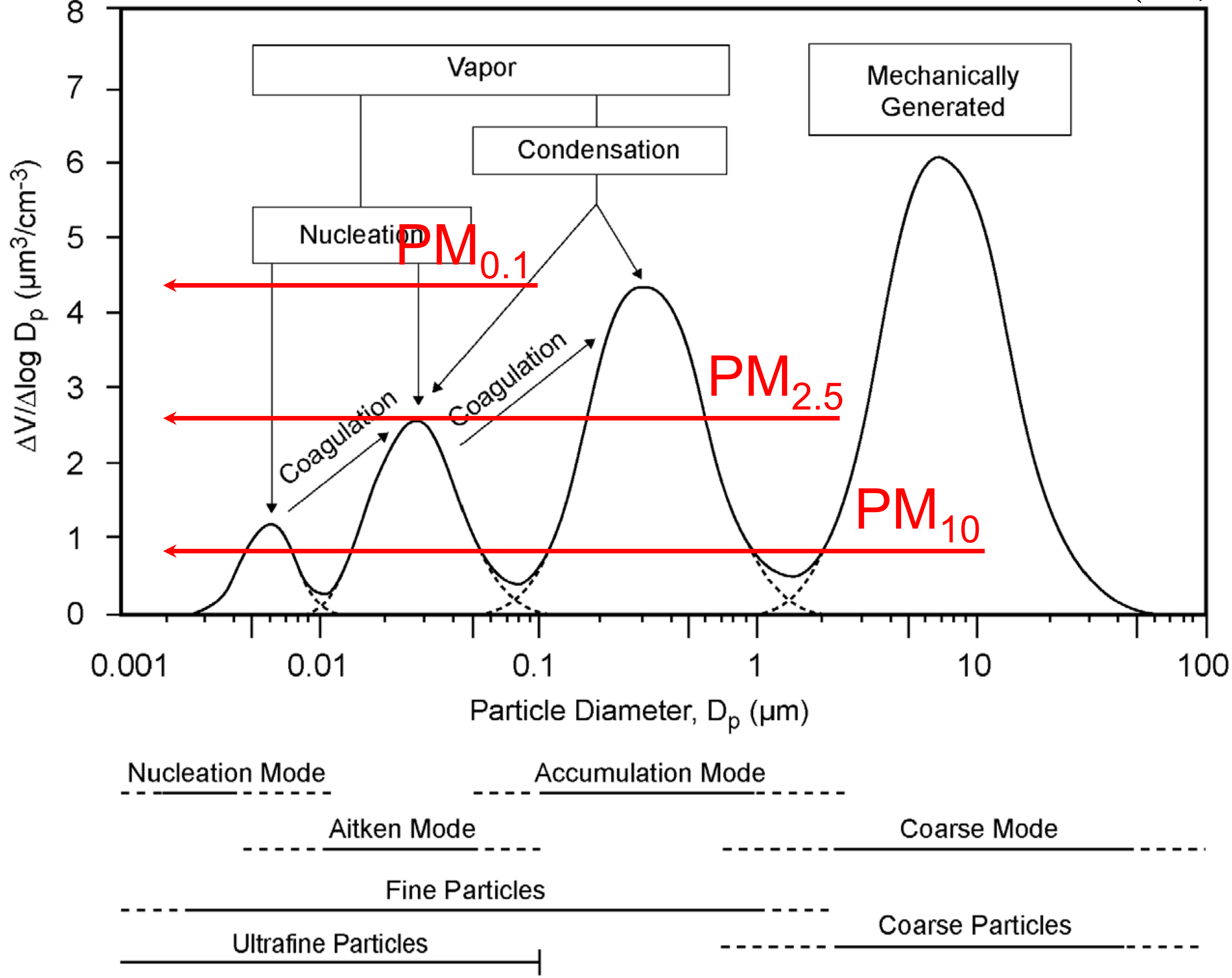
Idealized Size Distribution of Traffic-Related Particulate Matter

(EPA, 2004)



Idealized Size Distribution of Traffic-Related Particulate Matter

(EPA, 2004)

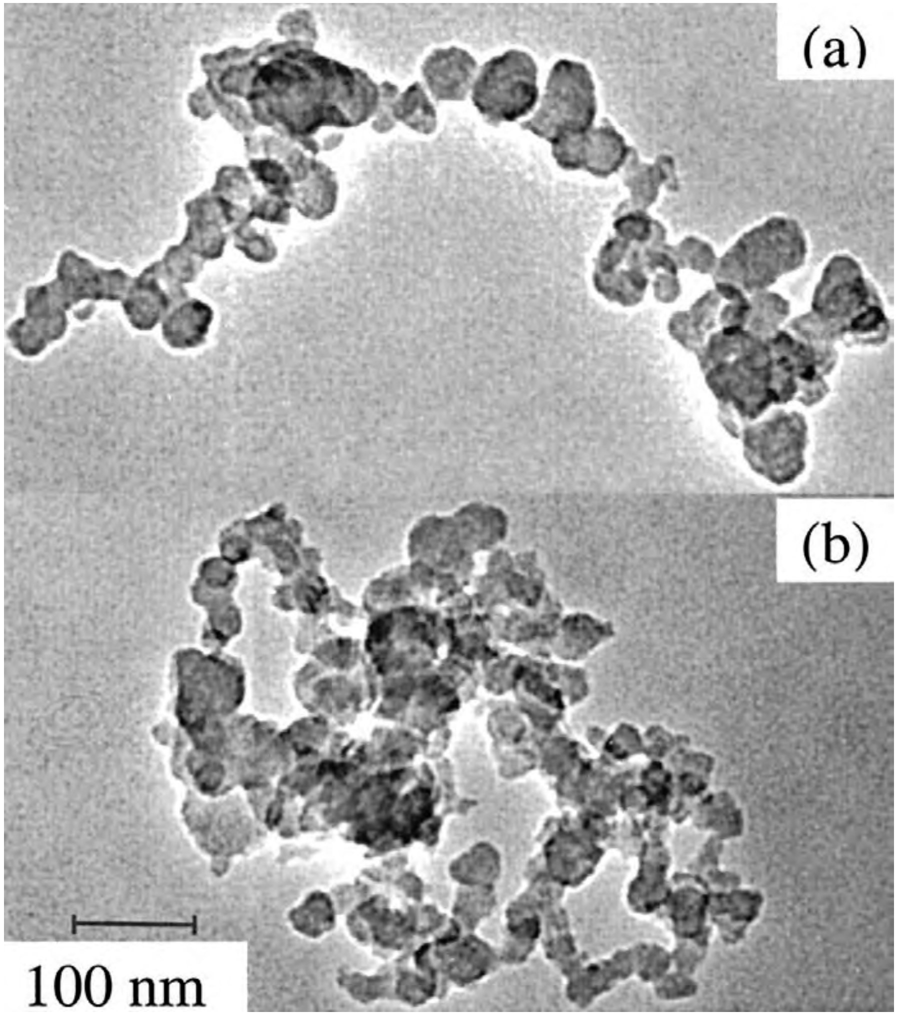


Source emission inventory for South Coast Air Basin surrounding L.A.:

Primary ultrafine particle emission rate:
<u>13 tonnes per day</u>

(Cass et al, 2000)

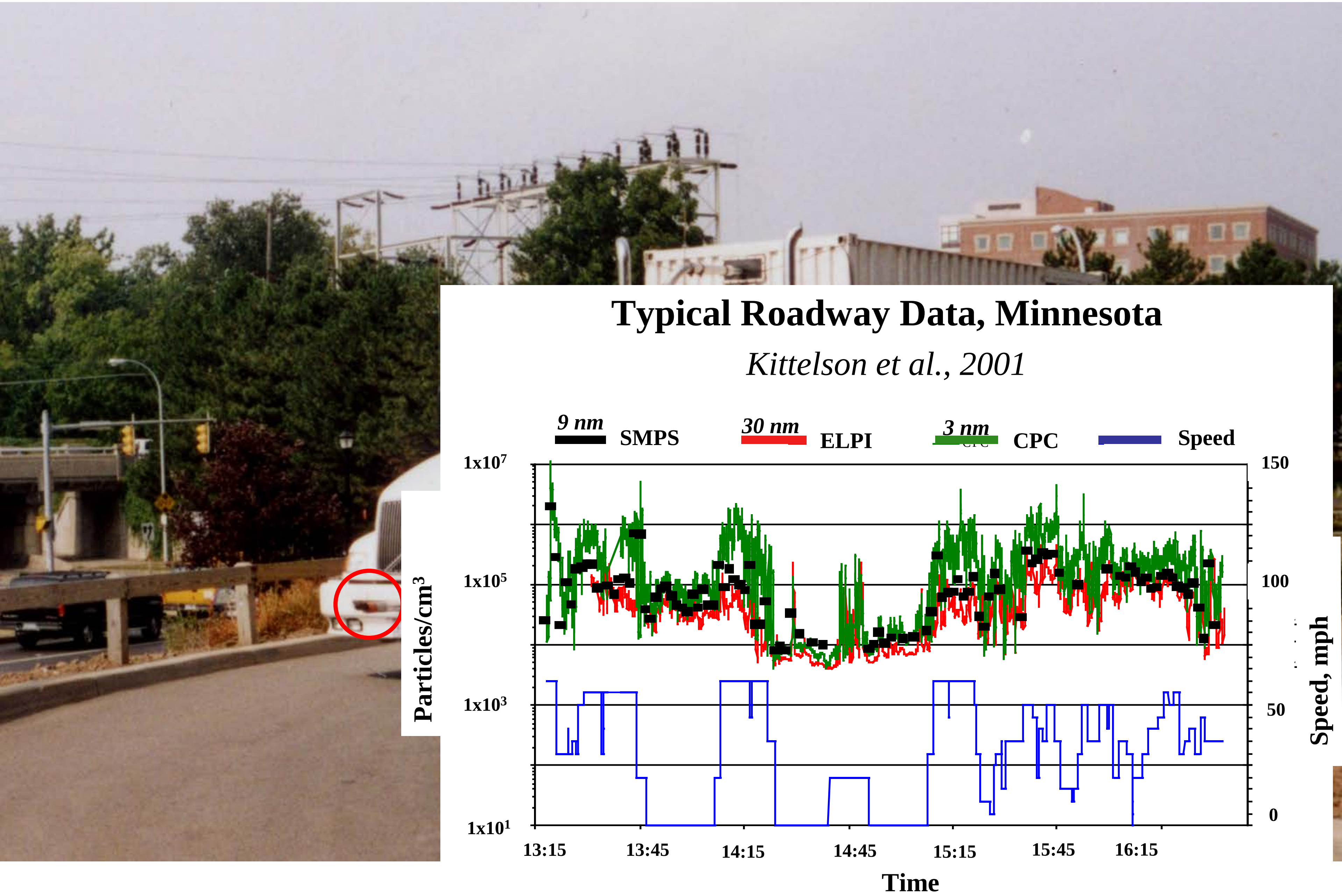
Chain aggregates of ultrafine particles from stage 7. *a* shows a short chain with low *Df* and *b* a longer chain with high *Df*. The sample was taken on Feb 20, 2001, at the San Jacinto Air Quality Management District (AQMD) site.



Xiong, C. and Friedlander, S. K. (2001) Proc. Natl. Acad. Sci. USA 98, 11851-11856

U of Minnesota Mobile Laboratory

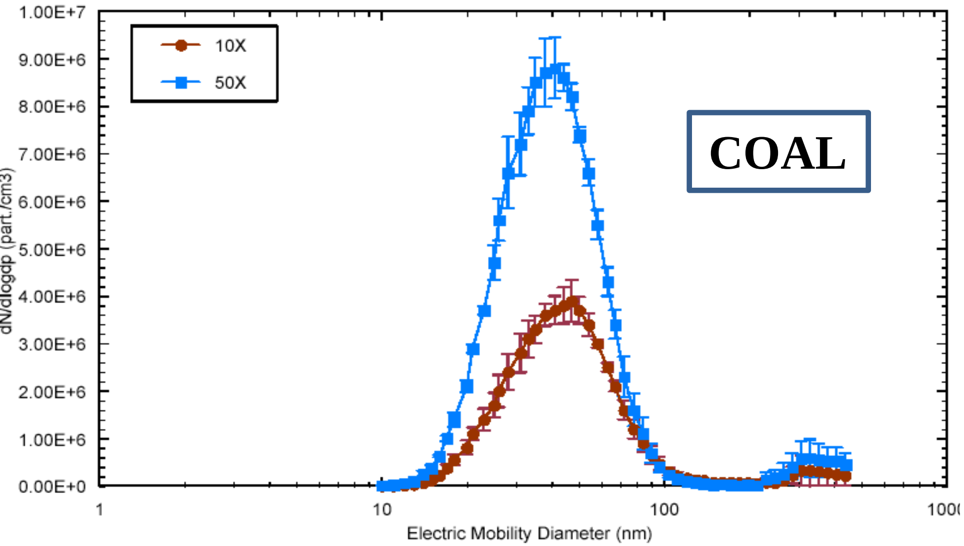
U of Minnesota Mobile Laboratory

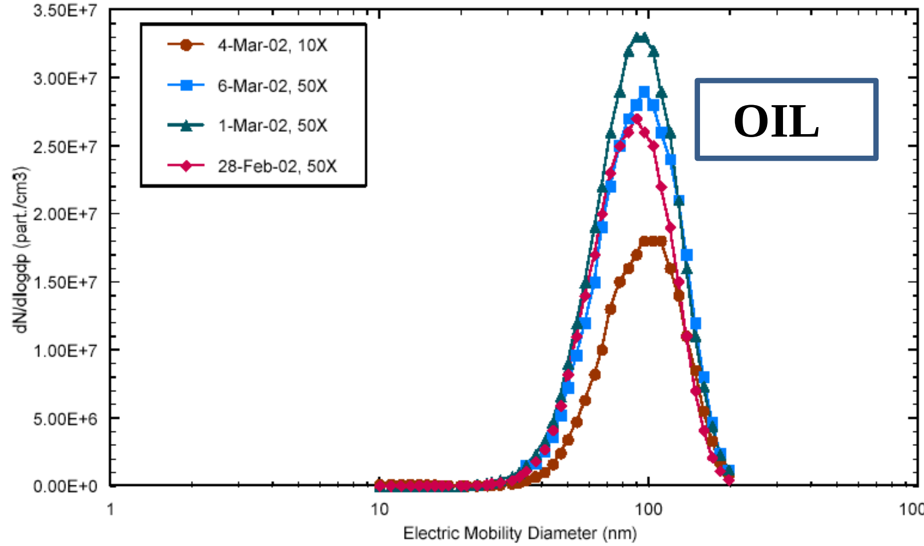


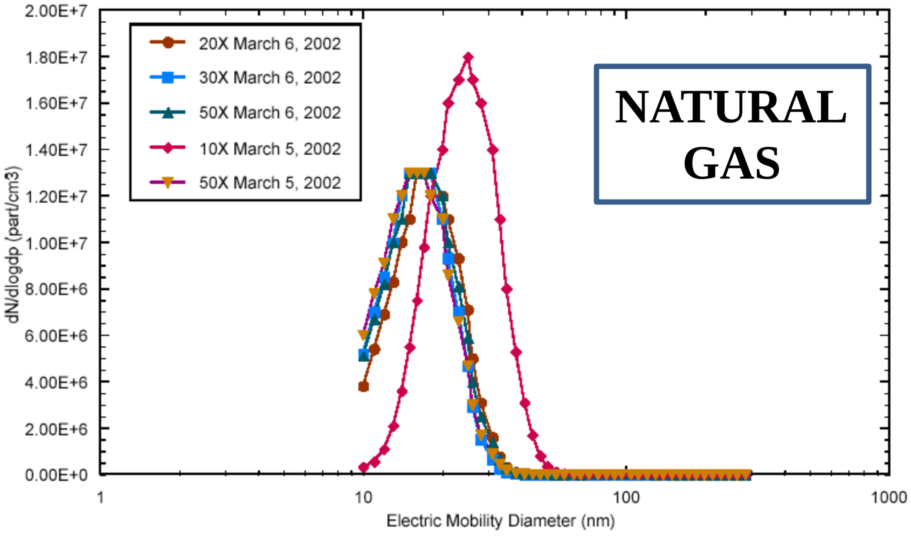
Powerplants: Ultrafine Particle Size Distribution at 10, 20, 30 and 50 X Dilution Air Ratios

(Exhaust temp. 450° K; residence time 80 sec)

(Chang et al., 2003)







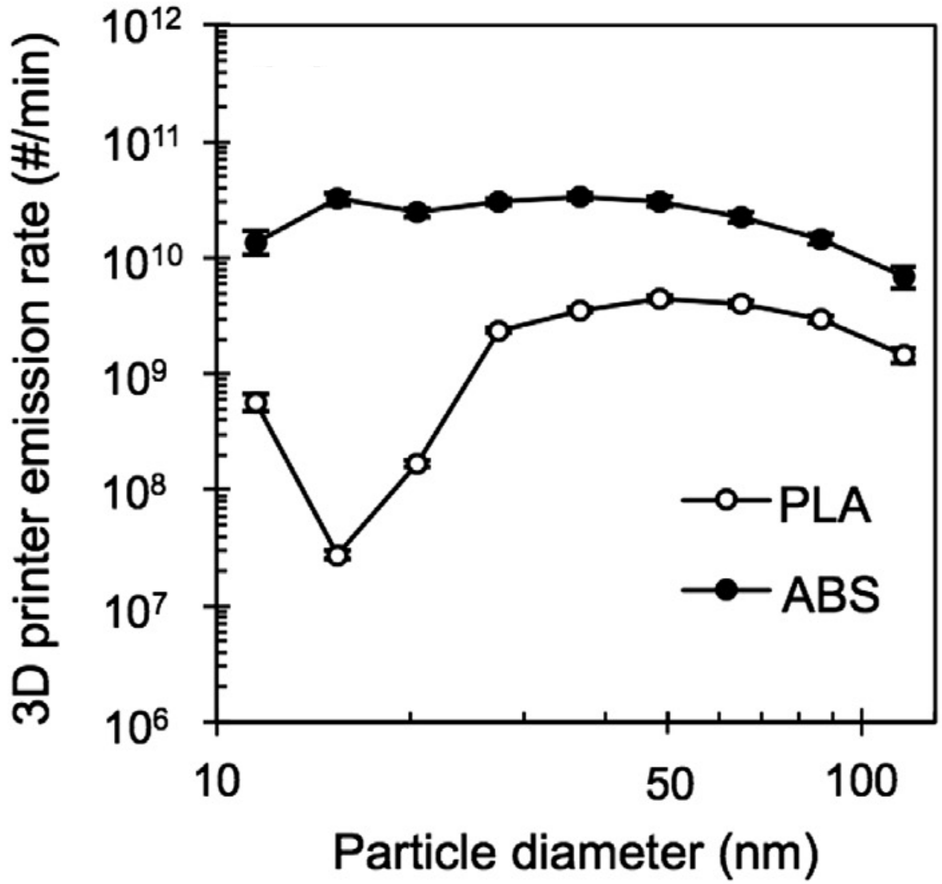
3-D Printing

Printed medical model

Printed acoustic guitar

Ultrafine Emission Rates from 3-D Printers Using Different Feedstocks

Polylactic Acid (PLA)



Acrylonitrile Butadiene Styrene (ABS)