The Respiratory Tract as Portal of Entry for Inhaled Ultrafine/Nanosized Particles

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

Primary ultrafine particle emission rate:
13 tonnes per day

(Cass et al, 2000)

ULTRAFINE/NANO PARTICLES (<100 nm): NATURAL AND ANTHROPOGENIC SOURCES

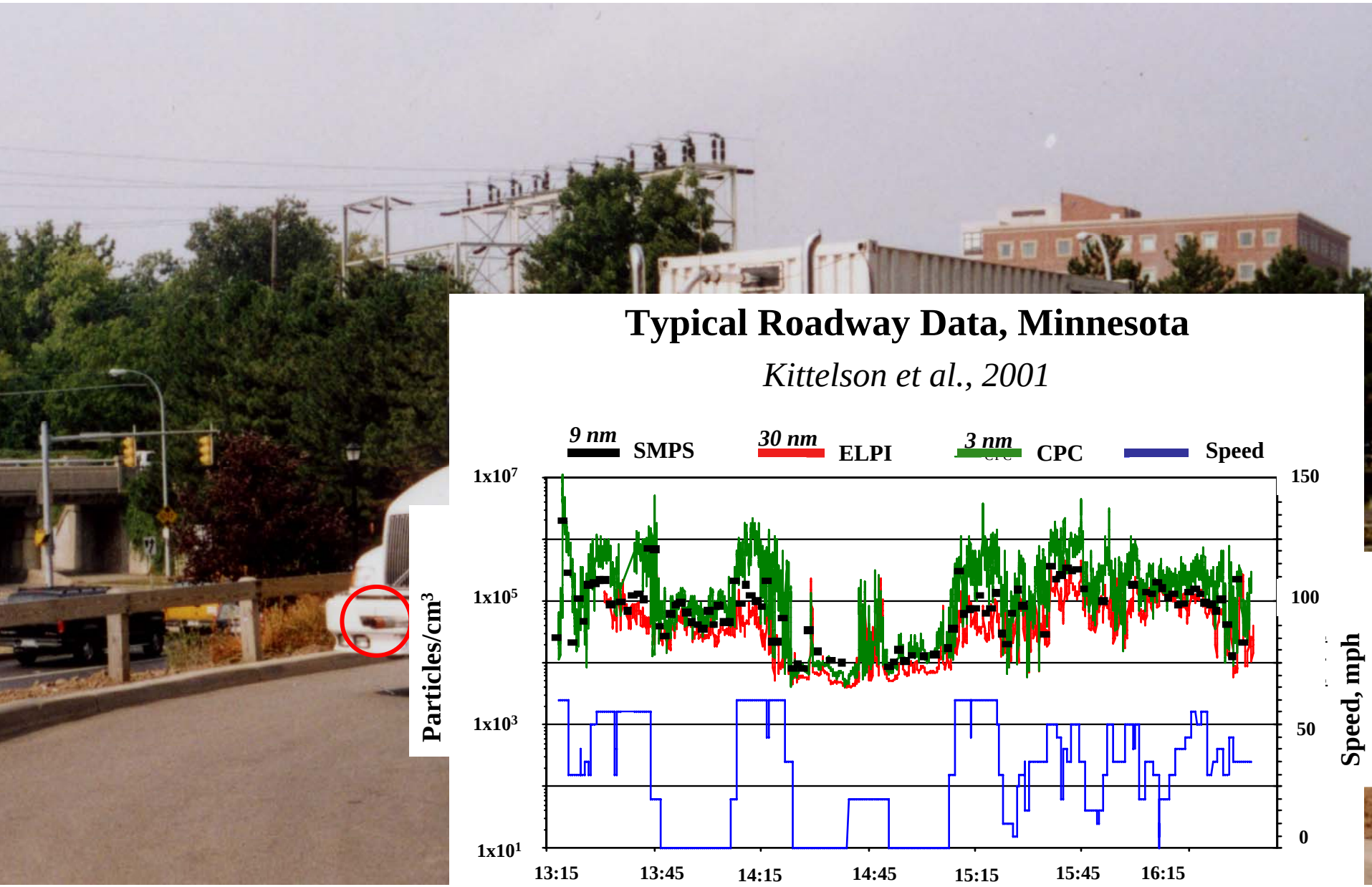
Natural	Anthropogenic	
	Unintentional	*Intentional*
gas to particle conversions **forest fires** **volcanoes (*hot lava)*** **viruses** **biogenic magnetite:** ***magnetotactic bacteria;*** ***protoctists, mollusks,*** ***arthropods, fish, birds,*** ***human brain, meteorite?*** **ferritin (12.5 nm)** **microparticles** *(<100 nm)* ***(from activated cells)***	**internal combustion engines** **power plants** **incinerators** **airplane jets** **metal fumes** **(*smelting, welding, etc .*)** **polymer fumes** **other fumes** **heated surfaces** **frying, broiling, grilling** **electric motors**	**engineered nanoparticles:** ***(controlled size and shape,*** ***designed for functionality)*** ***metals, semiconductors, metal oxides*** ***quantum dots/rods*** ***fullerenes, nanotubes*** ***nanowires*** ***nanoshells*** ***nanorings….etc*** ***(nanotechnology applied to many products: cosmetics, medical, fabrics, electronics, optics, displays, etc.)***

<u>Human Exposure Routes:</u>

Polydispere Ambient Ultrafine Particles: ***Inhalation***
MonodisperseEngineered Nanoparticles: ***Inhalation, Ingestion, Dermal, Injection***

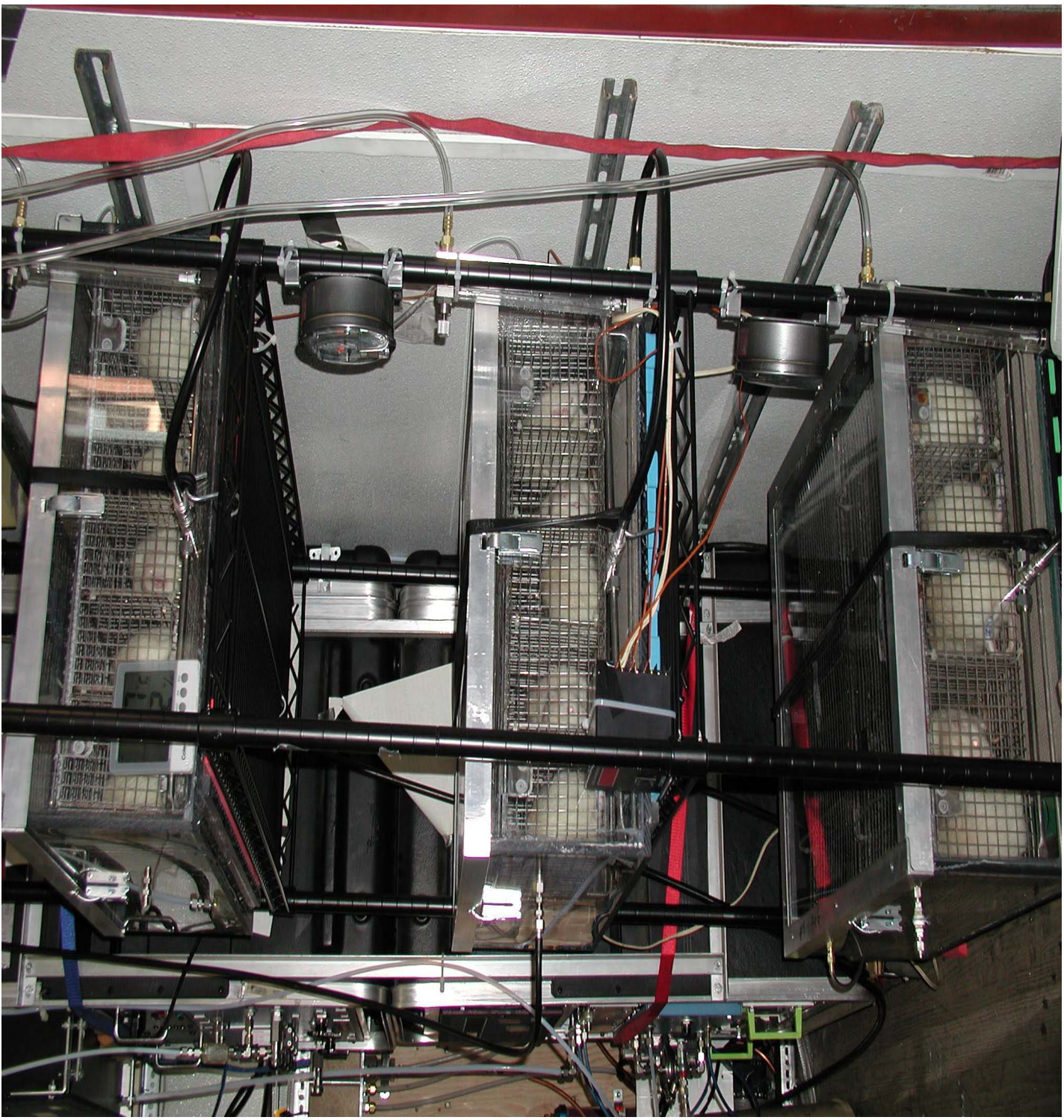
U of Minnesota Mobile Laboratory

U of Minnesota Mobile Laboratory

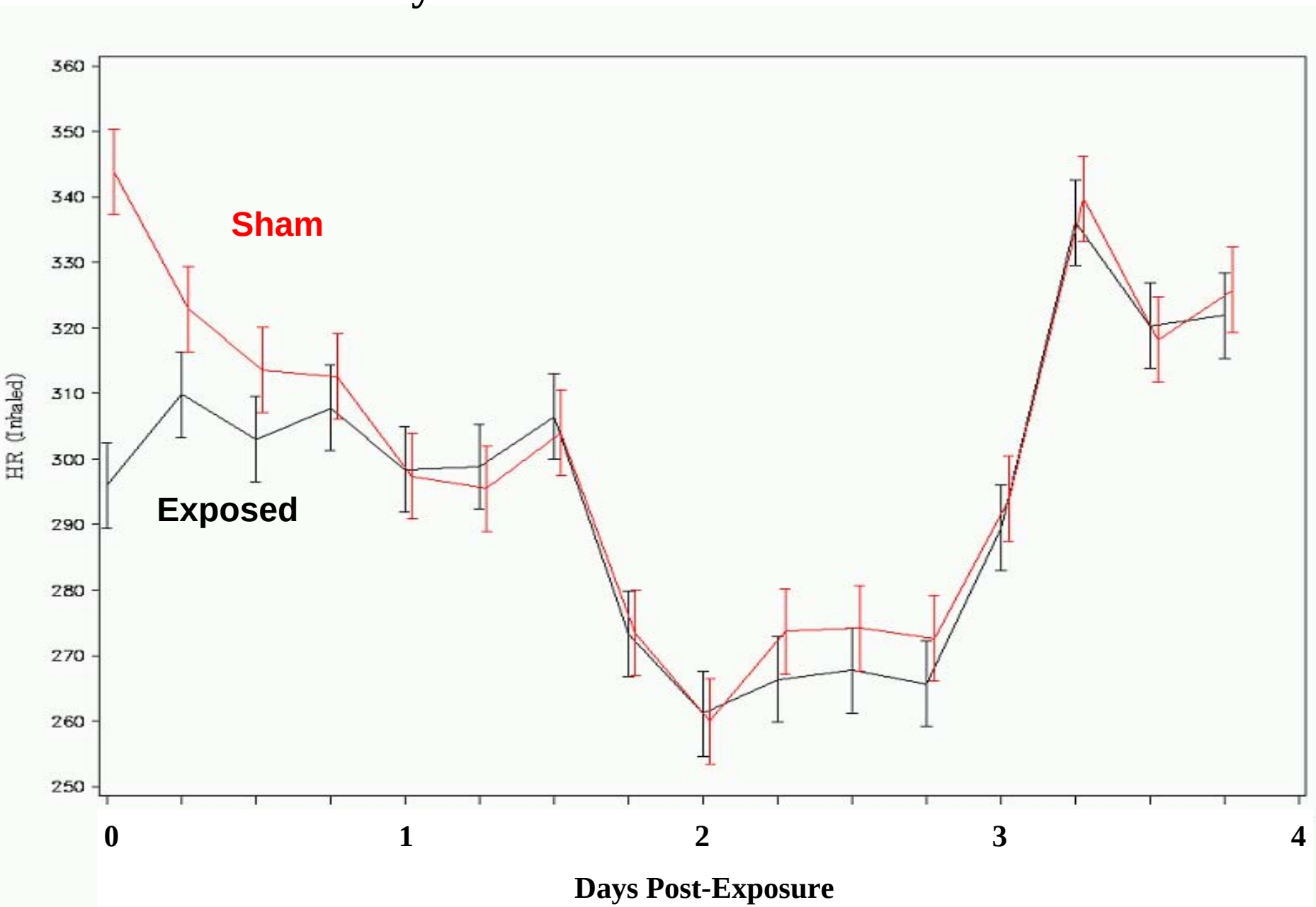


Typical Roadway Data, Minnesota

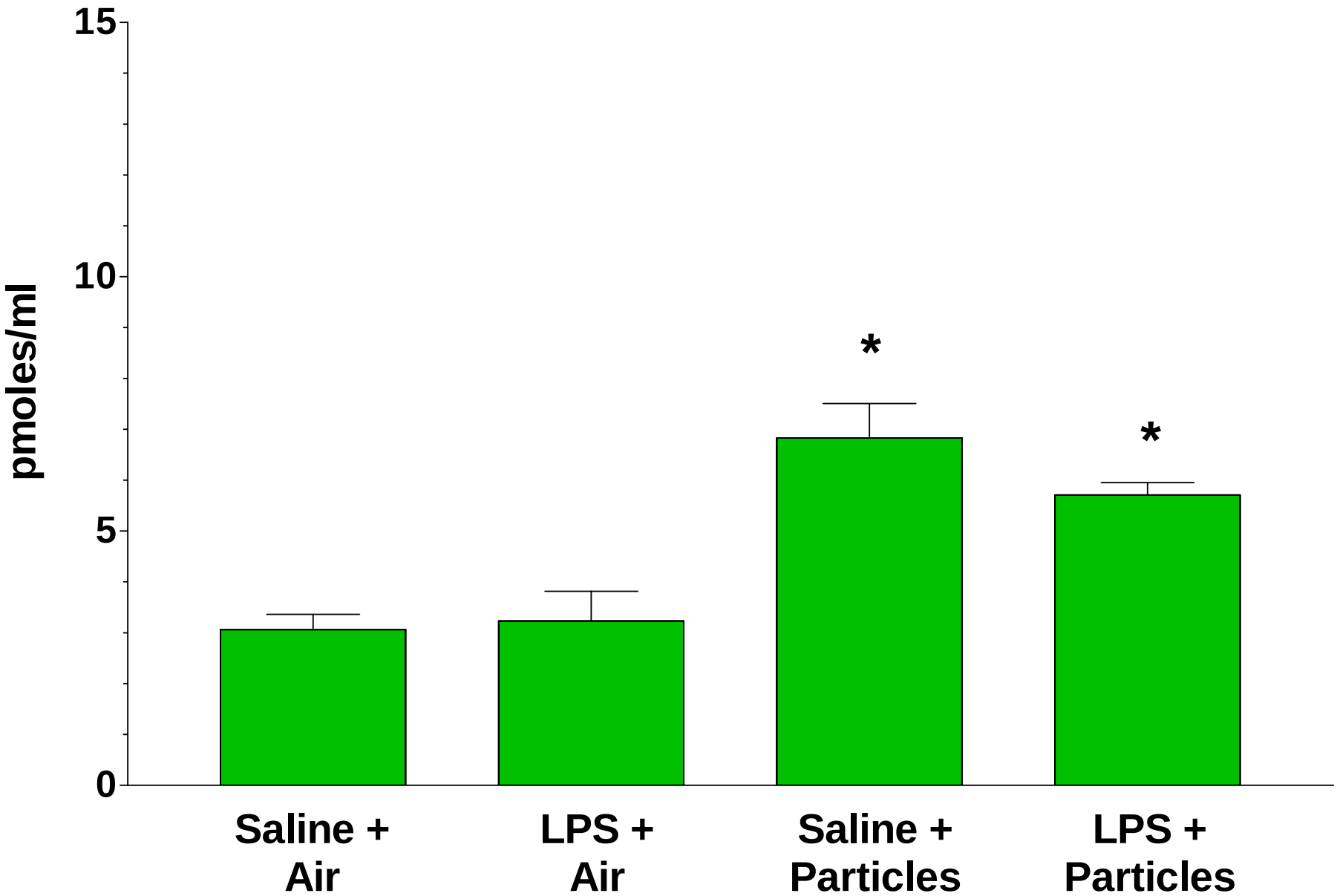
Kittelson et al., 2001



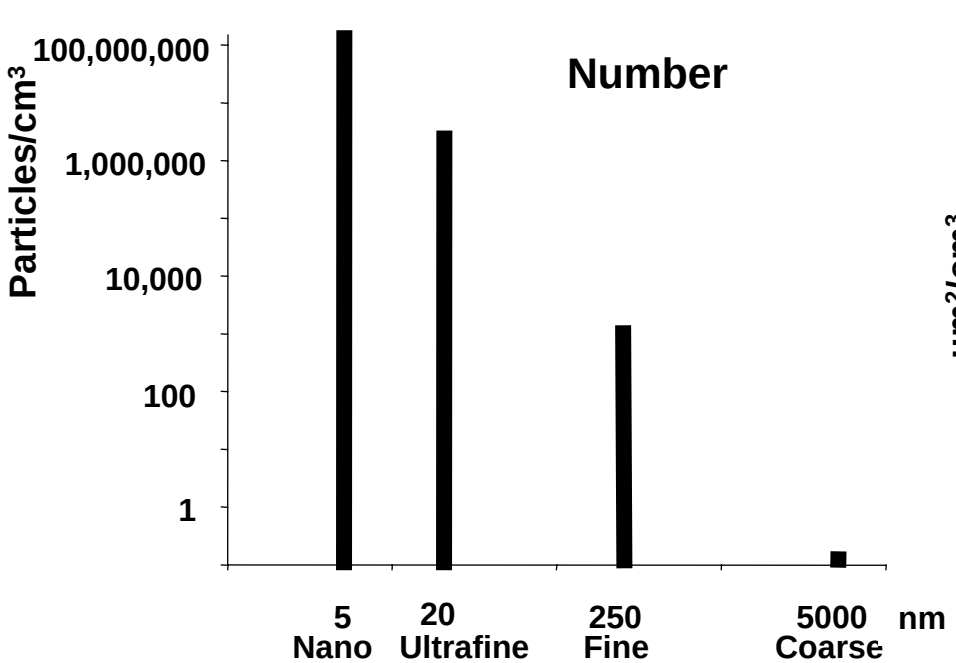
Changes in Heart Rate Following On-Road Exposures to Freshly-Generated On-Road Particles

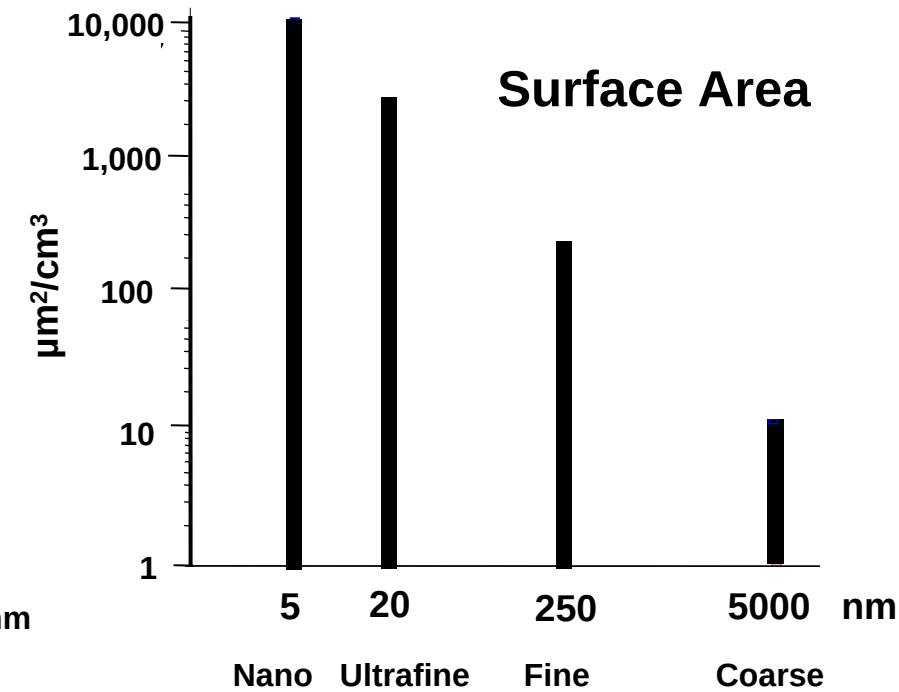


Plasma Endothelin-2 Levels from Old Rats Exposed to On-Road Ultrafine Particles or Filtered Air with and without LPS Priming

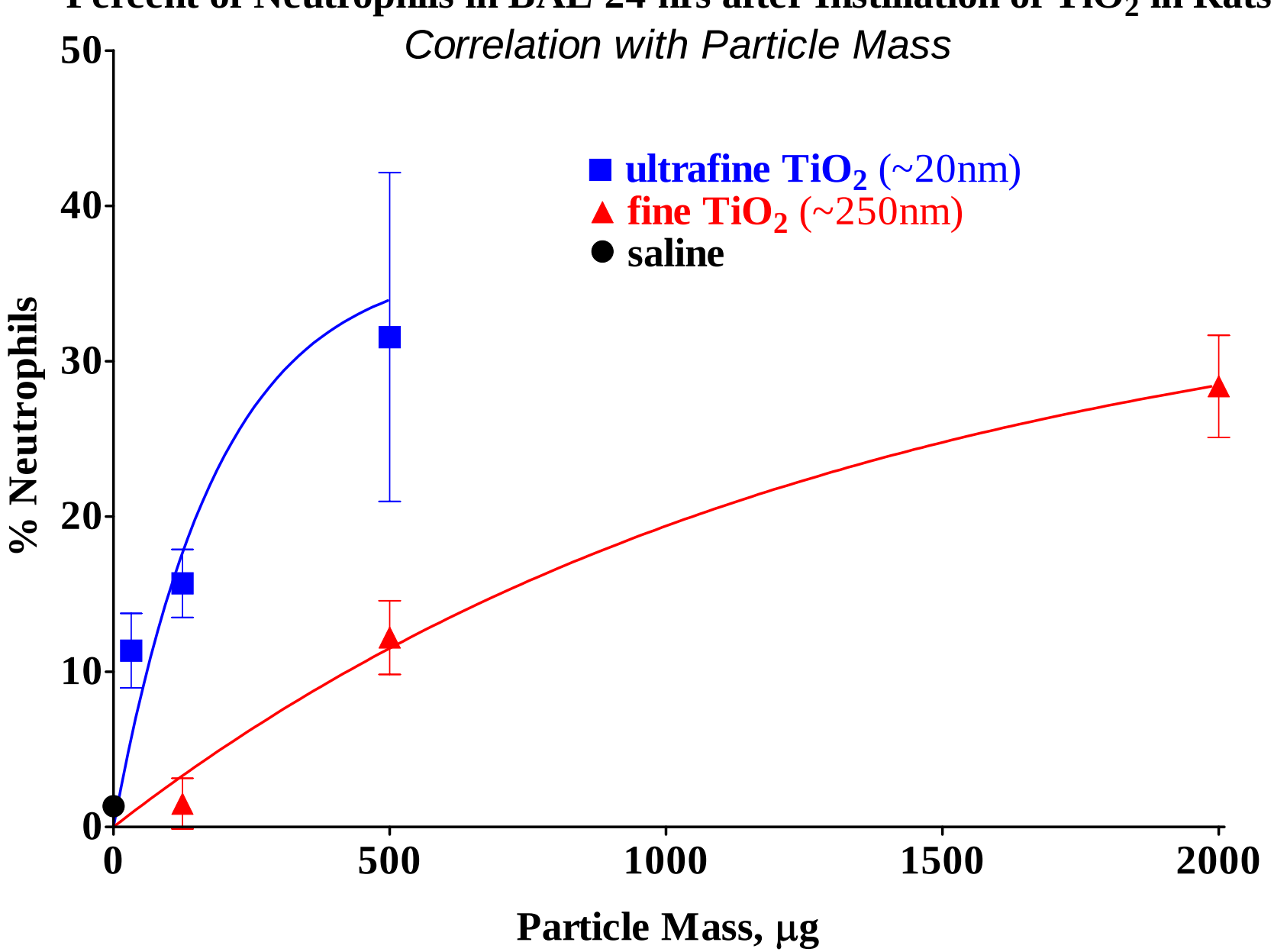


Number and surface area per 10 µg/m³ airborne particles



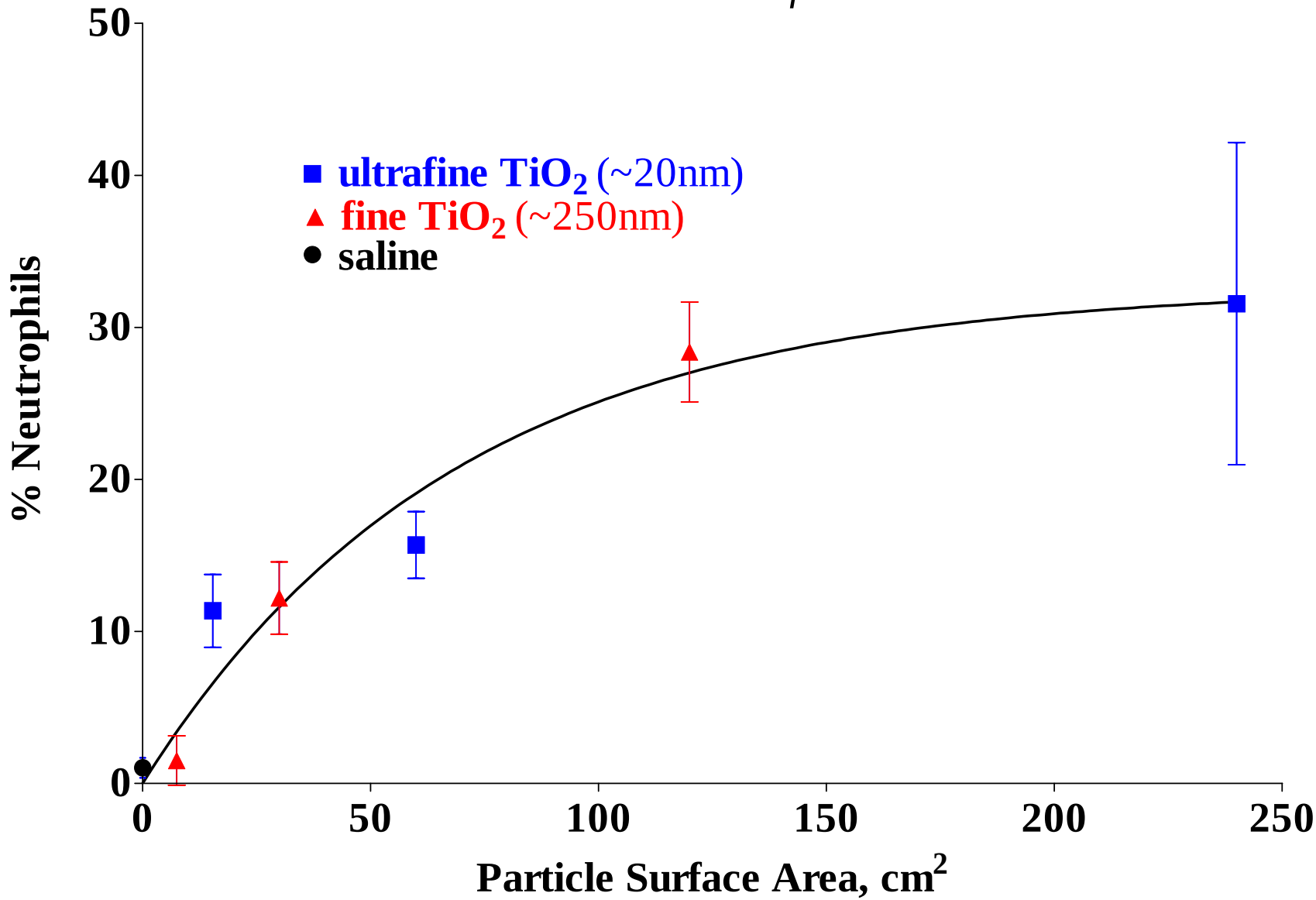


Principles of classical particle toxicology may no longer apply ….


Percent of Neutrophils in BAL 24 hrs after Instillation of TiO2 in Rats
Correlation with Particle Mass
ultrafine TiO2 (~20nm)
fine TiO2 (~250nm)
saline
% Neutrophils
0
10
20
30
40
50
0
500
1000
1500
2000
Particle Mass, μg

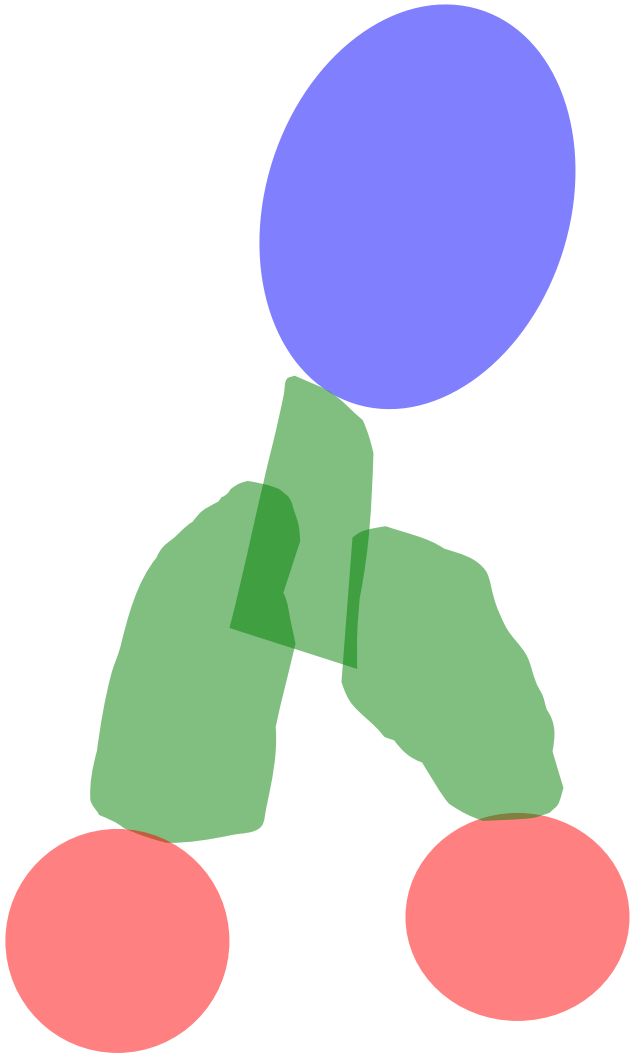
Percent of Neutrophils in BAL 24 hrs after Instillation of TiO_2 in Rats

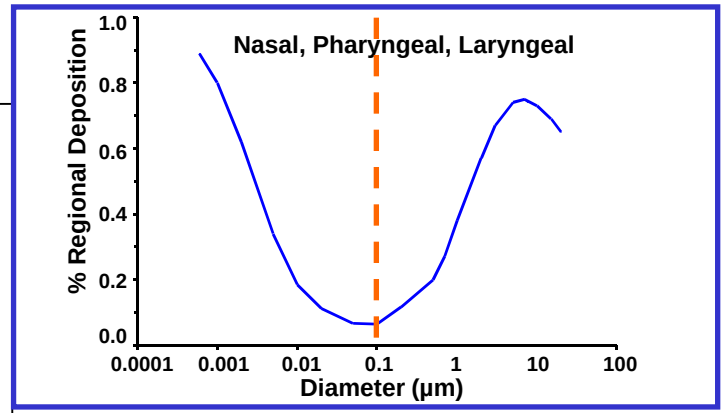
Correlation with Particle Surface Area

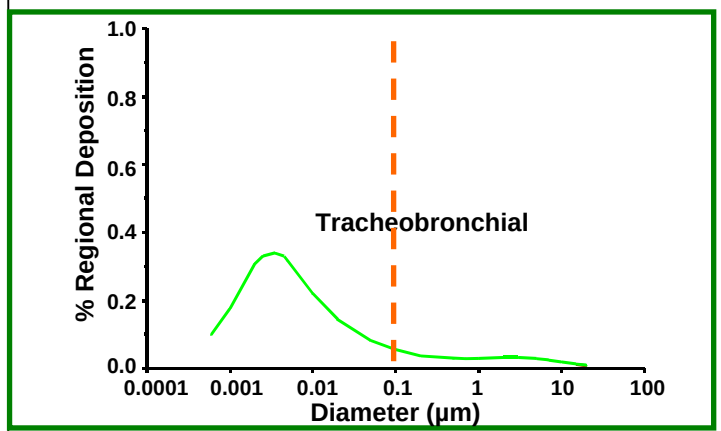


Fractional Deposition of Inhaled Particles in the Human Respiratory Tract

(ICRP Model, 1994; Nose-breathing)







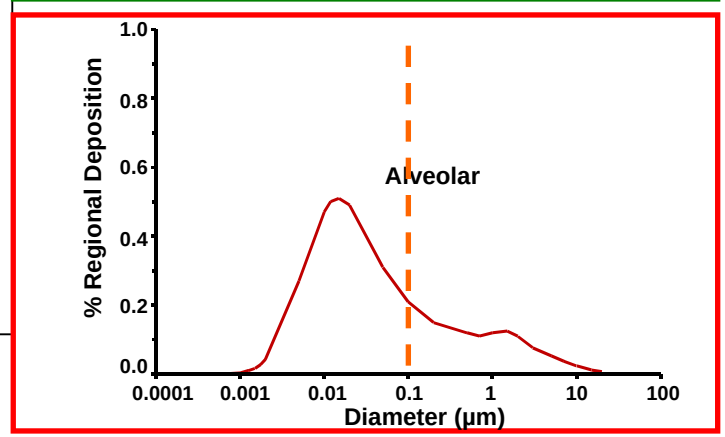
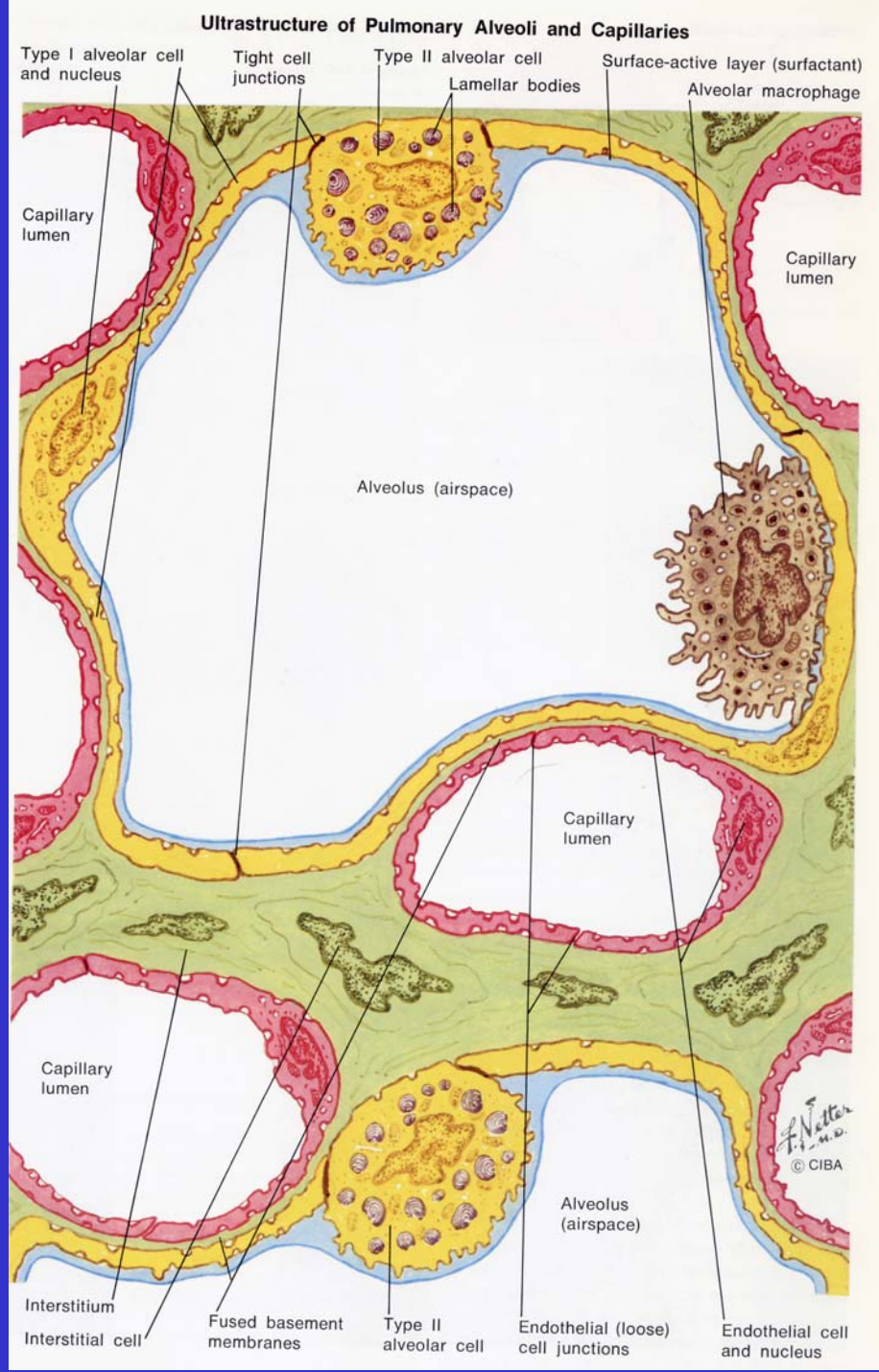


Figure courtesy of J.Harkema


Ultrastructure of Pulmonary Alveoli and Capillaries
Type I alveolar cell and nucleus
Tight cell junctions
Type II alveolar cell
Lamellar bodies
Surface-active layer (surfactant)
Alveolar macrophage
Capillary lumen
Capillary lumen
Alveolus (airspace)
Capillary lumen
Capillary lumen
© CIBA
Alveolus (airspace)
Interstitium
Interstitial cell
Fused basement membranes
Type II alveolar cell
Endothelial (loose) cell junctions
Endothelial cell and nucleus

Some Pathways of UltrafineParticle Translocation Within and Outside Respiratory Tract

AM-mediated Clearance

Interstitium
(via Epithelium)

Blood Circulation

Sensory Neurons
(olfactory, trigeminus, T.- bronchial)

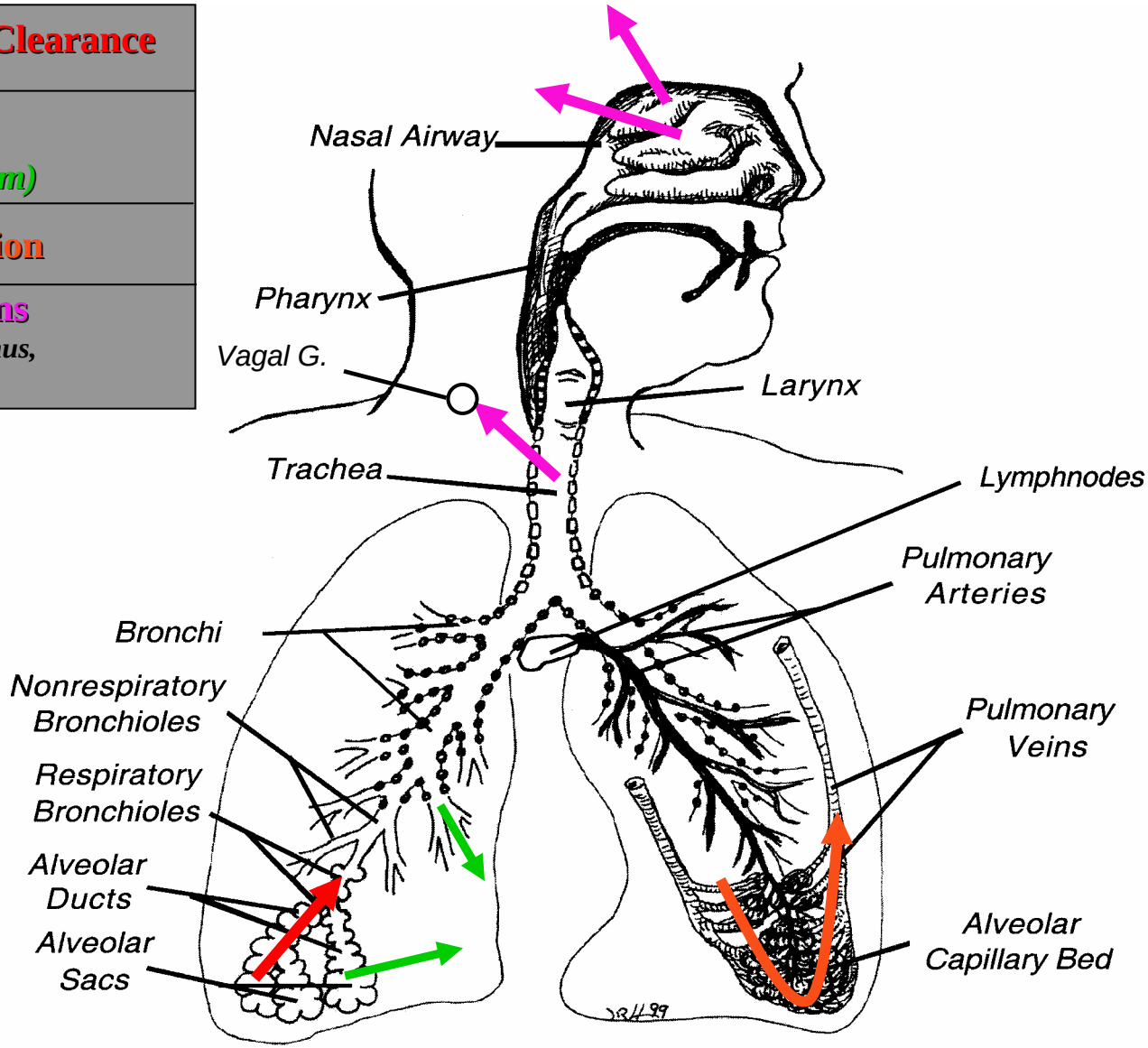
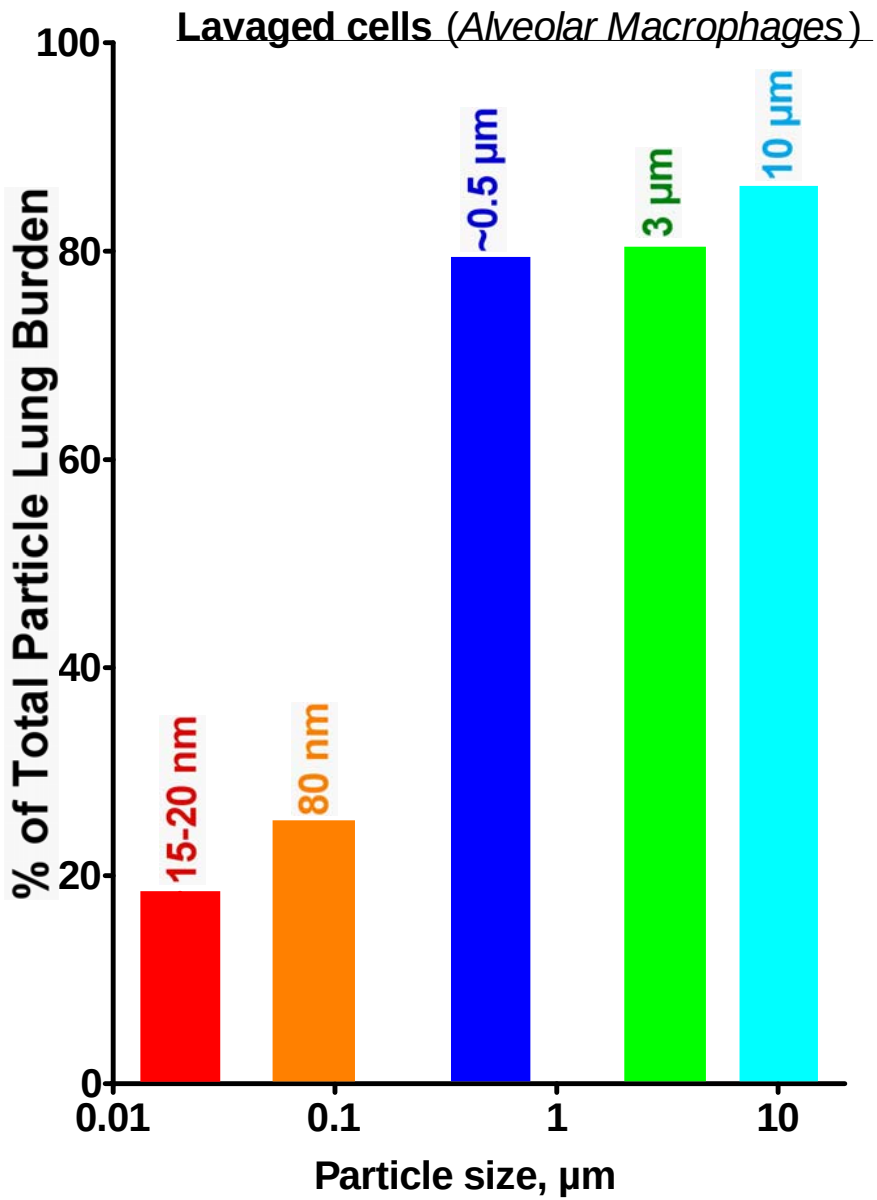


Figure courtesy of J.Harkema

Retention of Ultrafine, Fine and Coarse Particles in Alveolar Macrophages of Rats Determined 24 hrs. Post-exposure by Exhaustive Lung Lavage



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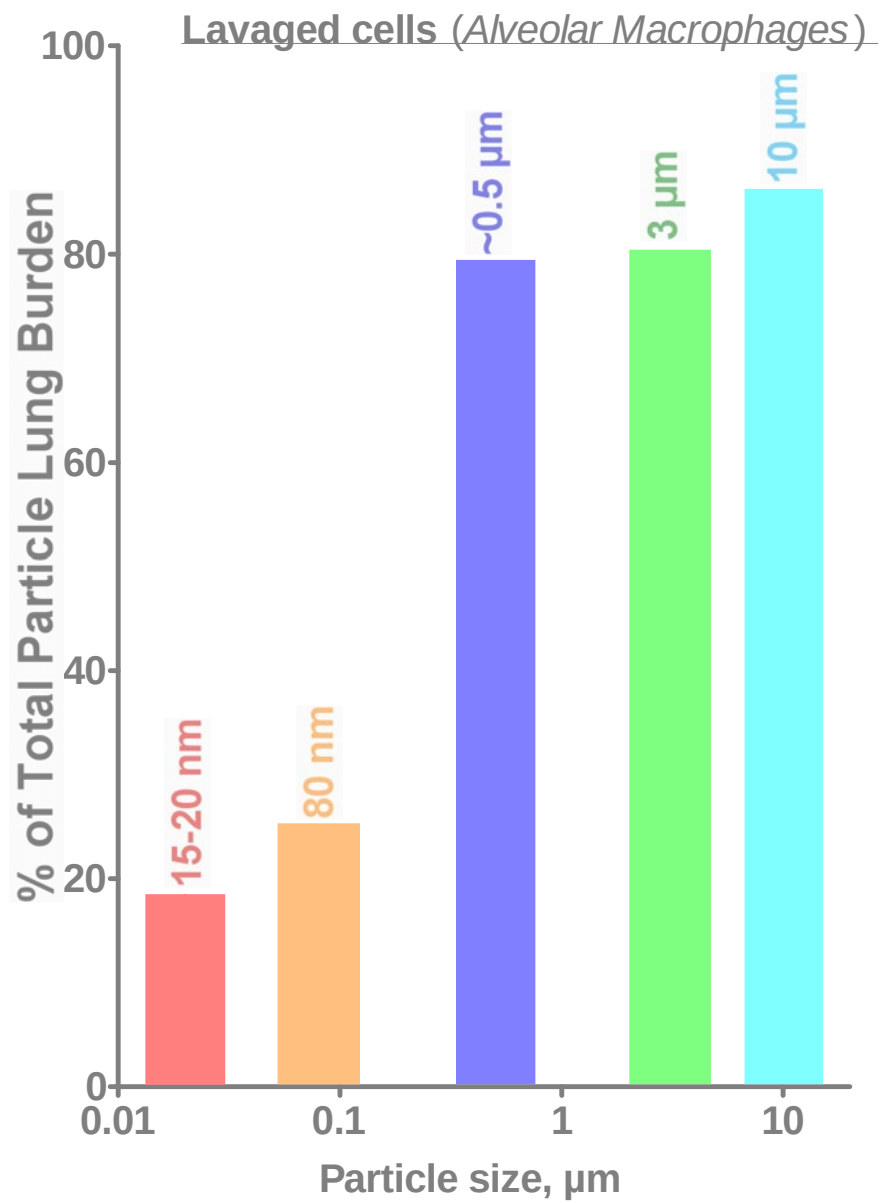
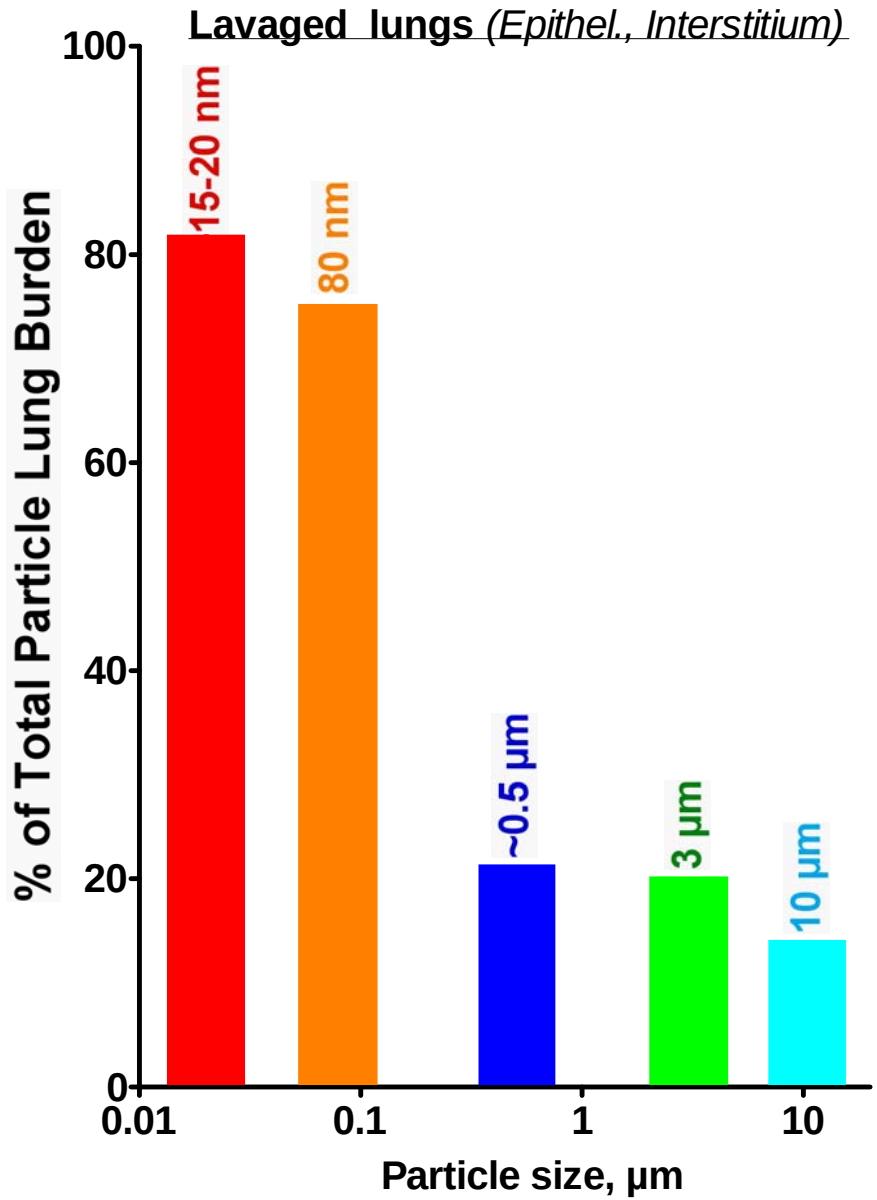
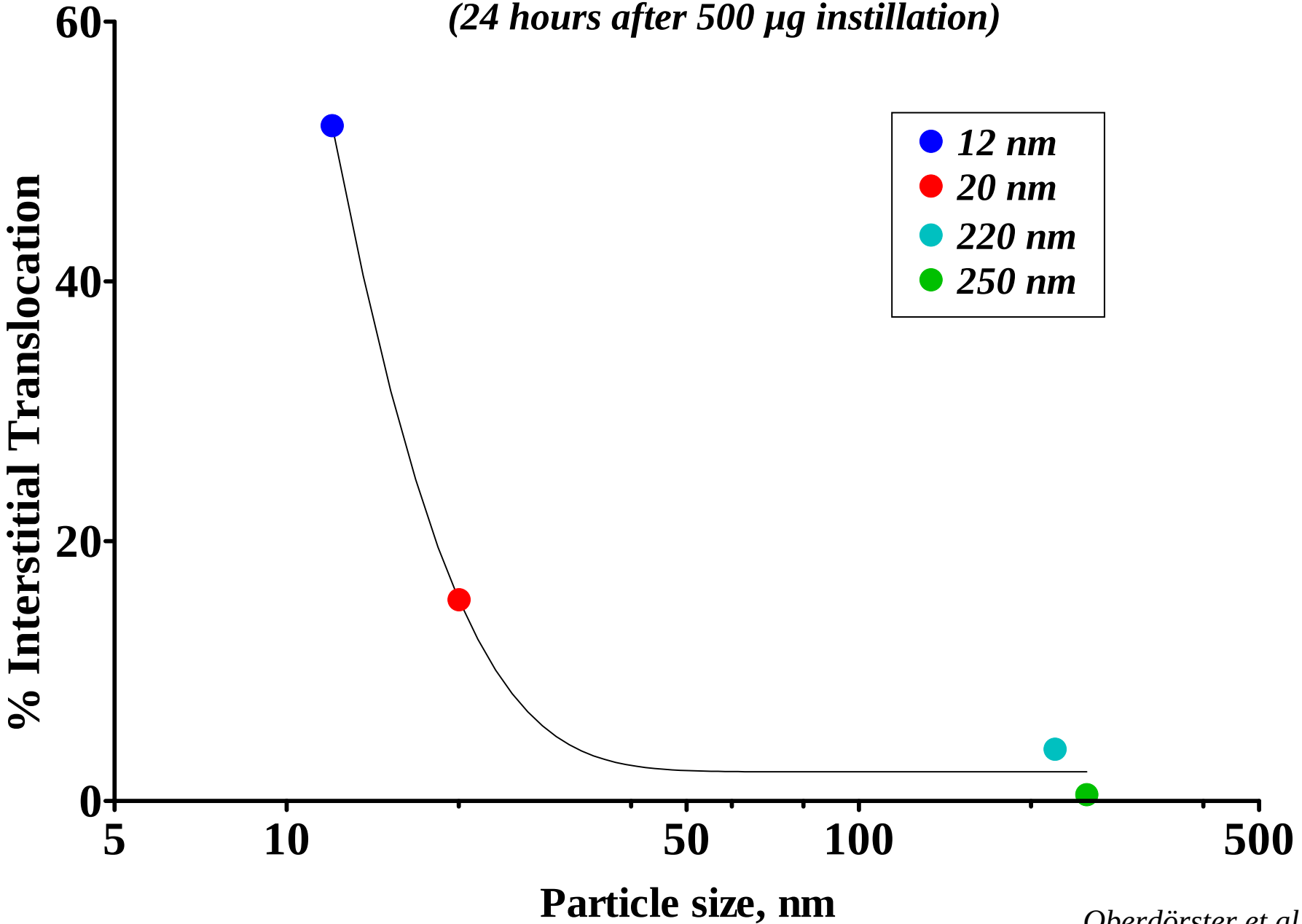


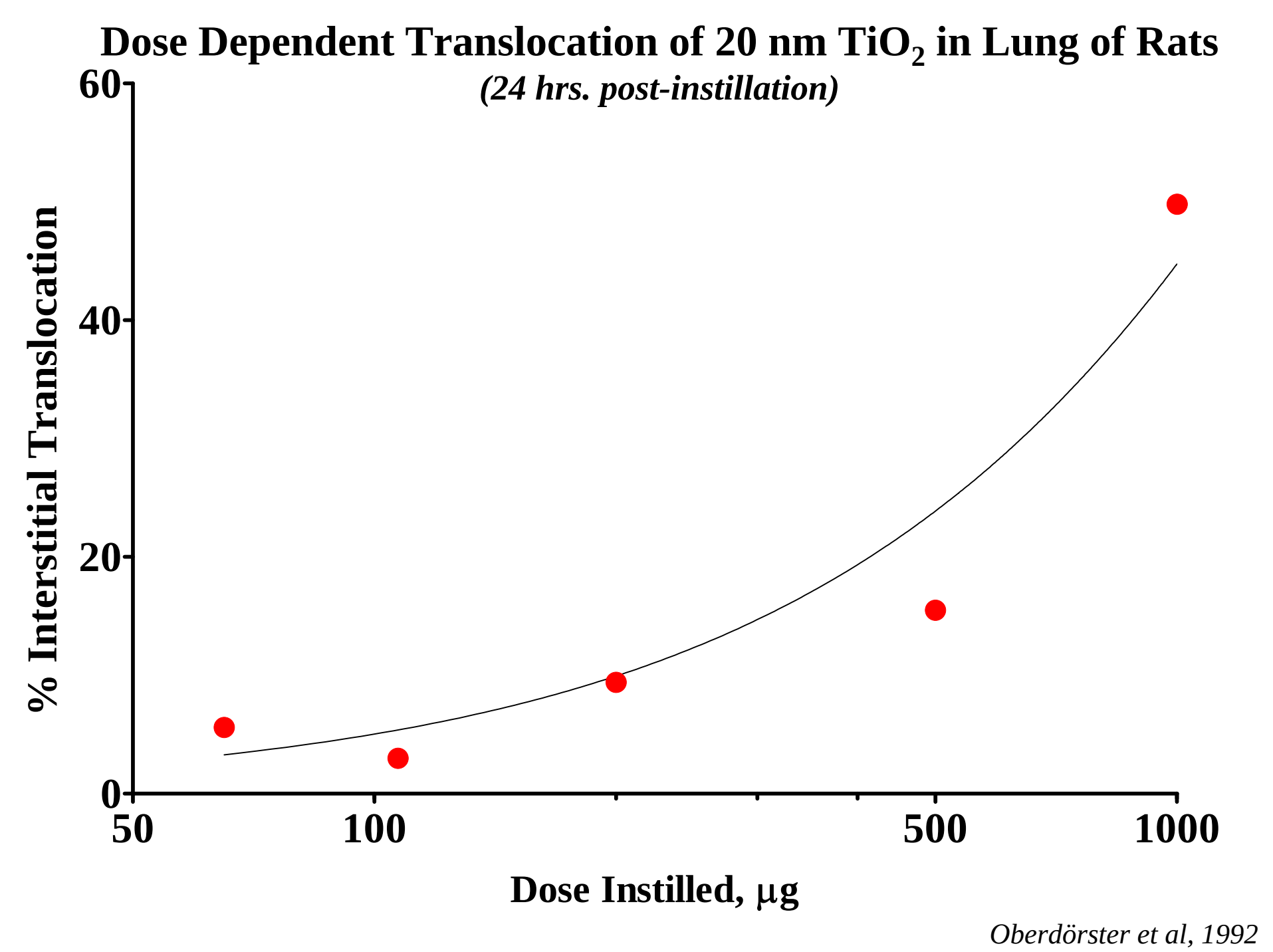


Size-dependent translocation of TiO_2 particles in lungs of rats

(24 hours after 500 µg instillation)

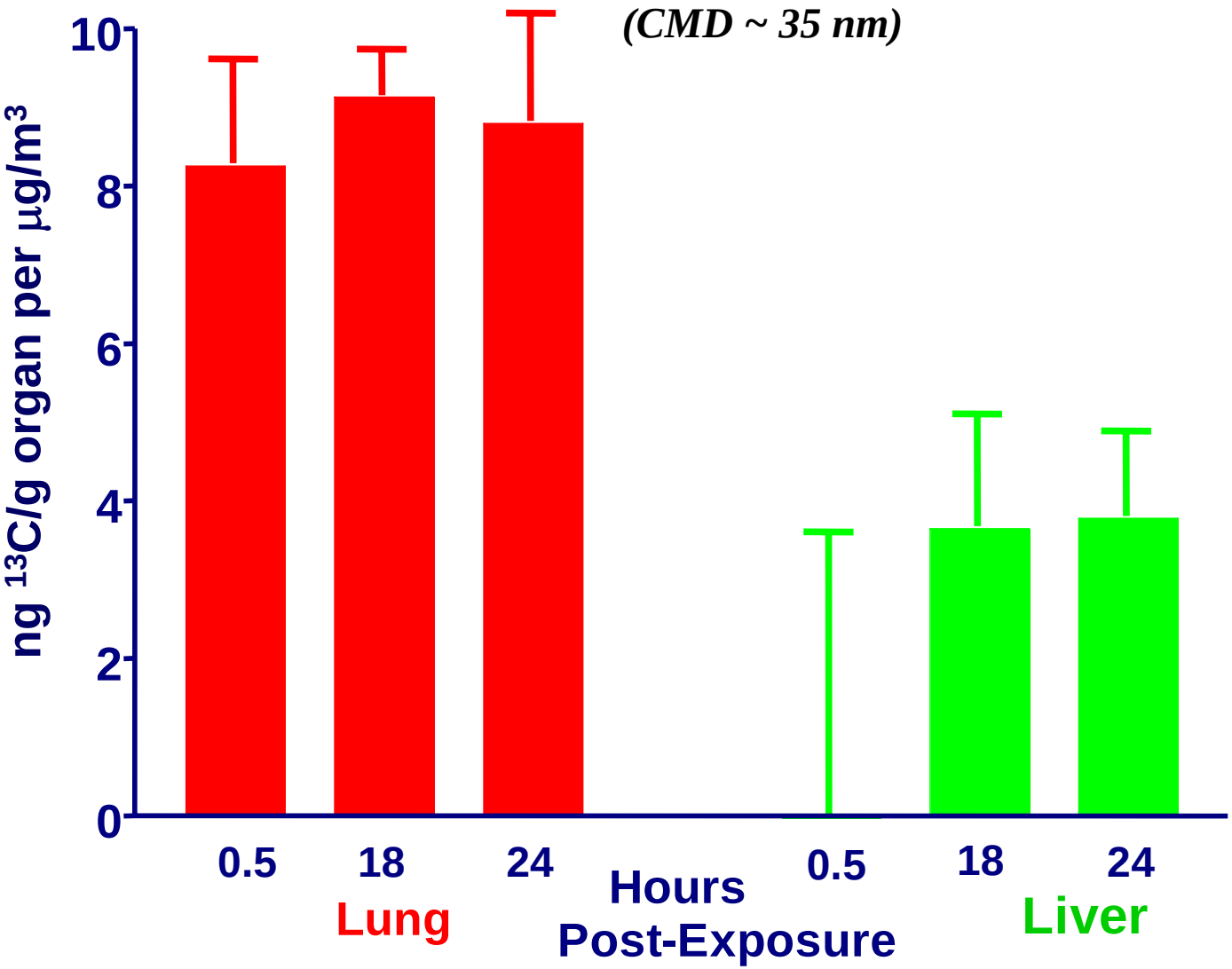


Oberdörster et al, 1992



Oberdörster et al, 1992

Normalized Lung and Liver Excess ^{13}C Concentration Following Ultrafine ^{13}C Particle Exposure in Rats (n=3)



Extrapulmonary Translocation of Inhaled Ultrafine Particles

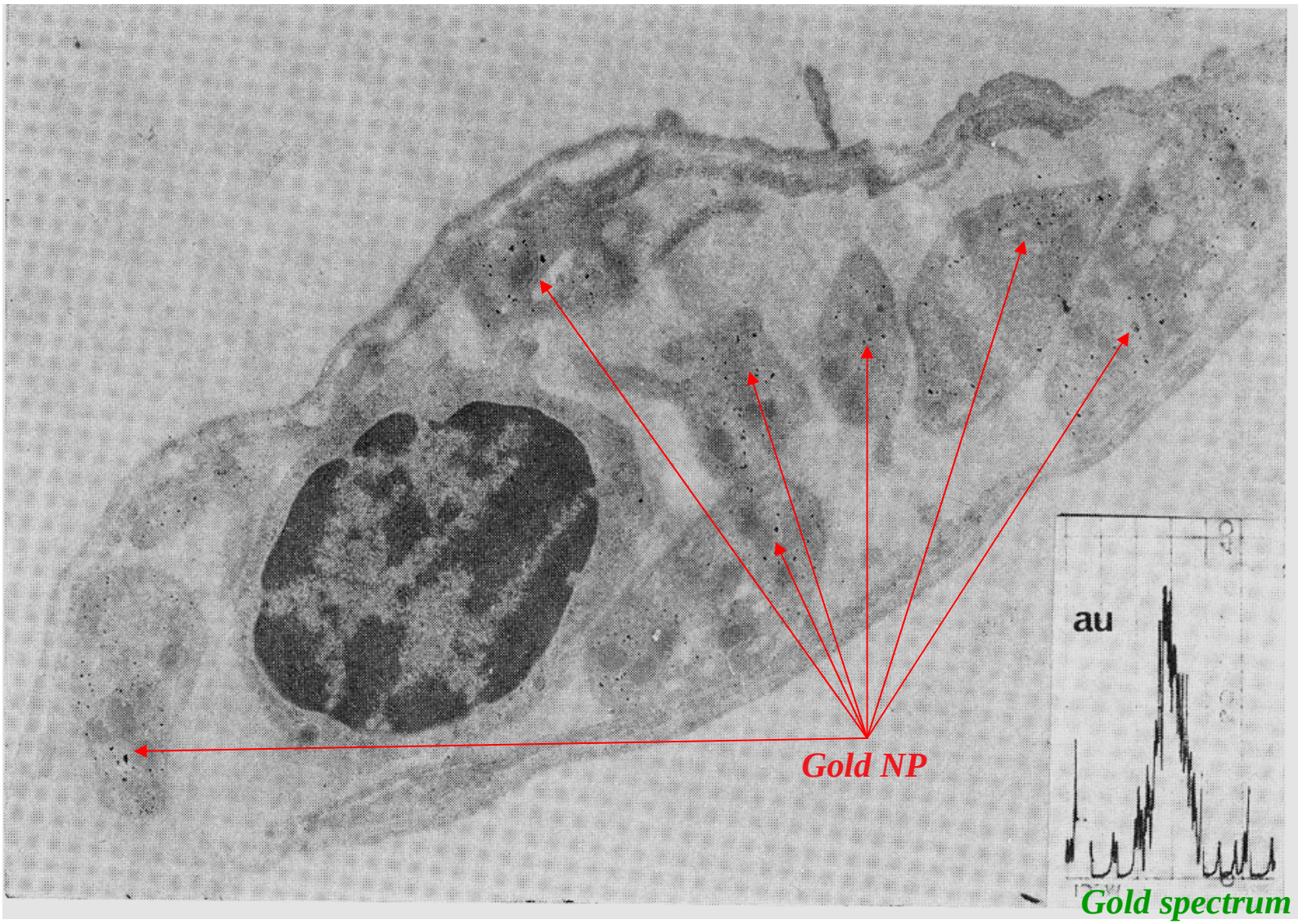
Kreyling et al., 2002: **15 nm and 80 nm Iridium:**
only minimal translocation (0.1 - 0.2%)

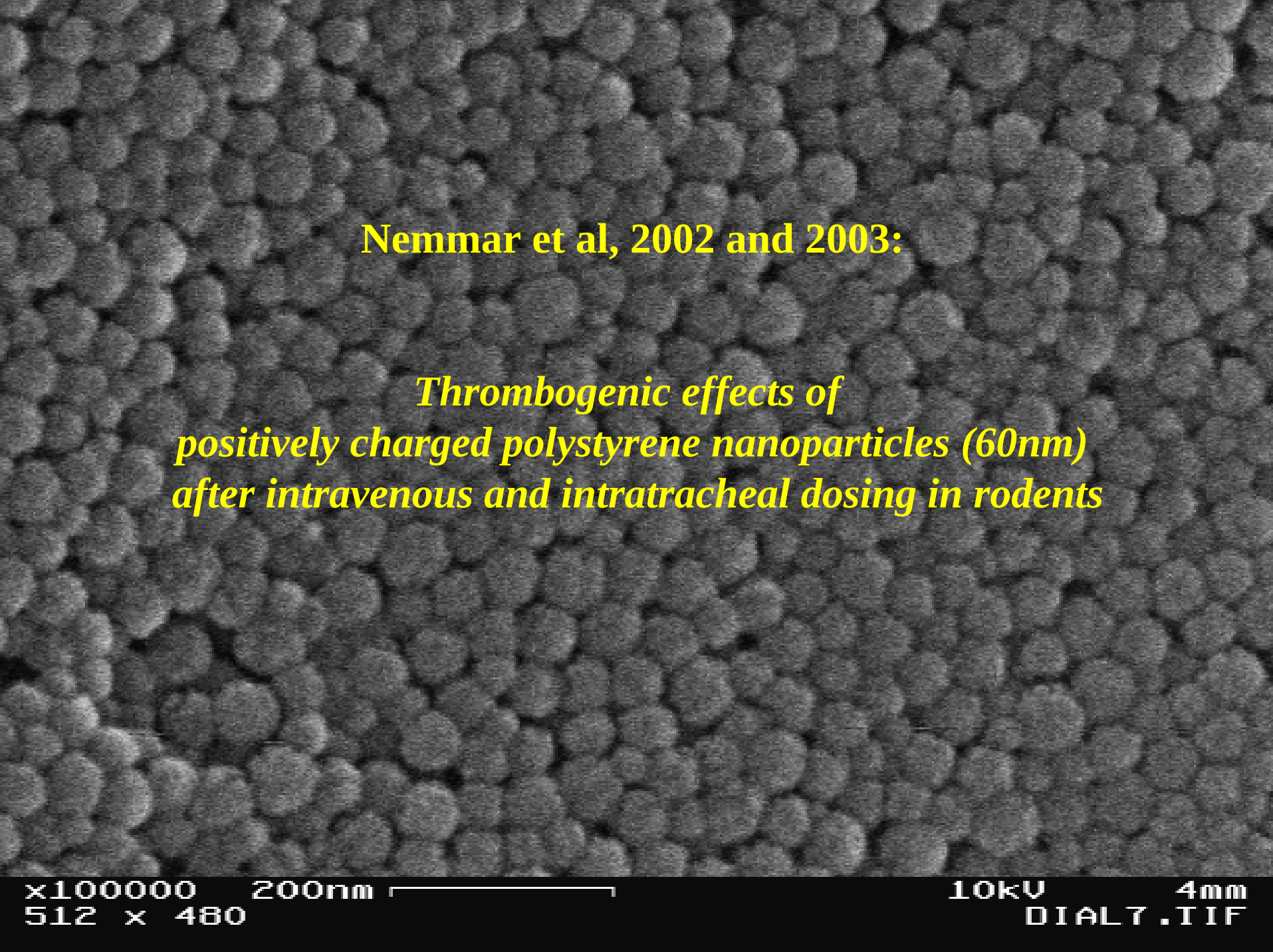
but: 10 times more for 15 nm vs. 80 nm!

Protein binding affecting translocation?

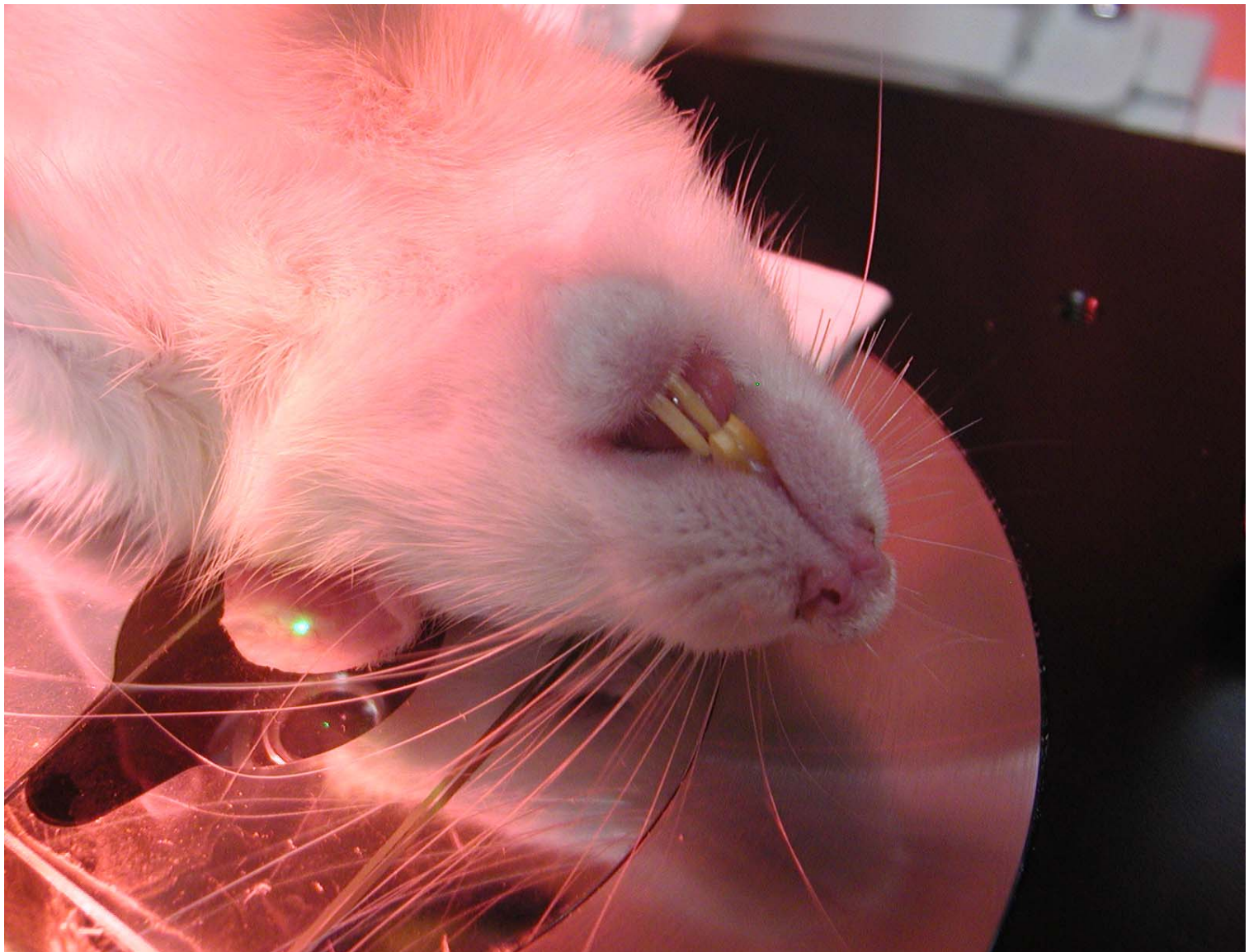
Gold nanoparticles (30 nm) in platelets of pulmonary capillary 30 mins. after intratracheal instillation into rats

(Berry et al., 1977)



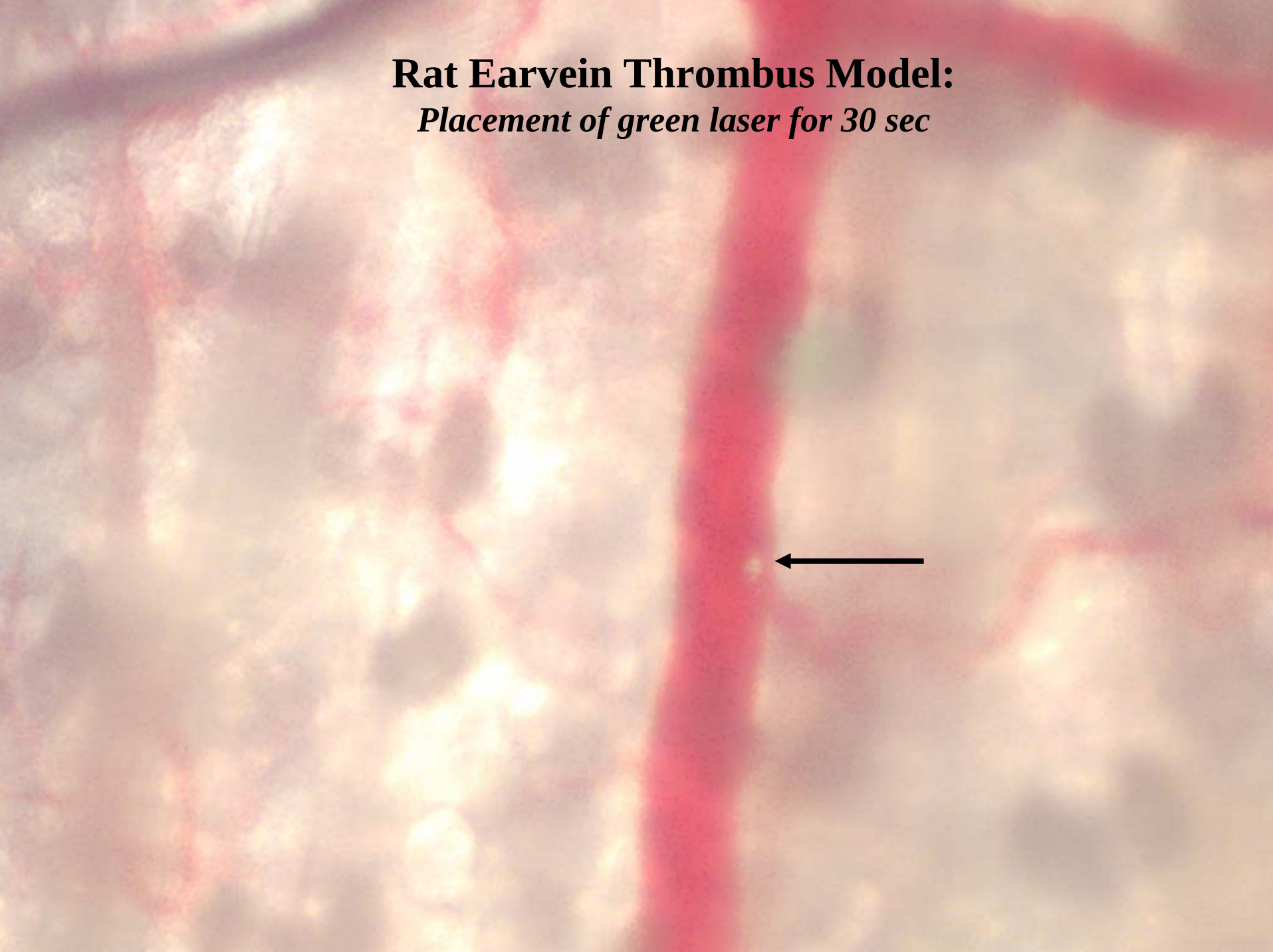

Nemmar et al, 2002 and 2003:
Thrombogenic effects of
positively charged polystyrene nanoparticles (60nm)
after intravenous and intratracheal dosing in rodents
x100000 200nm
512 x 480
10kV 4mm
DIAL7.TIF

Rat Ear Vein Model to Determine Particle Induced Thrombus Using Green Laser *(Silva et al, 2004)*



Rat Earvein Thrombus Model:

Placement of green laser for 30 sec

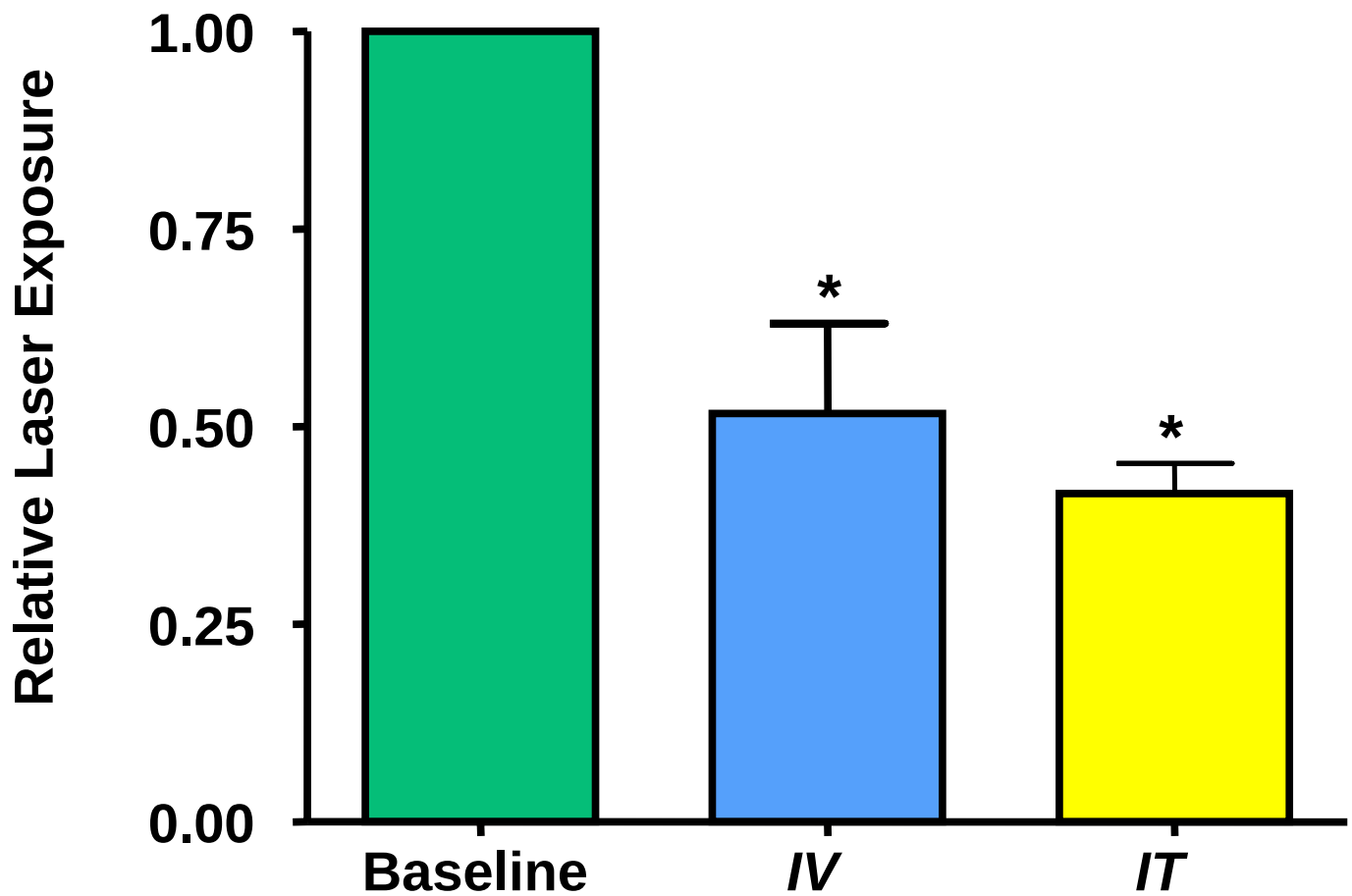


Rat Earvein Thrombus Model:

Thrombus formation following illumination.

Laser illumination time is significantly reduced after intravenous or intratracheal dosing with elemental ultrafine carbon particles

Reduction of Laser Exposure Time to Induce Thrombus in the Rat Ear Vein after *IV* or *IT* Instillation of Amine-coated (+) 60nm Polystyrene Particles *(125µg/rat)*



Silva et al, 2004

Translocation of ultrafine particles to CNS:

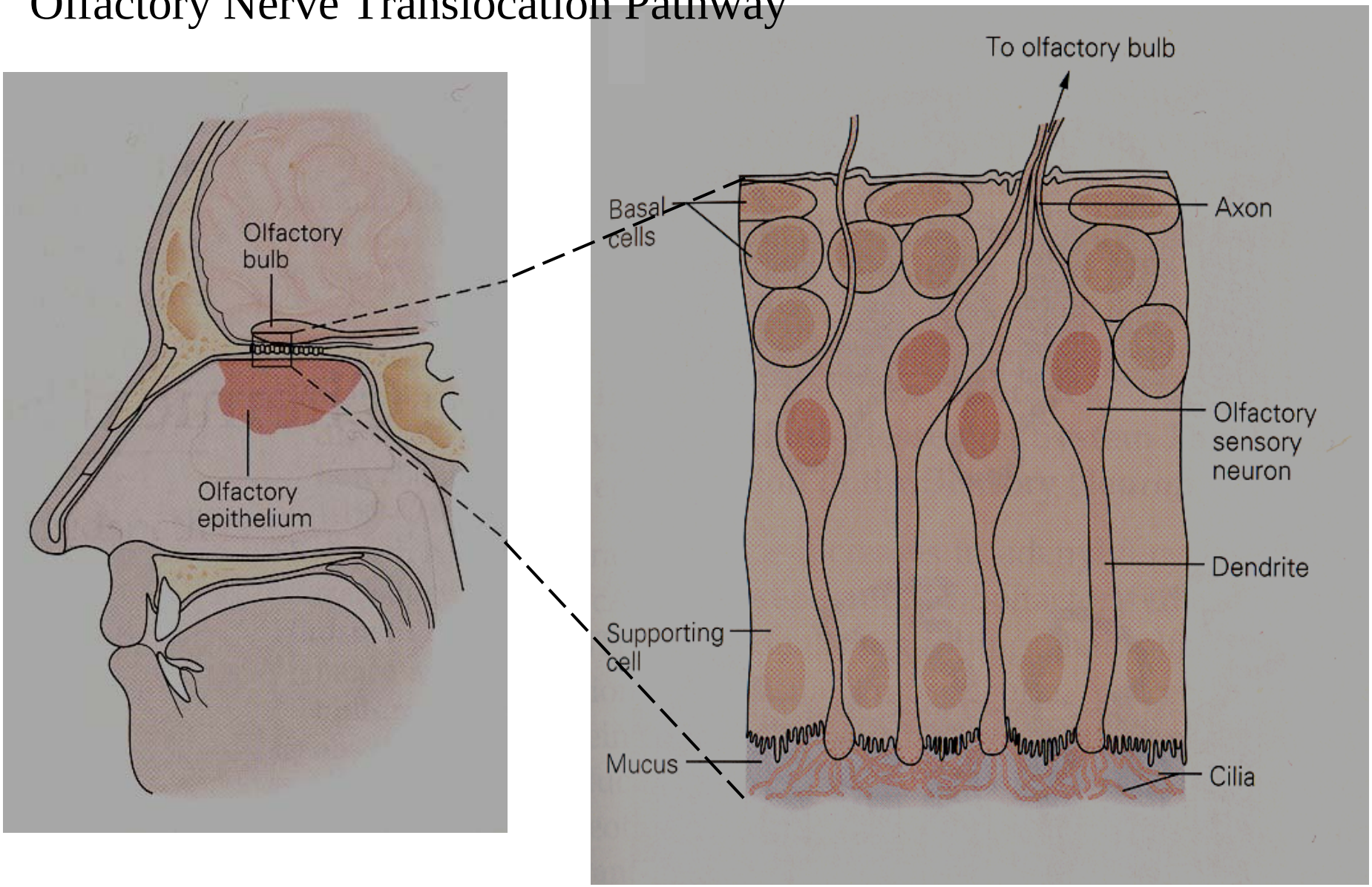
- via circulation – ***tight blood brain barrier!***

-via olfactory nerve – ***more likely*** *(has been shown before for inhaled soluble metal salts)*

-via perineural pathways into cerebrospinal fluid (CSF)

CSF-brain barrier!

Olfactory Nerve Translocation Pathway



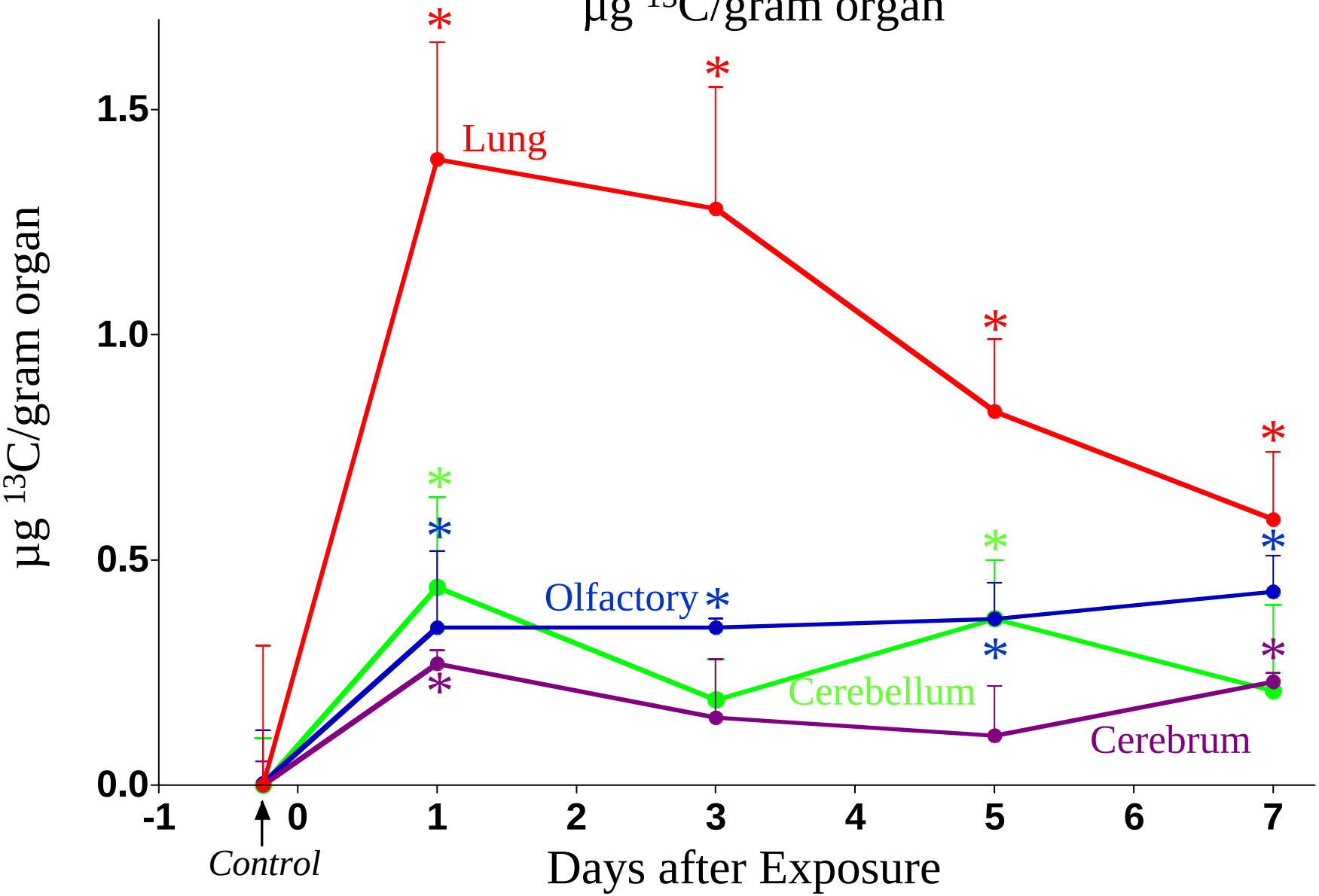
From: *Kandel, Schwartz and Jessel: Principles of Neural Science, 2000*

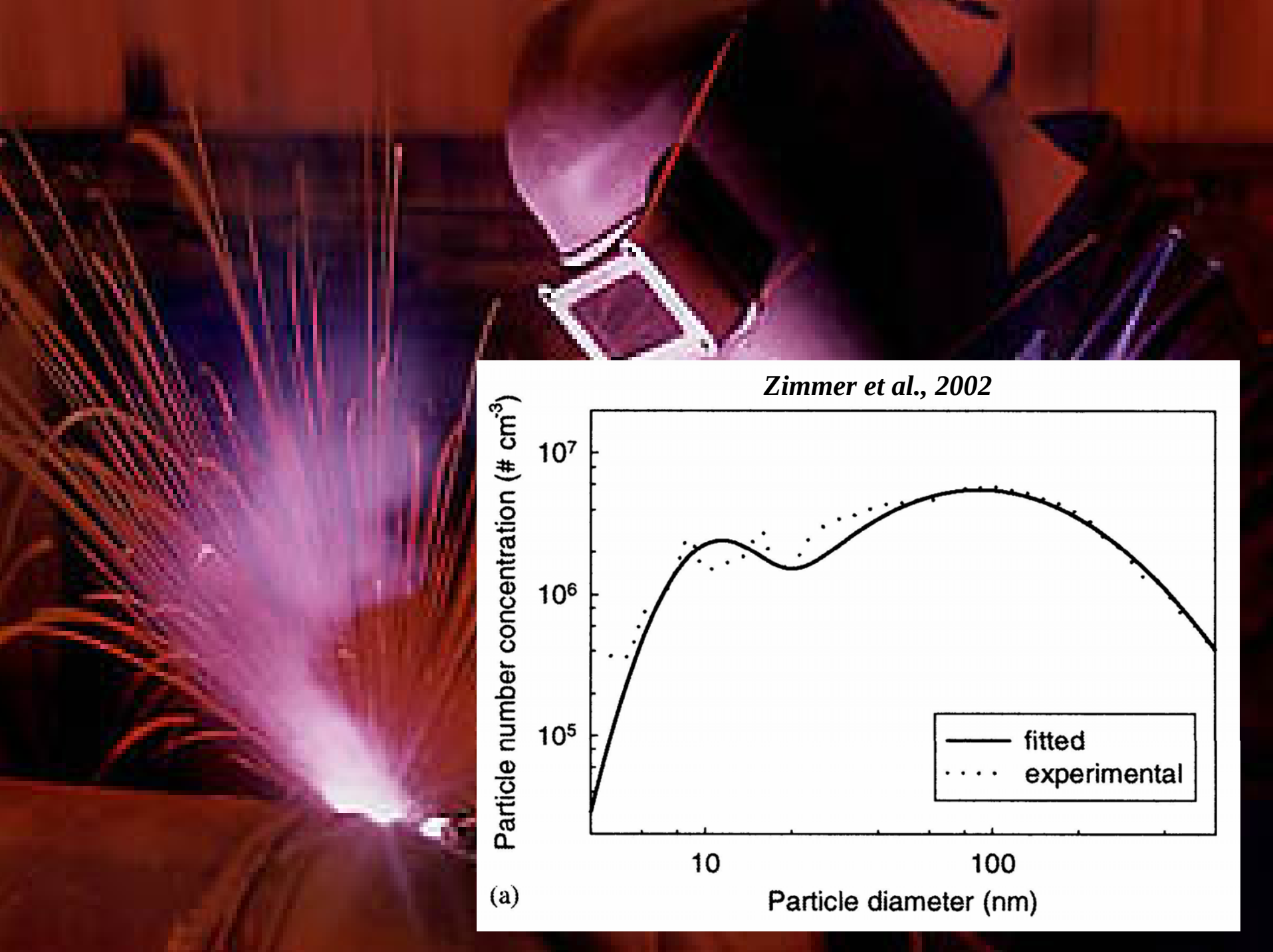
MRI Scan of Olfactory Bulbs

(from Turetsky et al., 2003)

Ultrafine ^{13}C Particle Inhalation Rat: Lung and CNS Tissue Concentrations

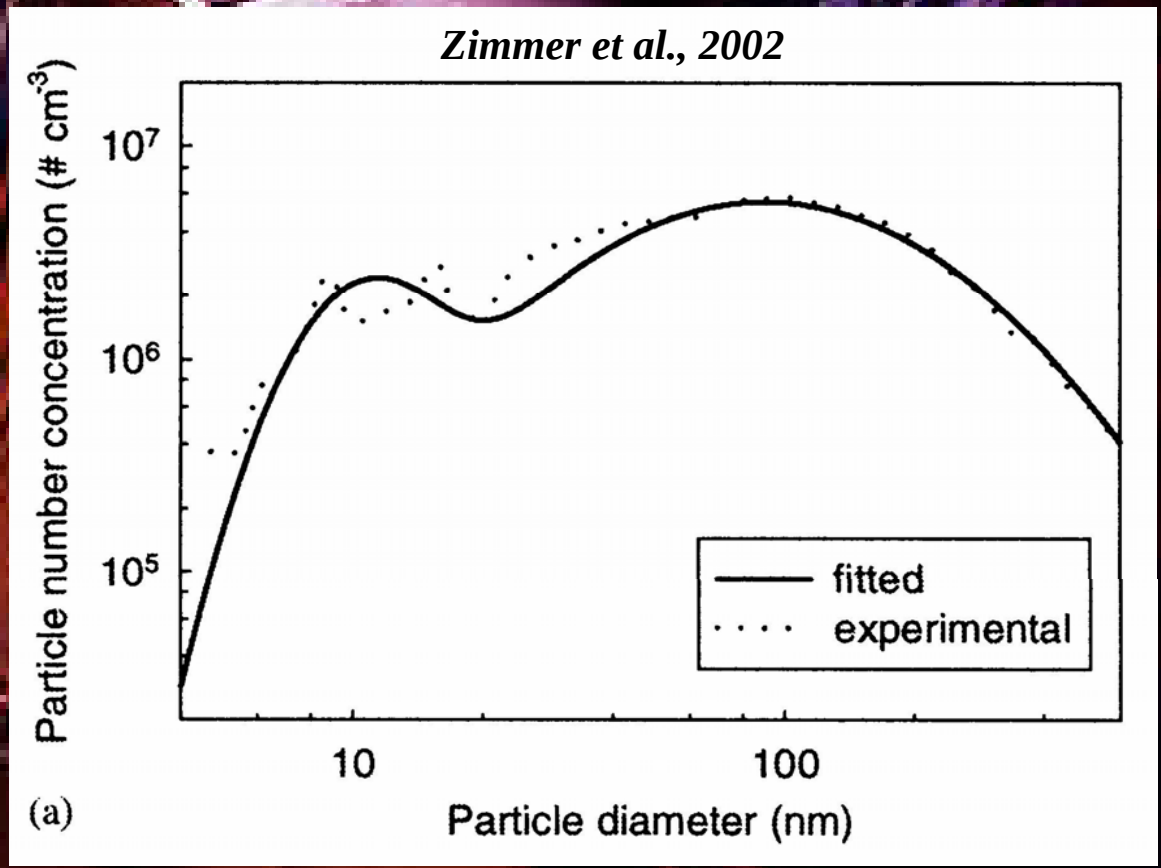
µg ^{13}C/gram organ




Zimmer et al., 2002
Particle number concentration (# cm-3)
10^7
10^6
10^5
10
100
Particle diameter (nm)
fitted
experimental
(a)

Racette et al., 2001:
Welding-related Parkinsonism

Zimmer et al., 2002



Summary: Inhaled Ultrafine/Nanoparticle Toxicology

- **High deposition efficiency throughout respiratory tract**
- **Translocation to extrapulmonary organs *via* circulation**
- **Neuronal transport *via* sensory nerves to CNS**
- **Variable toxicity in respiratory tract: from highly toxic to rather benign**
  - ***freshly-generated vs. aged***
  - ***pre-exposure history***
- **Can induce cardiovascular effects; oxidative stress**
- **Size, chemistry, surface properties** *(area, charge, reactivity)* **important**

Many open questions: Mechanisms of cardiovascular effects?
Organic carbon compounds?
CNS effects (Acute, long-term)?
Implications for ultrafine particle standard?
What is the significance for nanotechnology particles?

INVESTIGATOR TEAM, COLLABORATORS AND SUPPORT OF ROCHESTER-BASED RESEARCH WITH NANO-SIZED PARTICLES — PAST AND PRESENT —

Rochester Crew	**Outside Collaborators**
Alison Elder	Viorel Atudorei *(Univ. of Minnesota)*
Jurai Ferin	Janet Carter *(Procter & Gamble Co.)*
Jacob Finkelstein	Glenn Cass *(Georgia Tech)*
Mark Frampton	Vincent Castranova *(NIOSH)*
Bob Gelein	Christopher Cox *(NIEHS)*
Todd Kraus	Kevin Driscoll *(Procter & Gamble Co.)*
Paul Morrow	John Godleski *(Harvard)*
David Oakes	Jack Harkema *(Michigan State U.)*
Günter Oberdörster	Phil Hopke *(Clarkson University)*
Rick Phipps	Wolfgang Kreyling *(GSF, Germany)*
Vanessa Silva	David Kittelson *(Univ. of Minnesota)*
Mark Utell	Andrew Maynard *(NIOSH)*
Hong Yang	Zachary Sharp *(Univ. of New Mexico)*
	Renaud Vincent *(Health Canada)*

Support: ***EPA; NIEHS; NASA***