Effects of Nanoscale Particles in the Brain

SOT Medical Device and Combination Product Specialty Section Webinar

January 23, 2017

Alison Elder, University of Rochester, USA

Excess Mortality Associated With PM_{10} Exposure

per 10 µg/m^3 increase *(Dockery & Pope, 1996):*

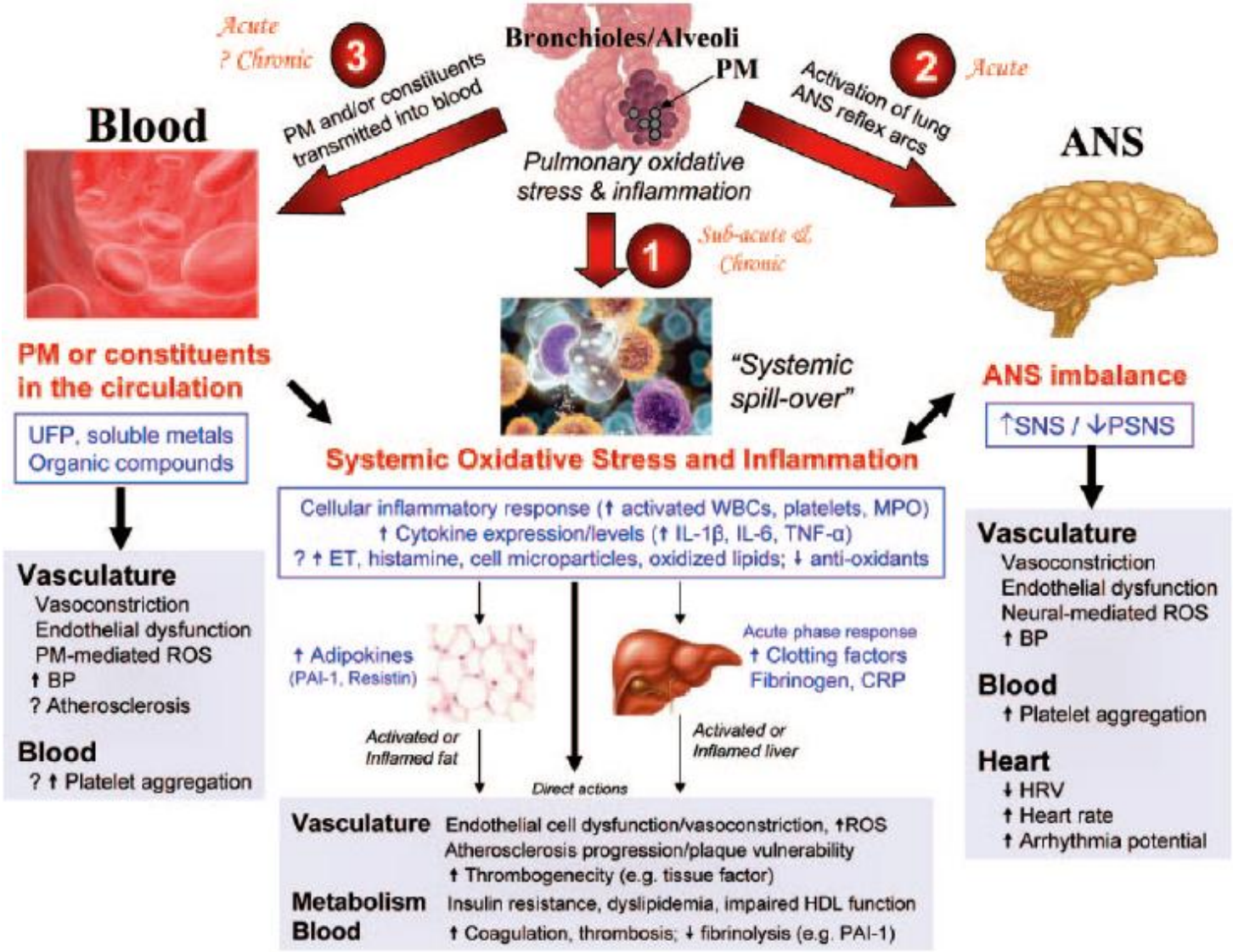
- **Total:** **1.0 %**
- **Respiratory:** **3.4%**
- **Cardiovascular:** **1.4 %**

Excess Annual Mortality in US:

28,000 to 124,000

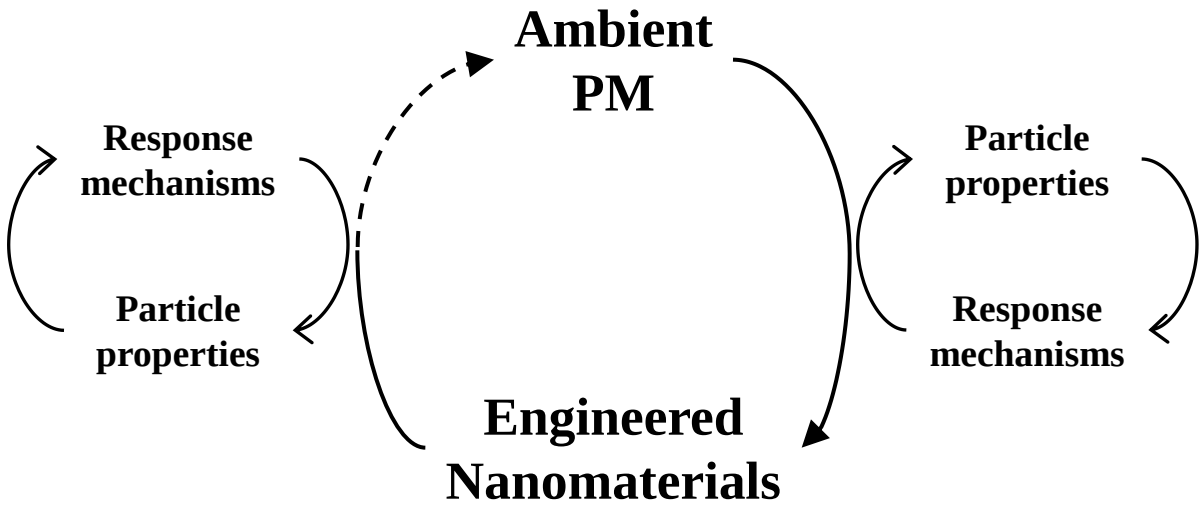
Particulate Matter —**?**→ **Adverse Health Outcomes**

Possible Mechanisms of Particulate Effects



Brook et al., 2010 (AHA Scientific Statement)

Lessons from Ambient Pollutant Ultrafine Particles and 'Legacy' Nanomaterials



Lessons from Ambient Ultrafine Particles and 'Legacy' Nanomaterials

- Oxidative stress and inflammation are consequences of exposure; can be persistent if retention is prolonged
- Nanoscale particles produce greater adverse effects at the same mass dose as compared to larger particles with same chemistry
- Physicochemical properties of nanomaterials are determinants of toxicological responses
- Nanoscale particles can breach epithelial barriers (translocation)
- Particles (or their constituents) have effects outside of the lungs

Outline of Talk

- Mechanisms and pathways of **particulate transport**
- **Consequences of particulate accumulation** in the CNS

Respiratory Tract

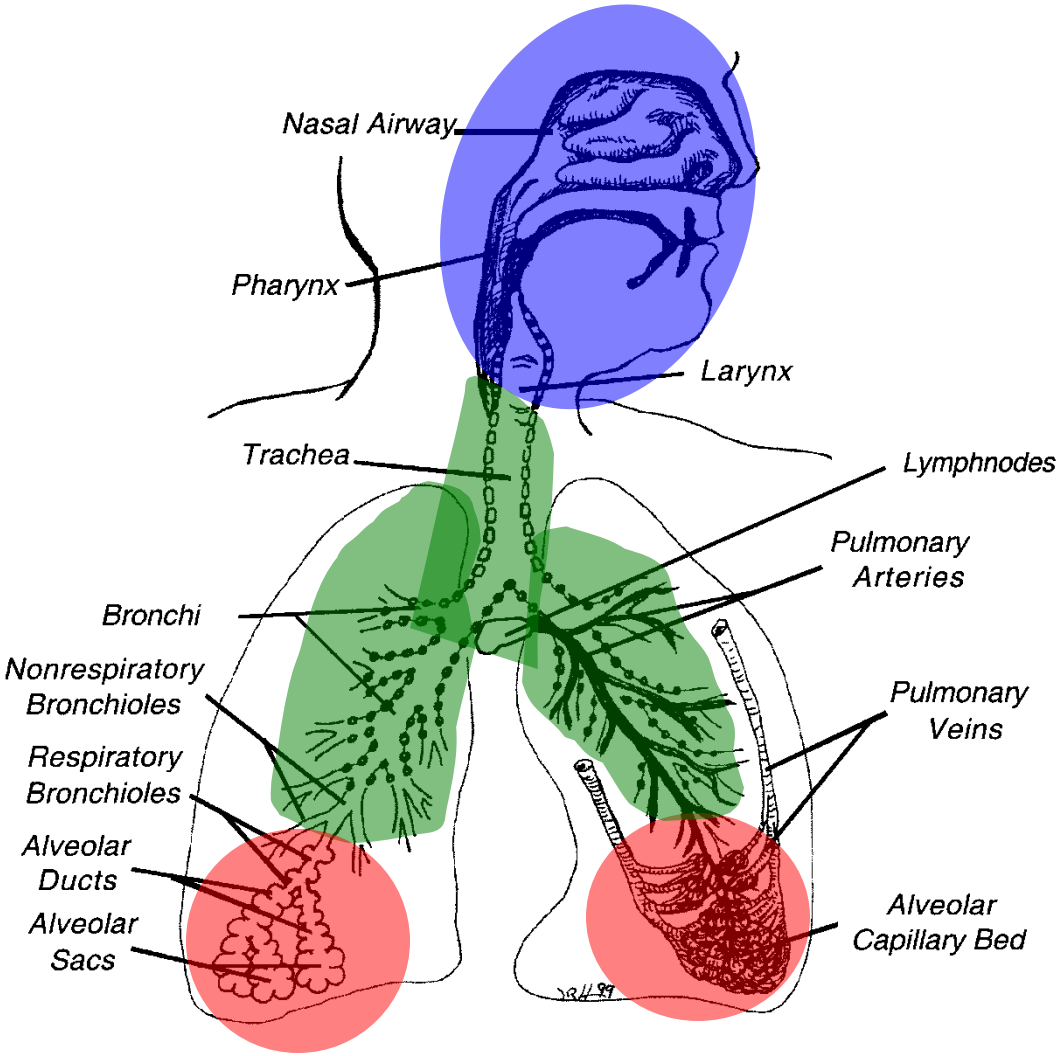
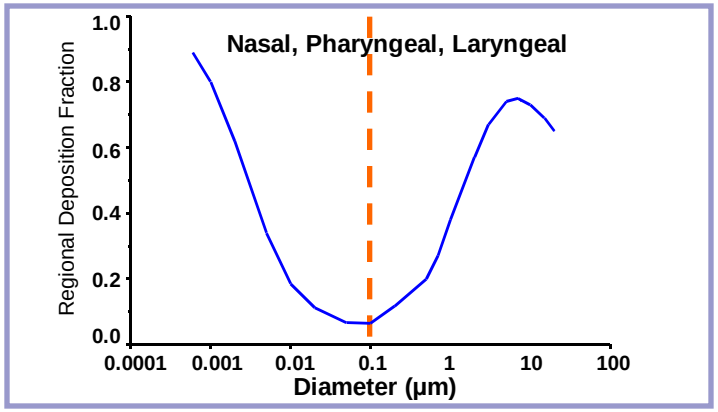
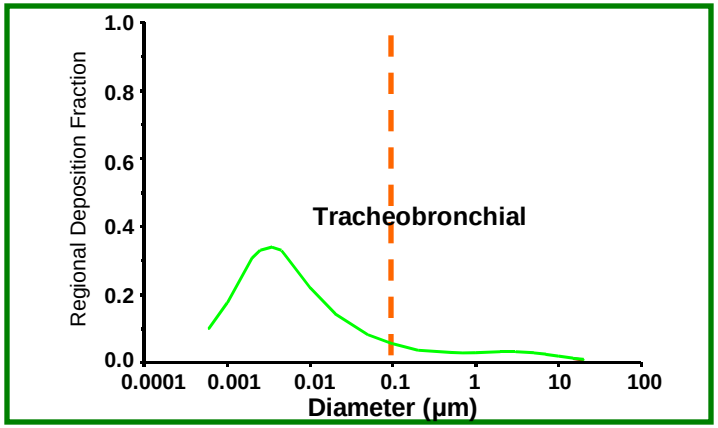
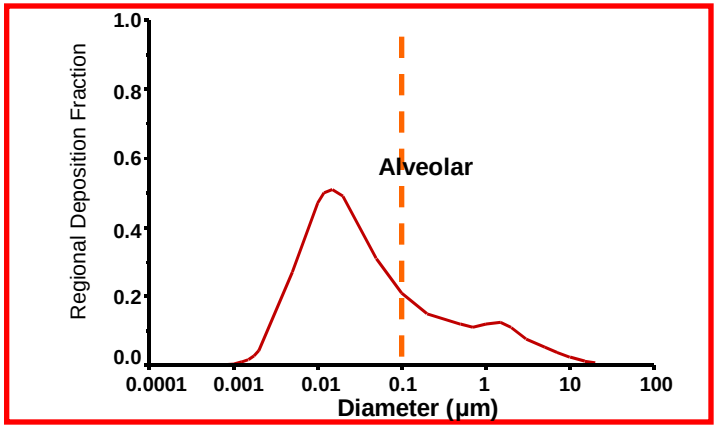


Figure courtesy of J. Harkema; adapted from ICRP, 1994

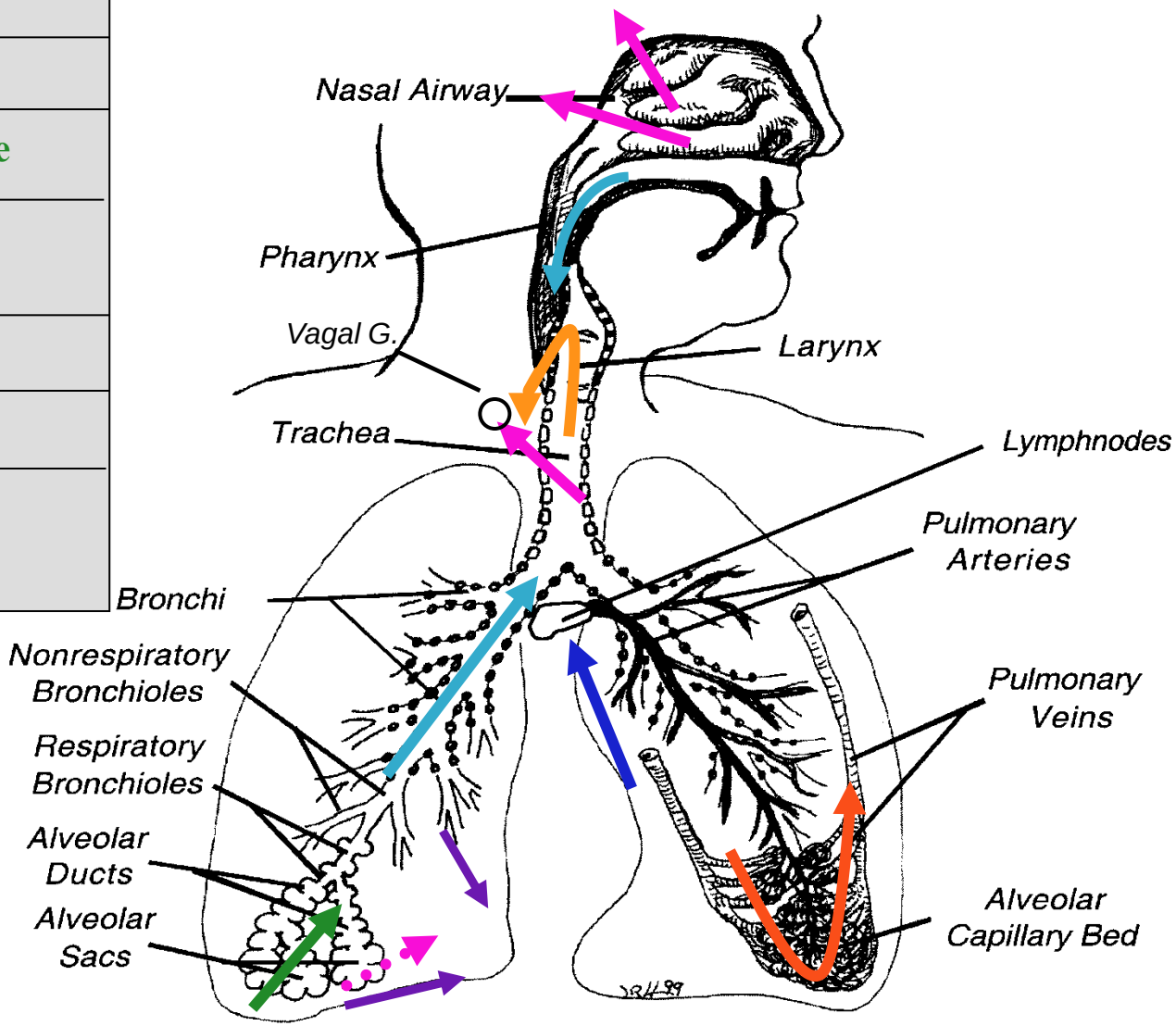






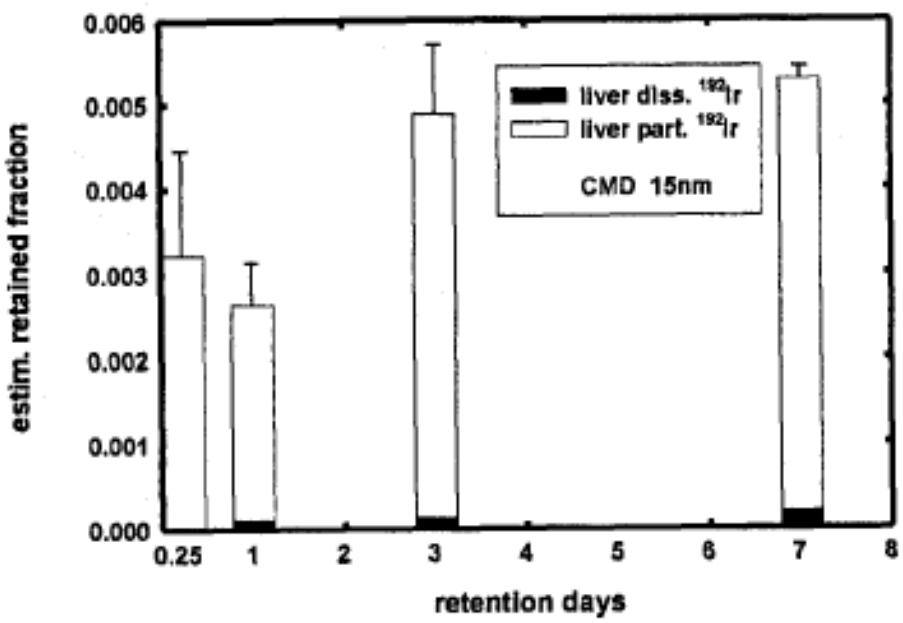
Pathways of Particle Translocation

- Mucociliary Clearance
- GI Tract
- AM-mediated Clearance
- Interstitium *(via Epithelium)*
- Lymphatic Circulation
- Blood Circulation
- Sensory Neurons *(olfactory, trigeminus, T.- bronchial)*

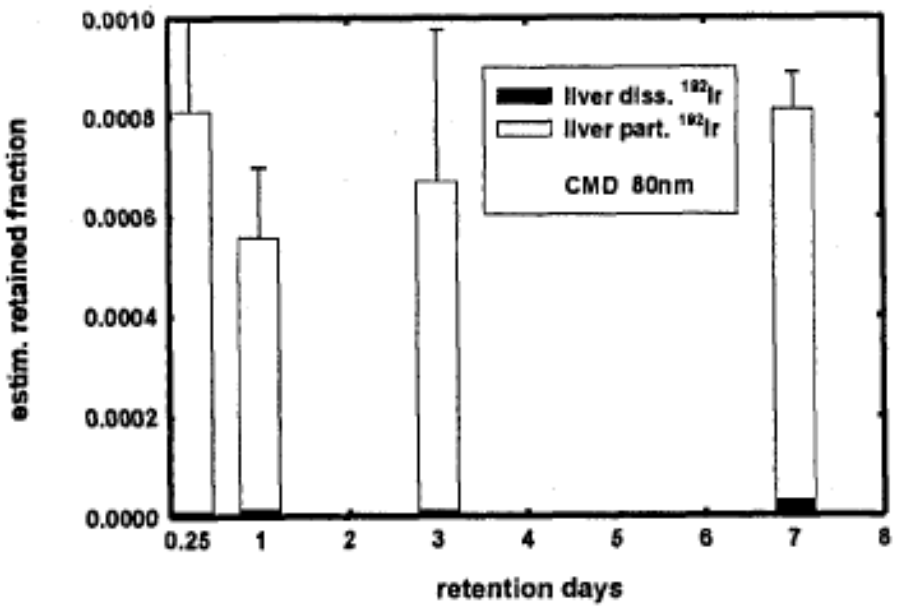


Oberdörster et al., 2009

Translocation of Inhaled Particles:
Uptake and Retention of Nanosized ^{192}Ir Particles:
Intratracheal Inhalation, Rats



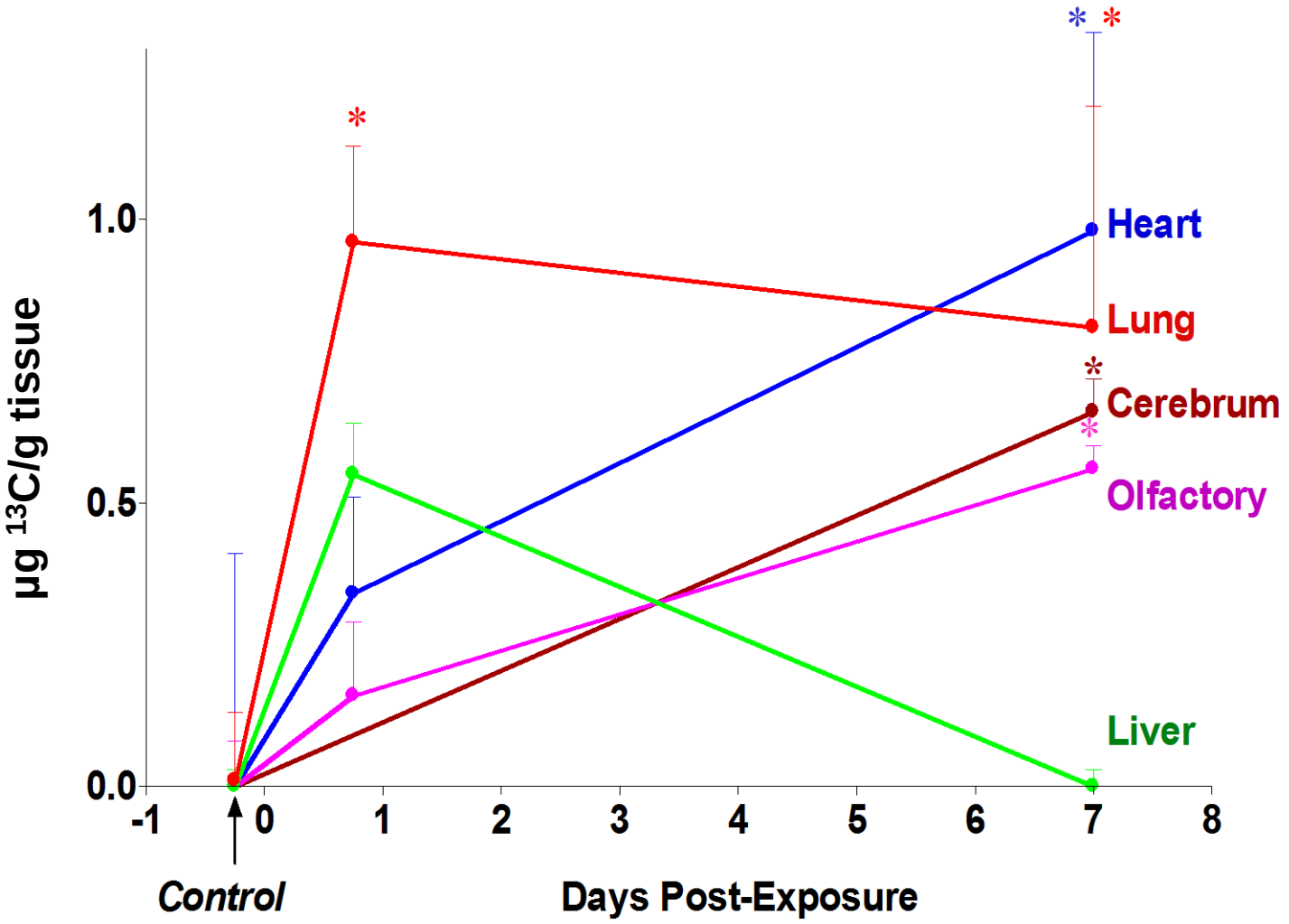
15 nm Ir



80 nm Ir

Kreyling et al., 2002

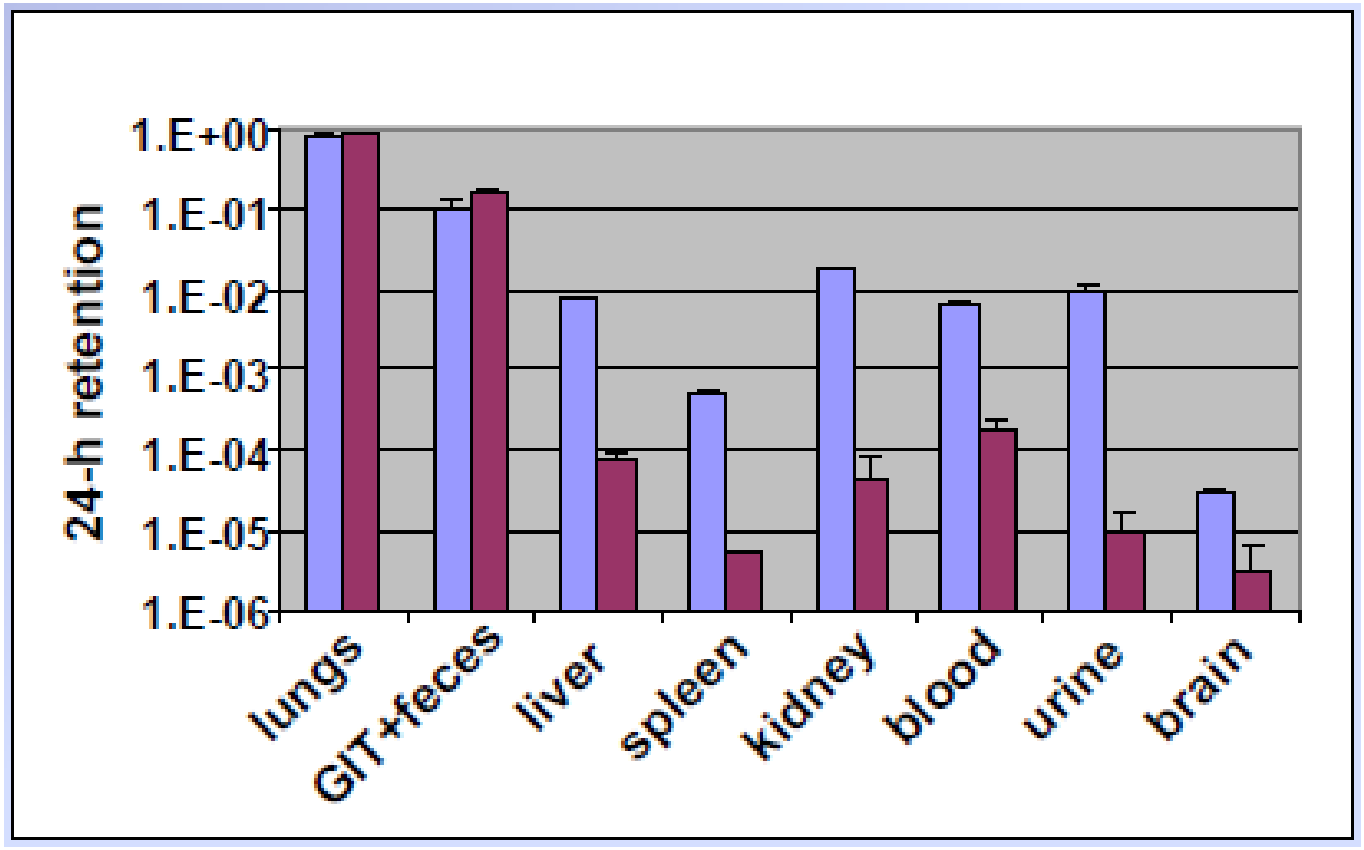
Transport of Ultrafine (35 nm; 150 µg/m^3) ^{13}C Particles to Extrapulmonary Tissues



from Oberdörster et al., 2002

Translocation of ^{198}Au nanoparticles:

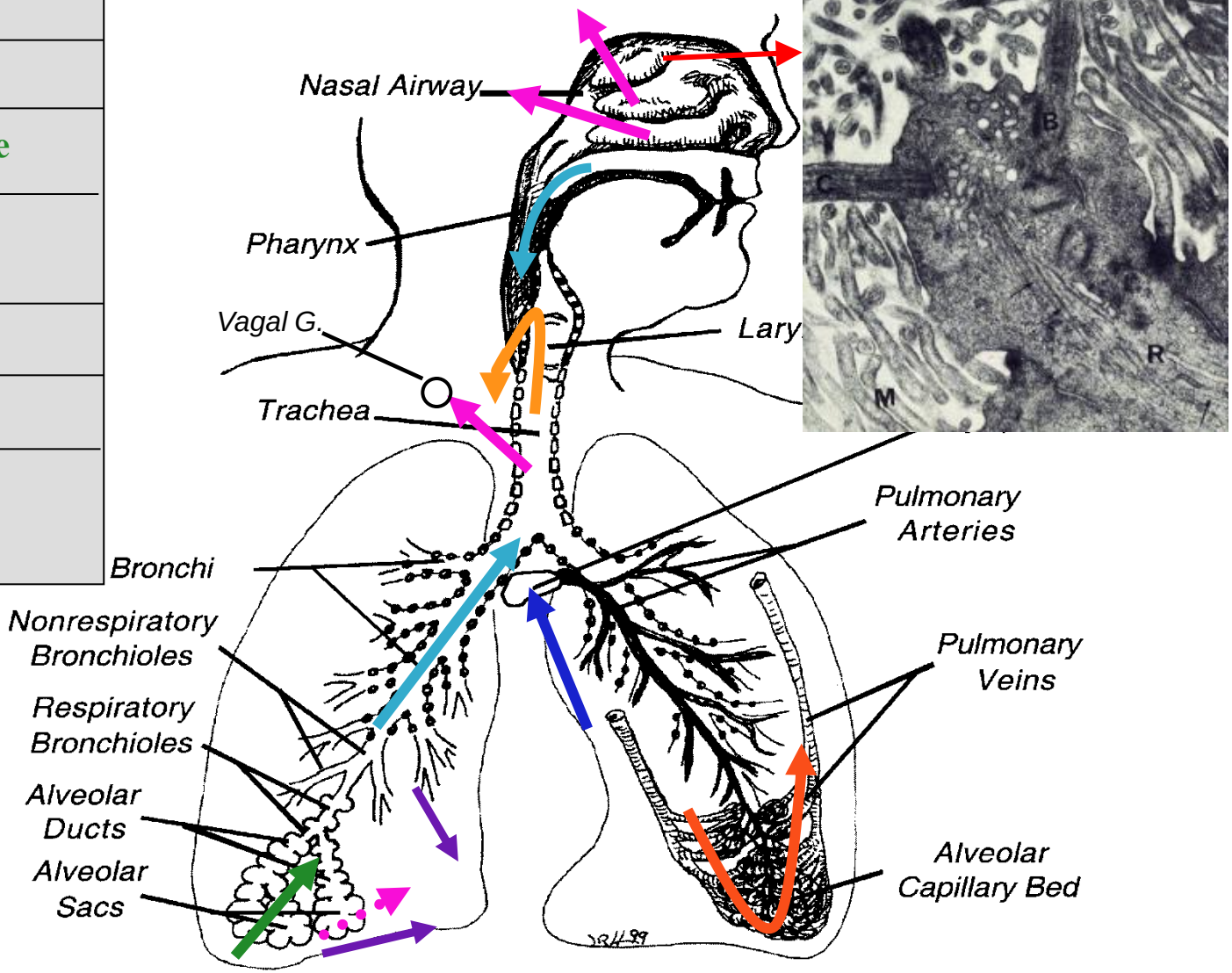
Effect of particle size (mass fractions of Au in organs 24 hrs PE)



Semmler-Behnke et al., 2008

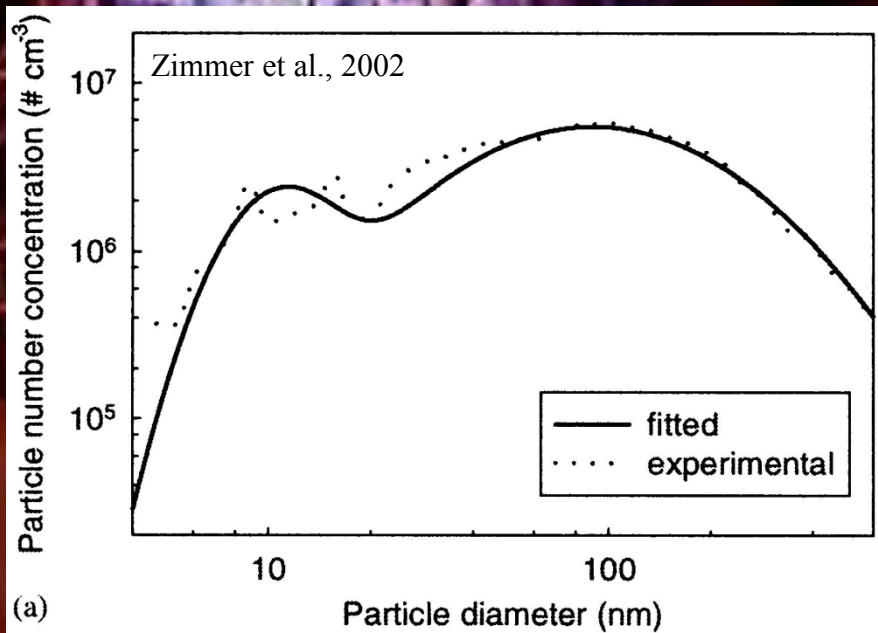
Pathways of Particle Translocation

- Mucociliary Clearance
- GI Tract
- AM-mediated Clearance
- Interstitium *(via Epithelium)*
- Lymphatic Circulation
- Blood Circulation
- Sensory Neurons *(olfactory, trigeminus, T.- bronchial)*



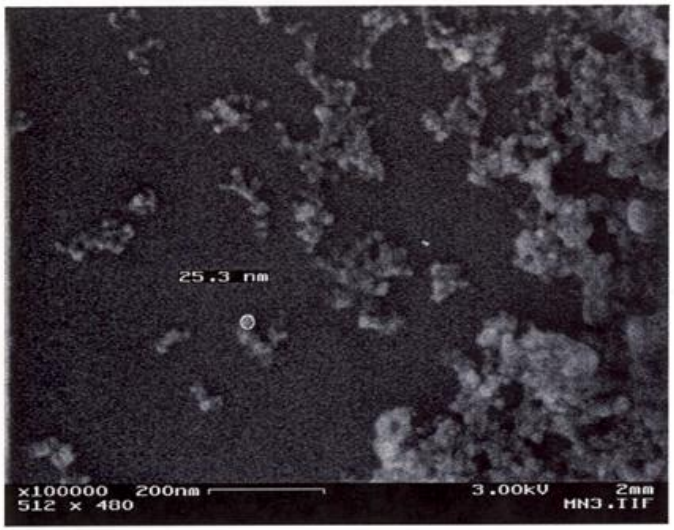
Oberdörster et al., 2009

Racette et al., 2001:
Welding-related Parkinsonism

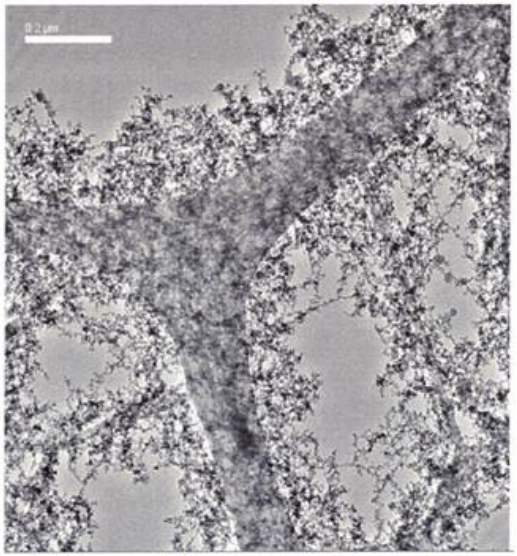


Size Distribution of Mn Oxide Particles:
Simulating Welding Fume

SEM



TEM

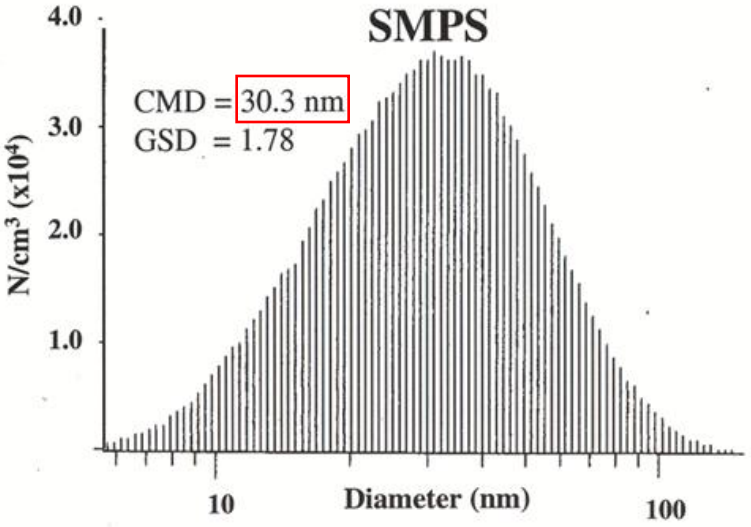


61% MnO (II)

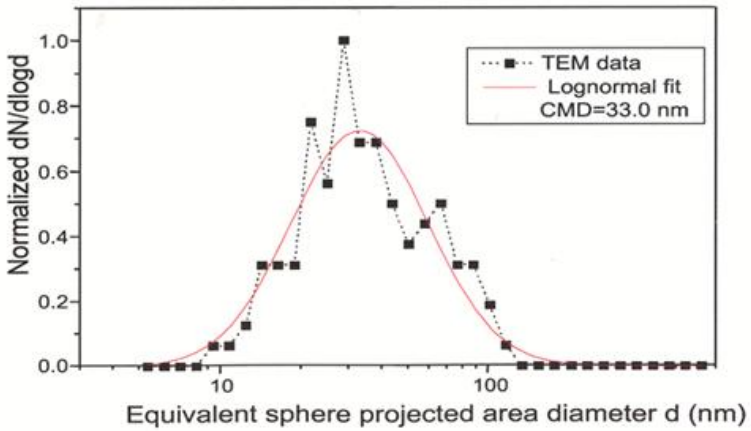
39% Mn_2O_3 (III)

Solubility:
1-1.5% per day
(at pH 7.4)

SMPS



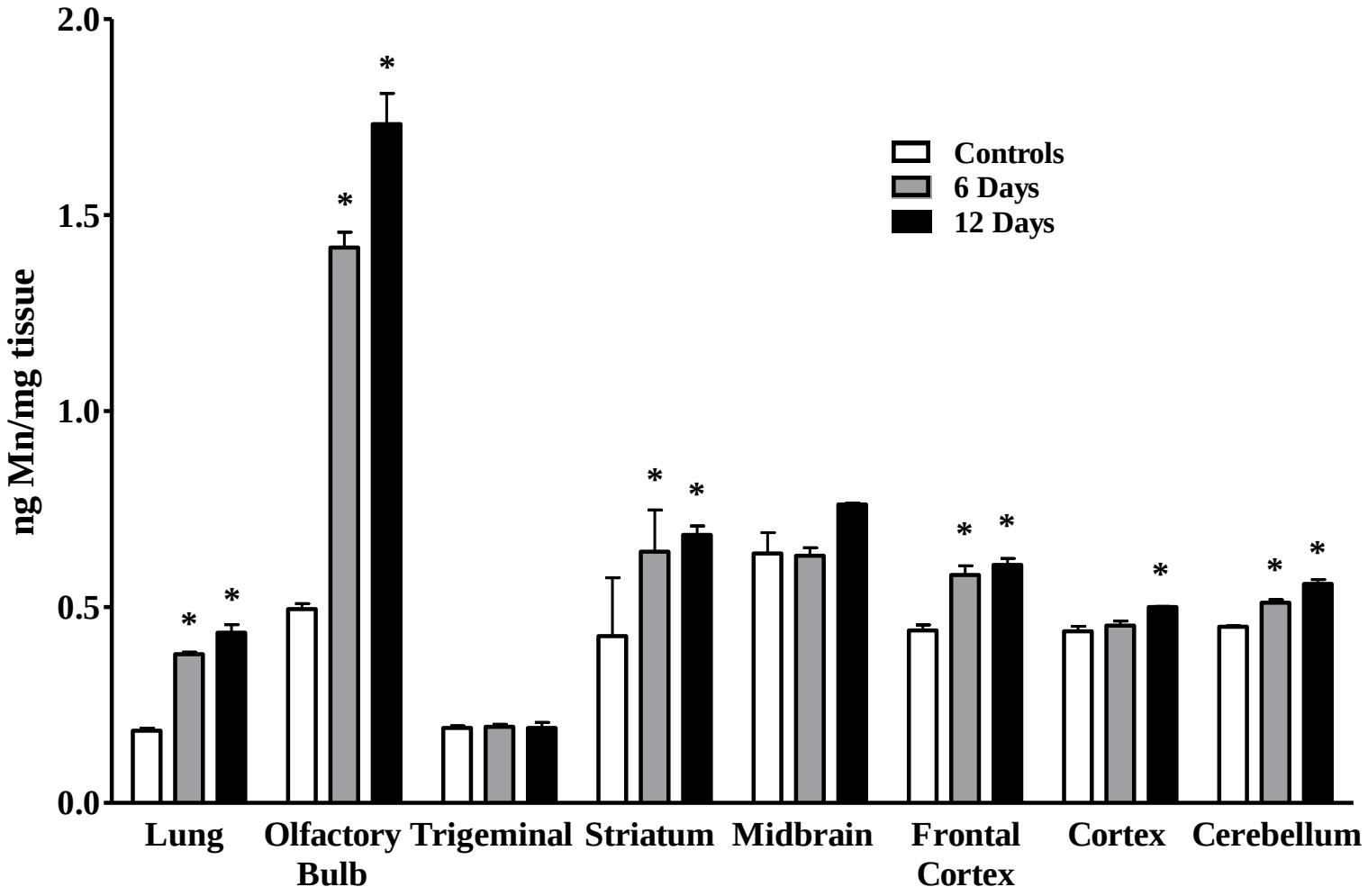
TEM - size distribution



Elder et al., 2006

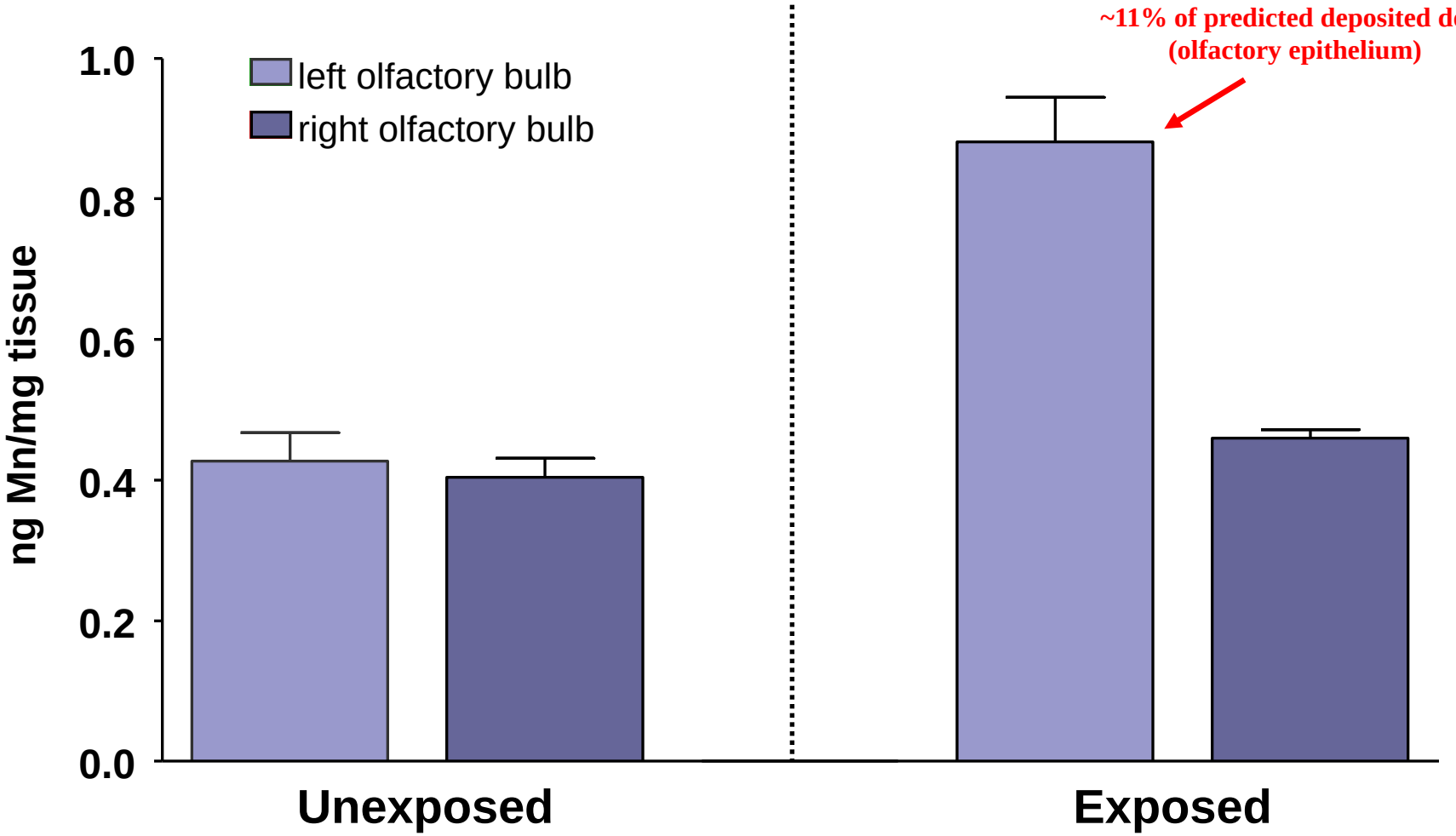
Accumulation of Mn in the CNS Following Exposure to Ultrafine Mn Oxide Particles

(~500 µg/m^3; 18 x 10^6/cm^3)



Elder et al., 2006

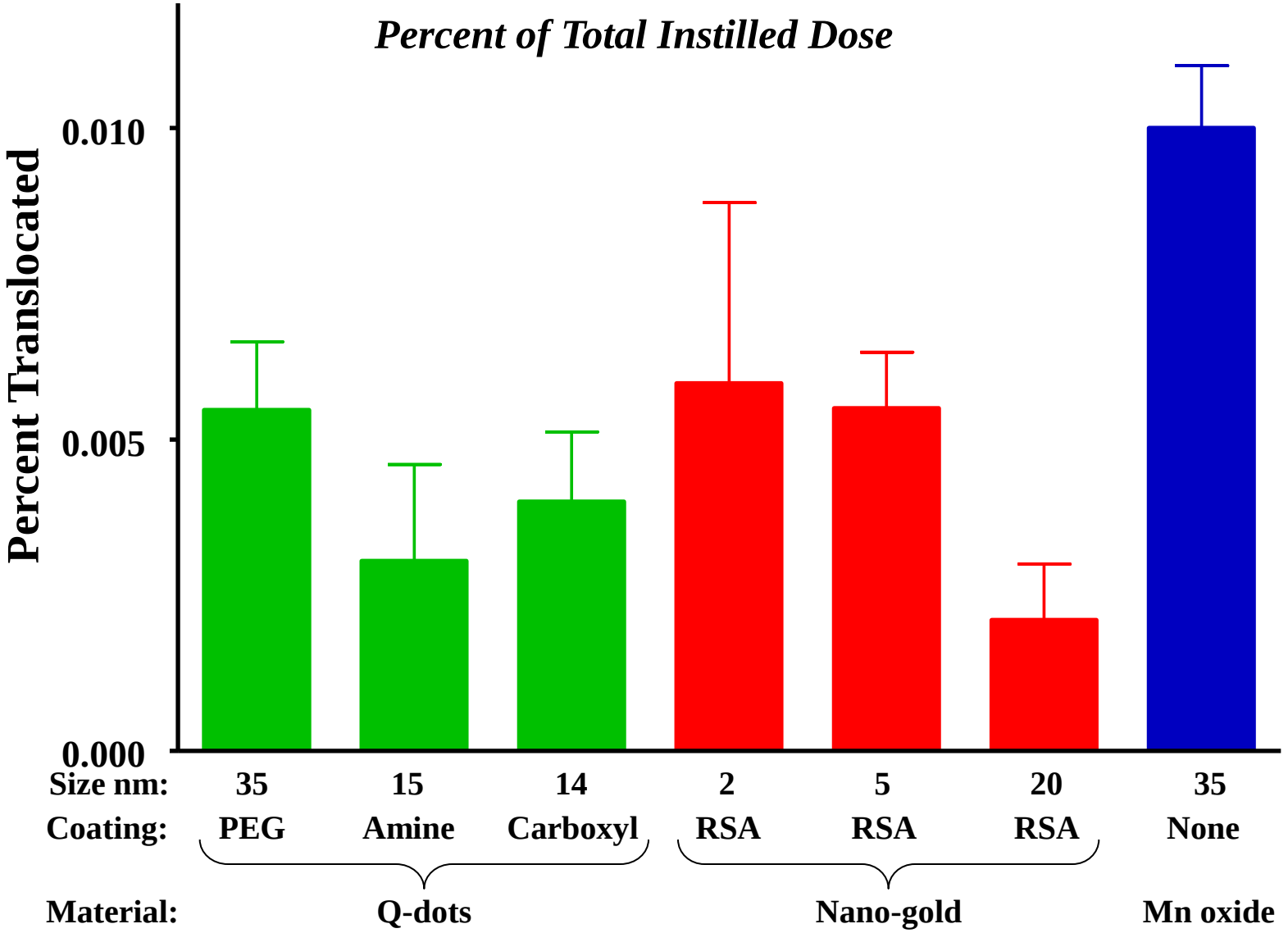
Accumulation of Mn Oxide UFPs in Olfactory Bulb after Aerosol Inhalation with One Naris Occluded



from: Elder et al., 2006

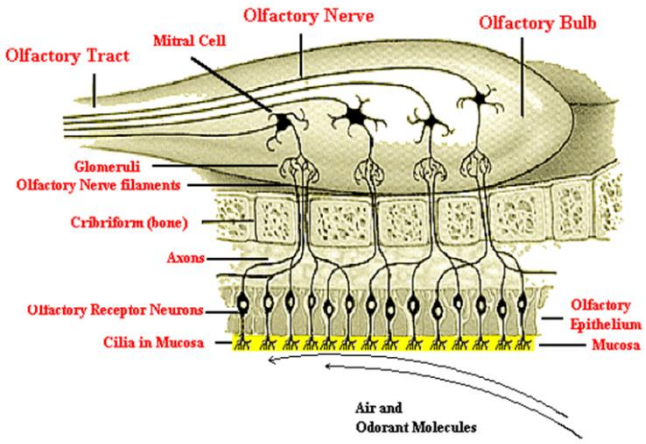
Nanoparticle Translocation to Olfactory Bulb 24 hrs After Intranasal Instillation

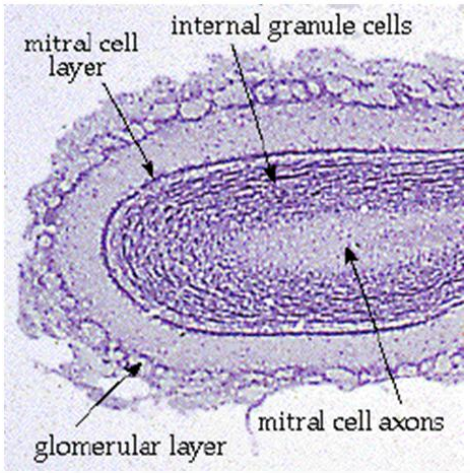
Percent of Total Instilled Dose

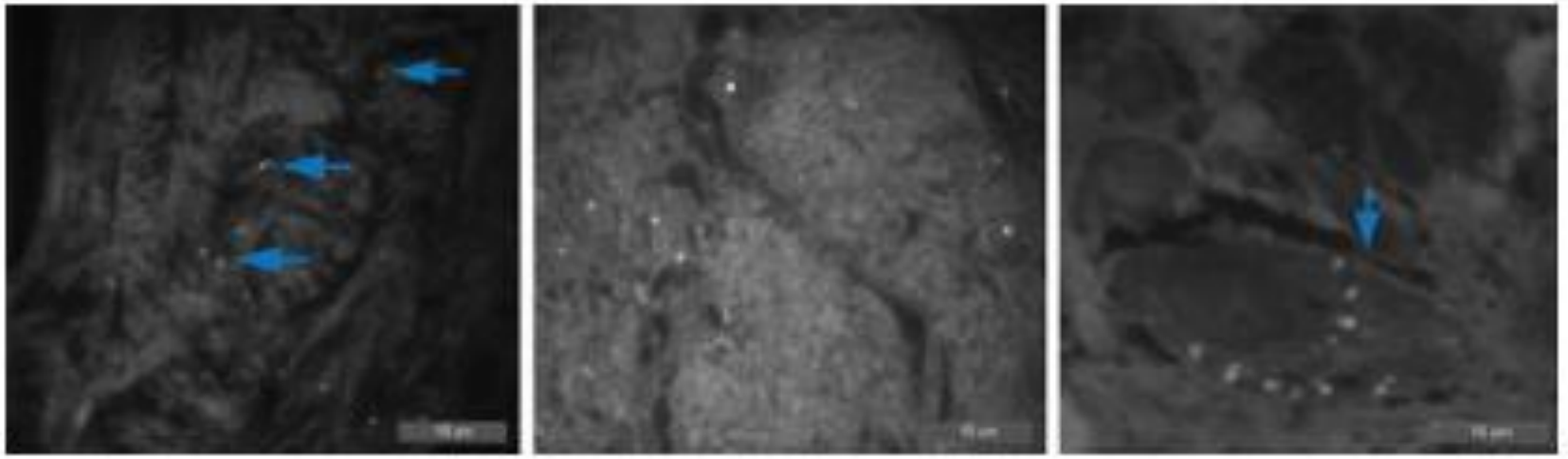


Oberdörster et al., 2009

Accumulation of Quantum Dots in Olfactory Tissue Following Nose-Only Inhalation Exposure







olfactory nerve layer

glomerular layer

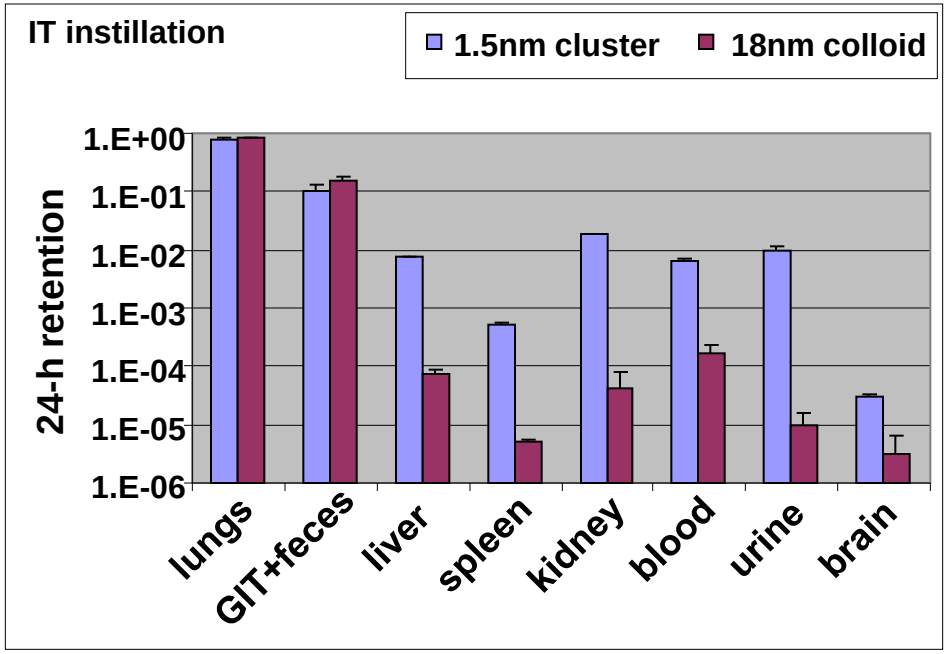
CdSe-ZnS semiconductor nanocrystals, which have characteristic fluorescence – when intact – depending on the particle size

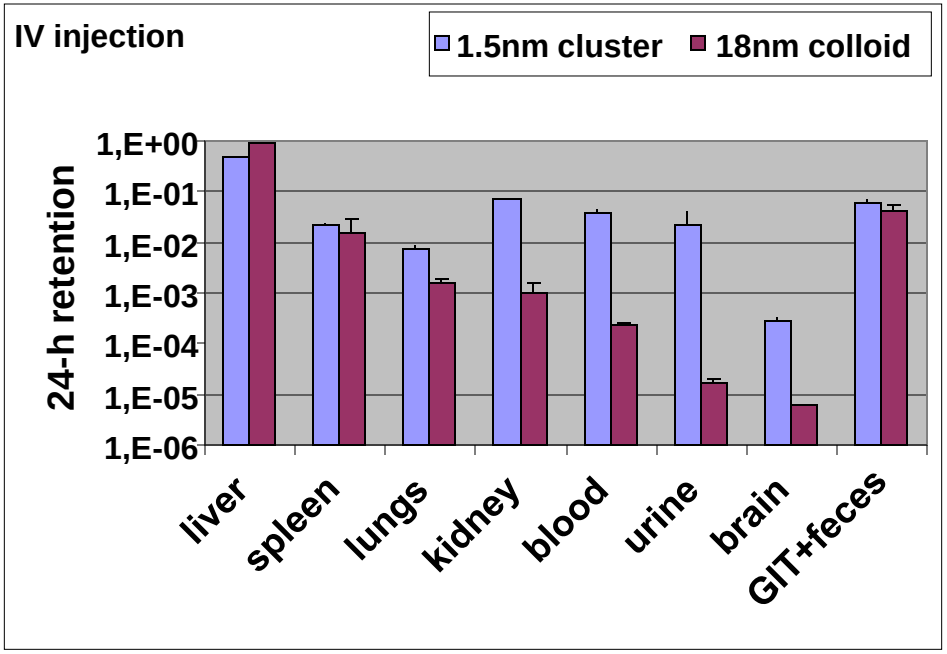
from Hopkins et al., 2014

Translocation of gold nanoparticles: Effect of particle size

Intratracheal instillation or intravenous injection of 1-10 µg ^{198}Au particles in rats

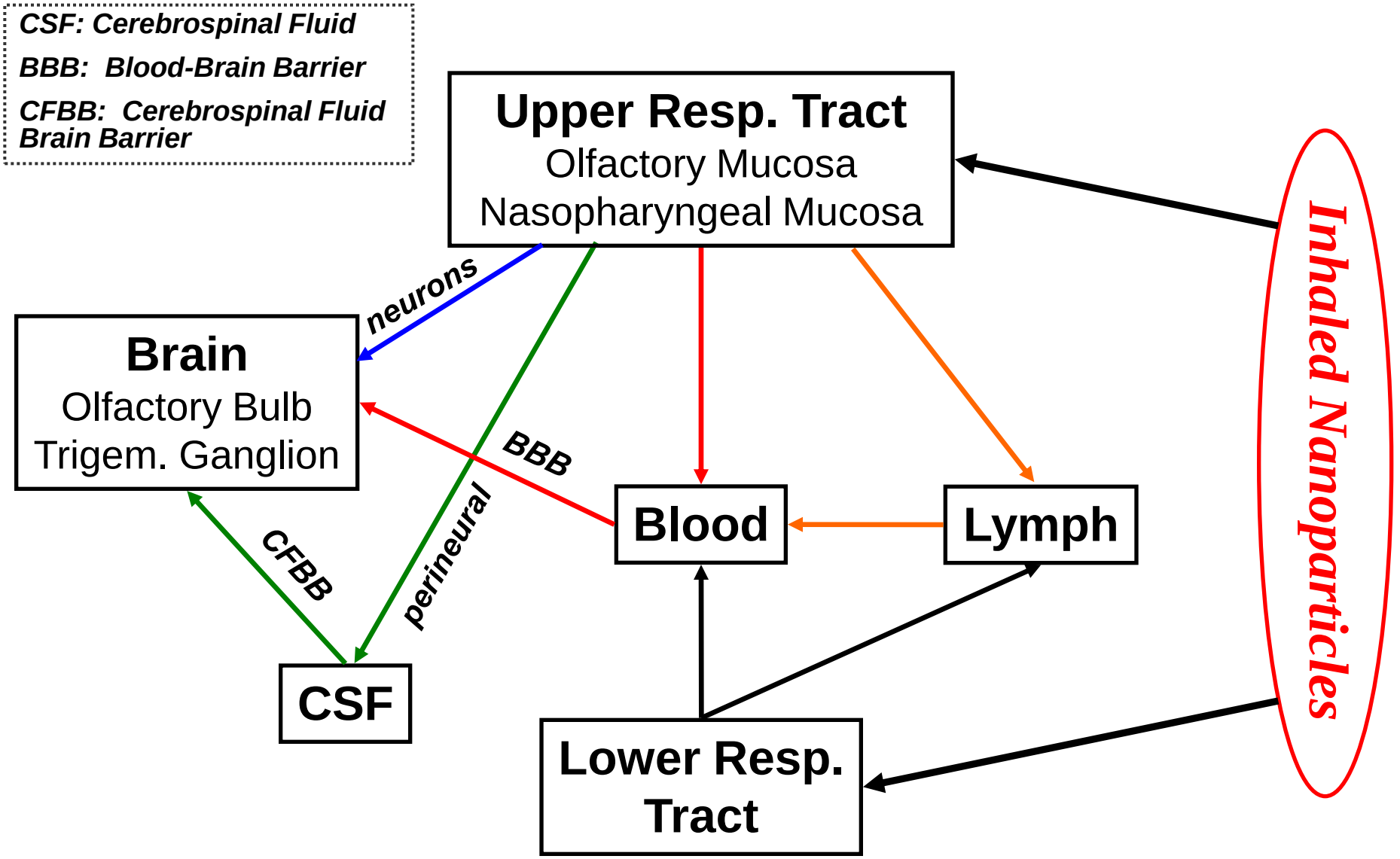
Mass fractions of gold nanoparticles in different organs after 24 h





Semmler-Behnke et al., 2008

POTENTIAL TRANSLOCATION PATHWAYS FOR NANOPARTICLES



from Oberdörster et al., 2008

Particle Properties that May Impact Their Transport to and Effects in the CNS

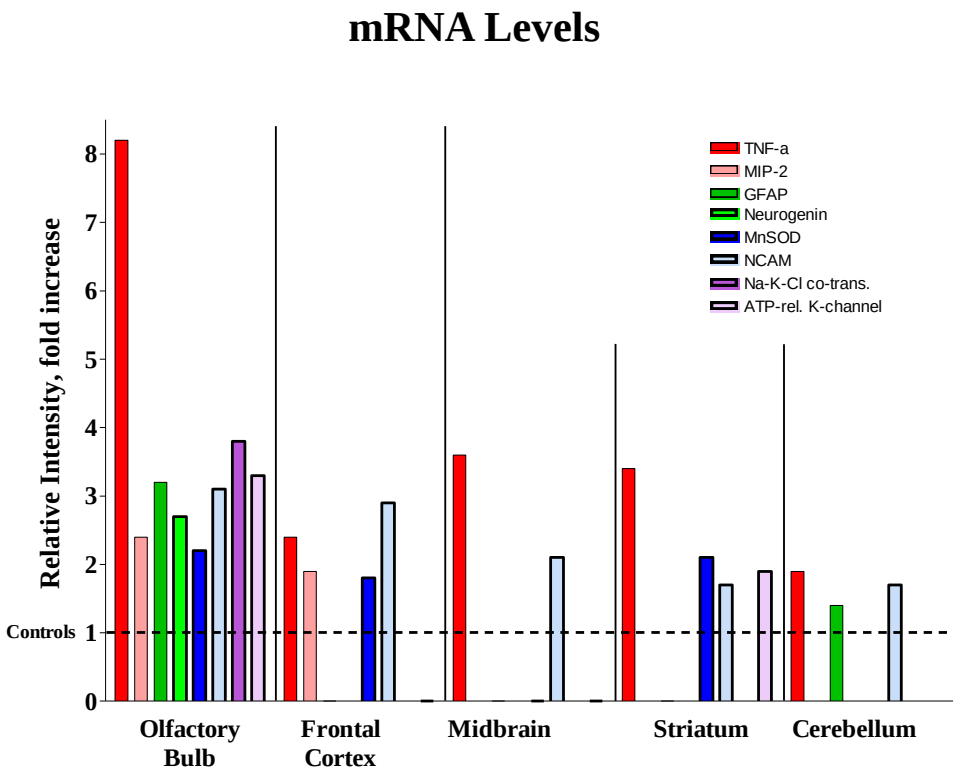
- Dose and dose rate
- Chronicity of exposure
- Particle size distribution and agglomeration state in air and after deposition in respiratory tract
- In vivo dissolution (extracellular >> intracellular ?)
- Particle surface reactivity

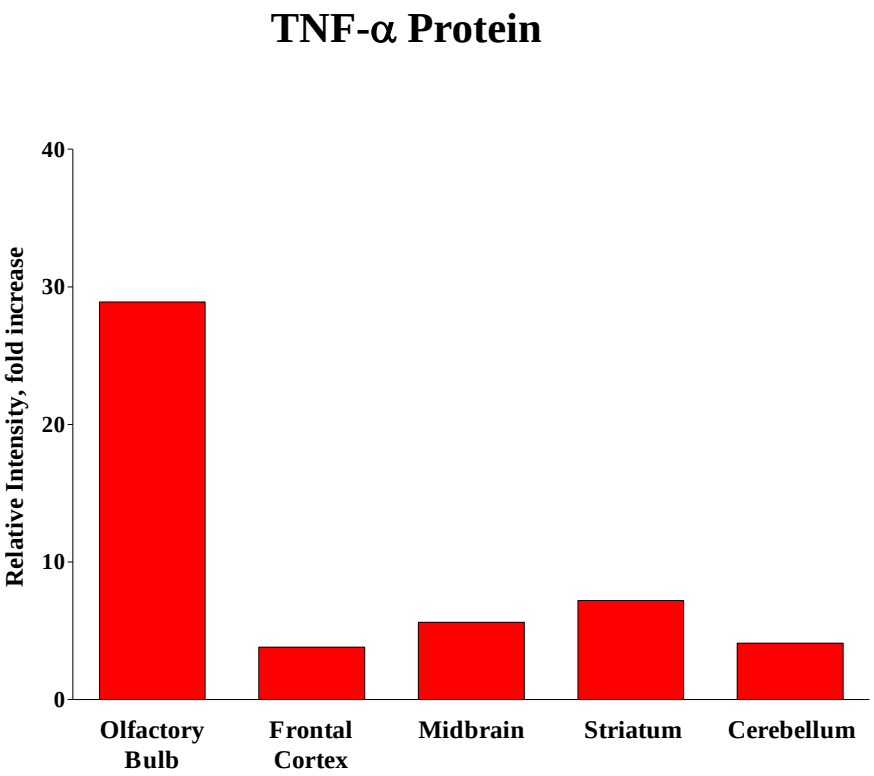
* Health of the barrier epithelium

Outline of Talk

- Mechanisms and pathways of **particulate transport**
- **Consequences of particulate accumulation** in the CNS

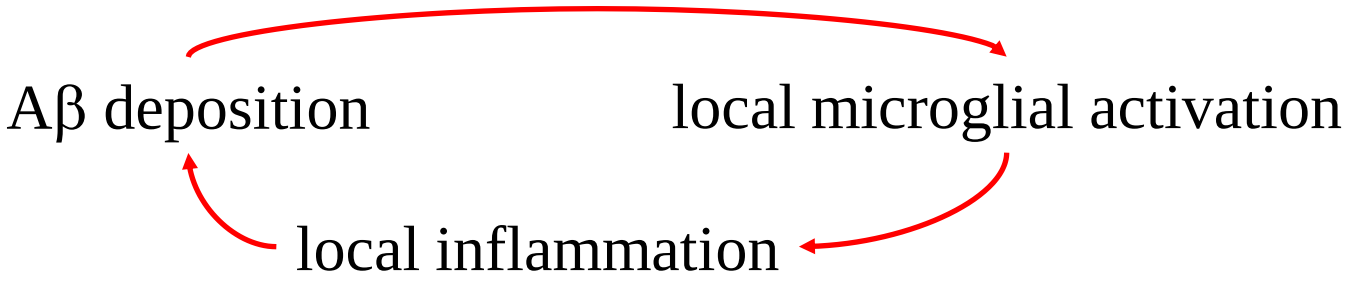
Inflammation in the Brain Regions where Mn Signal was Found





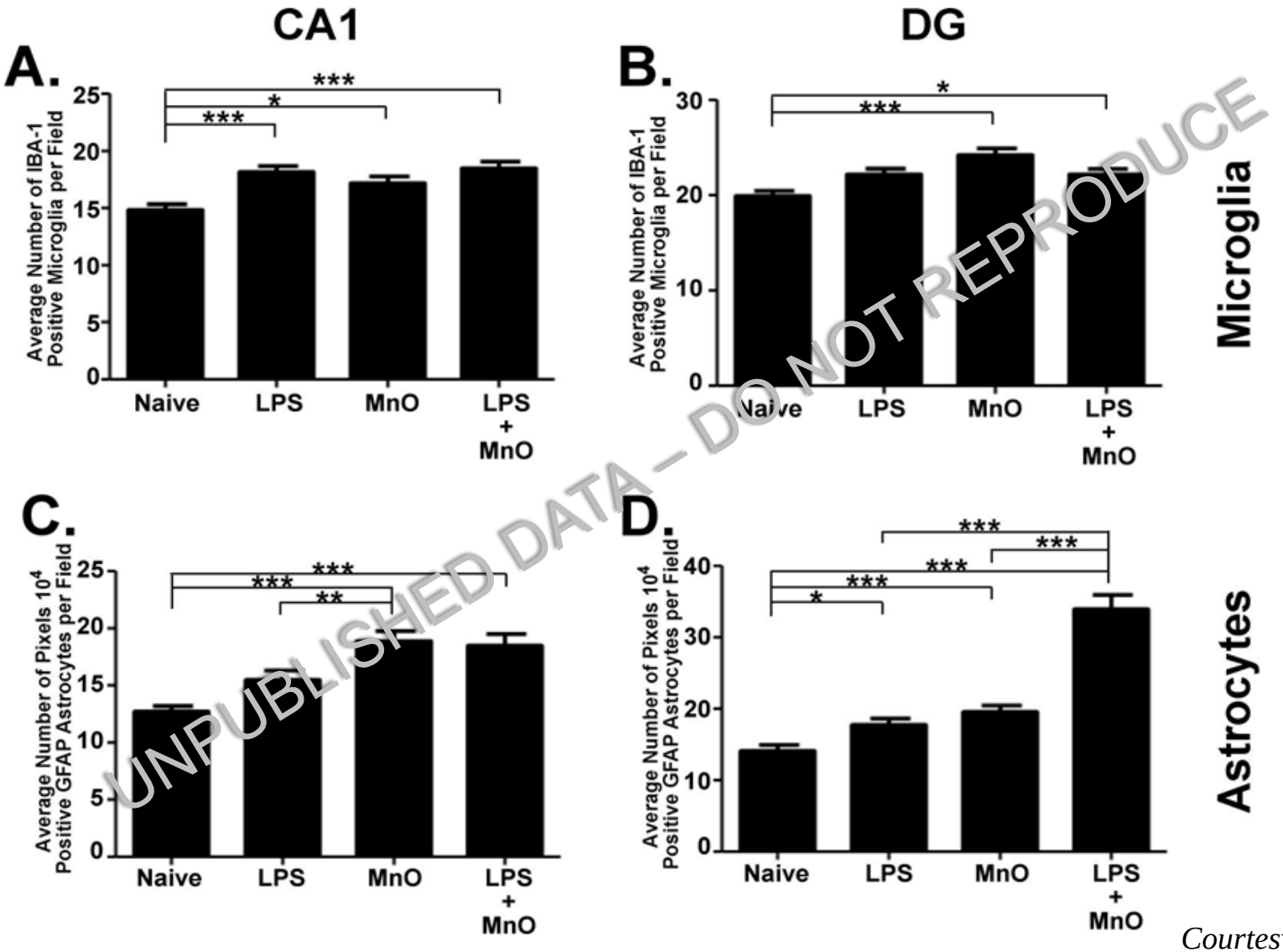
from: Elder et al., 2006

Inflammation to Neurodegeneration?



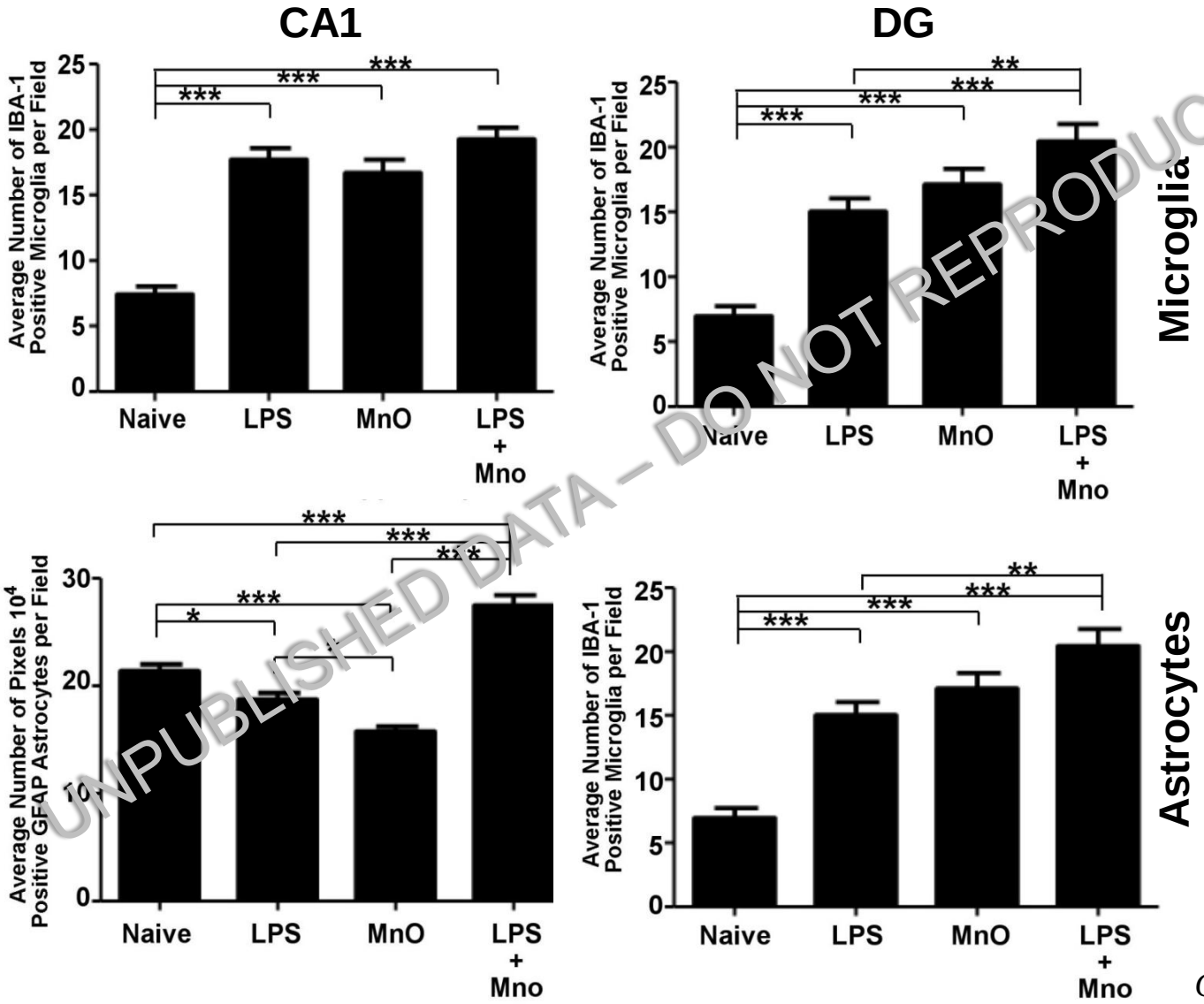
- Acute inflammation (serum TNFα) associated with a 2-fold faster rate of cognitive decline in an Alzheimer's cohort (Holmes et al., 2009).
- Significant association between 'pro-inflammatory' TLR4 SNPs and AD (Balistreri et al., 2008, 2009; Minoretti et al., 2006).
- Inhibition of TNF signaling after intraperitoneal LPS injections significantly reduced Aβ deposition in 3xTg-AD mice (McAlpine et al., 2009).

Enhanced Glial Cell Activation in 3xTg-AD Mouse Hippocampus following Mn Oxide NP +/- LPS Exposure



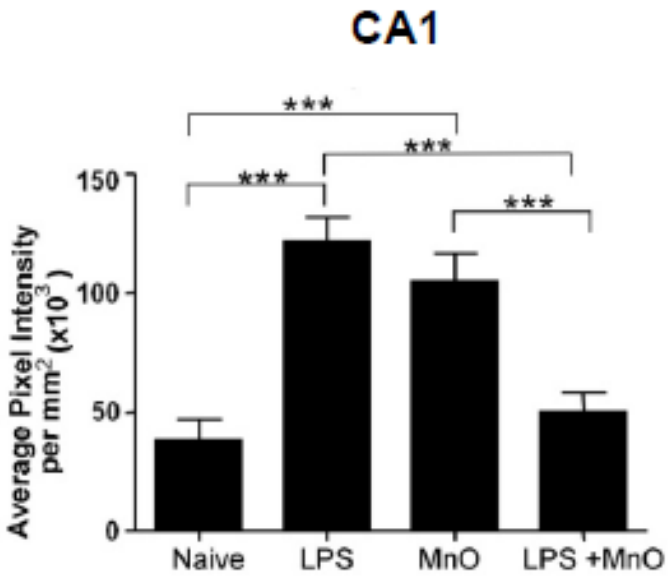
Courtesy of Dr. W. Bowers

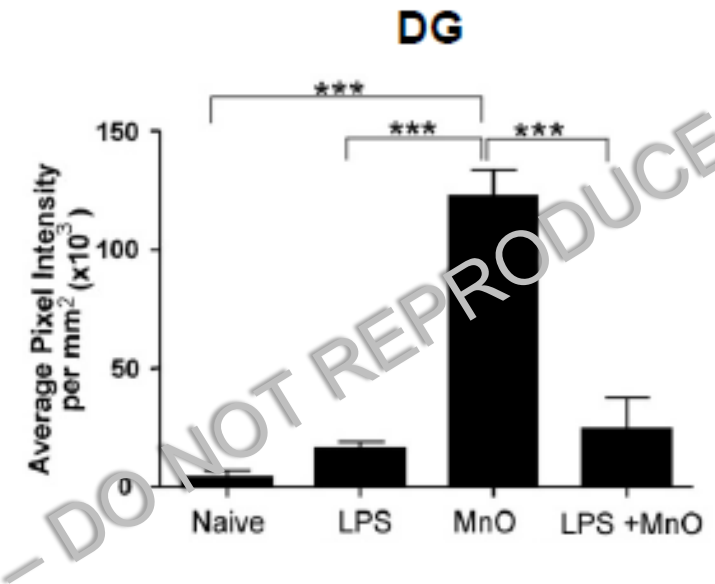
Persistent Glial Cell Activation in 3xTg-AD Mouse Hippocampus: 2 months Post-Exposure



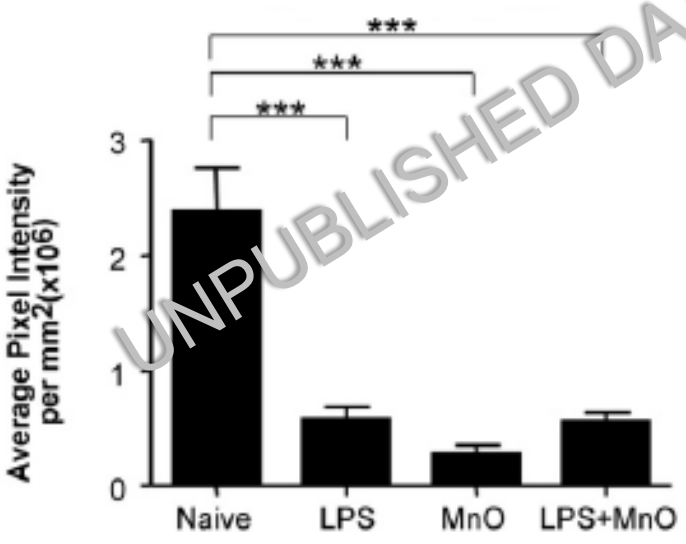
Courtesy of Dr. W. Bowers

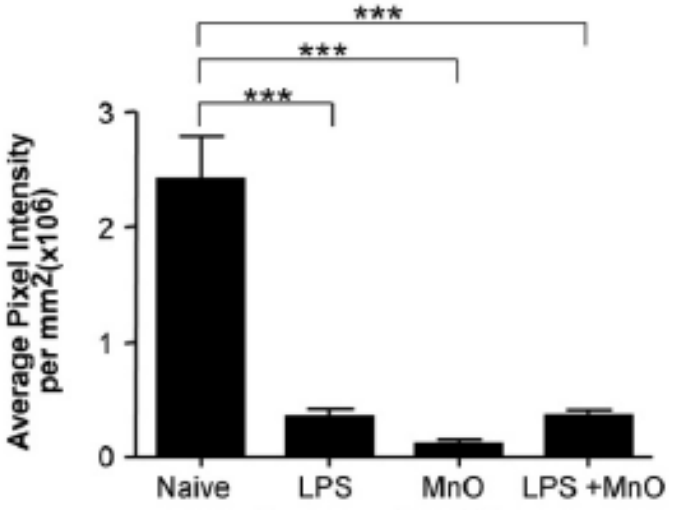
Persistent Glial Cell Activation in 3xTg-AD Mouse Hippocampus: 2 months Post-Exposure





Aβ42





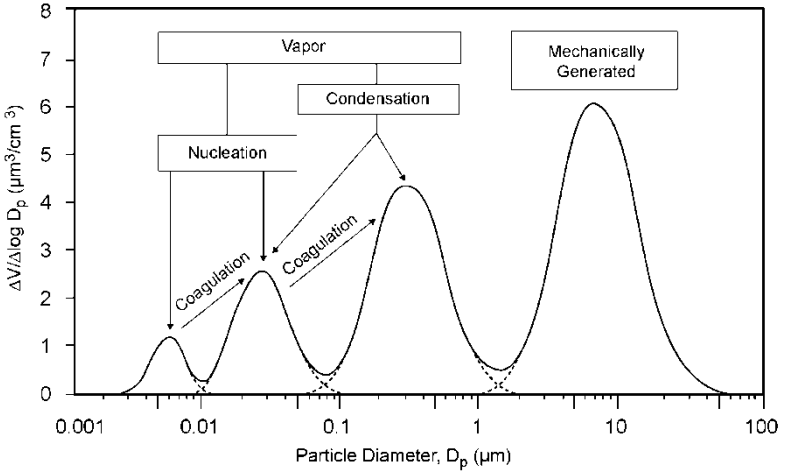
synaptophysin

Dr. W. Bowers

Can Air Pollution Adversely Affect Brain Health?

Air Pollution:

- Mixture of particulates and gas-phase components
- Is transported over long distances and undergoes atmospheric aging
- Significant temporal and spatial heterogeneity



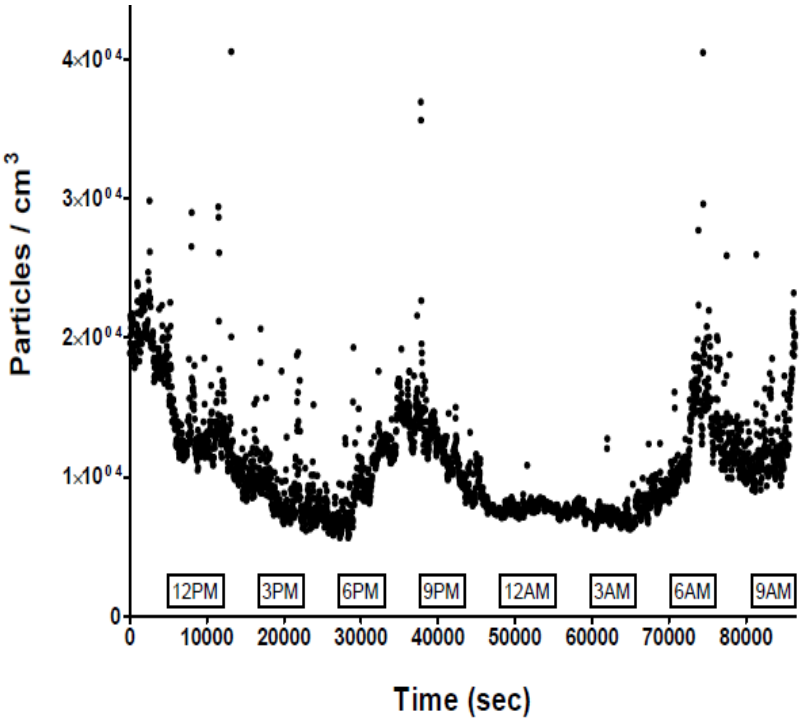
Are There Adverse CNS Effects Related to Particulate Exposure?

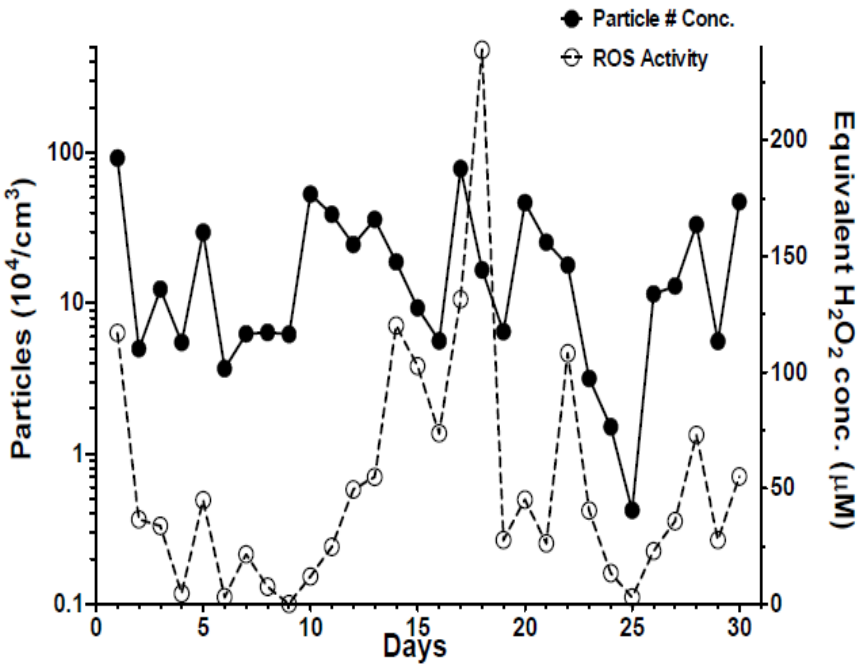
- Increased brain NF-κB activity and IL-1α levels in mice exposed to concentrated traffic-related particles (diam. <180 nm) (Campbell et al., 2005).
- High brain expression of COX-2, β-amyloid accumulation, DNA damage, AD-like pathology in people and dogs living in Mexico City (Calderón-Garcidueñas et al., 2003, 2004).
- Changes in cognition (Calderón-Garcidueñas et al., 2008, 2011) and decreases in measures of verbal and nonverbal intelligence and memory in children (Suglia et al., 2008)
- Neonatal exposures in mice to concentrated ambient UFP leads to persistent microglial activation and ventriculomegaly (Allen et al., 2014).
- Subchronic exposure of mice to $PM_{2.5}$ led to depression-like symptoms and impairments in spatial learning and memory (Fonken et al., 2012).

Growing Epidemiological Evidence Regarding Adverse CNS Effects of Air Pollution

- Positive association between higher levels of $PM_{2.5}$ exposure and time to 1st hospitalization for **AD** (HR, 1.15; 95% CI: 1.11-1.19 per 5 μg/m^3 increase annual $PM_{2.5}$) and **PD** (HR 1.08; 95% CI: 1.04-1.12) (9.8 million Medicare enrollees, NE US; Kioumourtzoglou et al., 2016)
- Highest tertile of PM_{10} (≥49.23 μg/m^3) or ozone (≥21.56 ppb) exposure is associated with an increase in **AD** (OR 4.17; 95% CI: 2.31-7.54) and **vascular dementia** risk (Wu et al., 2015)
- Men and women 50 years and older living in areas with annual $PM_{2.5}$ concentrations that exceed EPA standards (12 μg/m^3) tested worse on **cognitive function** scores (β=0.26, 95% CI: -0.47, -0.05), indicating harmful effects to adult cognition (Ailshire and Crimmins, 2014).
- US women age 70-81 years old: a 10 μg/m^3 increase in long term PM_{10} or $PM_{2.5}$ exposure corresponded to a decline in **global cognitive score** associated with aging 2 years (Weuve et al,, 2012).

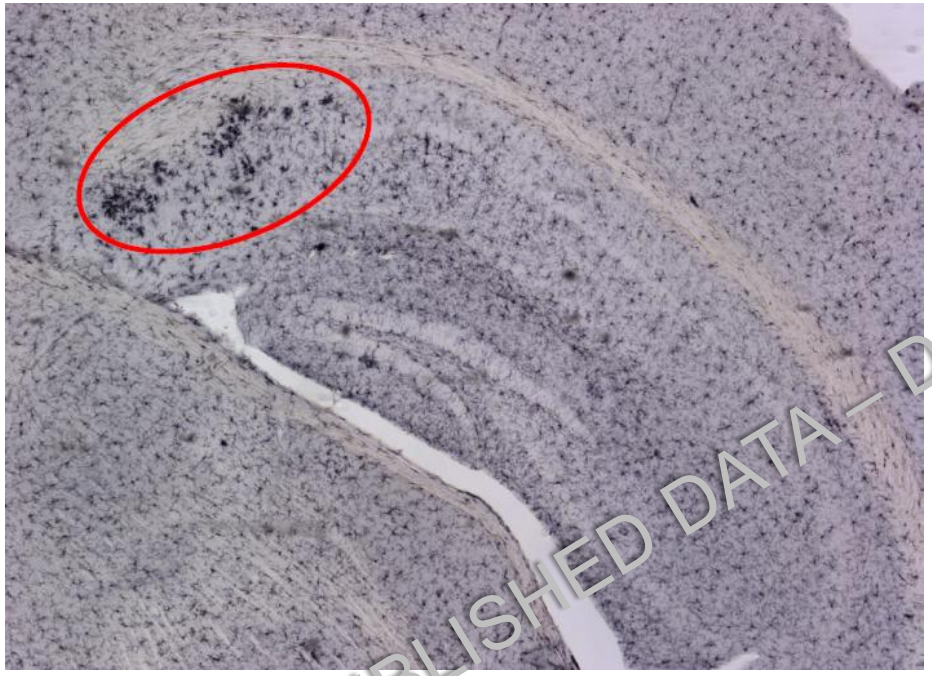
HUCAPS (Gupta et al., 2004) Aerosol Output: UFP Number Concentrations and Inherent Oxidant Activity



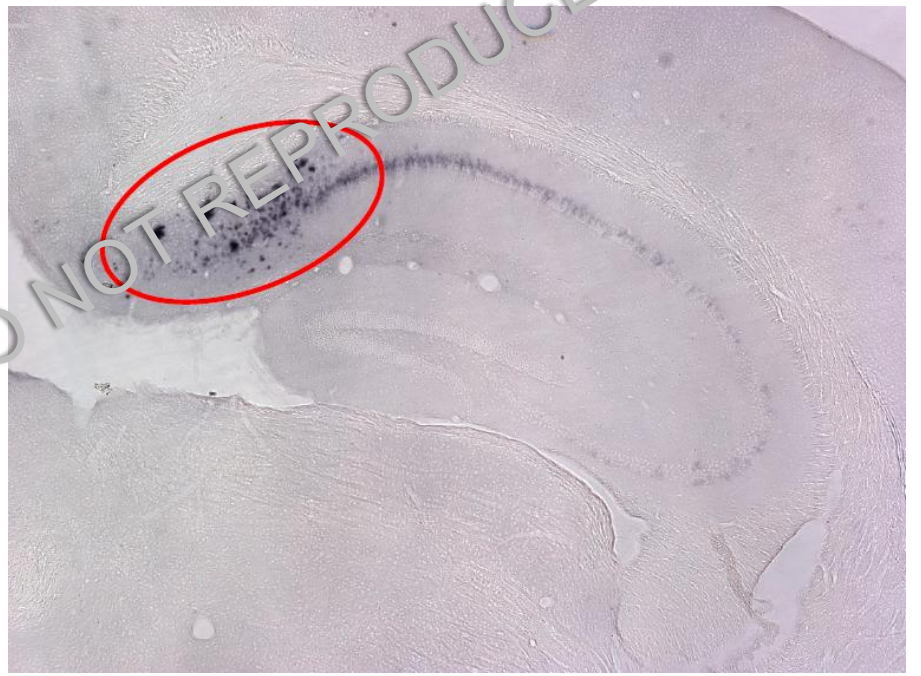


Effects of HUCAPS Exposure on Microglial Activation and Amyloid β Levels

Iba-1



6E10



Filtered air-exposed – not observed in HUCAPS-exposed mice

Herr, unpublished data

Conclusions

- The translocation of particles from the respiratory tract to the CNS following a single exposure is small but statistically significant
- Particles can be transported via several pathways, although the relative importance of each and the impact of particle properties on transport are not well-understood
- Transport of particles and/or their bound constituents into the CNS could contribute to the progression of pathology
- Little is known thus far about the nature of any vulnerable populations or susceptibilities

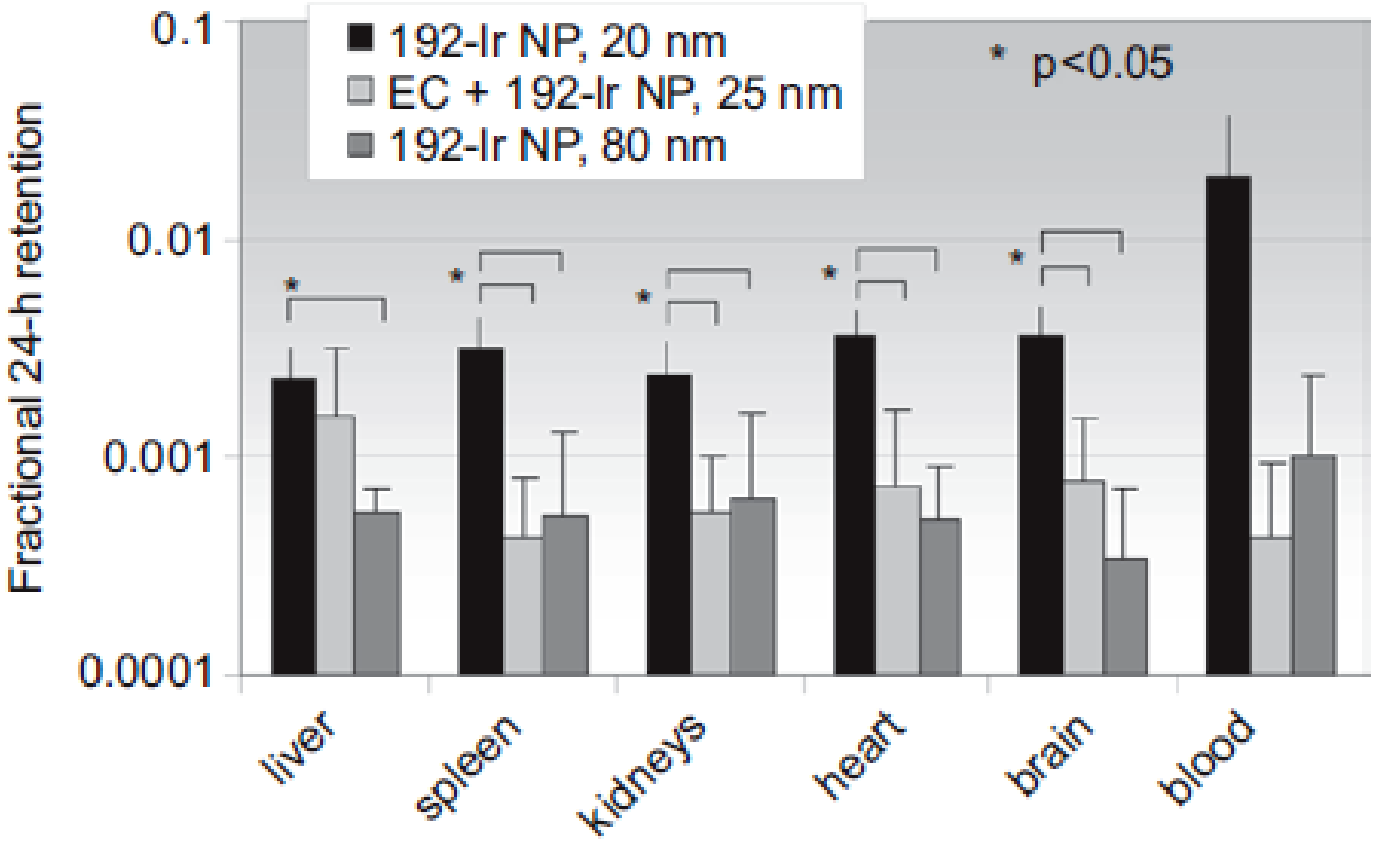
Acknowledgements

Brittany Baisch, PhD
Karen Bentley, MS
David Chalupa, MS
Nancy Corson
Bob Gelein
Alex Lunts
Günter Oberdörster, DVM, PhD
Pamela Wade-Mercer
Andrea Kennell

Donald Baer, PhD (PNNL)
Mark Engelhard, PhD (PNNL)
Hong Yang, PhD (Univ. Illinois)
Miao Shi, PhD (BASF)
David Pui, PhD (Univ. MN)
Jing Wang, PhD (ETH)
Sara Brenner, MD, MPH (SUNY CNSE)

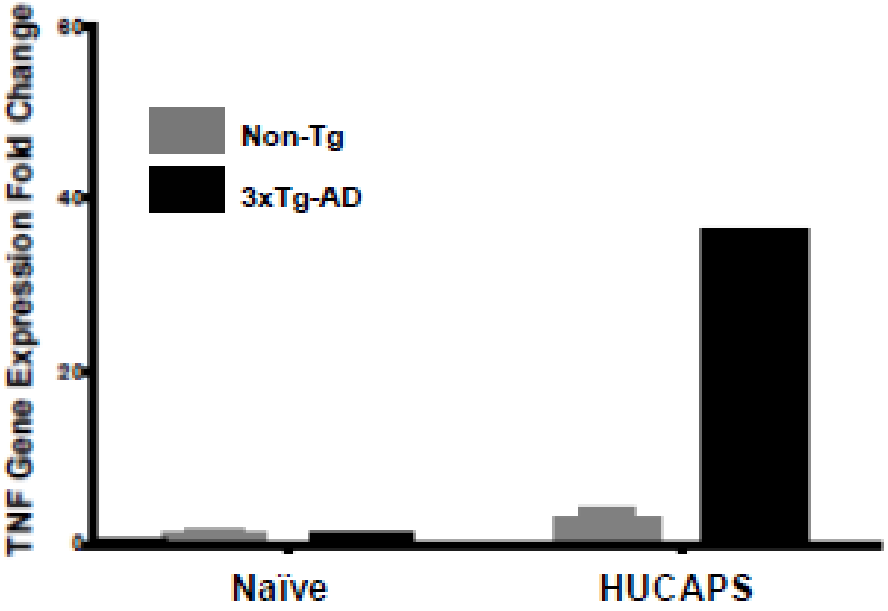
Grant Support:
NIH R01 ES020332
NIEHS Center P30 ES01247
NY State

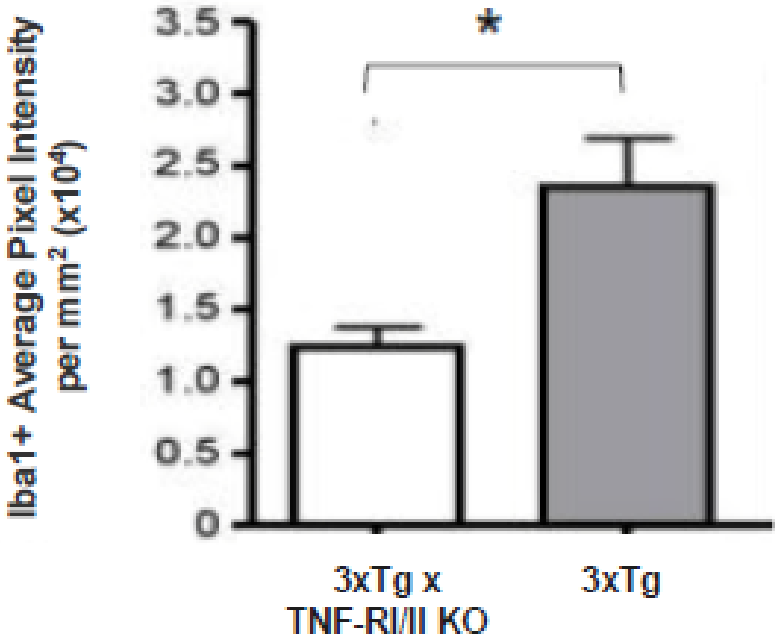
Translocation of inhaled nanoparticles: Fractional retention 24 hrs after exposure



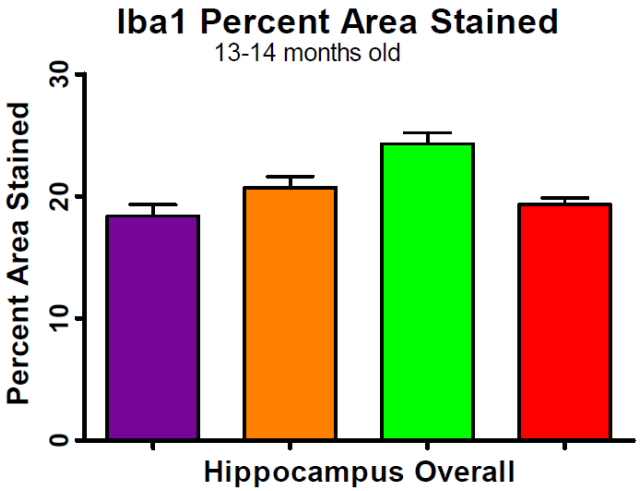
Kreyling et al., 2009

Role of TNF in Response to Inhaled Ambient UFP Aerosols (2 week exposure, 2 month recovery)

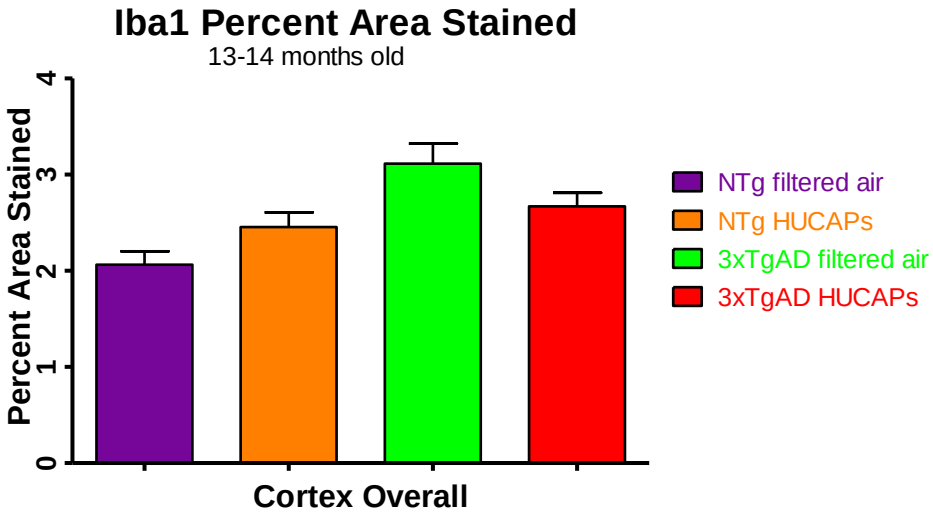




Effects of HUCAPS Exposure on Microglial Activation and Amyloid β Levels

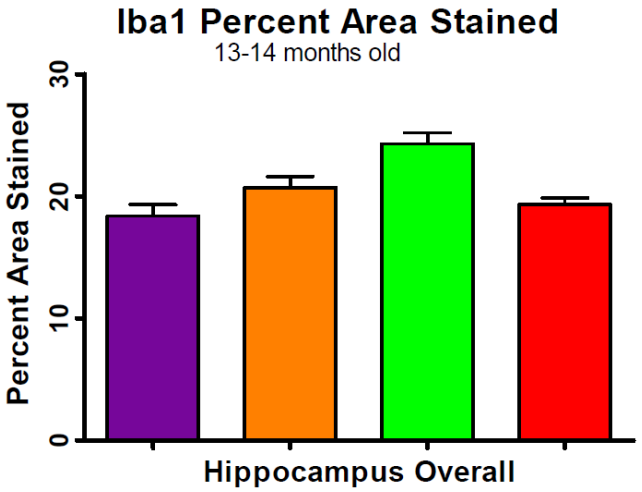


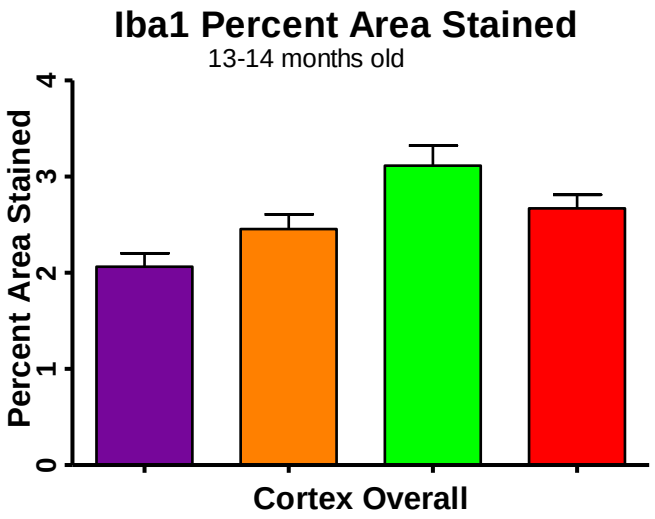
Iba-1, microglia marker (does not indicate activation status)



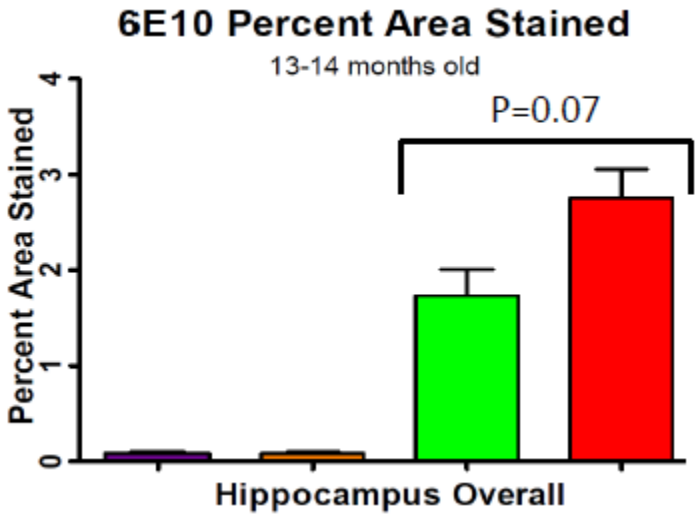
Herr, unpublished data

Effects of HUCAPS Exposure on Microglial Activation and Amyloid β Levels





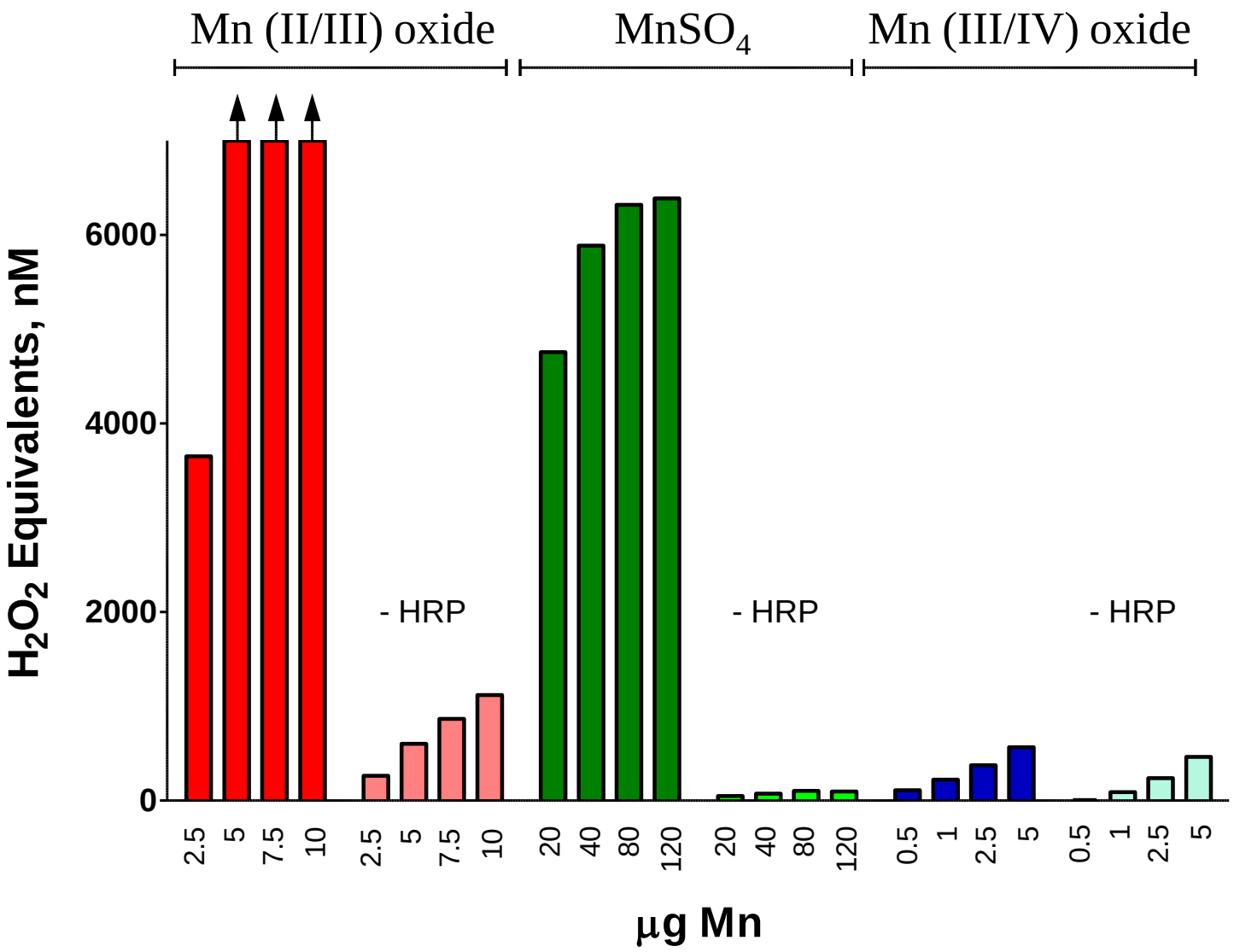
NTg filtered air
NTg HUCAPs
3xTgAD filtered air
3xTgAD HUCAPs



6E10, binds to APP and to monomeric and fibrillar Aβ

Herr, unpublished data

Inherent Oxidant Capacity of Manganese Compounds



Effects of HUCAPS Exposure on Microglial Activation and Amyloid β Levels