EXTRAPULMONARY EFFECTS OF INHALED NANO-SIZED PARTICLES

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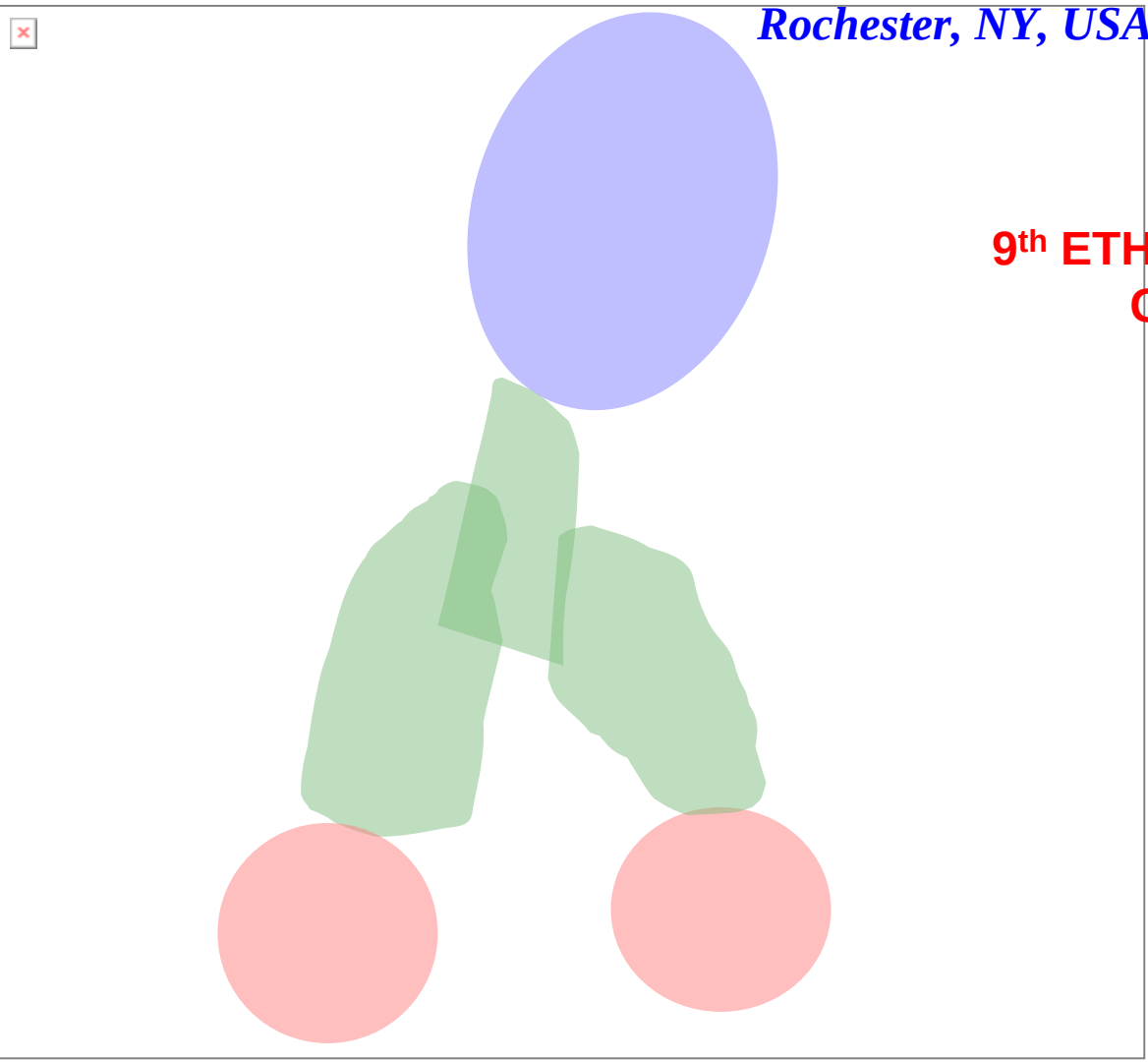
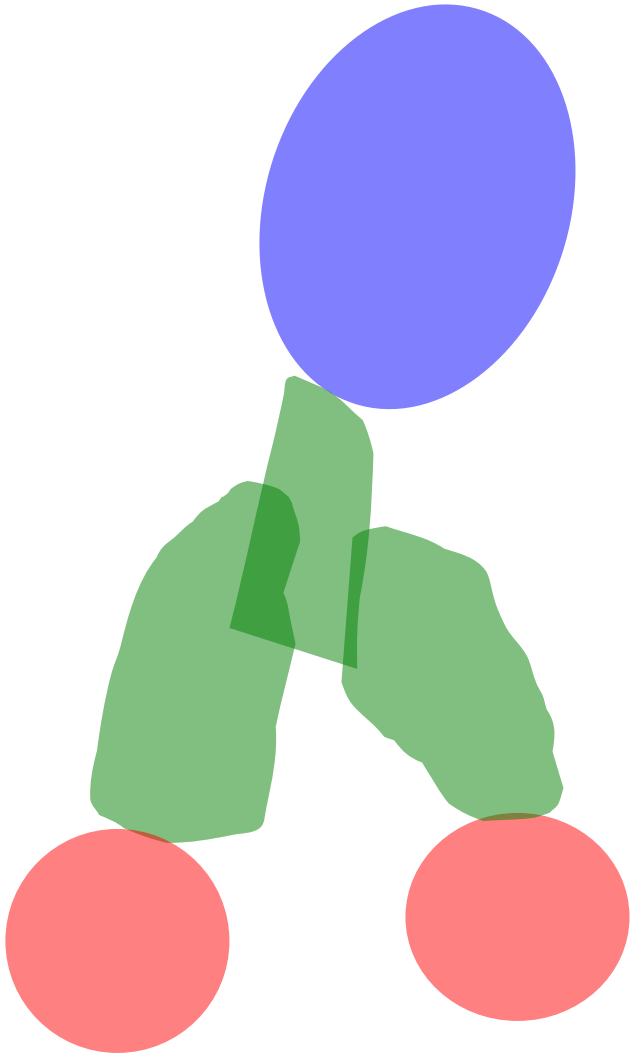


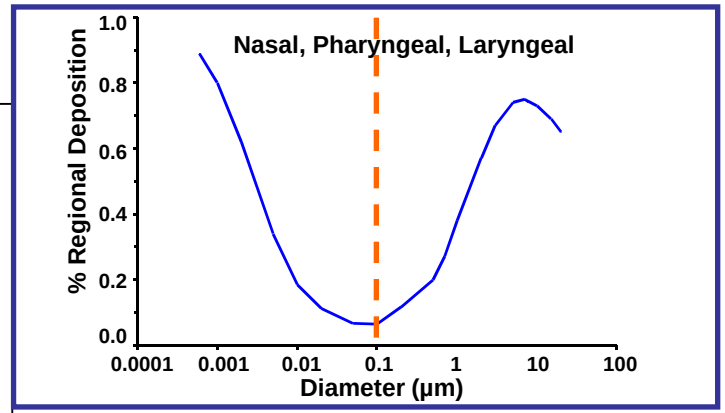
9th ETH Conference on Combustion Generated Nanoparticles

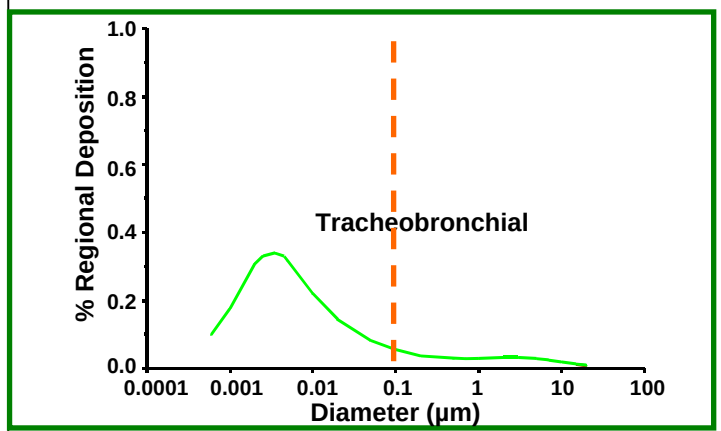
Zürich, Switzerland
August 15 - 17, 2005

Fractional Deposition of Inhaled Particles in the Human Respiratory Tract

(ICRP Model, 1994; Nose-breathing)







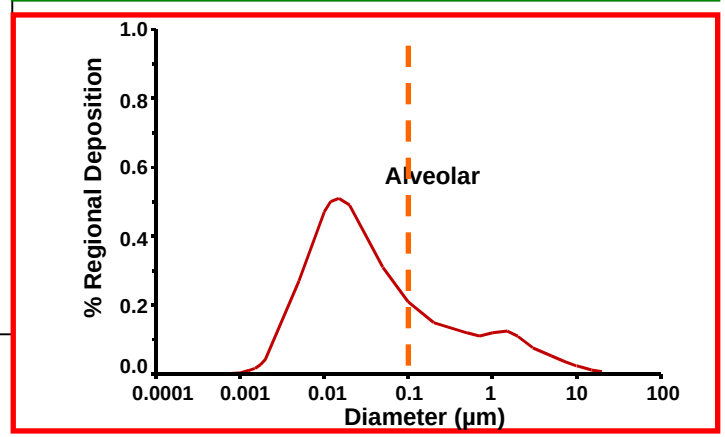
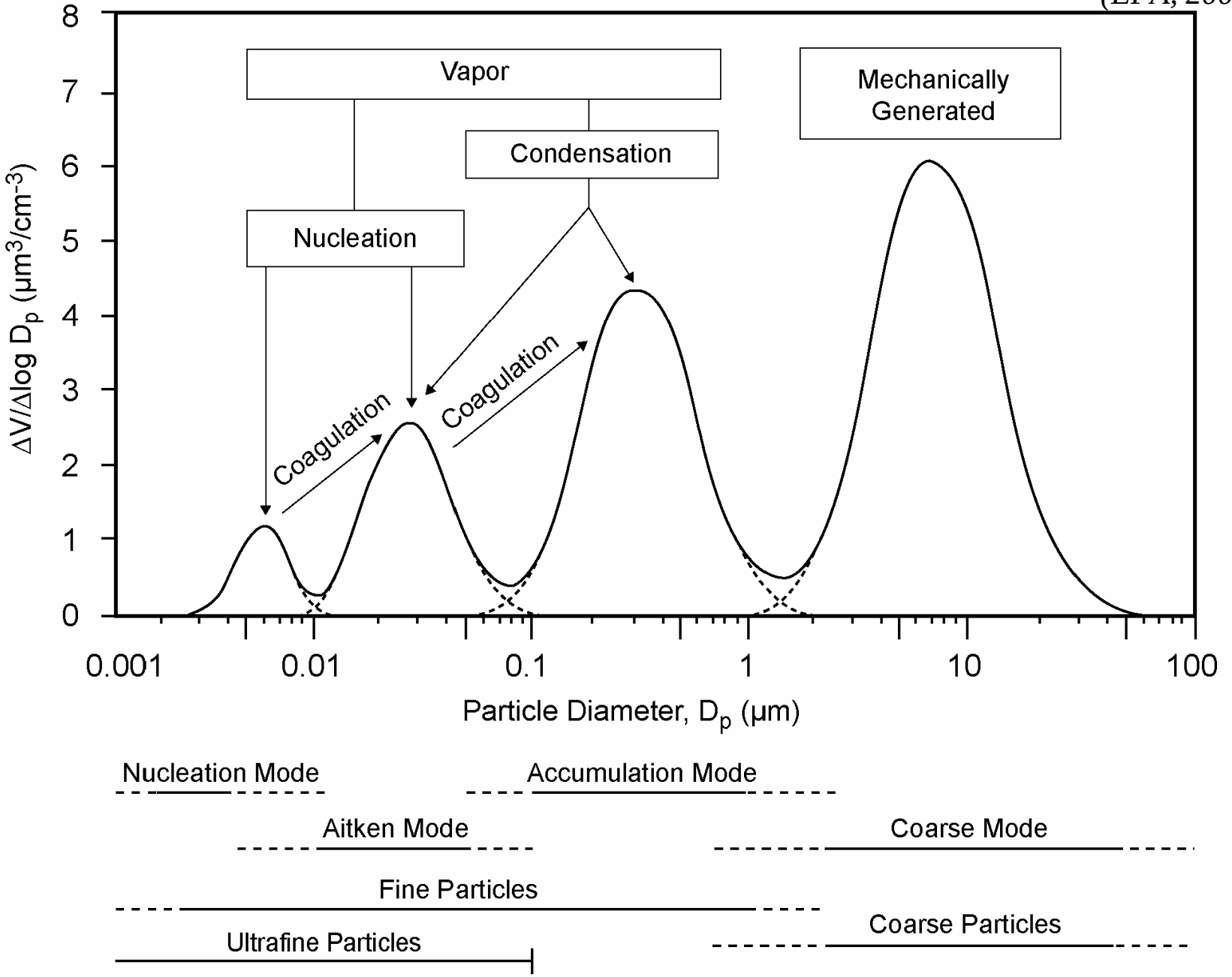


Figure courtesy of J.Harkema

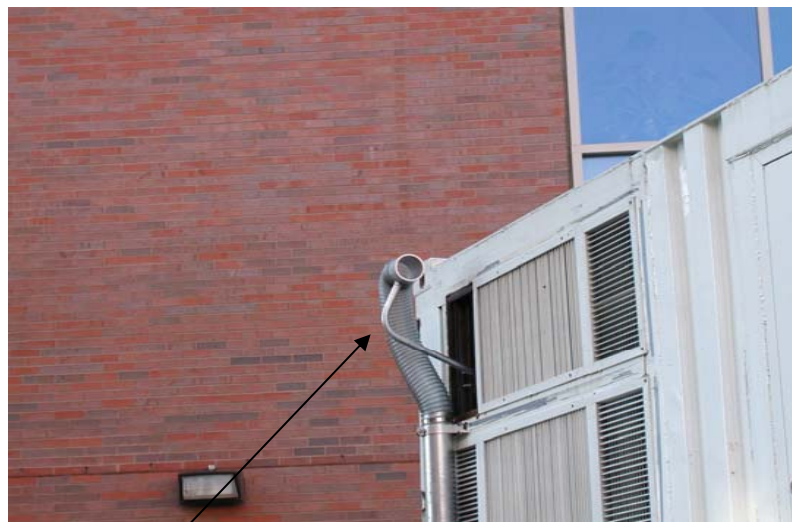
Idealized Size Distribution of Traffic-Related Particulate Matter

(EPA, 2004)



University of Minnesota Mobile Emissions Laboratory (MEL)

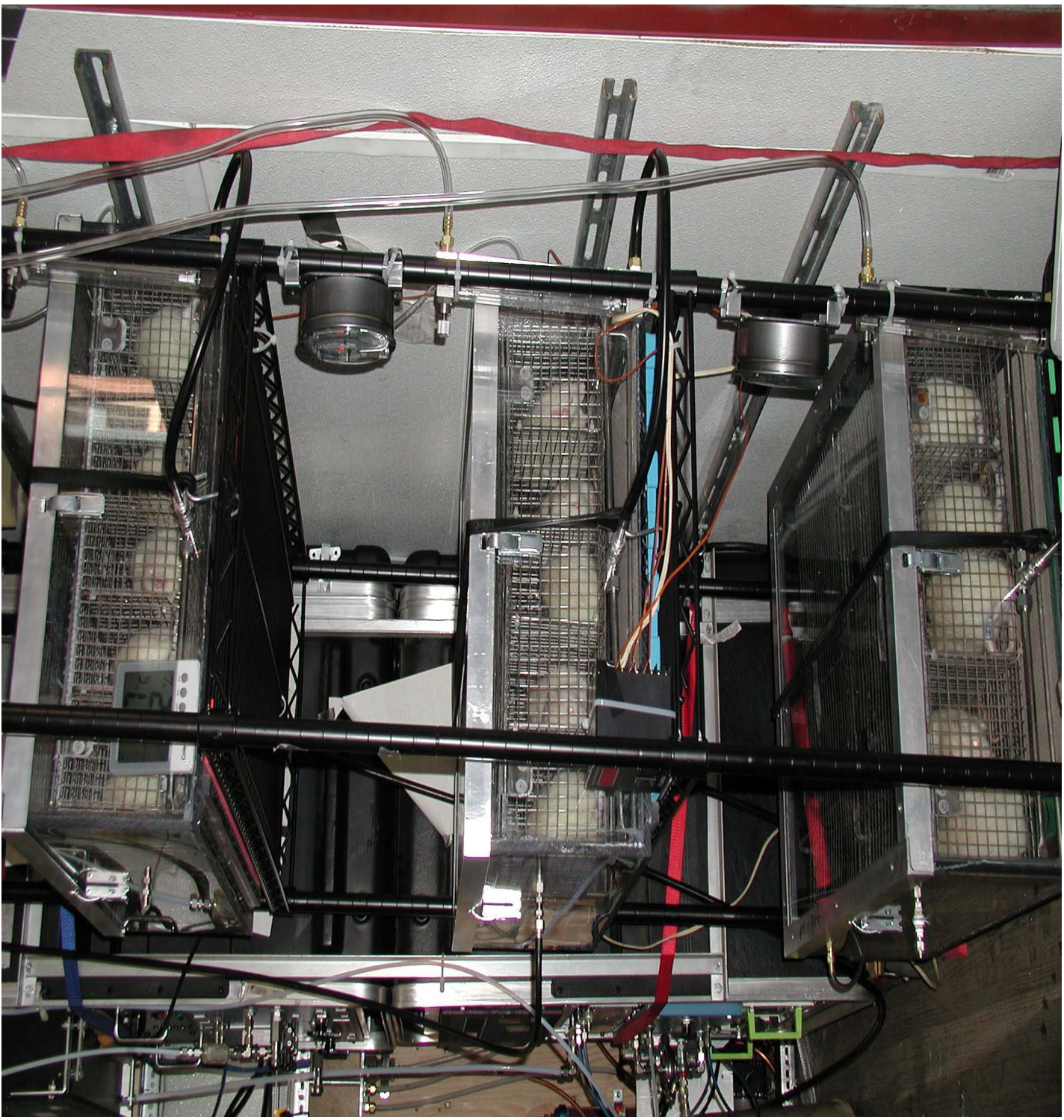
air-conditioned compartment



Year 1

Year 2

exhaust intake



Description of On-Road Experiments using MEL

Air-conditioned trailer

Animals: 21 month-old F-344 rats; ~15 month-old SH rats

Respiratory tract **priming exposures**:

Inhaled LPS

Instilled influenza virus (2 days prior to or 18 hrs after last on-road exposure)

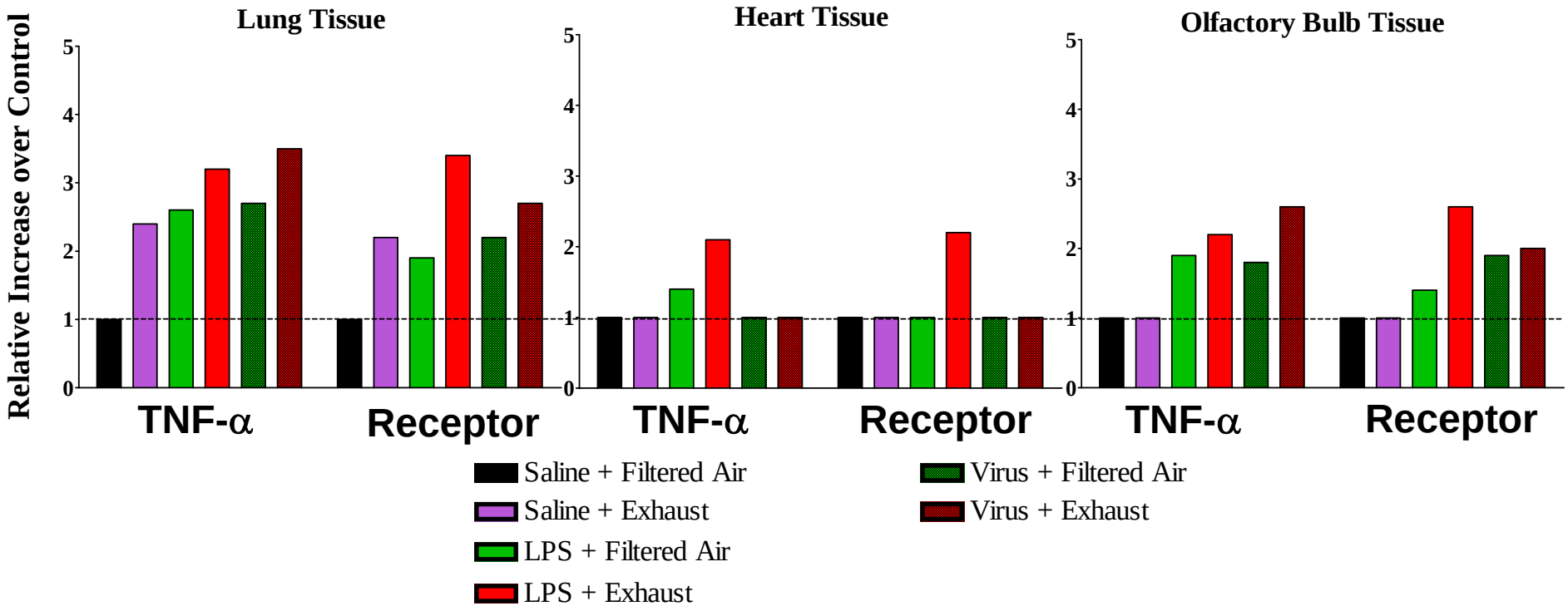
Atmospheres: filtered air, gas phase only, particles/gas phase

Duration of exposure: 6 hrs **or** 3 days x 6 hrs

Particle Size (CMD): 13 – 19 nm

Number concentration: 1.3 – 7.6 x $10^5/cm^3$

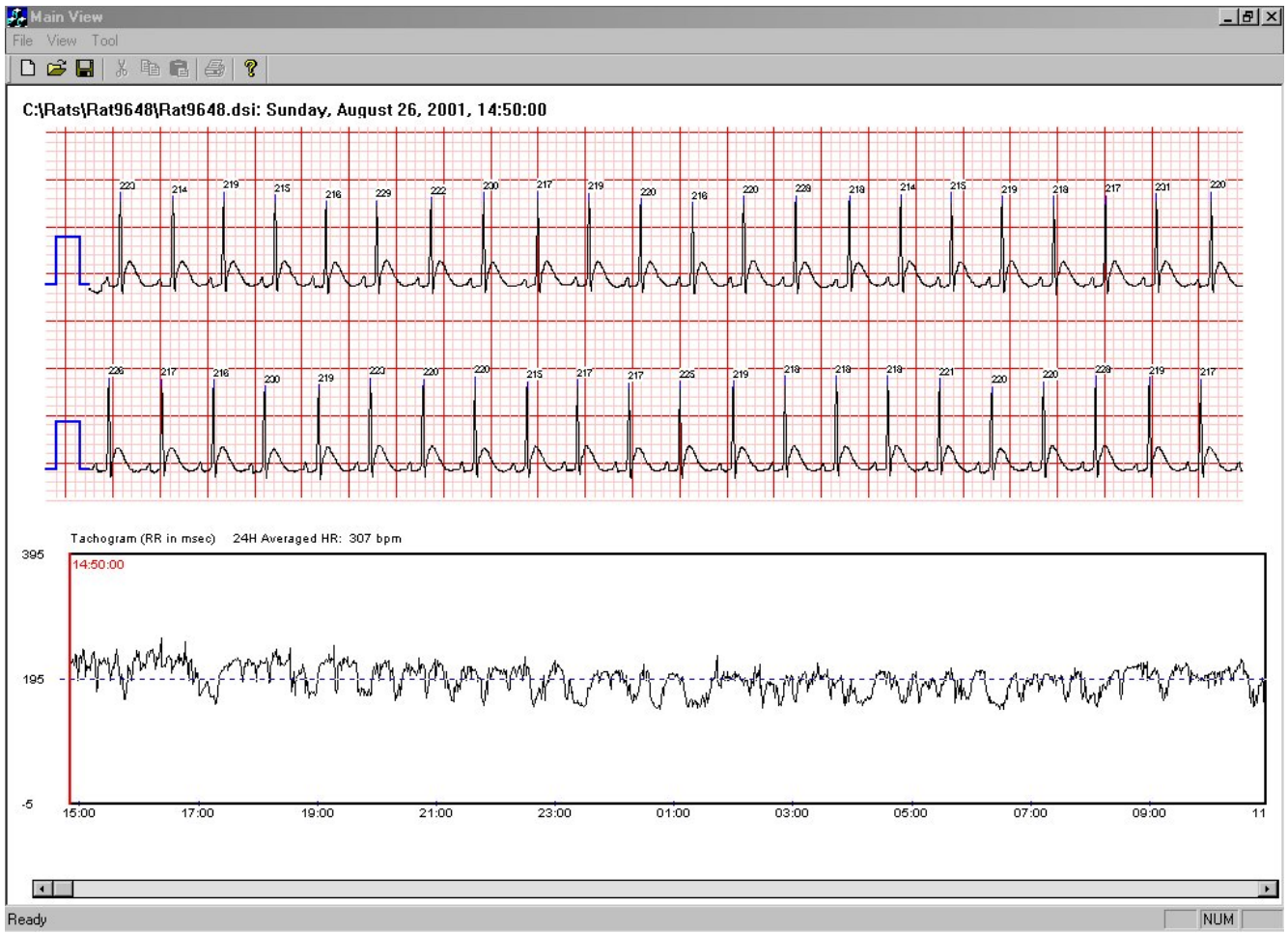
TNF-α and TNF-α Receptor I Gene Expression in 21 month-old Rats Exposed for 1 Day in MEL



Method

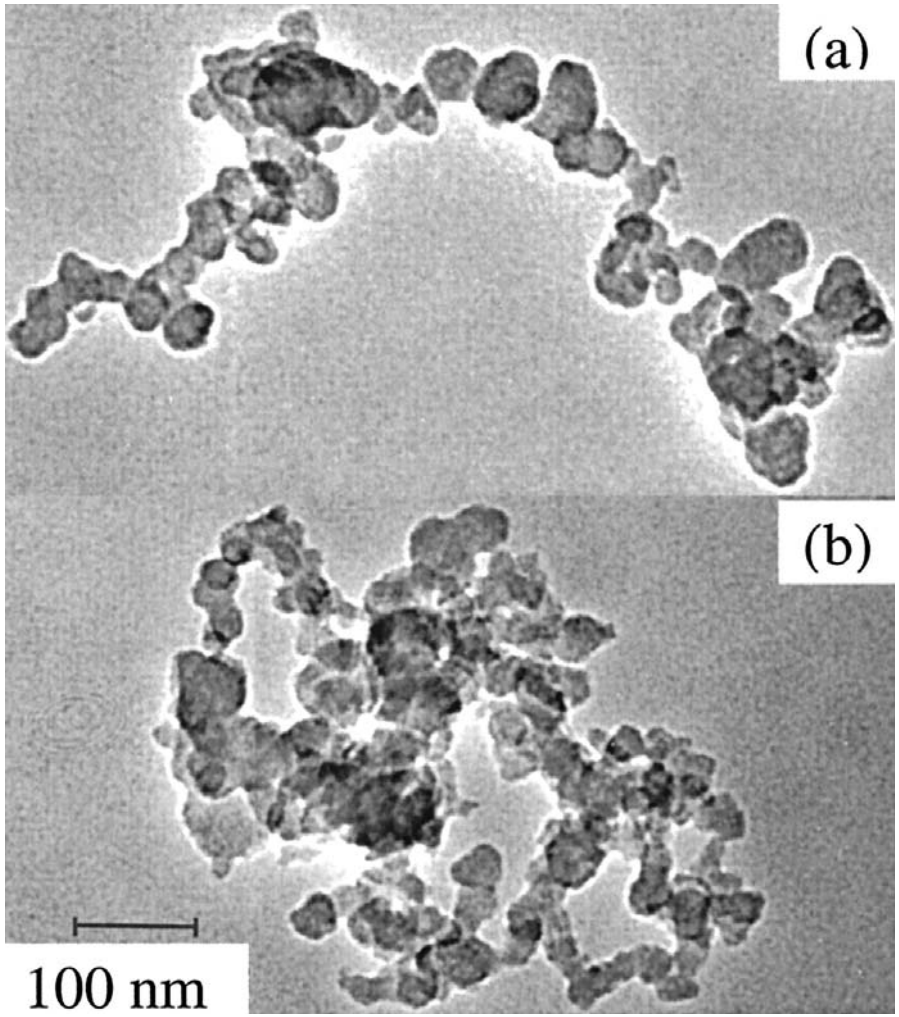
T.H.E. R.A.T.

Tracking **H**RV in **E**lectrocardiographic **R**ecordings from **A**nimals using **T**elemetry.



Couderc et al, 2005

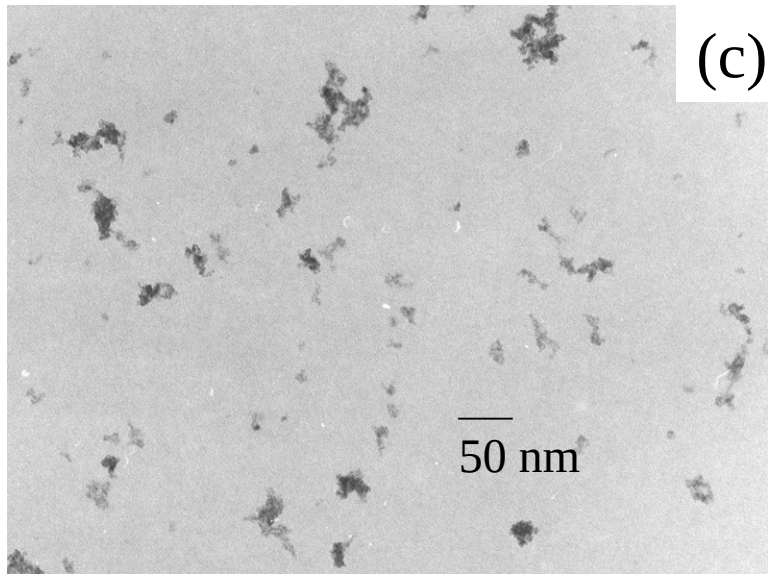
Nano-sized Ambient and Engineered Particles

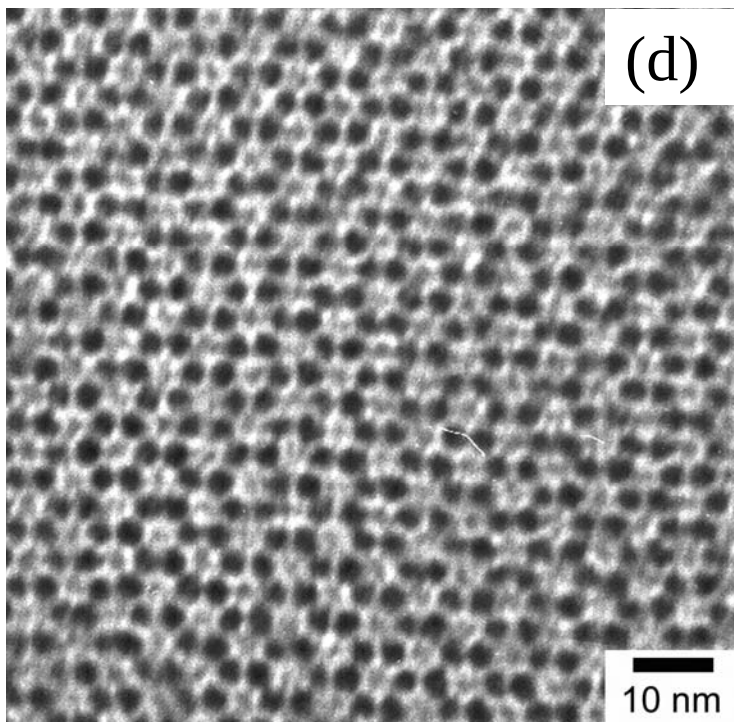


(a,b) Primary chain aggregates from internal combustion emissions with low (a) and high (b) fractal dimensions from L.A. basin (*Xiong & Friedlander, 2001*).

(c) Fe-oxide particles generated by electric spark discharge: note branched chain-like structures (*Roth et al., 2004).*

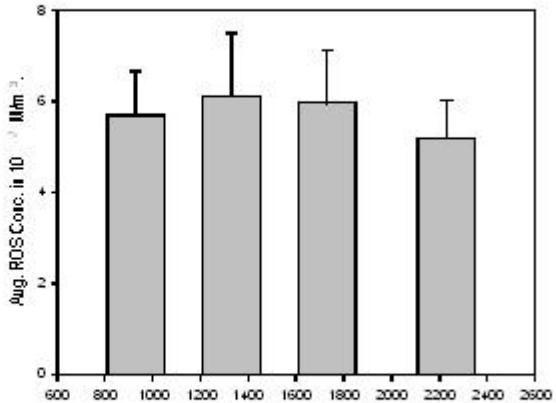
(d) Engineered γ-Fe_2o_3 nanoparticles, monodispersed singlets (3 nm). *(Yang & Teng, unpublished results).*



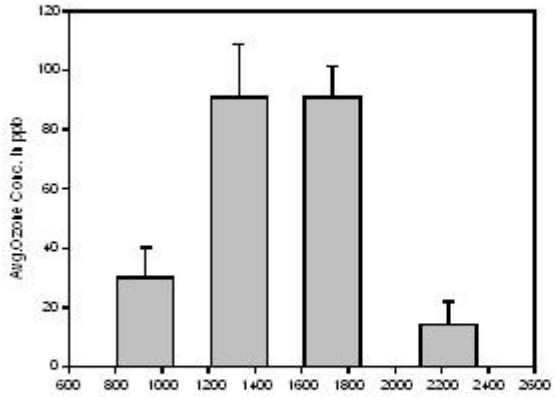


Reactive Oxygen Species

ROS

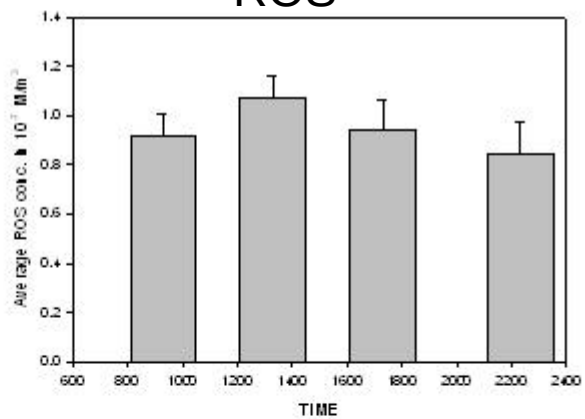


Ozone

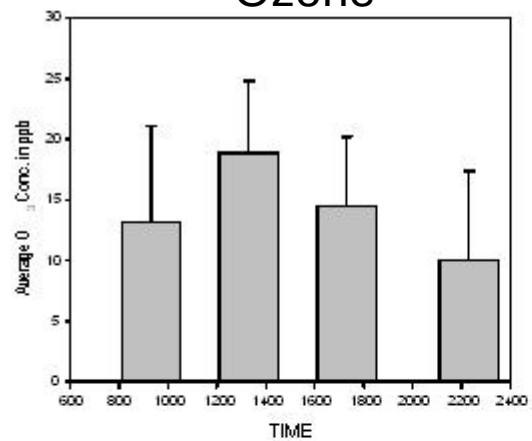


Measurements in Rubidoux, CA, July 2003

ROS



Ozone



Measurements in New York City, February 2004

Particle bound reactive oxygen species (ROS) on PM2.5 were found in both locations. The contribution of these ROS to adverse health effects will be evaluated in future studies.

Hopke, 2005

CELL FREE REACTIVE OXYGEN SPECIES (ROS) ANALYSIS

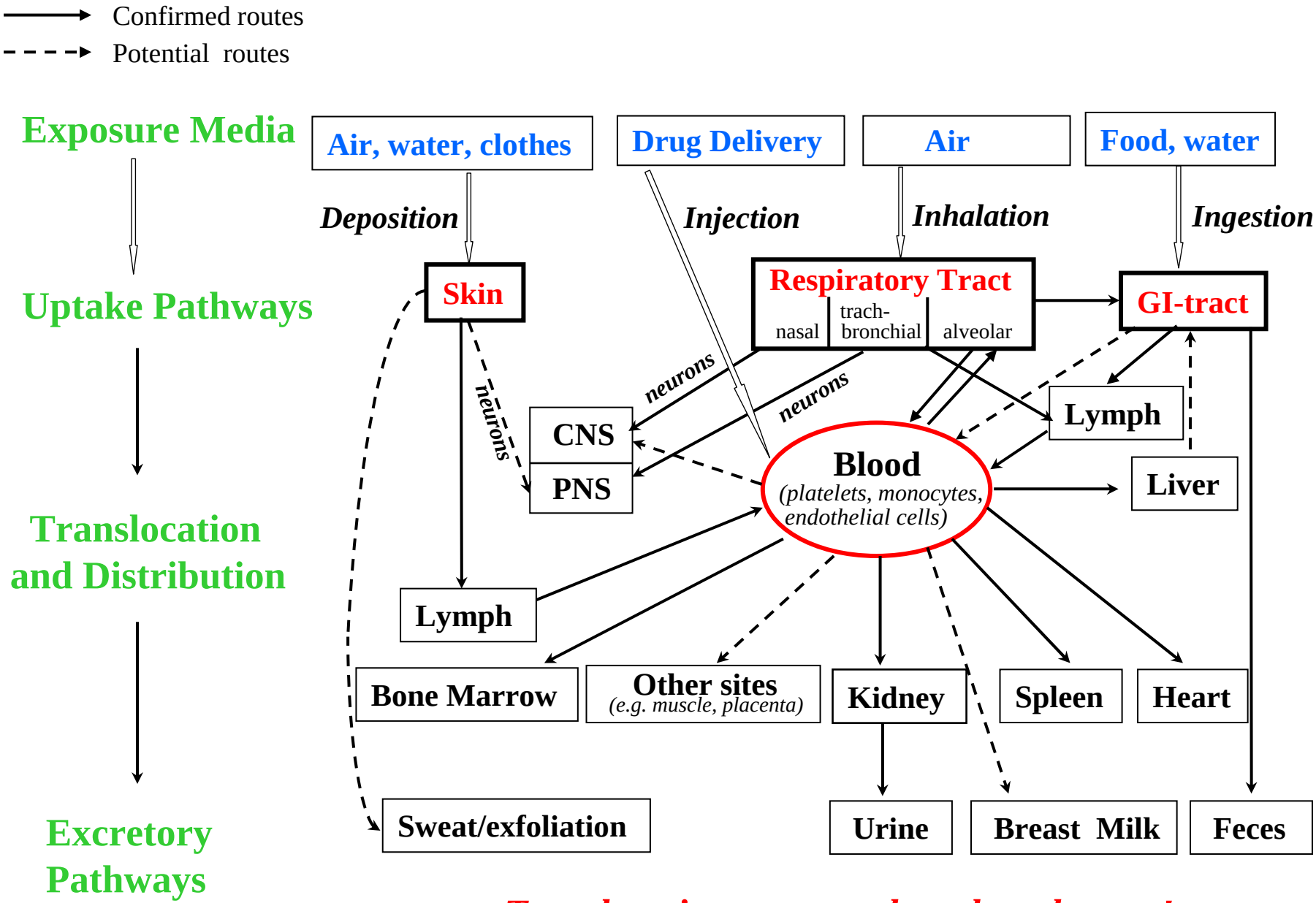
Principle:

2'-7' Dichlorodihyddrofluorescein diacetate (DCFD) oxidation by nanoparticles in PBS-buffer in presence of HRP

H_2O_2 as standard oxidant

Expression of oxidative potential of nanoparticles as H_2O_2 equivalents

Exposure and Biokinetics of Nanosized Particles

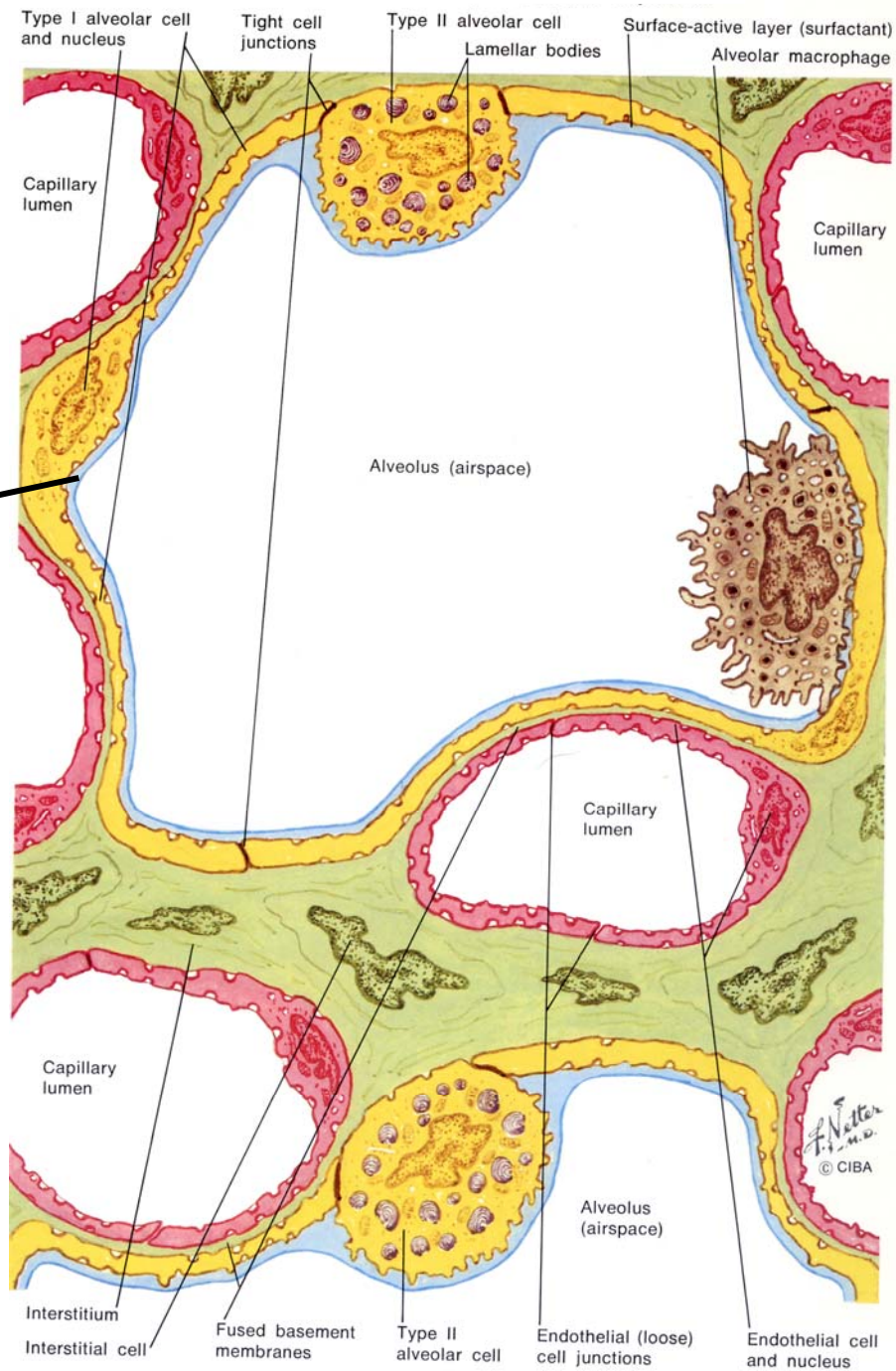


Translocation rates are largely unknown!

Oberdörster et al. 2005

Ultrastructure of Pulmonary Alveoli and Capillaries

Surfactant layer:
Phospholipids, proteins



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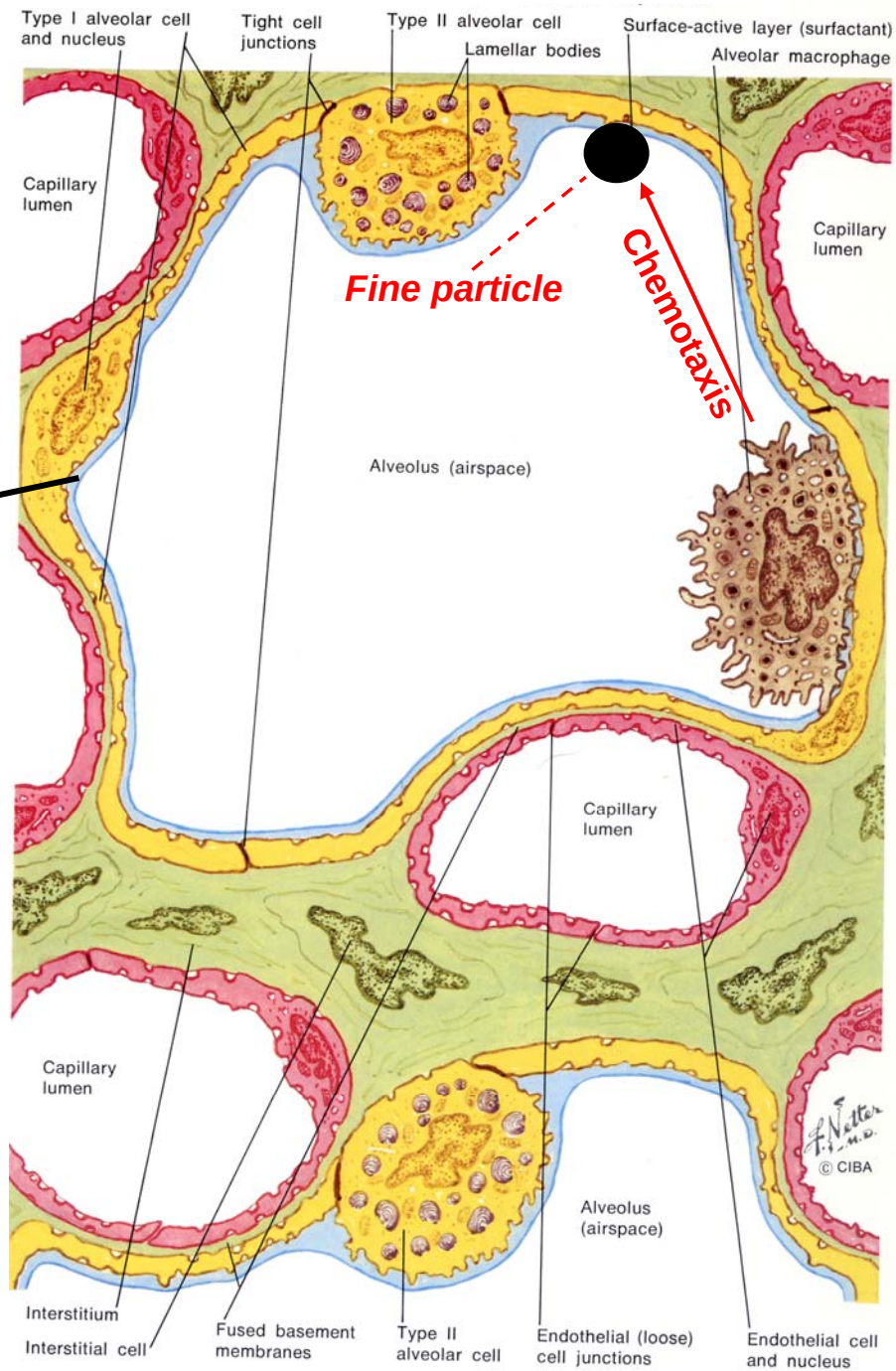
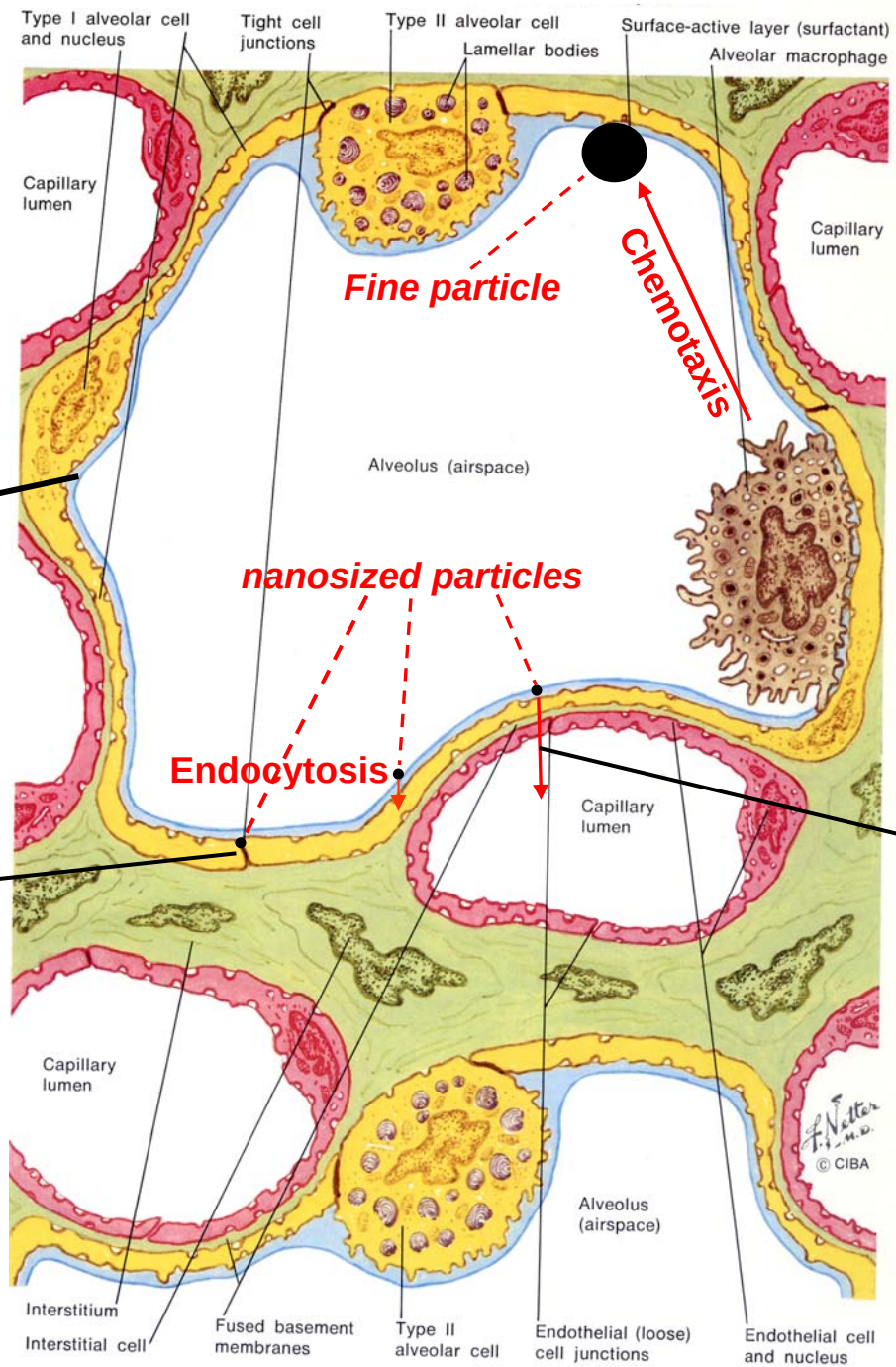


Ultrastructure of Pulmonary Alveoli and Capillaries

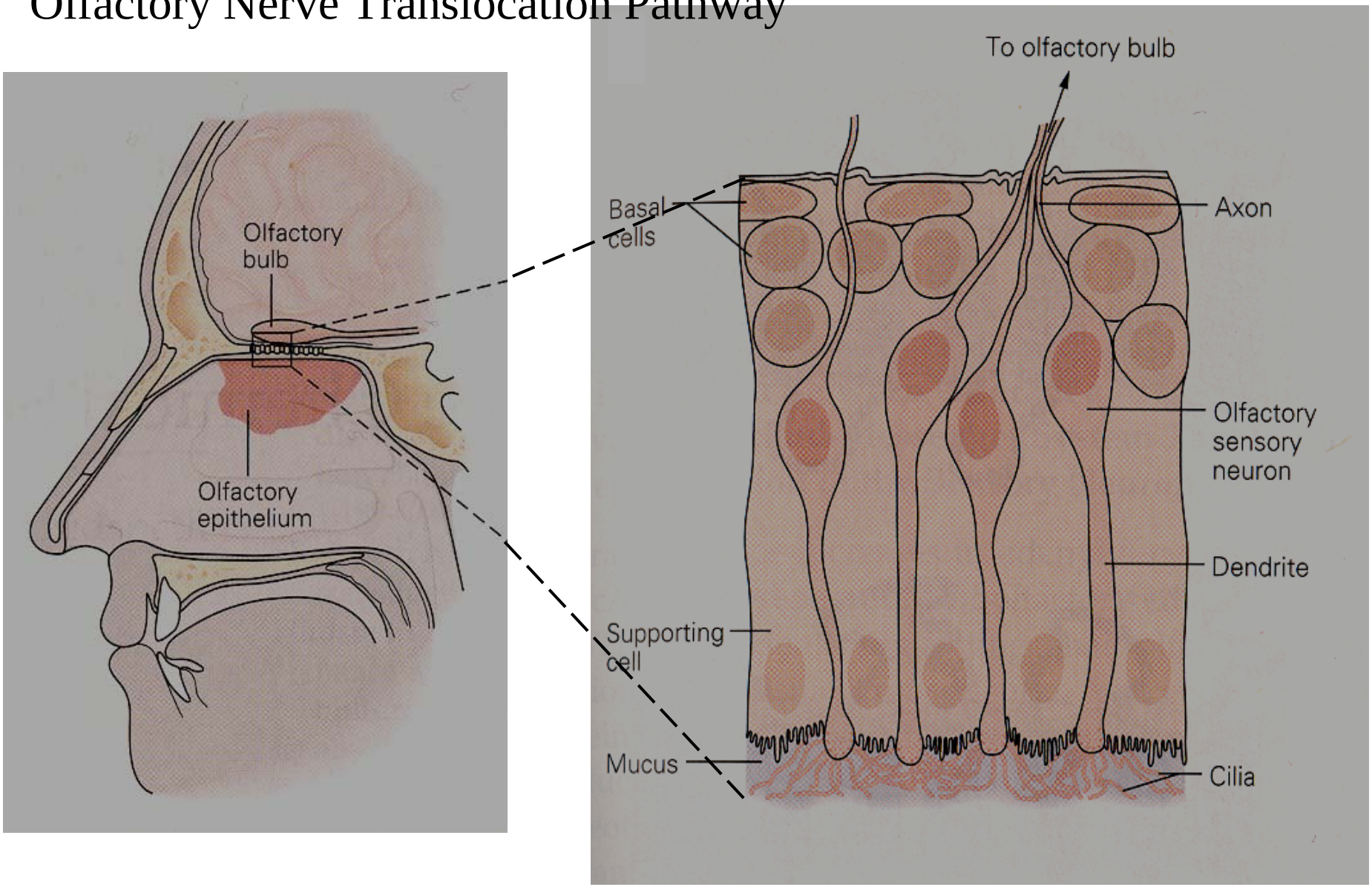


Surfactant layer:
Phospholipids, proteins

Tight junction (paracellular) Translocation

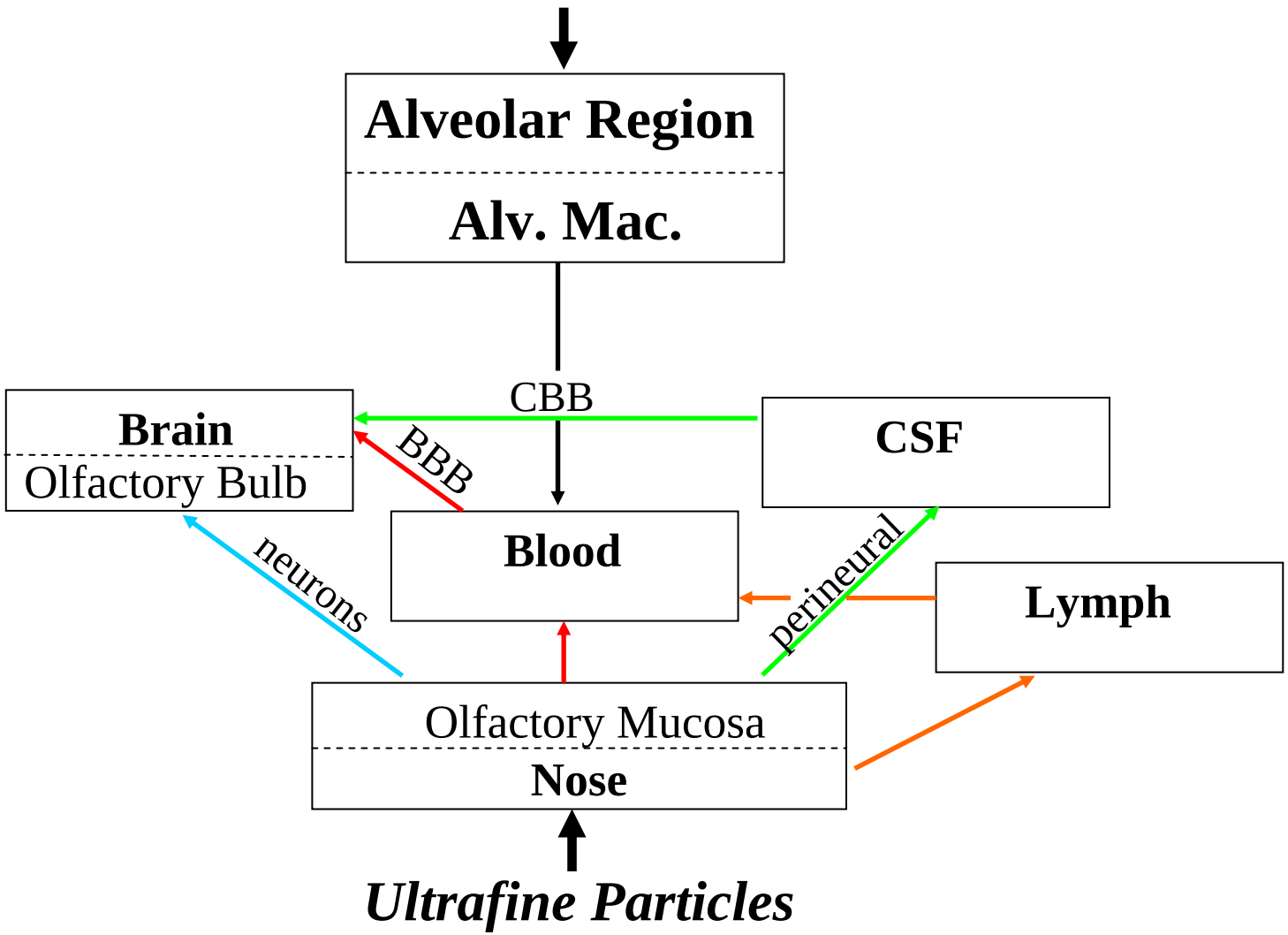
Transcytosis

Olfactory Nerve Translocation Pathway



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

FROM NOSE TO BRAIN:
POTENTIAL TRANSLOCATION PATHWAYS OF NANOPARTICLES



Studies of Neuronal Translocation of UFP from Respiratory Tract

1941: *Bodian and Howe*: ***Olfactory*** axonal transport of Polio-virus (30 nm) after intranasal instillation in chimpanzee.
Transport velocity: 2.4 mm/h

1970: *de Lorenzo*: ***Olfactory*** axonal transport of 50 nm silver coated gold after intranasal instillation in squirrel monkey.
Transport velocity: 2.5 mm/h

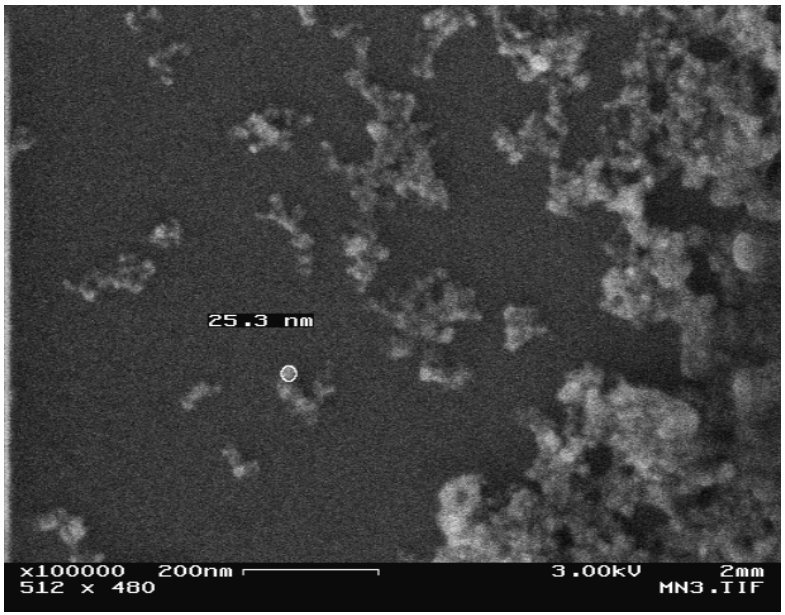
1998: *Hunter and Undem*: Rhodamine-labelled 40 nm micro-spherest ranslocation via sensory nerves of ***TB region*** to ganglion nodosum in hamster after intratracheal instillation.

1999: *Hunter and Dey*: Retrograde tracing of ***trigeminal*** neurons from nasal epithelium with microspheres

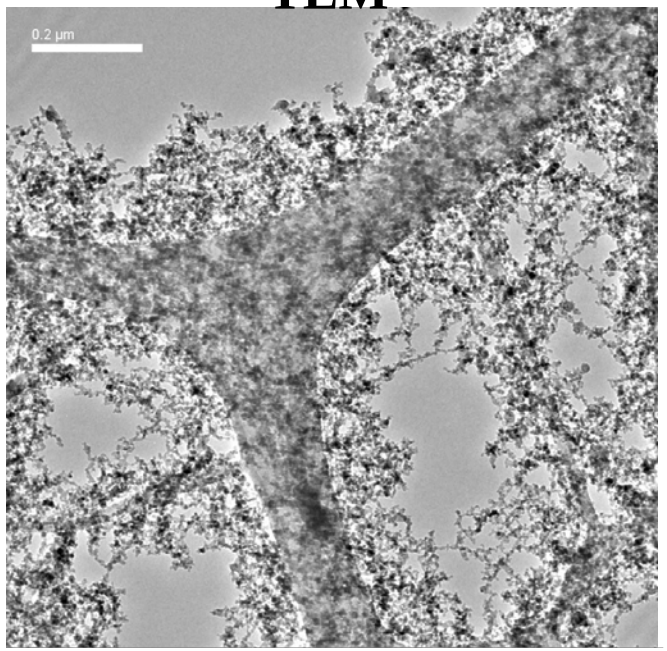
2004: *Oberdörster et al.*: ^{13}C particles (CMD ~36 nm) in ***olfactory*** bulb after whole-body inhalation exposure in rats.

Nanosized Mn-oxide particles *(Vapor-phase generated)*

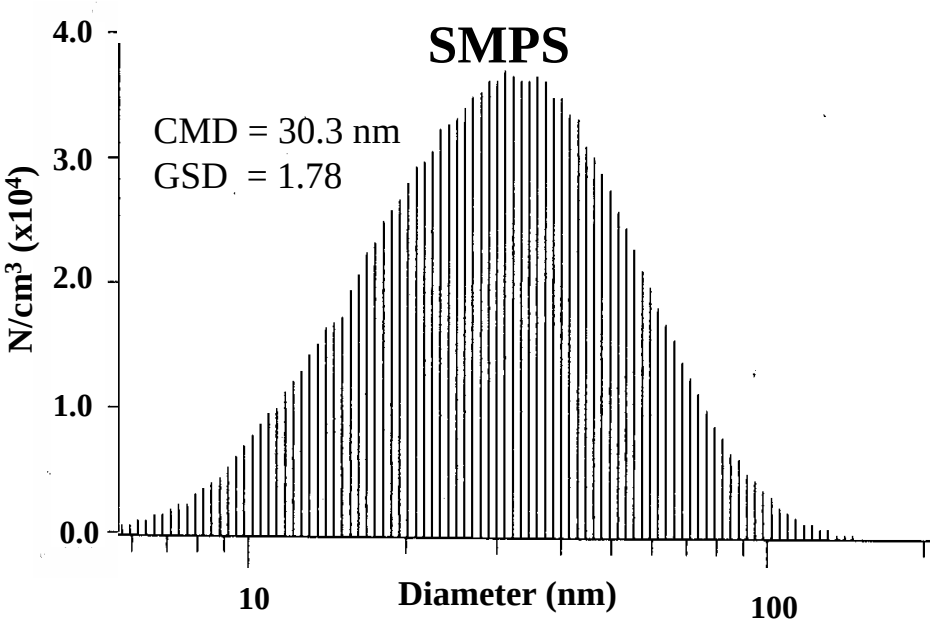
SEM



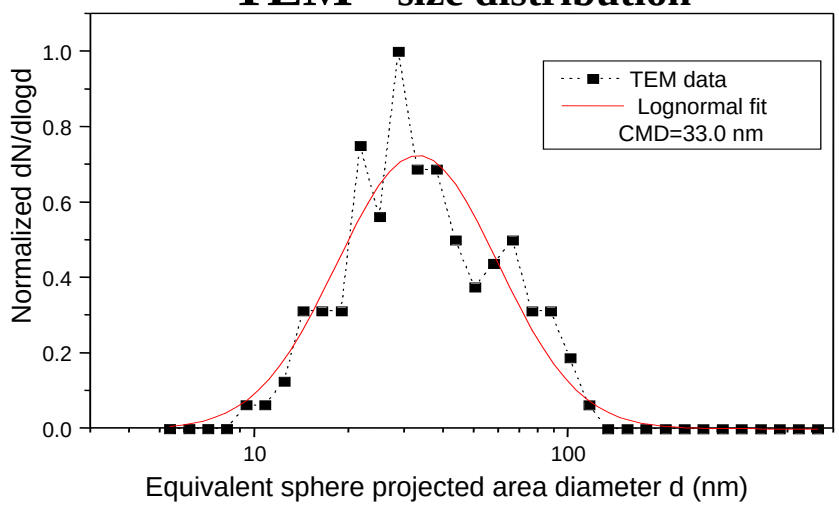
TEM



SMPS



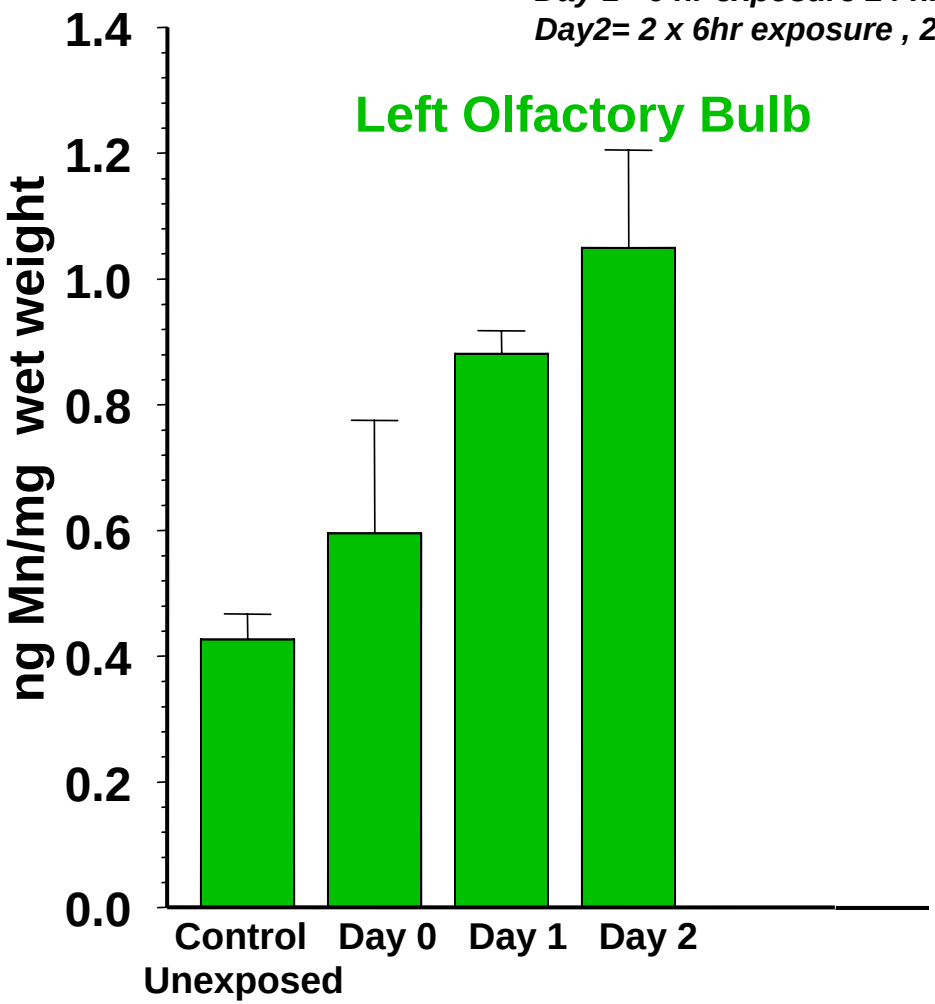
TEM - size distribution



Rat, Right Nostril Occlusion Model:

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

Day 0= 6 hr exposure, immediate sac.
Day 1= 6 hr exposure 24 hr sac.
Day2= 2 x 6hr exposure , 24 hr sac.



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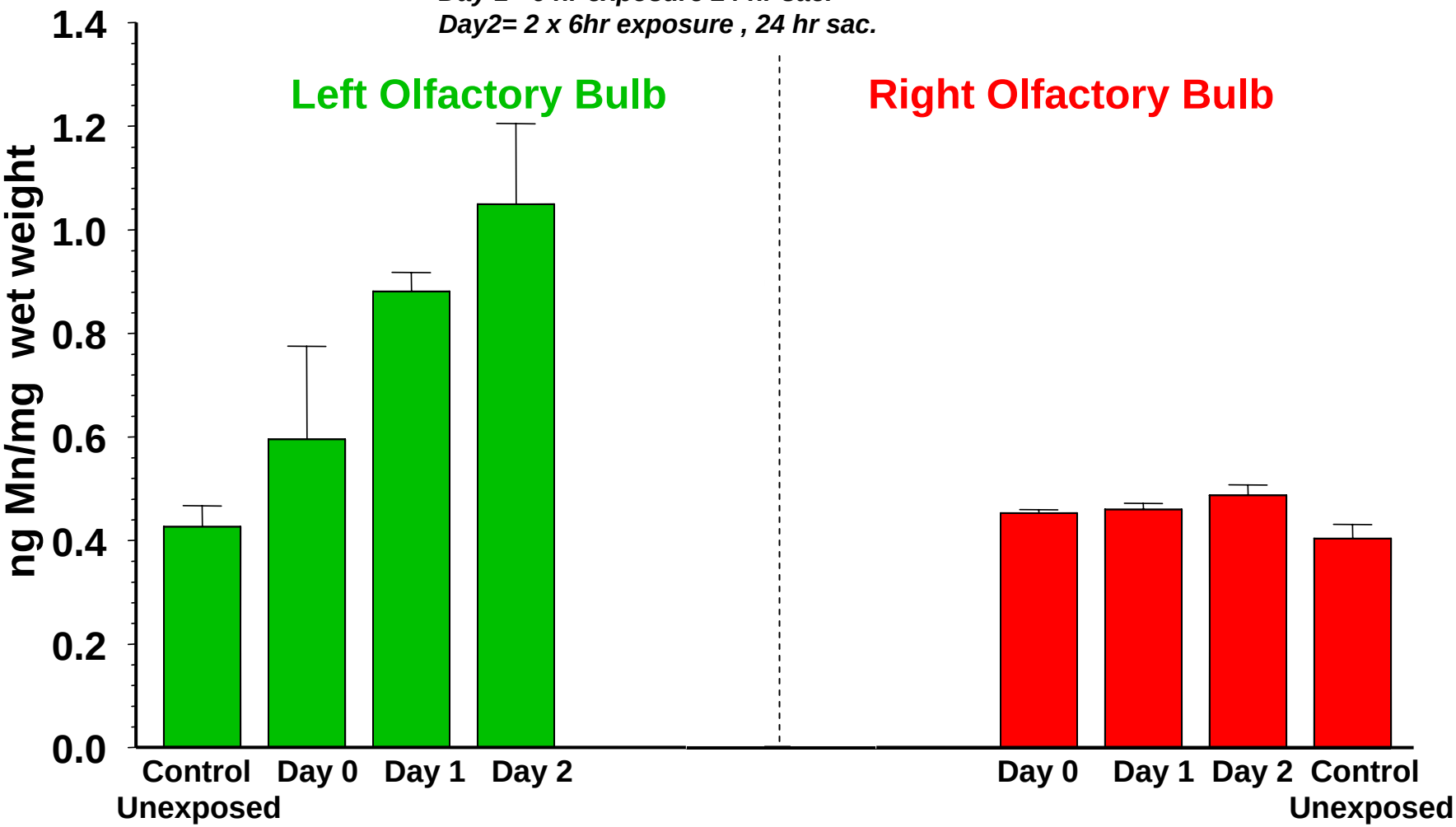
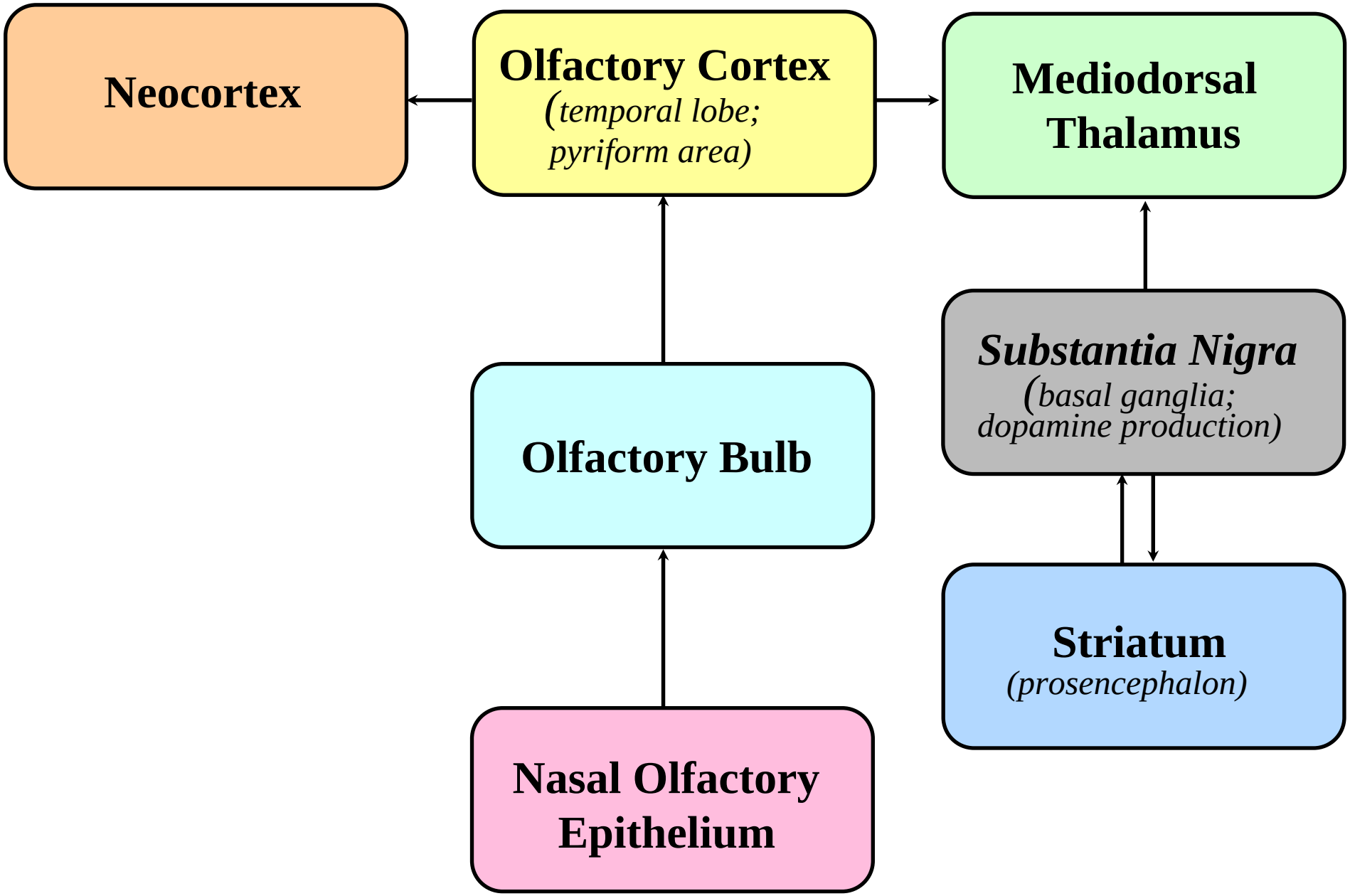
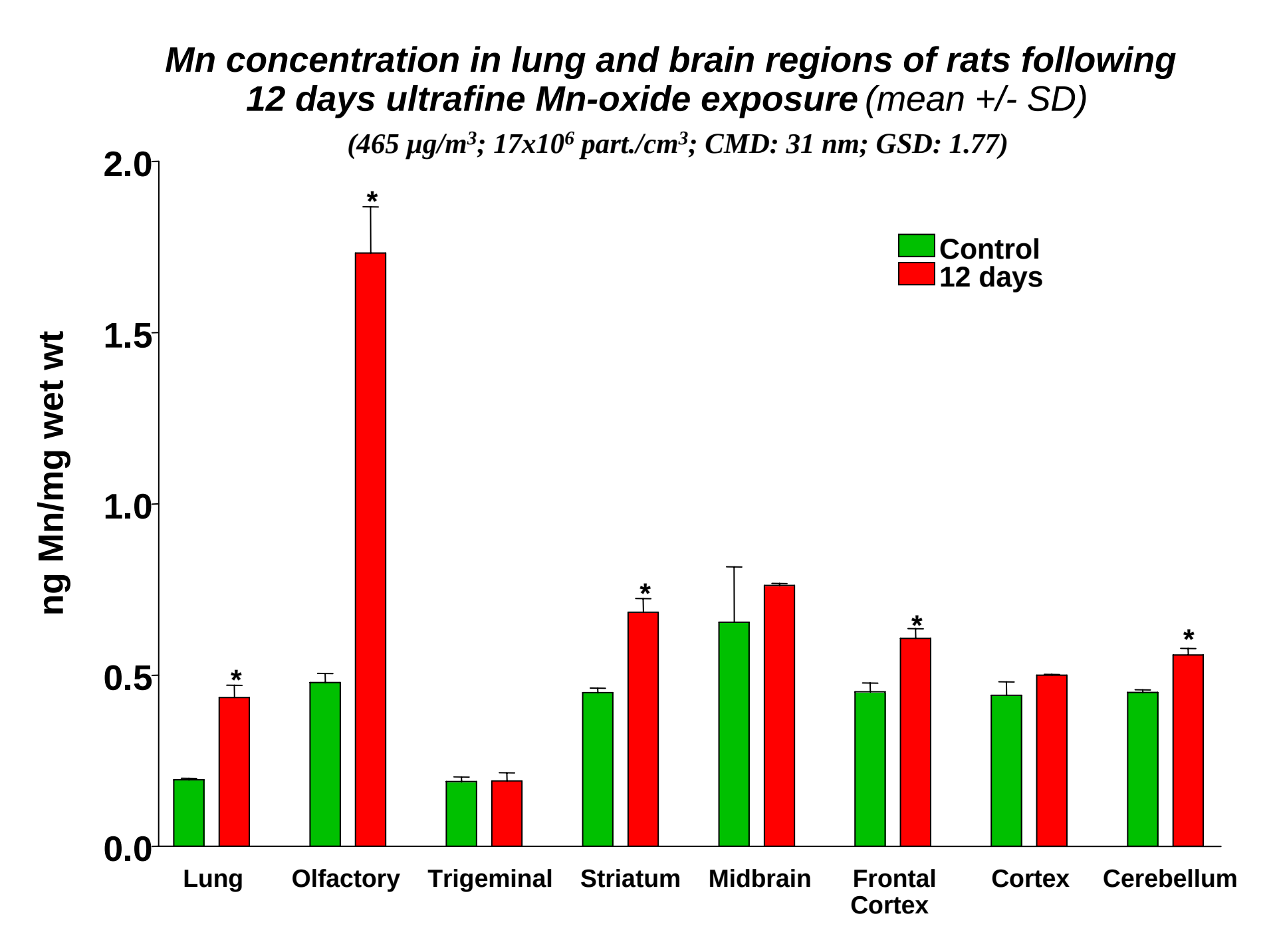
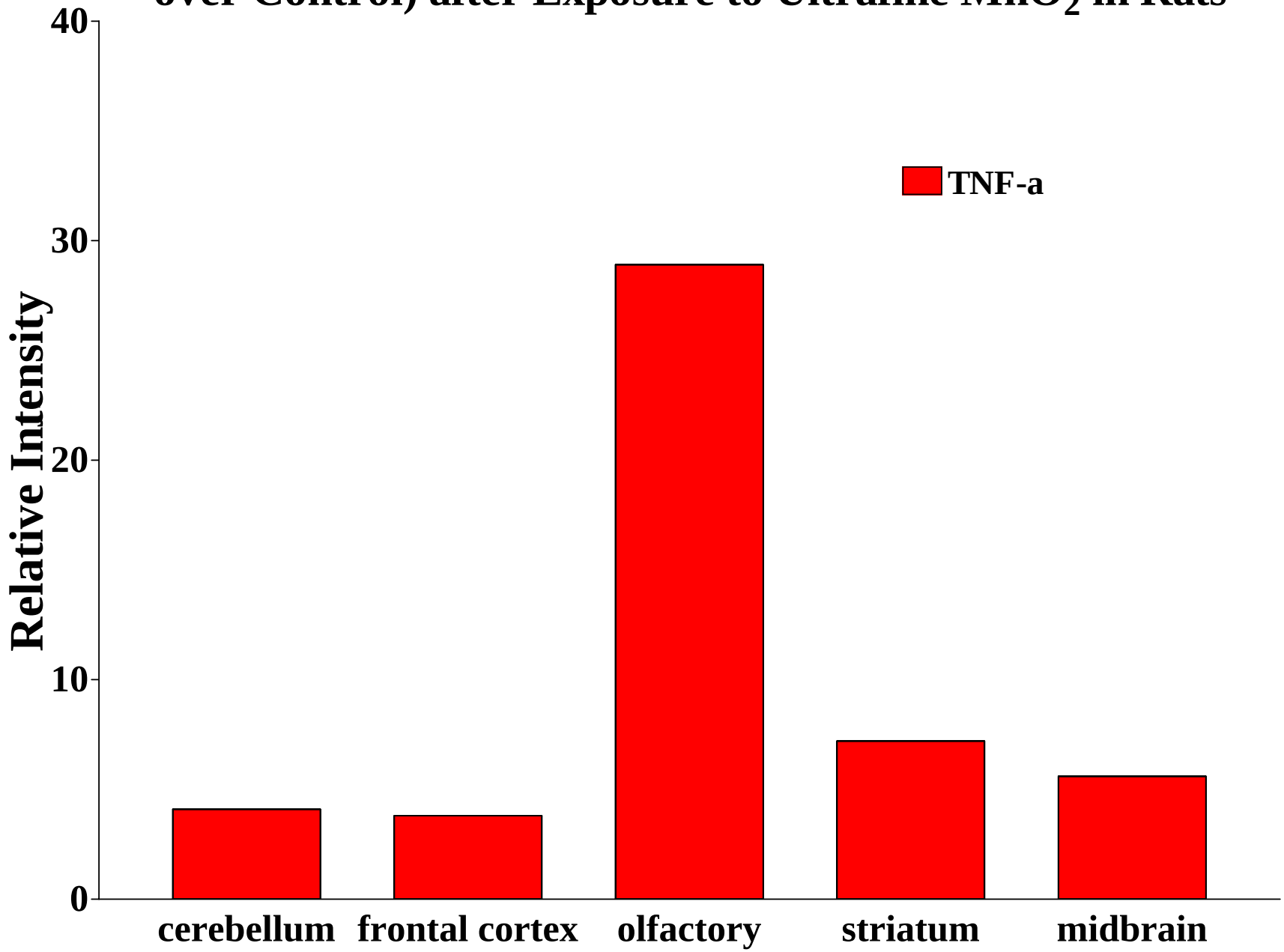


Nanoparticles: From the Nose to the Olfactory Bulb, and Beyond?




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)
ng Mn/mg wet wt
2.0
1.5
1.0
0.5
0.0
Control
12 days
*
Lung
Olfactory
Trigeminal
Striatum
Midbrain
Frontal Cortex
Cortex
Cerebellum

Brain Region Protein Expression Changes (fold increase over Control) after Exposure to Ultrafine MnO_2 in Rats



Conclusions

Biokinetics of nano-sized particles are different from larger particles:

— **when inhaled:**

efficient deposition in all regions of respiratory tract,
evade specific defense mechanisms,
can translocate via different pathways
endocytosis, transcytosis into lymph and blood circulation
neuronal pathways to CNS

— **when in blood circulation:**

distribution to whole organism,
uptake into liver, spleen, heart, bone-marrow, others

Important: Evaluation of potential toxicity (oxidative stress, inflammation!)

Conclusions (cont)

Biological activity and biokinetics are dependent on many parameters:

-size; -shape; -chemistry; -crystallinity;
-surface properties *(area, porosity, charge, coating)*
-agglomeration state; -biopersistence; -dose

Dose and dosemetric for combustion nano-sized particles:

- ***mass*** *small compared to fine and coarse*
- ***-number*** *easy measurement, indicative of ultrafines*
- ***- surface*** *measurement more involved, not in real time*

} **Chemistry** *(solubility, volatility)*

Essential for Nanotoxicology Research : Multidisciplinary Approach!

INVESTIGATORS AND COLLABORATORS OF ROCHESTER-BASED RESEARCH WITH NANO-SIZED PARTICLES

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