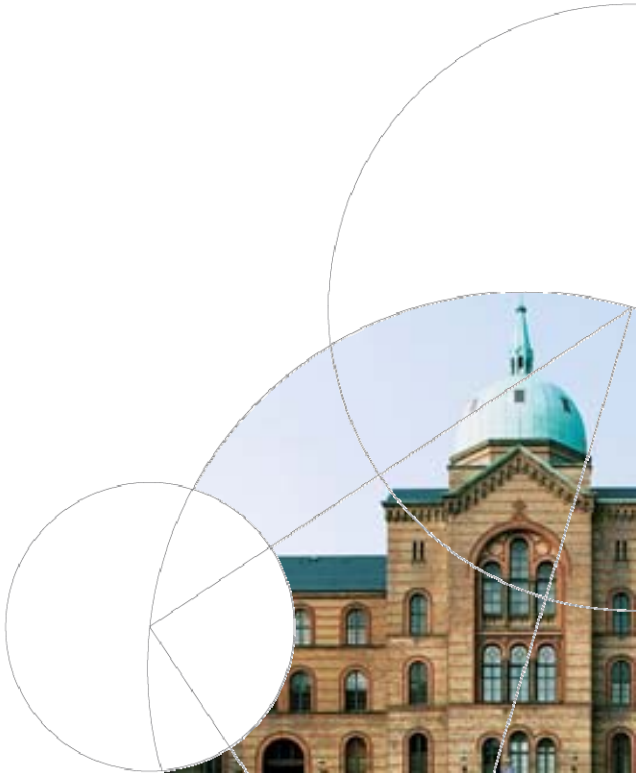
Faculty of Health Sciences

In vivo in vitro associations of oxidative stress-induced genotoxicity of nanomaterials

Steffen Loft, Dept.of Environmental Health, University of Copenhagen, Denmark

HESI-ILSI Webinar February 9, 2009

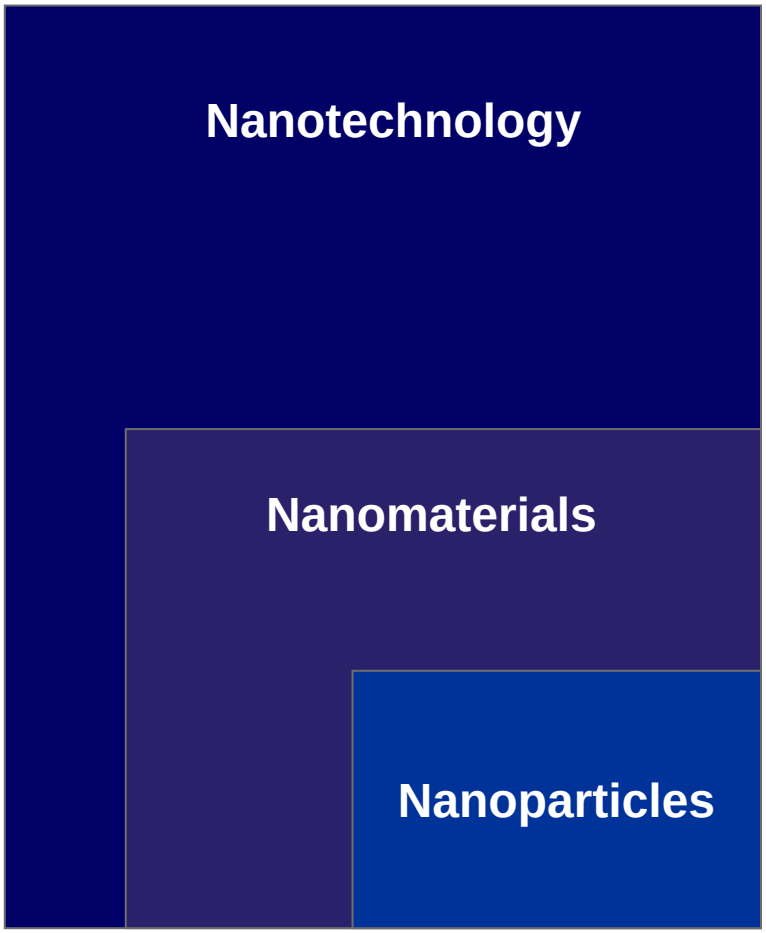


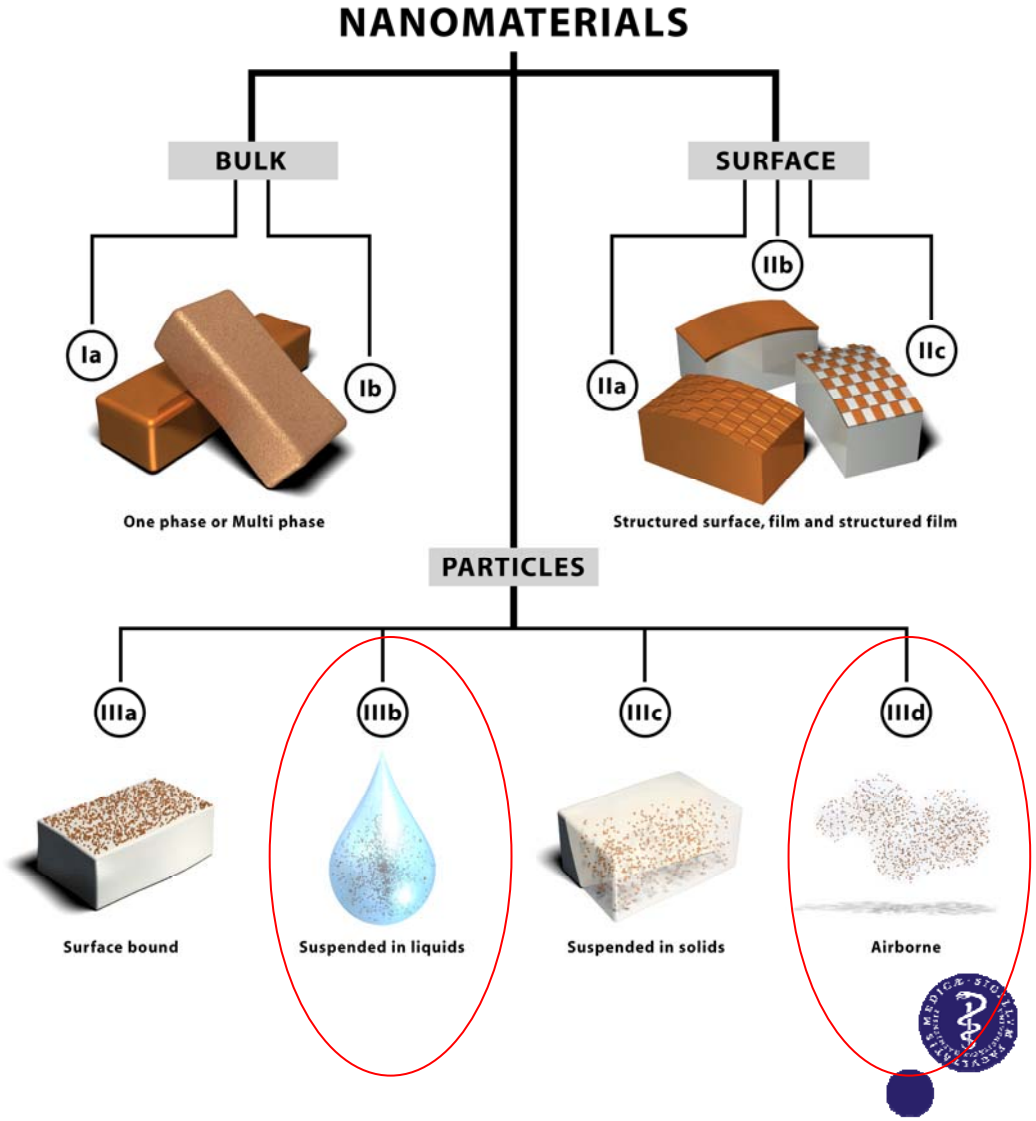
ecnis

AIRPOLIFE

Danish Agency for Science Technology and Innovation
Ministry of Science Technology and Innovation

Airborne or suspended nanoparticles are considered to pose a potential hazard



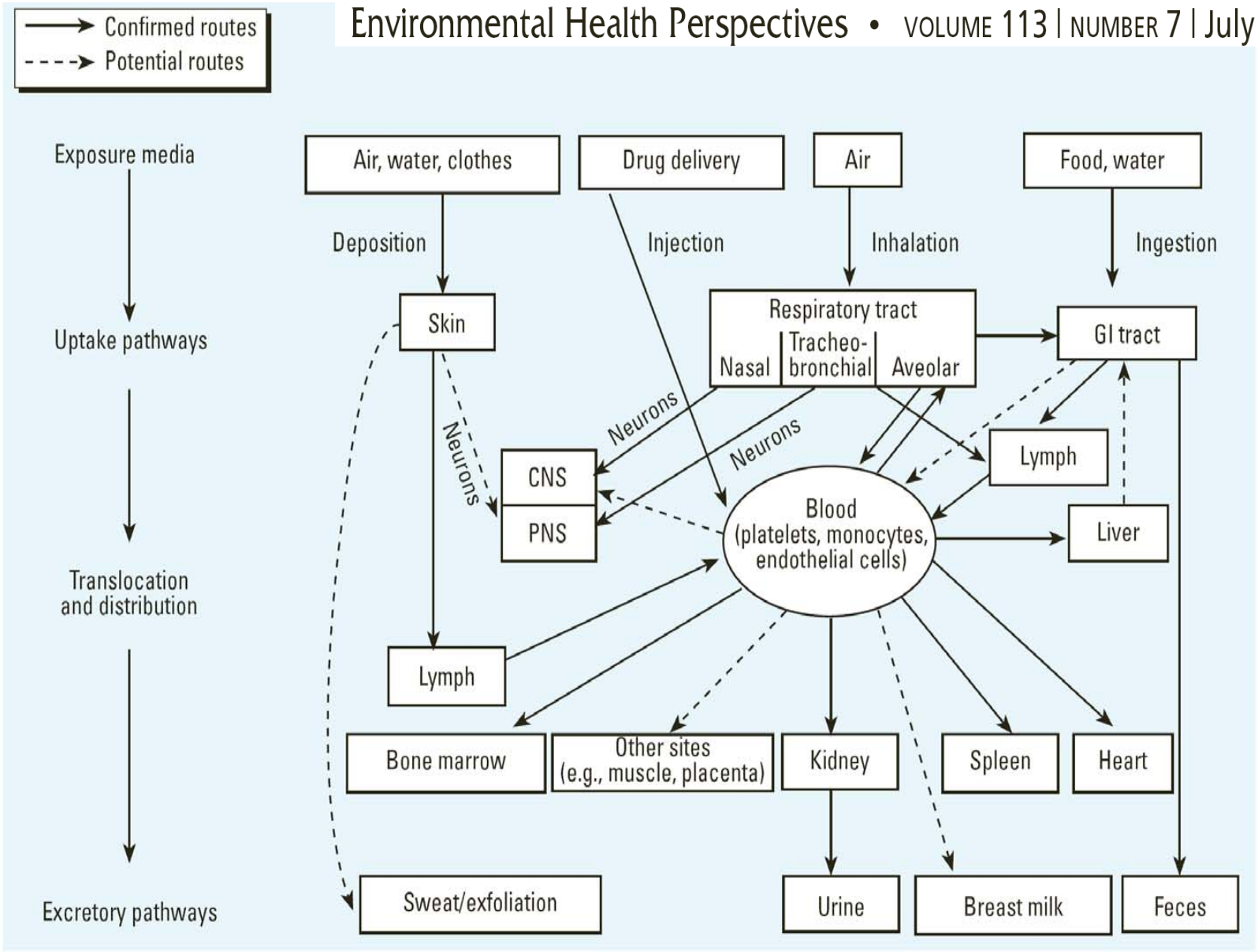


Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles

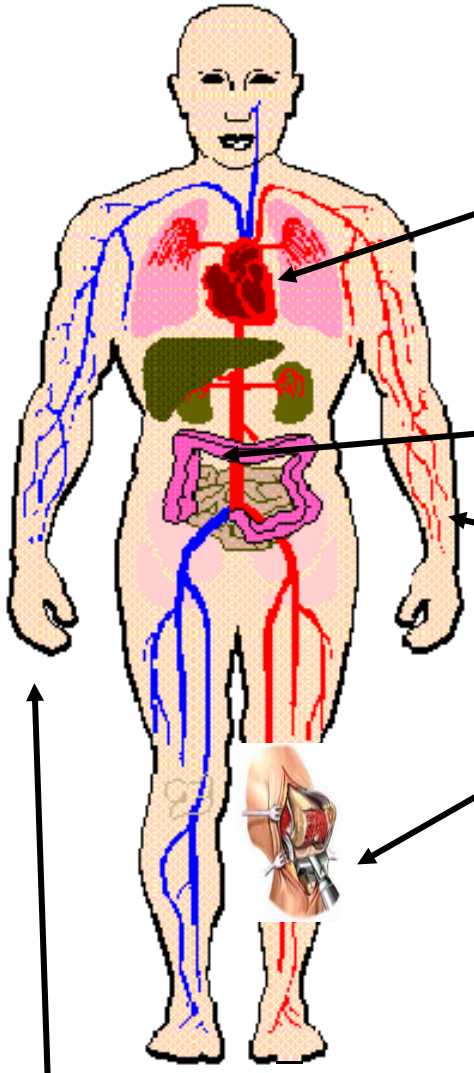
Biokinetics of NP

Günter Oberdörster,[1] Eva Oberdörster,[2] and Jan Oberdörster[3]

Environmental Health Perspectives • VOLUME 113 | NUMBER 7 | July 2005



In vivo genotoxic hazards of nanoparticles



Inhalation (mainly lung)

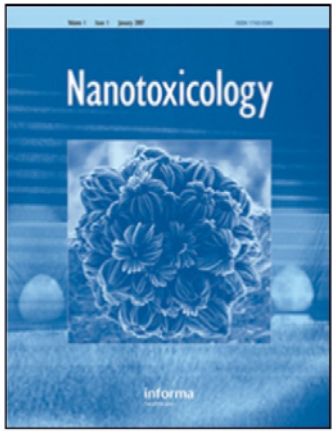
Ingestion (systemic)

Systemic diagnostic and therapeutics

Wear on implants: autoimmune disease

Dermal exposure

In vivo – in vitro correlations of oxidative stress and DNA damage
Lung and liver as targets



Nanotoxicology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t716100760

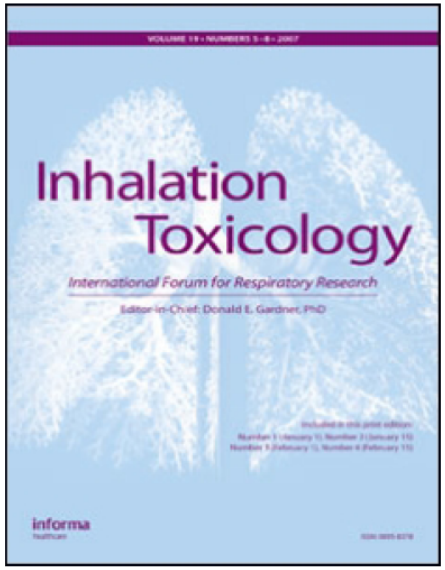
Genotoxicity of engineered nanomaterials: A critical review

Laetitia Gonzalez [a]; Dominique Lison [b]; Micheline Kirsch-Volders [a]
[a] Laboratory of Cell Genetics, Department of Biology, Vrije Universiteit Brussel, Brussels [b] Industrial Toxicology and Occupational Medicine Unit, Université catholique de Louvain, Brussels, Belgium

First Published on: 20 November 2008

Table II *(Continued)*

Np Type	Route of exposure	Animal	Cell Type	Test	Top dose	Concentration/dose	Result	Reference
In vivo studies								
Carbon								
MWCNT (11.3 nm/ 0.7μm)	Intratracheal instillation	Female Wistar rats	AT-II cells	CBMN	Data on inflammation	0.5 and 2 mg/rat-72 h	+ (2 mg/rat)	(Muller et al. 2008 [4]
Iron								
Magnetoliposomes 14 nm?	Endovenous injection	Female Swiss mice	Anucleated polychromatophylic erythrocytes Female Swiss mice	MN	/?	100 μl of $1{,}8 \times 10^{15}$ particles/ml (12, 24, 48 h)	(+) 24 h	(Garcia et al. 2002)[19]
Polaspartic acid coated Fe								
8.5 nm	Endovenous injection	Female Swiss mice	Anucleated polychromatophylic erythrocytes	MN		50 μl of $0{,}6 \times 10^{16}$ particles/ml		(Sadeghiani et al. 2005)[20]
						1 day	+	
						7 days	−	
						15 days	−	
						30 days	−	
						50 μl of $1{,}6 \times 10^{16}$ particles/ml		
						1 day	+	
						7 days	+	
						15 days	−	
						30 days	−	
Titaniumdioxide								
20 nm (hydrophilic and hydrophobic surface)	Intratracheal instillation	Female Wistar rats	Lung parenchyma cells	8-oxo-gua		0,15–1,2 mg/ml 90 days	(+)	(Rehn et al. 2003) [21]



Inhalation Toxicology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713657711

Twenty-Eight-Day Oral Toxicity, Genotoxicity, and Gender-Related Tissue Distribution of Silver Nanoparticles in Sprague-Dawley Rats

Yong Soon Kim [a]; Jin Sik Kim [a]; Hyun Sun Cho [a]; Dae Sik Rha [a]; Jae Min Kim [a]; Jung Duck Park [b]; Byung Sun Choi [b]; Ruth Lim [b]; Hee Kyung Chang [c]; Yong Hyun Chung [d]; Il Hoon Kwon [e]; Jayoung Jeong [e]; Beom Seok Han [e]; Il Je Yu [a]
[a] Korea Environment & Merchandise Testing Institute, Incheon, Korea [b] College of Medicine, Chung-Ang University, Seoul, Korea [c] Deparment of Pathology, Kosin University, Busan, Korea [d] Occupational Safety and Health Research Institute, Daejeon, Korea [e] National Institute of Scientific Investigation, Seoul, Korea

Online Publication Date: 01 April 2008

Silver nanoparticles of 60 nm by daily gavage (10 rats in each group):
- vehicle control (10 ml/kg)
- low-dose group (30 mg/kg),
- middle-dose group (300 mg/kg)
- high-dose group (1000 mg/kg).

After 28 days of exposure no effect on
- micronucleated polychromatic erythrocytes (MN PCEs)
- ratio of polychromatic erythrocytes among total erythrocytes

Cardiovascular Effects of Pulmonary Exposure to Single-Wall Carbon Nanotubes

Zheng Li,[1] Tracy Hulderman,[1] Rebecca Salmen,[1] Rebecca Chapman,[1] Stephen S. Leonard,[2] Shih-Houng Young,[2] Anna Shvedova,[2] Michael I. Luster,[1] and Petia P. Simeonova[1]

[1]Toxicology and Molecular Biology Branch, and [2]Pathology and Physiology Research Branch, Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, West Virginia, USA.

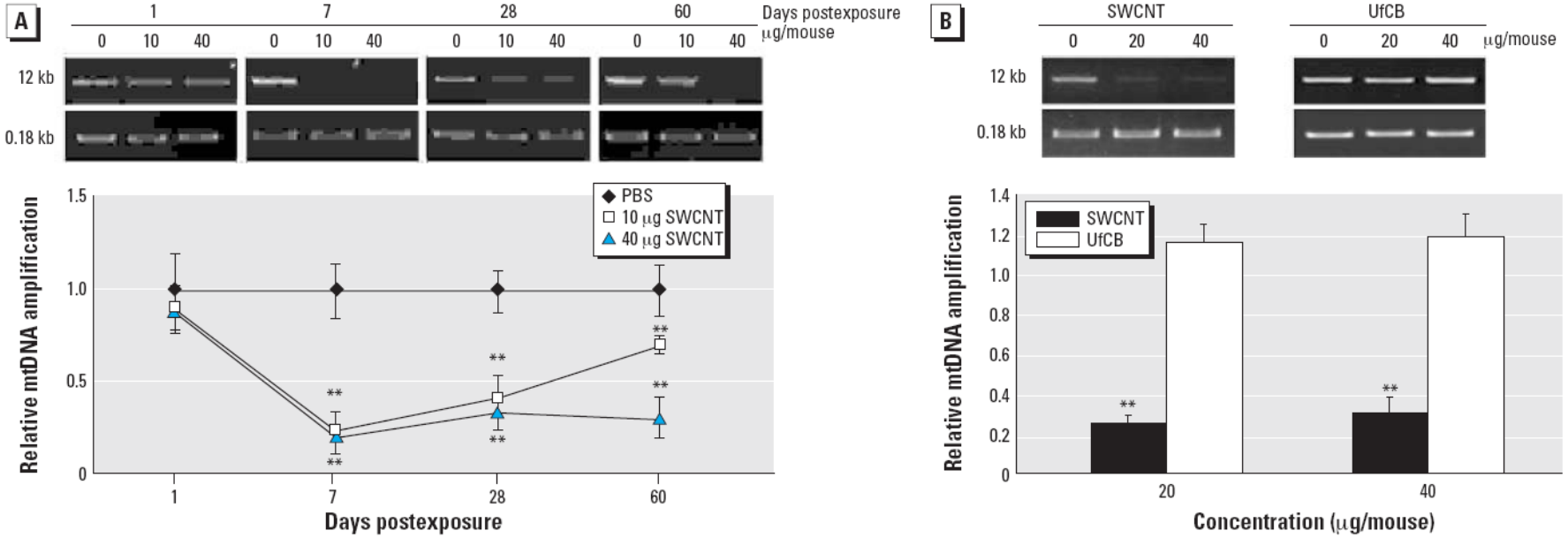
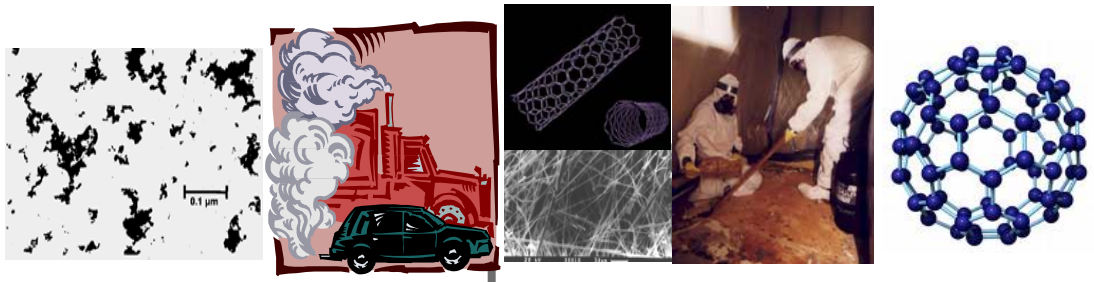
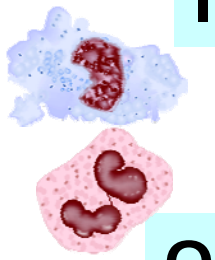


Figure 2. Aortic mtDNA damage in C57BL/6 mice exposed to SWCNTs shown as representative gel images of the long (12 kb) and short fragment (0.18 kb) mtDNA amplification products and quantitative analyses of the mtDNA damage (a reduction in the amplification) presented as a fold difference between each SWCNT-treated group and the vehicle-treated group. (*A*) Mice were treated with SWCNTs (0, 10, or 40 μg) and aortas were collected at 7, 28, and 60 days postexposure. (*B*) Mice were treated with SWCNTs (0, 20, or 40 μg) or UfCBs (0, 20, or 40 μg) and aortas were collected 60 days postexposure. The 12 kb mtDNA expression was normalized to 0.18 kb mtDNA expression. Each value represents the mean ± SE of four mice.
$^{**}p < 0.01$.

Nanoparticles





Inflammation ↔ **Oxidative stress**

ROS
RNS

Oxidative stress → **Inflammation**

Genotoxicity

DNA repair
- Upregulation
- Inhibition

Cancer **Cancer**

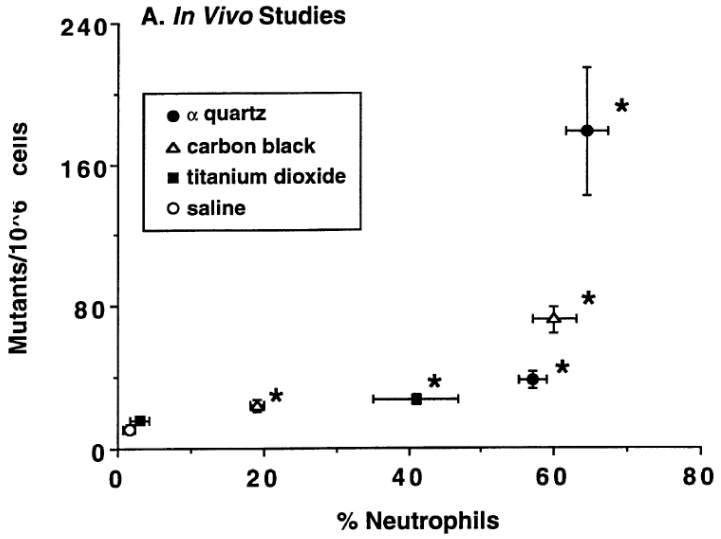
Carcinogenesis vol.18 no.2 pp.423–430, 1997

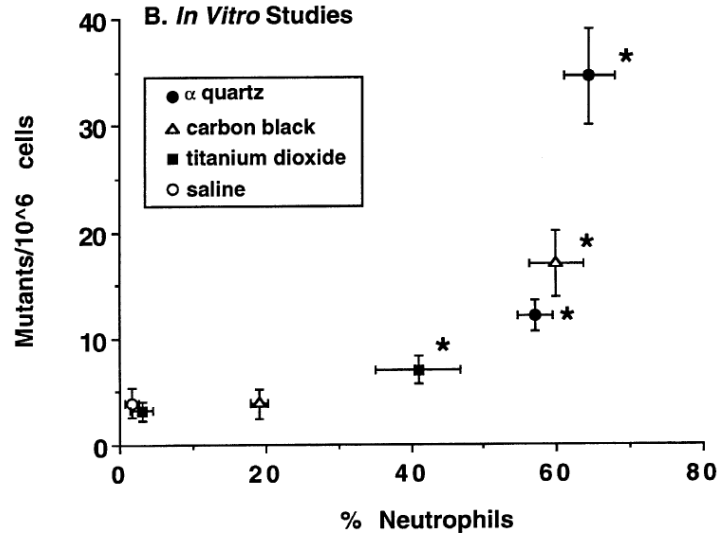
Effects of particle exposure and particle-elicited inflammatory cells on mutation in rat alveolar epithelial cells

Kevin E.Driscoll[1], Laurie C.Deyo, Janet M.Carter, Brian W.Howard, Diana G.Hassenbein and Timothy A.Bertram

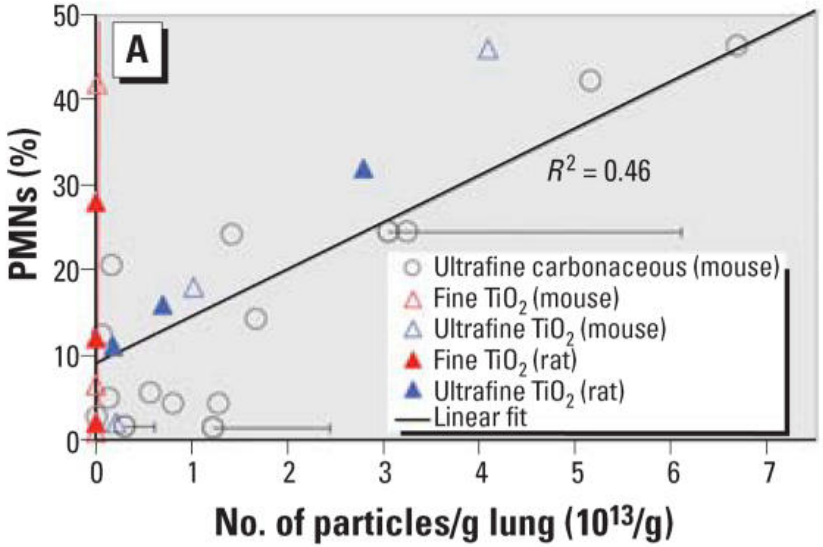
The Procter and Gamble Company, Miami Valley Laboratories, PO Box 538707, Cincinnati, OH 45253, USA

Relationship between mutations in rat lung epithelial cells 15 months after exposure in vivo and in vitro in In vivo exposed BAL and epithelial cell line coculture

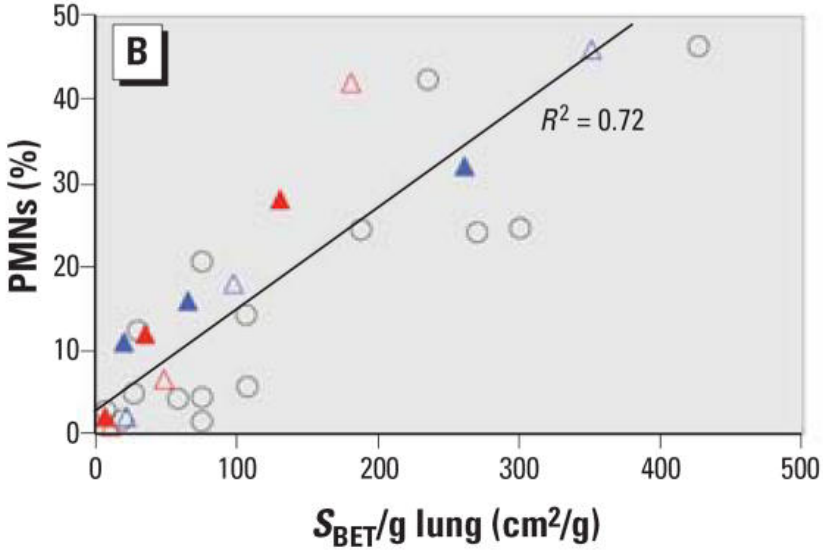




Lung inflammation after particle administration



Stoeger T, Schmid O, Takenaka S, Schulz H. Inflammatory response to TiO2 and carbonaceous particles scales best with BET surface area. Environ Health Perspect. 2007 Jun;115(6):A290-1

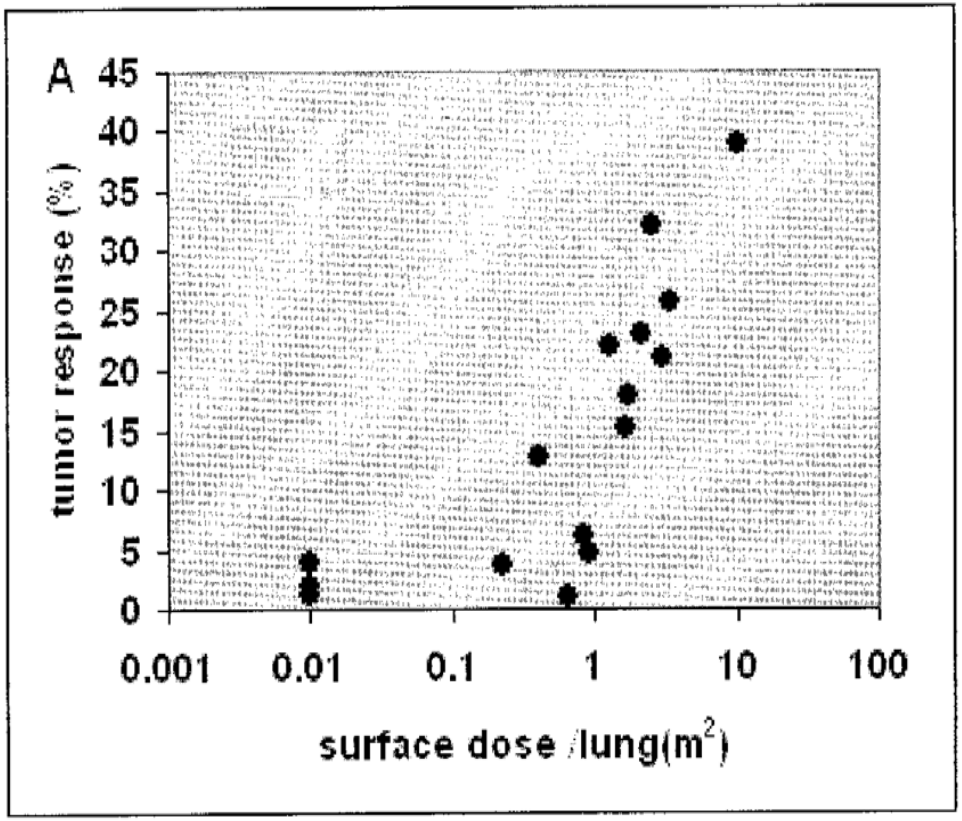


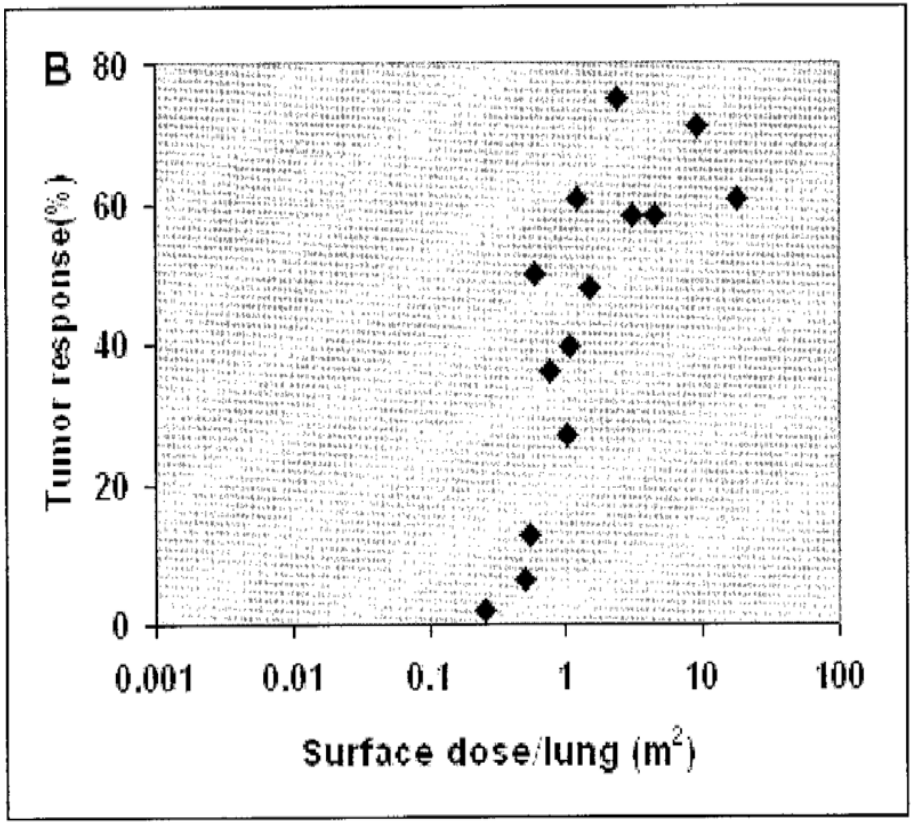
Surface area may be most important

Similar association for lung tumors

Tumor induction correlates with particle surface area much better than with mass independent on chemical composition with few exception (quarts)

Inhalation studies of different particles - Instillation studies





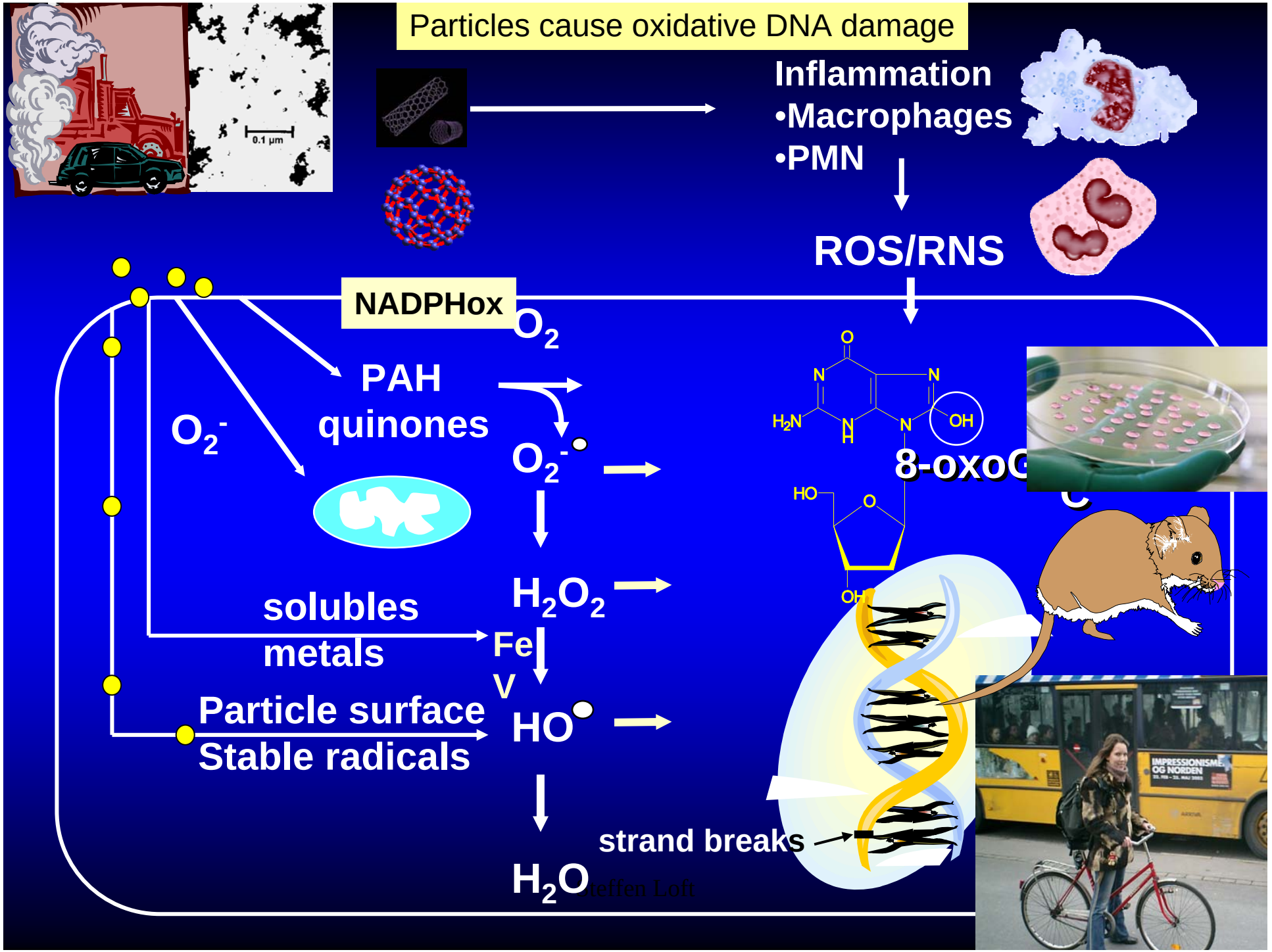
Int. J. Cancer: 110, 3–14 (2004)

Publication of the International Union Against Cancer

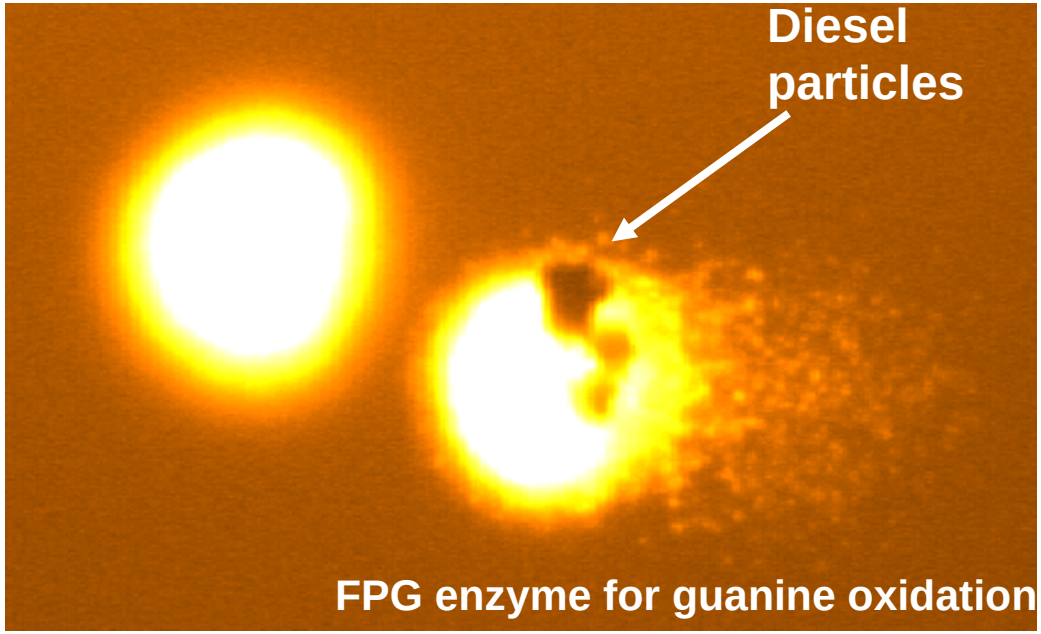
MINI REVIEW

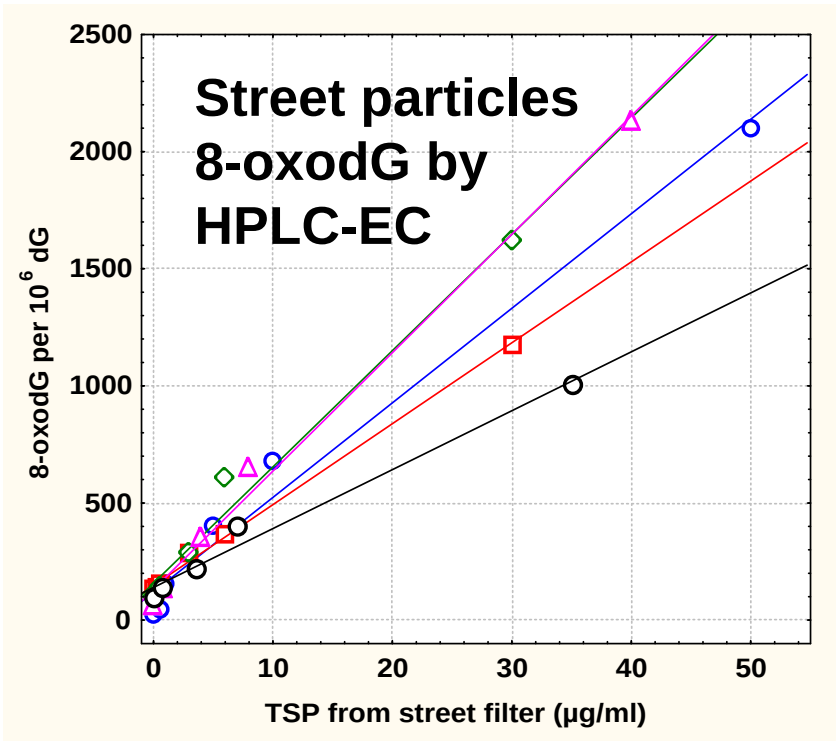
INHALED PARTICLES AND LUNG CANCER, PART B: PARADIGMS AND RISK ASSESSMENT

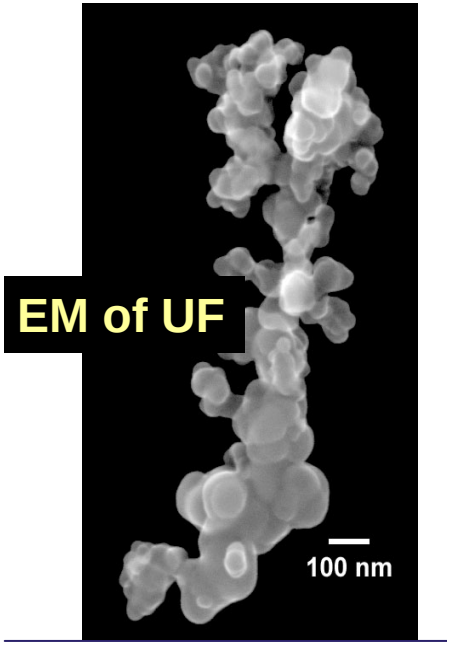
Paul J.A. Borm*, Roel P.F. Schins and Catrin Albrecht


Particles cause oxidative DNA damage
0.1 µm
Inflammation
•Macrophages
•PMN
ROS/RNS
NADPHox
O_2
PAH
quinones
O_2^-
O_2^-
H_2O_2
solubles
metals
Fe
V
Particle surface
Stable radicals
HO
H_2O
strand breaks
8-oxoG
Steffen Loft

DNA damage by particles in A549 lung epithelial cell and in isolated DNA







Increased strand breaks, guanine oxidation and TNF, IL1, 6, 8 mRNA expression (20-500 ug/ml) in cells by NIST 1650 or 2975 diesel or street particles

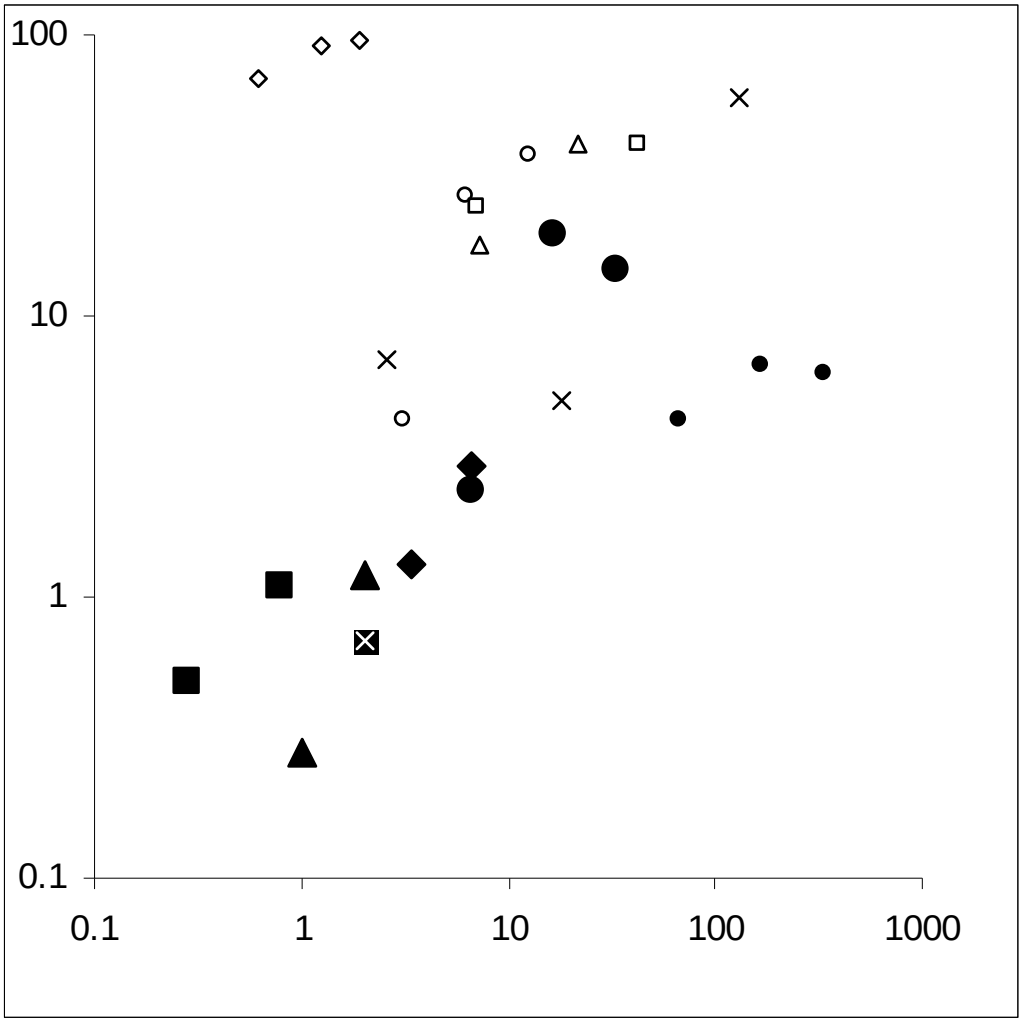
Similarly increased strand breaks in human lymphocytes (from 20 ug/mL)

Only effect of street particles and not of diesel particles on 8-oxodG in isolated DNA (HPLC-EC)

Dybdahl et al., Mutation Res 2004
Danielsen et al. Particle Fibre Toxicol 2008

Dose response of 8-oxodG in the lung across in vivo studies

8-oxodG per 10^5 dG



Mainly diesel a few carbon black

applied dose (mg/g lung weight) by inhalation or instillation

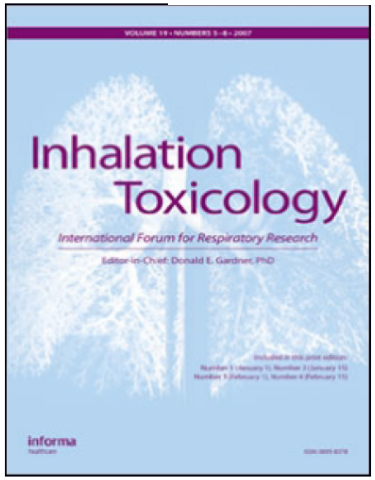
Møller et al. Tox Lett 2008

Exposure to Ultrafine Particles from Ambient Air and Oxidative Stress–Induced DNA Damage

FPG sites and strandbreaks in monoclear blood cells

Elvira Vaclavik Bräuner,[1] Lykke Forchhammer,[1] Peter Møller,[1] Jacob Simonsen,[1] Marianne Glasius,[2] Peter Wåhlin,[2] Ole Raaschou-Nielsen,[3] and Steffen Loft[1]*

Environmental Health Perspectives • VOLUME 115 | NUMBER 8 | August 2007



Inhalation Toxicology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713657711

No

Effects of Ambient Air Particulate Exposure on Blood-Gas Barrier Permeability and Lung Function

Elvira Vaclavik Bräuner [a]; Jann Mortensen [b]; Peter Møller [a]; Alfred Bernard [c]; Peter Vinzents [a]; Peter Wåhlin [d]; Marianne Glasius [d]; Steffen Loft [a]
[a] Institute of Public Health, Department of Environmental Health, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark [b] Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Faculty of Health Sciences, University hospital of Copenhagen, Copenhagen, Denmark [c] School of Public Health. Faculty of Medicine, Catholic University of Louvain, Louvain, Belgium [d] Department of Atmospheric Environment, National Environmental Research Institute, Roskilde, Denmark

First Published:January2009

Particle and Fibre Toxicology

BioMed Central

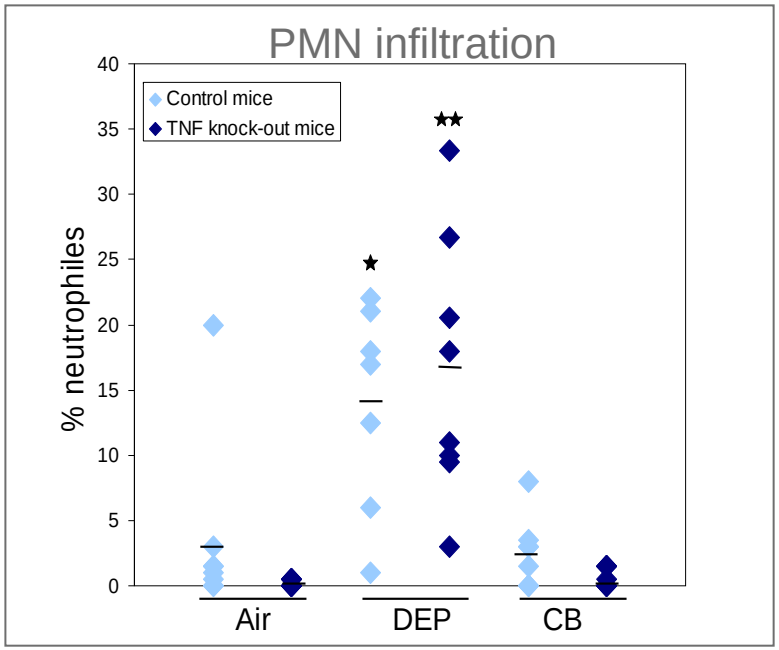
Research

Open Access

Exposure to ambient concentrations of particulate air pollution does not influence vascular function or inflammatory pathways in young healthy individuals

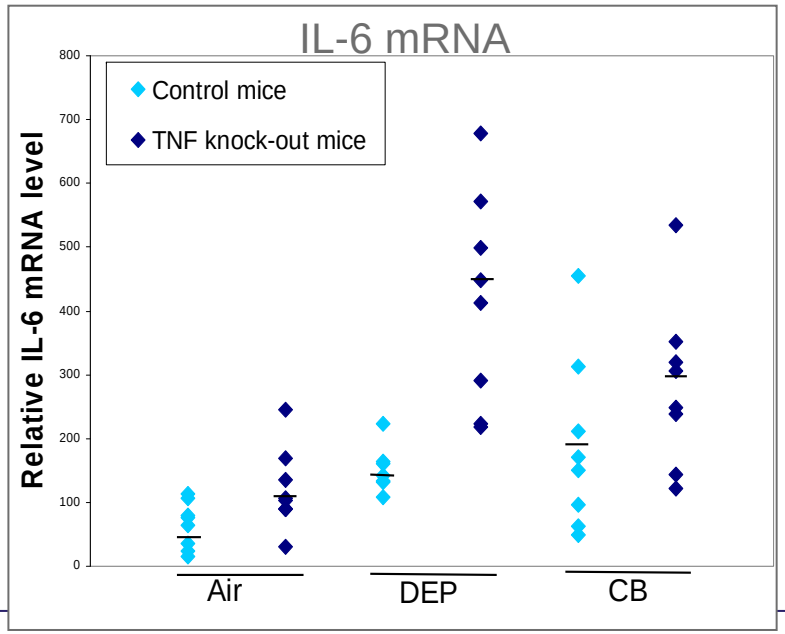
Elvira V Bräuner[1], Peter Møller[1], Lars Barregard[2], Lars O Dragsted[3], Marianne Glasius[4,5], Peter Wåhlin[5], Peter Vinzents[1,6], Ole Raaschou-Nielsen[7] and Steffen Loft*[1]

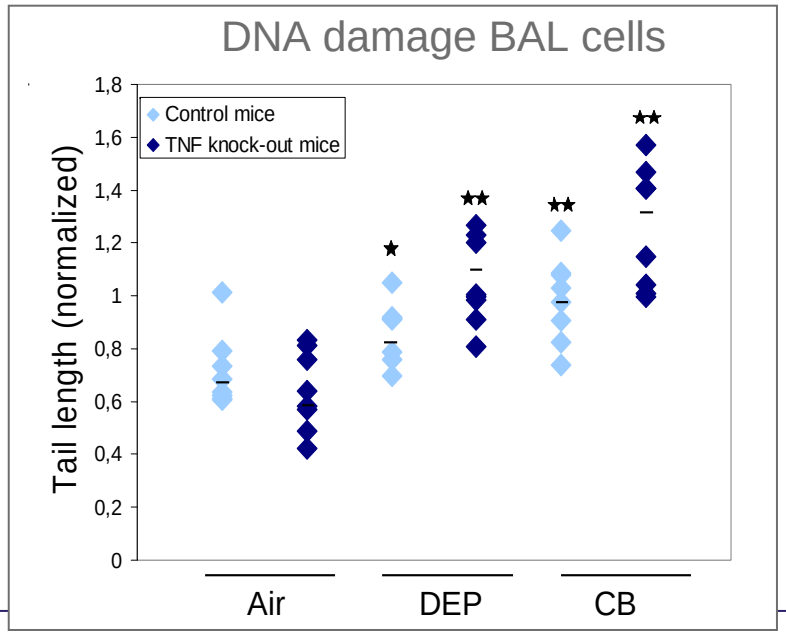
Role of TNF and PMN in *TNF-/-* inhaling diesel particles or carbon black x 4



TNF-signalling and PMN infiltration not required for DNA damage after repeated dosage

(Saber et al. Arch Toxicol 2005)





Particle and Fibre Toxicology 2009, **6**:2 doi:10.1186/1743-8977-6-2

Particle and Fibre Toxicology

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Lung inflammation and genotoxicity following pulmonary exposure to nanoparticles in ApoE$^{-/-}$ mice

Nicklas Raun Jacobsen[1], Peter Møller[2], Keld Alstrup Jensen[1], Ulla Vogel[1,3,4], Ole Ladefoged[3], Steffen Loft[2] and Håkan Wallin*[1]

Compare wild type and ApoE-/- mice for susceptibility (carbon black)

Compare inhalation and instillation for effect (carbon black)

Use instillation to compare a nanoparticle battery

- **Carbon black 14 nm**
- **C_{60} 0.7 nm**
- **SWCNT 0.9-1.7 x <1000 nm**
- **Au 2 nm**
- **Quantum dots 5 nm**

Characterize the aerosol

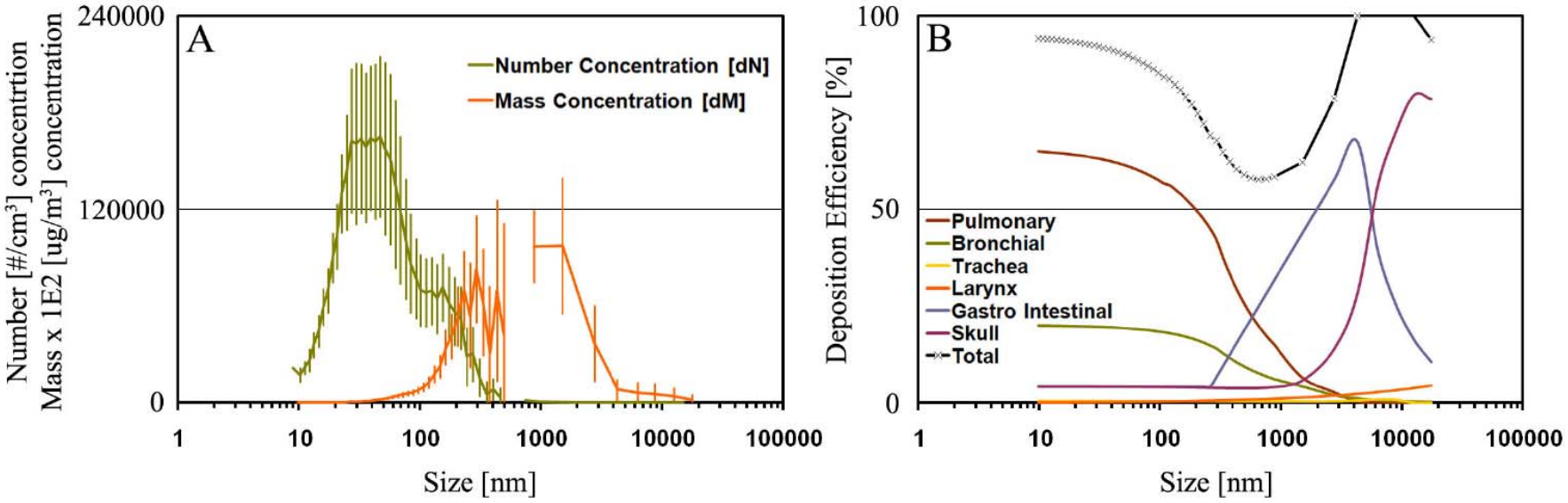


Figure 2
A) The average number and mass distribution of aerosolized CB during a 1-hour experiment. The mass concentration was calculated assuming spherical particles with a density of 2.1 μg/μm³. Error bars denote the standard deviation of the measured concentrations over the whole test period. B) A conservative model for deposition efficiency for particles in mice based on data from Raabe and co-workers [27]. The crosses plotted for the "Total" deposition efficiency curve indicates the model resolution, which fits the GRIMM SMPS+C and the GRIMM Dustmonitor.

Characterize the suspensions

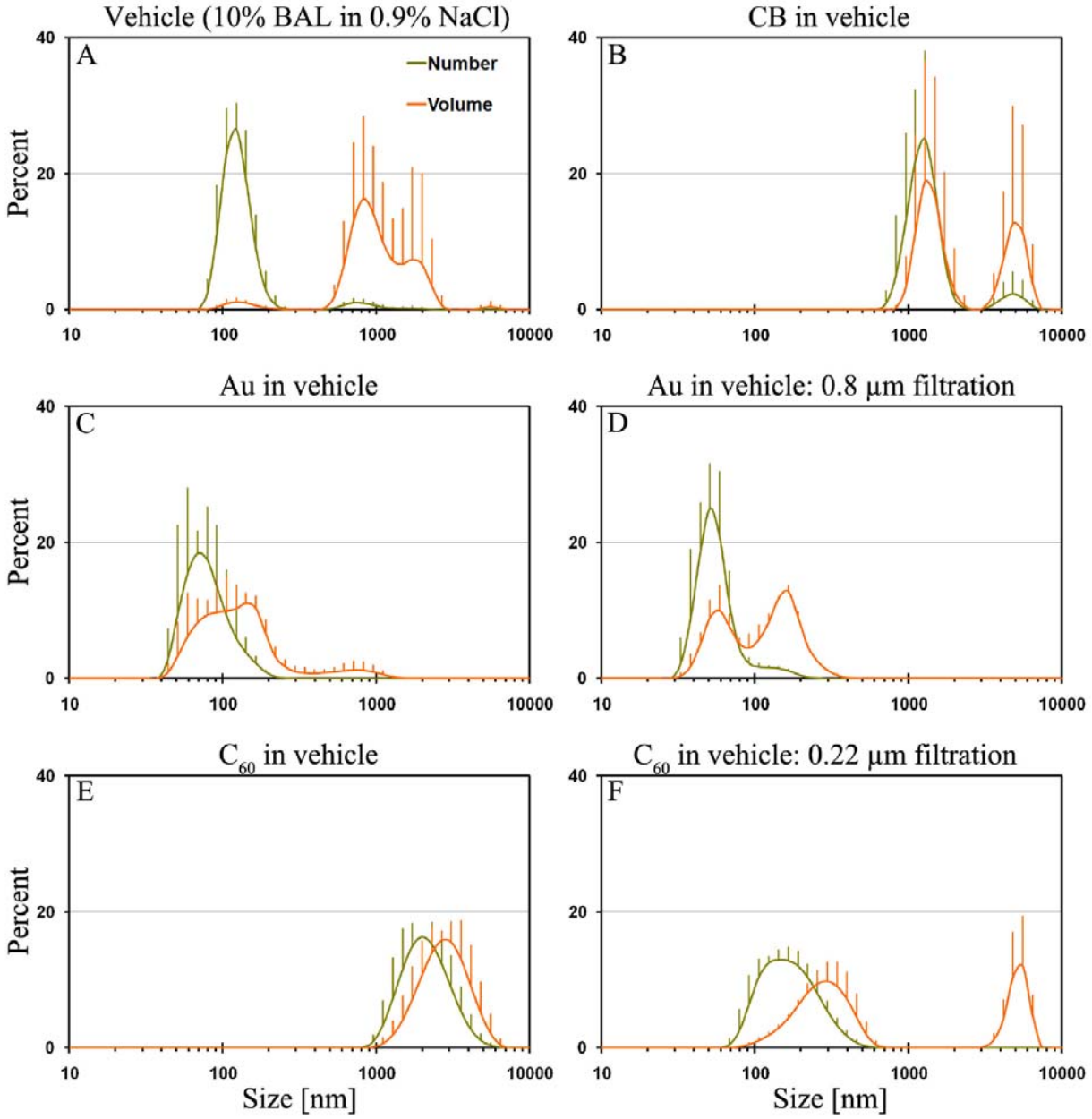


Figure 1
Number and volume size distribution of the particle suspensions used for instillation determined by DLS anal-

Much stronger inflammatory response to instillation of carbon black (CB 14 nm) 54 µg in ApoE$^{-/-}$ mice than in C57 mice after both 3 and 24 hr

Table 1: mRNAs of *Mip-2*, *Mcp-1* and *Il-6* in lung tissue and cell distribution and protein in BAL fluid 3 and 24 h after instillation of carbon black in C57 and ApoE$^{-/-}$ mice.

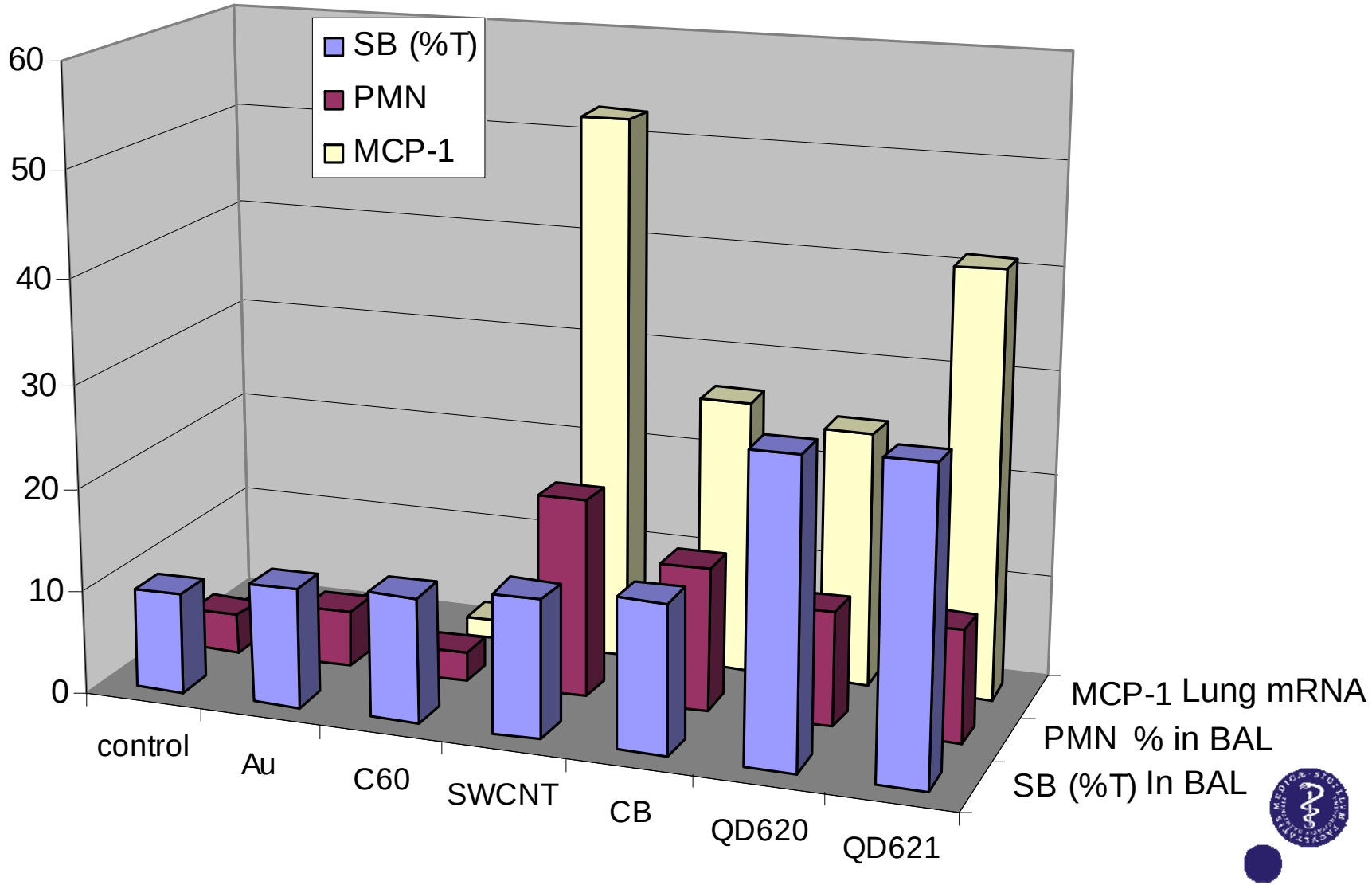
		C57 Control	C57 CB 54 µg	ApoE$^{-/-}$ Control	ApoE$^{-/-}$ CB 54 µg
3 h					
lung tissue	***Mip-2***	9.6 ± 2.5	20.4 ± 5.9	10.2 ± 3.2	108.1 ± 15.1***
	Mcp-1	12.1 ± 4.6	20.6 ± 5.4	10.1 ± 1.2	265.5 ± 163.9***
	Il-6	4.0 ± 1.9	5.8 ± 2.3	2.1 ± 0.4	31.4 ± 4.8***
BAL	**Neutrophils%[a]**	3.4 ± 2.4	4.5 ± 0.4	3.7 ± 1.2	13.8 ± 10.9
	Macrophages%[a]	94.5 ± 2.6	93.8 ± 0.4	93.9 ± 2.0	83.1 ± 10.7
	Total BAL cells	55732 ± 14617	73407 ± 9267	83262 ± 4819	49417 ± 7700
	Protein	133.3 ± 21.7	82.4 ± 6.0*	102.5 ± 5.2	139.3 ± 17.3**
24 h					
lung tissue	***Mip-2***	7.8 ± 1.0	82.8 ± 24.8***	5.1 ± 0.5	134.8 ± 33.2***
	Mcp-1	39.1 ± 10.4	434.1 ± 145.8***	28.3 ± 2.7	1087.0 ± 310.6***
	Il-6	2.1 ± 0.6	20.3 ± 12.3*	1.1 ± 0.1	44.0 ± 13.0***
BAL	**Neutrophils%[a]**	5.2 ± 1.2	51.0 ± 12.6**	5.3 ± 1.6	75.8 ± 3.4***
	Macrophages%[a]	92.6 ± 2.3	47.9 ± 12.7**	93.6 ± 1.5	22.1 ± 3.7***
	Total BAL cells	49022 ± 3589	98857 ± 11618	65290 ± 5246	78596 ± 21414
	Protein	114.5 ± 13.7	124.7 ± 10.6	110.6 ± 5.7	182.4 ± 7.1***

Much stronger inflammatory response to instillation of carbon black (CB 14 nm) 18 or 54 µg than to inhalation of the same dose in ApoE$^{-/-}$ mice after 24 hr

Table 2: Expression (mRNA) of *Mip-2*, *Mcp-1* and *Il-6* in lung tissue and cell distribution and protein in BAL fluid 24 h after inhalation or instillation of carbon black in ApoE$^{-/-}$ mice.

		Control	Low dose	High dose	significant dose-related differences[b]
Inhalation		**HEPA air 1/2–1 1/2 h**	**CB 60 mg/m³, 1/2 h**	**CB 60 mg/m³, 1 1/2 h**	
lung tissue	***Mip-2***	9.9 ± 1.6	11.6 ± 2.9	17.6 ± 3.1	High dose ≈ Low dose
	Mcp-1	44.4 ± 10.5	97.2 ± 24.8*	79.9 ± 18.7	Low dose ≈ High dose
	Il-6	3.4 ± 0.6	4.3 ± 0.9	3.2 ± 0.5	Low dose ≈ High dose
BAL	**Neutrophils%[a]**	1.1 ± 0.4	0.7 ± 0.3	5.6 ± 3.2	High dose ≈ Low dose
	Macrophages%[a]	97.5 ± 0.3	97.9 ± 0.2	92.5 ± 4.1	High dose ≈ Low dose
	Total BAL cells	54750 ± 4891	66567 ± 6304	77867 ± 4896	
	Protein	91.2 ± 3.7	108.1 ± 7.5*	118.5 ± 5.5**	High dose ≈ Low dose
Instillation		**Vehicle control**	**CB 18 µg**	**CB 54 µg**	
lung tissue	***Mip-2***	5.1 ± 0.5	37.1 ± 13.4***	134.8 ± 33.2***	High dose>>>Low dose
	Mcp-1	28.3 ± 2.7	511.2 ± 246.7***	1087 ± 310.6***	High dose ≈ Low dose
	Il-6	1.1 ± 0.1	14.3 ± 7.2***	44.0 ± 13.0***	High dose>Low dose
BAL	**Neutrophils%[a]**	5.3 ± 1.6	41.3 ± 10.2*	75.8 ± 3.4***	High dose ≈ Low dose
	Macrophages%[a]	93.6 ± 1.5	57.7 ± 10.2***	22.1 ± 3.7***	High dose>>>Low dose
	Total BAL cells	65290 ± 5246	88173 ± 19861	78596 ± 21414	
	Protein	110.6 ± 5.7	150.4 ± 7.7***	182.4 ± 7.1***	High dose>Low dose

Inflammation and DNA damage 3 hr after instillation of 54 µg nanoparticles of gold (Au, C60, SWCNT, carbon black CB 14 nm) or to quantum dots (QD620, QD621) in Apo$^{-/-}$ mice



Animal experiments show increased oxidative stress, DNA damage and gene expression in colon, liver and lungs after low oral doses of diesel particles in feed or by gavage and without signs of inflammation or mutagenicity (after 21 days)

Carcinogenesis vol.24 no.11 pp.1759–1766, 2003
DOI: 10.1093/carcin/bgg147

DNA adduct formation and oxidative stress in colon and liver of Big Blue® rats after dietary exposure to diesel particles

Marianne Dybdahl[1,6], Lotte Risom[2], Peter Møller[2], Herman Autrup[3], Håkan Wallin[1], Ulla Vogel[1], Jette Bornholdt[1], Bahram Daneshvar[4], Lars Ove Dragsted[4], Allan Weimann[5], Henrik Enghusen Poulsen[5] and Steffen Loft[2]

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Fundamental and Molecular Mechanisms of Mutagenesis

Mutation Research 550 (2004) 123–132

DNA damage in lung after oral exposure to diesel exhaust particles in Big Blue® rats

Anne K. Müller[a,*], E. Olatunde Farombi[b], Peter Møller[c], Herman N. Autrup[d], Ulla Vogel[e], Håkan Wallin[e], Lars O. Dragsted[a], Steffen Loft[c], Mona-Lise Binderup[a]

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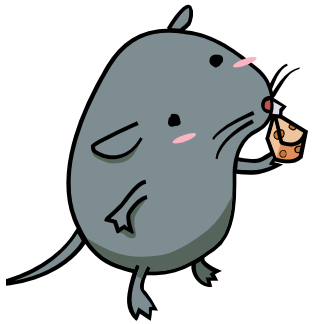
Mutation Research 637 (2008) 49–55

Fundamental and Molecular Mechanisms of Mutagenesis

www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

DNA damage in rats after a single oral exposure to diesel exhaust particles

Pernille Høgh Danielsen[a], Lotte Risom[a], Håkan Wallin[b], Herman Autrup[c], Ulla Vogel[b], Steffen Loft[a], Peter Møller[a,*]



ehp ENVIRONMENTAL HEALTH PERSPECTIVES
ehponline.org

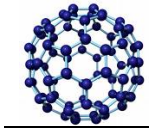
Janne K. Folkmann, Lotte Risom, Nicklas R. Jacobsen,
Håkan Wallin, Steffen Loft, and Peter Møller

doi: 10.1289/ehp.11922 (available at http://dx.doi.org/)
Online 12 November 2008

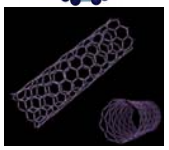
Oxidatively Damaged DNA in Rats Exposed by Oral Gavage to C_{60} Fullerenes and Single-walled Carbon Nanotubes

Groups of 8-10 rats received by gastric intubations

C60 Fullerenes

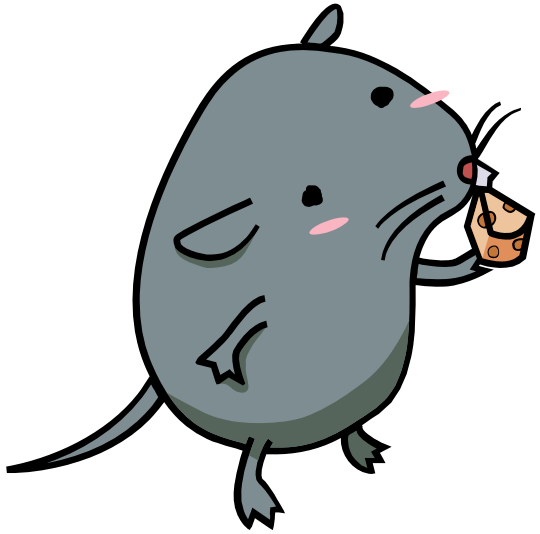


Single wall carbon nanotubes



0, 0,064 or 0,64 mg/kg

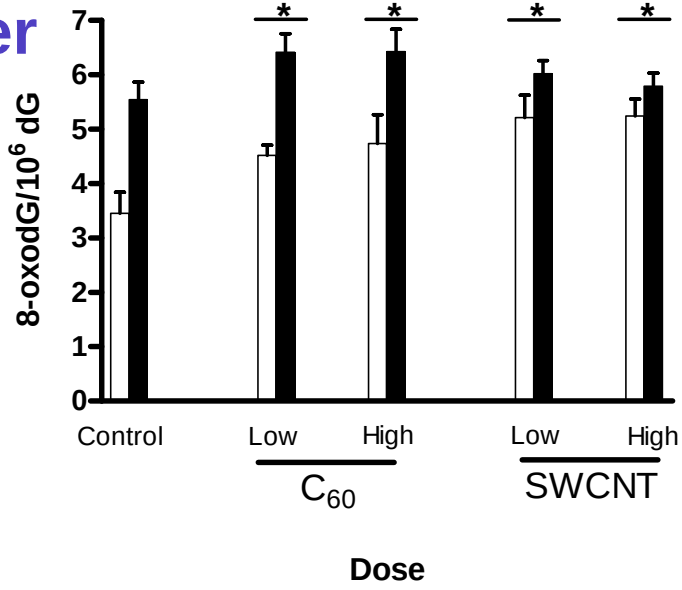
In saline or corn oil



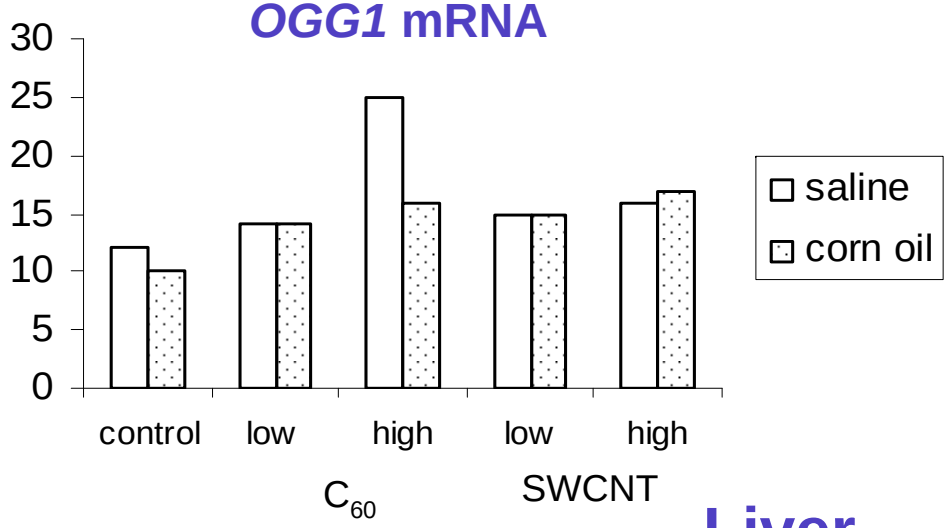
24 hr after oral exposure to C60 or SWCNT

Liver

8-oxodG

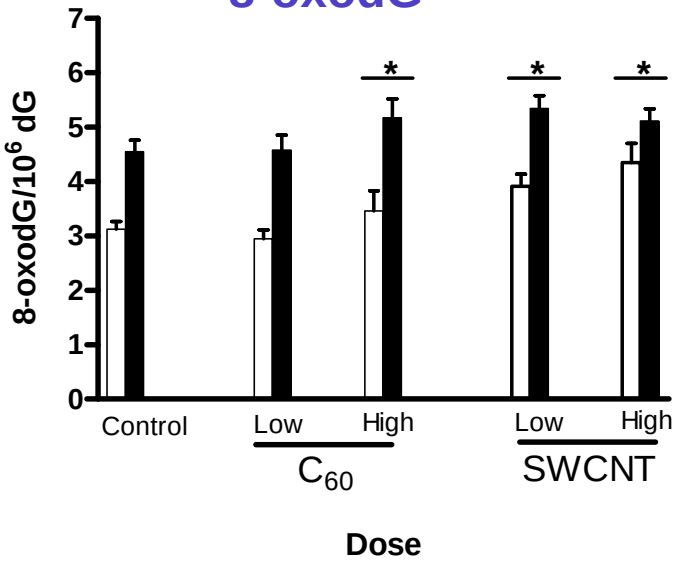


OGG1 mRNA



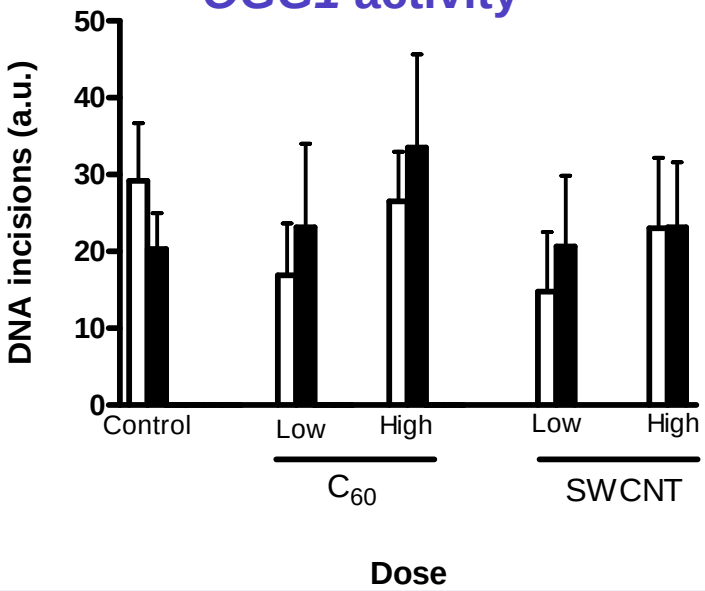
Lung

8-oxodG

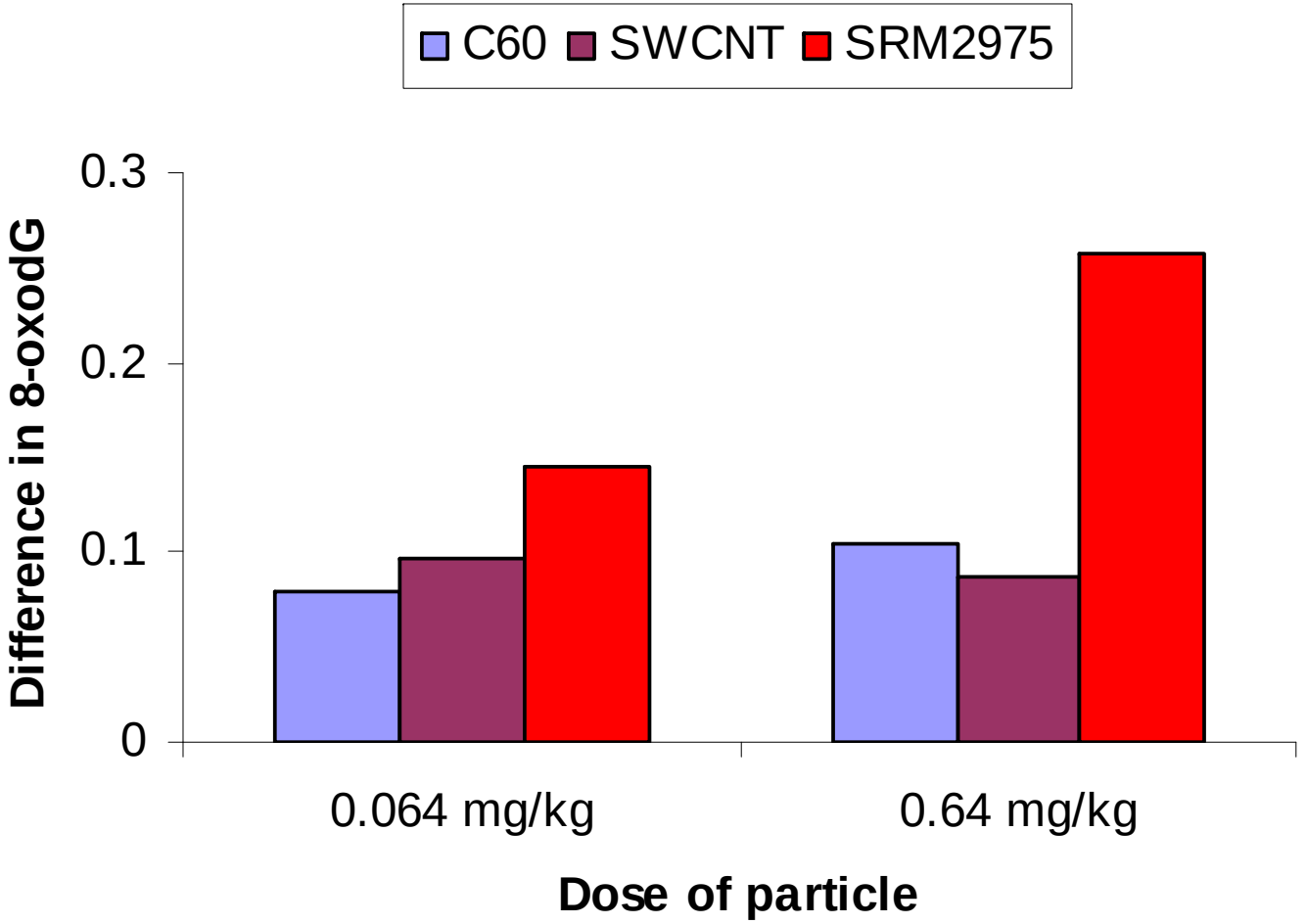


Liver

OGG1 activity



Difference in hepatic 8-oxodG (per 10^5 dG) compared to untreated group



Danielsen et al. Mutation Res 2008; Folkmann et al. EHP 2009

Environmental and Molecular Mutagenesis 48:451–461 (2007)

Research Article

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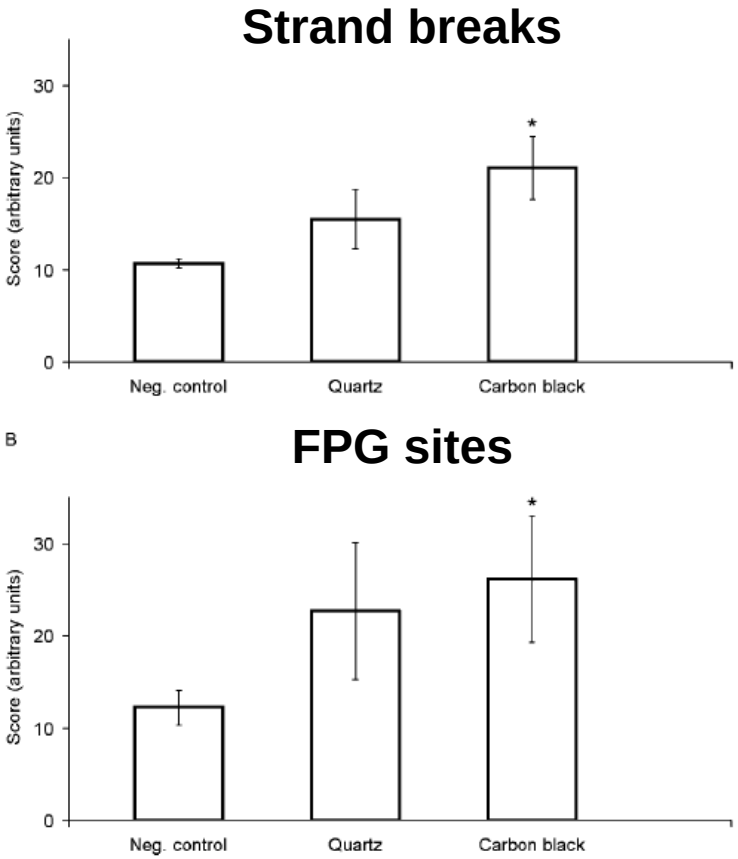

Environmental and Molecular Mutagenesis 49:476–487 (2008)

Research Article

Genotoxicity, Cytotoxicity, and Reactive Oxygen Species Induced by Single-Walled Carbon Nanotubes and C_{60} Fullerenes in the FE1-Muta™Mouse Lung Epithelial Cells

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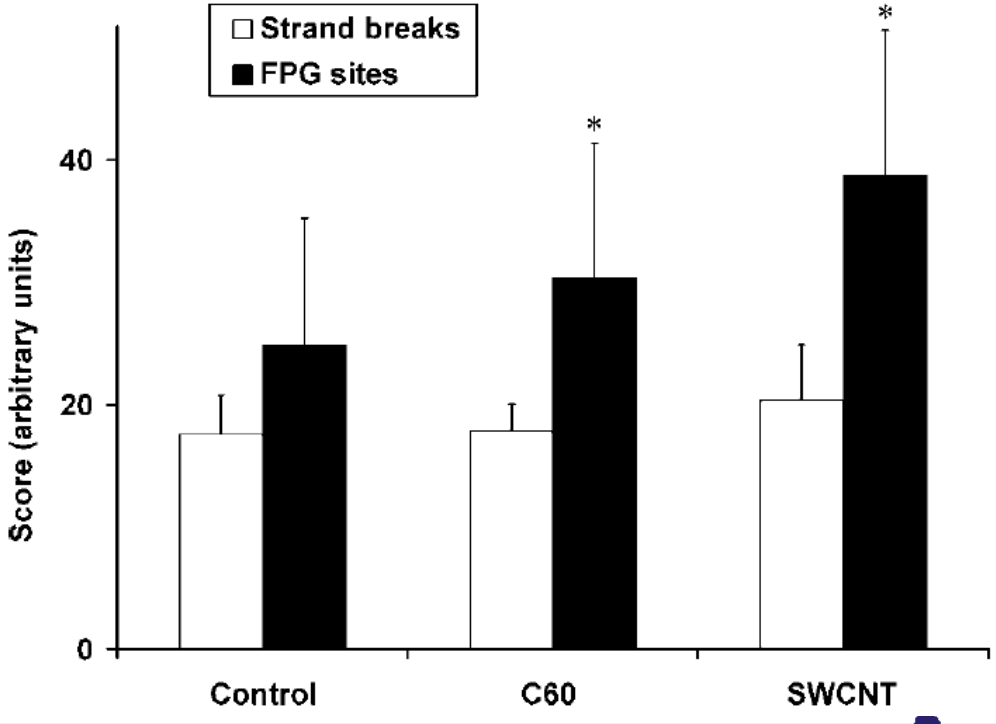

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Particle (75 µg/ml; 8 rounds)	CII mutation frequency
Carbon black	22±4 ★
Diesel	20±5 ★
C_{60} fullerenes	13±4
Single wall carbon nanotubes	14±4
Quartz	16±6
Negative control	12-15
Positive control	151-395

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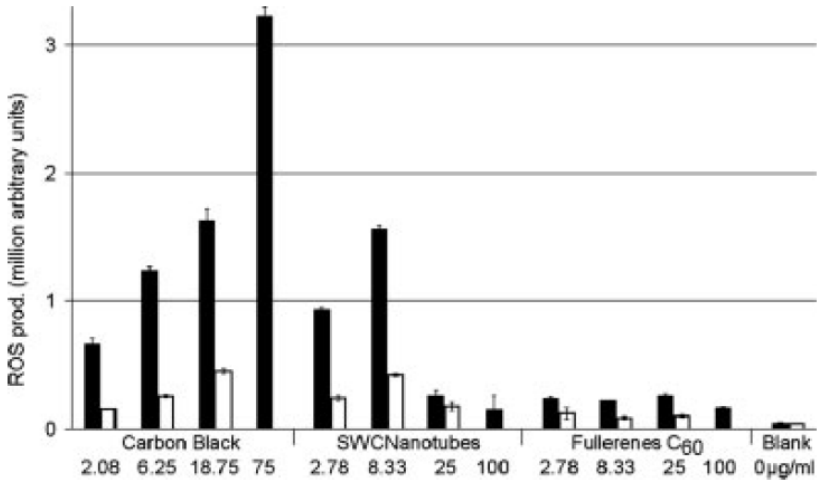

Fig. 4. ROS production measured by DCF in a cell-free environment (filled columns) or within FE1 Muta™Mouse lung epithelial cells (open columns) following 3 hr of incubation. The environment was stimulated with different mass loadings of CB, SWCNT, and C_{60}. Each bar represents the mean and SD of four replicates within one experiment. The blank contains no test particles.

Diesel: Environ Mol Mutagen 49:476-87, 2008

Summary of effects of particles in THP1, A549 and MML cells

Particles	ROS	IL1/6/8;TNF	SB	FPG	CII mutation
Diesel SRM1650/2975	+	++	++	++	++
Wood smoke	-	++	+++	++++	nd
Diesel extract	?	+	++++	+++	nd
Wood smoke extract	?	+	+++++	+++	nd
Carbon black	+++	+	++	++	++
C_{60} fullerenes	+/-	nd	+	+	-
Carbon nanotubes	++/-	nd	+	+	-
Quartz	+	++	-	-	-

Danielsen et al. Particle Fibre Toxicol 2008; Dybdahl et al. 2004; Jacobsen et al. Environ Mol Mutagen 2007+2008, Mutation Res 2007; Kocbach et al. Toxicology 2008, Toxicol Appl Pharmacol 2008

Summary of effects of particles in cell culture and in vivo in apoE-/- mice and rats

	in vitro					in vivo		
Particles	ROS	IL1-8 TNF	SB	FPG	CII mu-tation	MCP -1	SB BAL	8-oxodG oral/inhal.
Diesel	++	++	++	++	++	++	++	++ / +-
Carbon black	+++	+	++	++	++	++	++	/-
C_{60} fullerenes	+/-		+	+	-	+	-	+ /
SWCNT	++/-		+	+	-	+++	+	+ /
Quartz	+	++	-	-	-	(+++)	(++)	
QDots		highly cytoxic				+++	+++	

Danielsen et al. Particle Fibre Toxicol 2008; Dybdahl et al. 2004; Jacobsen et al. Environ Mol Mutagen 2007+2008, Mutation Res 2007, Particle Fibre Toxicol 2009; (Knaapen et al. Carcinogenesis 2002); Folkmann et al EHP 2009

Conclusions: In vivo vitro genotoxicity of nanomaterials

Dosimetry and biokinetics more required in vivo

Route of exposure
- ✓ **Inhalation or instillation - suspensions or aerosols**
- ✓ **Oral**
- ✓ **Injection**

Target tissues could include
- ✓**Lung**
- ✓**Liver**
- ✓**Bone marrow**
- ✓ **Germ cells**

Endpoints include
- ✓ **Comet assay strand breaks and base oxidation**
- ✓ **DNA base oxidation by chromatography**
- ✓ **Micronuclei**
- ✓ **Mutations**

Reasonable in vivo in vitro correlation for oxidative damage to DNA, mutations and inflammation with respect NP

No direct data on issues of size, charge etc. and genotoxicity of NP in vivo