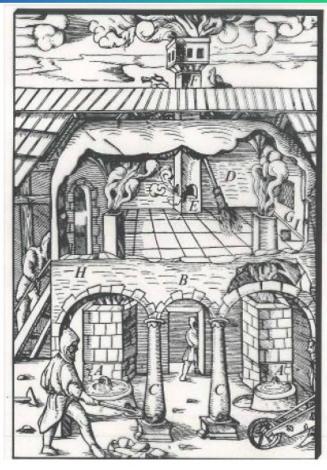
Farewell-Symposium Gerrit Alink, Wageningen University, July 9th, 2010

# Toxicity of (nano)particles

E. Dopp
Institute of Hygiene and Occupational Medicine
University of Duisburg-Essen



#### **History**



De re metallica
Georg Agricola
1556

long enough to reach to the elbow, and they should fasten loose veils over their faces; the dust will then neither be drawn through these into their wind-pipes and lungs, nor will it fly into their eyes. Not dissimilarly, among the Romans<sup>22</sup> the makers of vermilion took precautions against breathing its fatal dust.

p215

#### **History**

1661 John Evelyn wrote to King Charles II: "Smoake issuing from one or two Tunnels near Northumberland-house, and not far from Scotland-yard, did so invade the Court, that all the Rooms, Galleries and Plates about it were filled and infested with it; ..."

~ 1700 Ramazzini described bakery asthma which quite likely was linked to the amount of inhaled dust – first workplace hygienist

1775 Percivall Pott (1714-1788) was the first to establish a causal link between cancer and exposure to a substance in the environment. Scrotum cancer in a number of his male patients, whose common history included employment as chimney sweeps when they were young.

1870 Tissandier laid out papers of about 2 m<sup>2</sup> collecting dust for microscopic analysis

1878 Miquel introduced the *Aeroskop* for first quantitative sampling by "impaction"

#### London, December 1952



#### Public Health

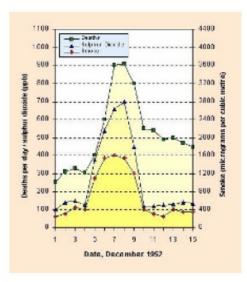
#### MORTALITY IN THE LONDON FOG INCIDENT, 1952

W. P. D. LOGAN M.D. Glasg., Ph.D. Lond.

CHIEF MEDICAL STATISTICIAN, GENERAL REGISTER OFFICE

The Meuse Valley fog episode in 1930 caused 64 deaths, and the Donora (Pennsylvania) episode in 1948 caused 20 deaths. In December, 1952, a four-day fog in London caused about 4000 deaths. This paper gives a short account of when and where these deaths occurred, the age-distribution, and the reported medical causes. No attempt is made here to present detailed meteorological data or to discuss clinical aspects; these and other features of the incident, including additional details about mortality, will no doubt be discussed in a report which, it is understood, will be made to the Minister of Hoalth when investigations have been completed. Two papers have already been published concerning the

TABLE 1—DEATHS REGISTERED IN GREATER LONDON FROM WEEK ENDED NOV. 15, 1952, TO JAN. 10, 1953, COMPARED

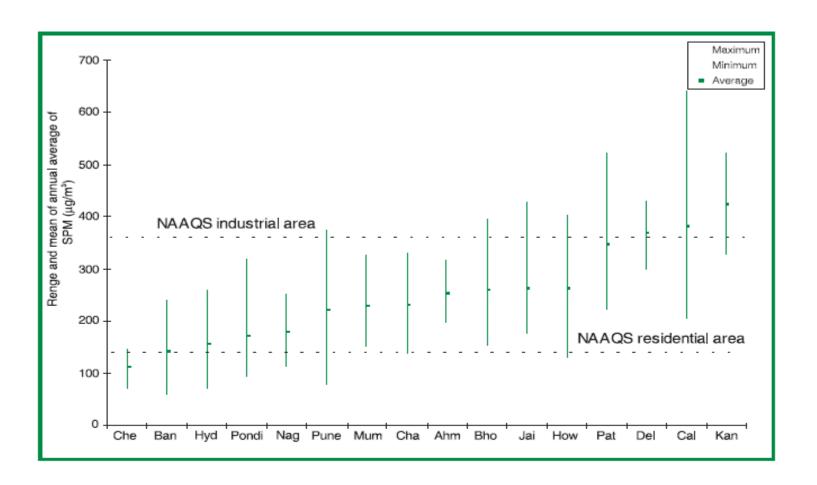




Beijing 2006

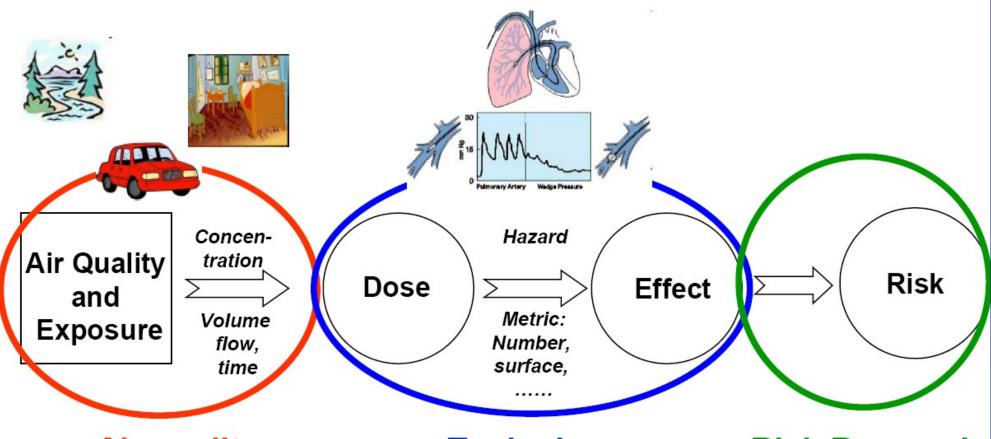
London 1952

### PM10-values (µg/m<sup>3</sup>) in different cities in India



Che – Chennai; Ban – Bangalore; Hyd – Hyderabad; Pondi – Pondicherry; Nag – Nagpur; Pune – Pune; Mum – Mumbai; Cha – Chandigarh; Ahm – Ahmedabad; Bho – Bhopal; Jai – Jaipur; How – Howrah; Pat – Patna; Del – Delhi; Cal – Calcutta; Kan – Kanpur.

#### Relevant Research Areas



Air quality Indoor air Personal Exposure Toxicology, Epidemiology Risk Research

# International Meeting on Environmental

Hygiene

An established event in the field of Environmental Hygiene and Environmental Medicine organized by Norbert H. Seemayer and Gerrit M. Alink

1.	1987	Düsseldorf (f	FRG)
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- 2. 1989 Düsseldorf (FRG)
- 3. 1991 Düsseldorf (Germany)
- 4. 1993 Wageningen (NL)
- 5. 1995 Prague (Czech Republik)
- 6. 1997 Graz (Austria)



Prof. N.H. Seemayer 1932 - 2005 †

# Environmental Hygiene IV

Edited by

G.M. Alink • N.H. Seemayer • G.A.H. Heussen • W. Hadnagy







ELSEVIER

# **Environmental Hygiene V**

Edited by

N.H. Seemayer • W. Hadnagy • G.M. Alink





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# **Environmental Hygiene VI**

**Edited** by

N.H. Seemayer • G.M. Alink





**ELSEVIER** 

Toxicology Letters

Vol. 88 Nos. 1-3

P. Nettesheim (USA),

F. Marano (France)

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## Research on Particle/Fibre Toxicology



Asbestos fibres, Man-made mineral fibres, Nanotubes

Coal dust, PM10, PM2.5, urban particles, ultrafine particles

Metal dust on workplaces, generated particles, nanoparticles

# Particle toxicology



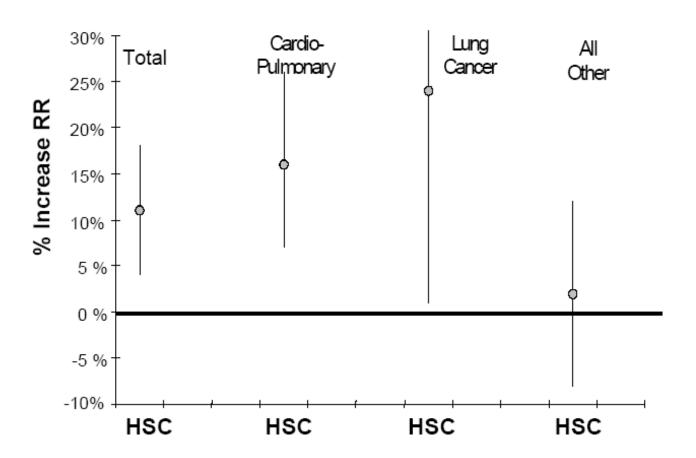
## **Epidemiology**

#### Studies long term effects

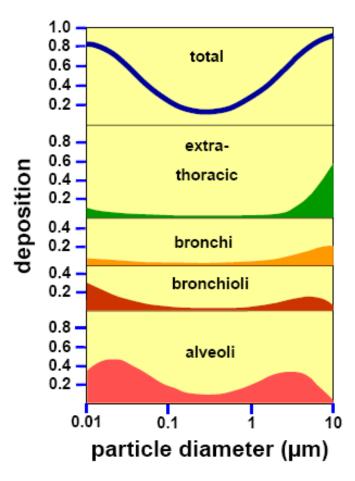
- Harvard Six Cities Study (Dockery et al., 1993)
- American Cancer Society (ACS) Study (Pope et al., 1995, 2002)
- Adventist Health Study of Smog (AHSMOG) (Abbey et al., 1999; McDonnell et al., 2000)
- Veterans' Administration Cohort Mortality Study (VA) (Lipfert et al., 2000)
- Dutch Cohort Study on Traffic (Hoek et al., 2002)

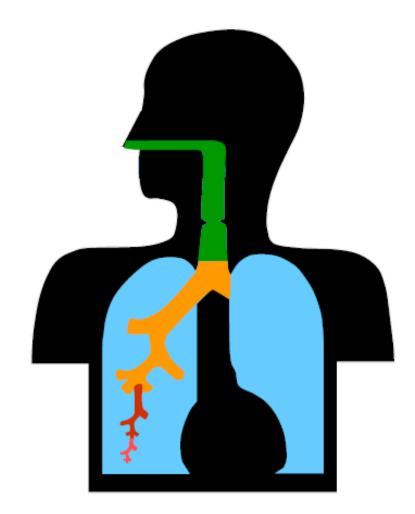
### $PM_{2.5}$ (10 $\mu g/m^3$ ) and mortality

**HSC: Harvard-Six-Cities Study** 



#### Lung deposition – inner exposure



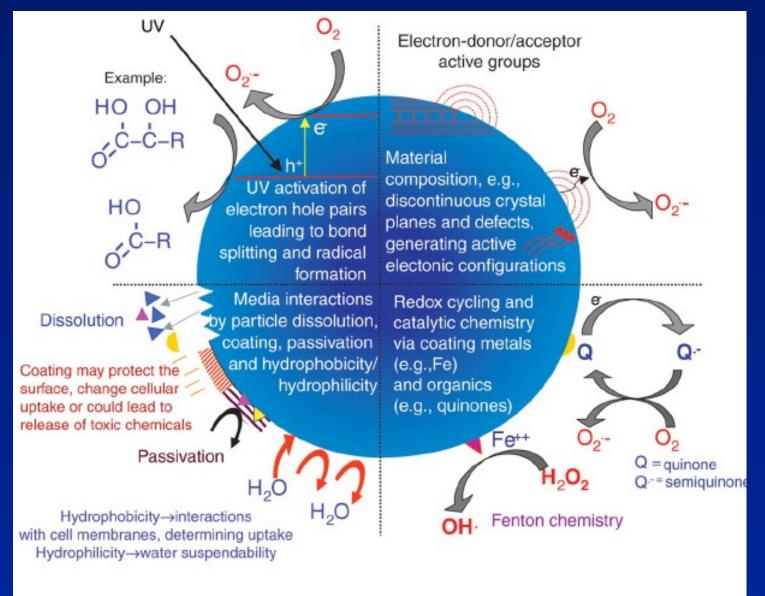


ICRP 66 (1994); MPPDep (2000)

#### Other metrics!

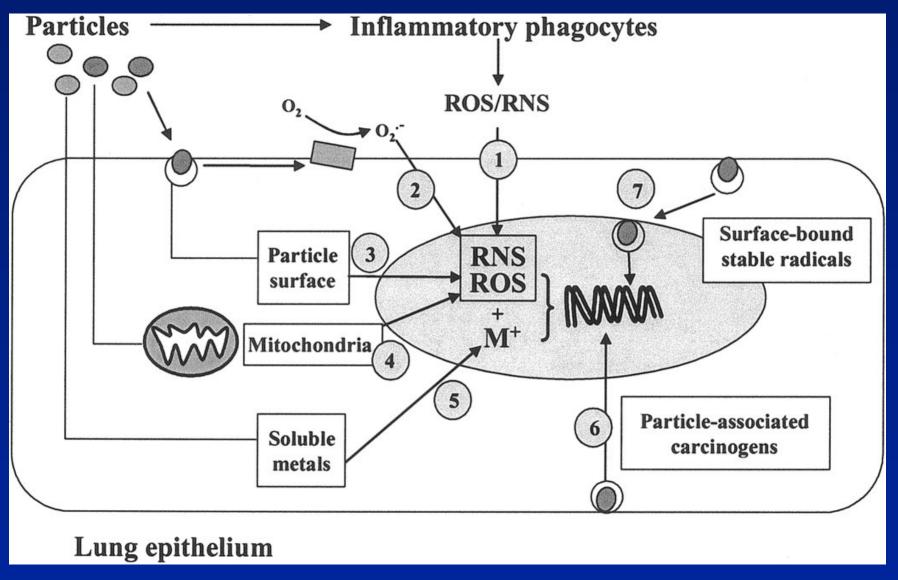
### Relevant particle properties!?

- Mass concentration
- Number concentration / Number size distribution
- Surface area concentration
- Chemical composition
- Particle reactivity (release of radicals, RedOx reactivity)
- surface structure / morphology
- Other properties (hygroscopicity, solubility, volatility, particle density, etc.)



Surface Reactivity of Nanoparticles Nel et al. Science 311: 622-627, 2006

### Intracellular effects after particle exposure



### Fields of interest in recent particle research

- 1.) Effects of nanoparticles on cardiomyocytes or neuronal cells at relevant concentrations
- 2.) Uptake and intracellular accumulation of NP
- 3.) Cyto- and genotoxic effects of particles in different cellular systems
- 4.) Intracellular radical formation after particle exposure dependent upon particle type

### Student exchange

### Wageningen University – University of Duisburg-Essen



Eik Hoffmann 2002



Cindy Katier 2006/2007



PhD defence Stefan Geh 2005

Kunal Bhattacharya 2008



© Kamla-Raj 2007

Int J Hum Genet, 7(1): 1-21 (2007)

### Oxidative Stress and Changed Gene Expression Profiles in Fiber-/Particle-Induced Carcinogenesis

Kunal Bhattacharya<sup>1</sup>, Gerrit Alink<sup>2</sup> and Elke Dopp<sup>1\*</sup>

<sup>1</sup>Institute of Hygiene and Occupational Medicine, University Hospital Essen, Germany <sup>2</sup>Department of Toxicology, University of Wageningen, The Netherlands

KEYWORDS Fibers; metals; gene expression; oxidative stress; cancer

ABSTRACT Exposure to ambient air pollution (particles, fibr. The mechanisms of induced health effects are believed to invol mediated by airborne particles and/or fibres may arise from dir the surface of particles/fibres, soluble compounds such as transinflammatory cells capable of generating ROS and reactive n directly cause covalent modifications to DNA or they can init. The resulting oxidative DNA damage can lead to changed gen

0090-9556/08/3605-971-979\$20.00
DRUG METABOLISM AND DISPOSITION
Copyright © 2008 by The American Society for Pharmacology and Experimental Therapeutics
DMD 36:971-979, 2008

Vol. 36, No. 5 19034/3327856 Printed in U.S.A.

### Subcellular Distribution of Inorganic and Methylated Arsenic Compounds in Human Urothelial Cells and Human Hepatocytes

Elke Dopp, Ursula von Recklinghausen, Louise M. Hartmann, Inga Stueckradt, Ilona Pollok, Sasan Rabieh, Liping Hao, Andreas Nussler, Cindy Katier, Alfred V. Hirner, and Albert W. Rettenmeier

Institute of Hygiene and Occupational Medicine, University Hospital Essen, University of Duisburg-Essen, Essen, Germany (E.D., U.v.R., I.S., I.P., A.W.R.); Institute of Environmental Analysis, University of Duisburg-Essen, Essen, Germany (L.M.H., S.R., A.V.H.); Chemical Research Department, Matís, Reykjavík, Iceland (S.R.); Department of Traumatology, Technical University of Munich, Munich, Germany (L.H., A.N.); Department of Toxicology, University of Wageningen, Wageningen, The Netherlands (C.K.)

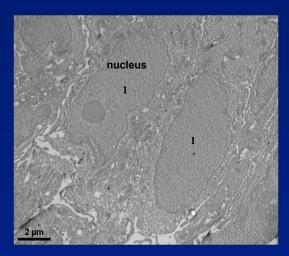
Received October 12, 2007; accepted January 31, 2008

#### ABSTRACT:

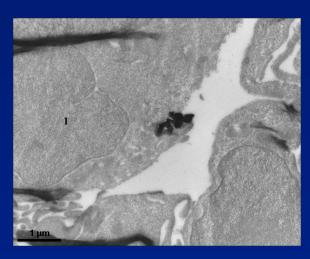
Epidemiological studies have indicated that exposure of humans to inorganic arsenic in drinking water is associated with the occurrence of bladder cancer. The mechanisms by which arsenic induces this malignancy are still uncertain; however, arsenic metabolites are suspected to play a pivotal role. The aim of the present study was the

uted into nuclei and ribosomes. After 24-h exposure, arsenic is mainly found in the ribosomes of UROtsa cells and in the nuclei and mitochondria of phH. In contrast to the pentavalent arsenic species, the trivalent species induced a 4- to 5-fold increase of DNA damage in hepatocytes. Radical generation, measured by thiobarbituric acid

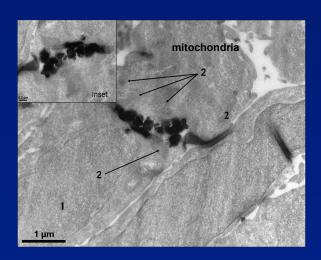
### Uptake and intracellular localization of particles



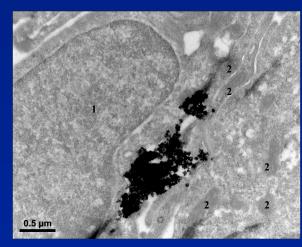
Control (TEM x 5.000)



Hematite Ø 1,5  $\mu$ m (x 12.500)

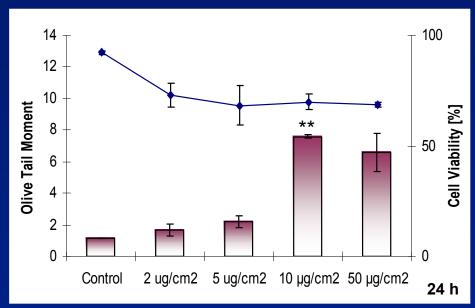


- Particles are taken up by human lung cells and are always located near the nucleus
- NP are surrounded by mitochondria
- No particles can be found within the nucleus!



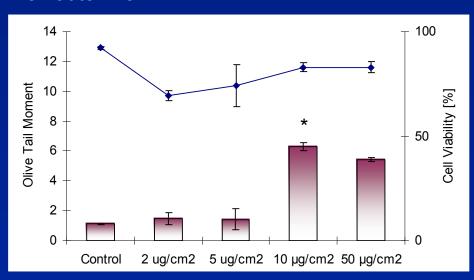
Hematite NP (x 20.000)

### Genotoxic effects in human lung fibroblasts

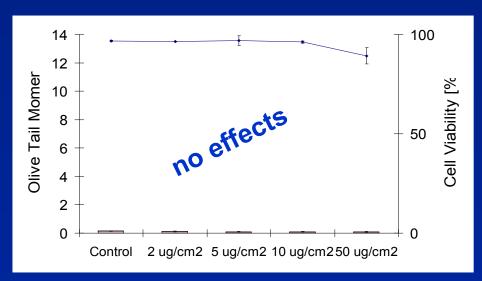


#### 14 100 \*\*\* 12 \*\* Olive Tail Moment Cell Viability [%] 50 2 ug/cm2 5 ug/cm2 10 μg/cm2 50 μg/cm2 24 h

#### Hematite fine



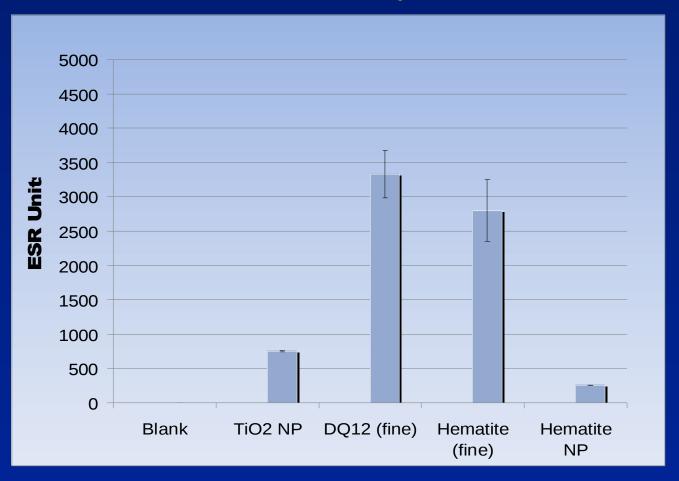
#### Hematite ultrafine



#### TiO<sub>2</sub> ultrafine

#### Radical formation

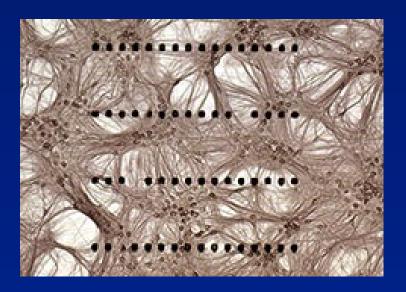
Acellular measurement of radicals by ESR (Electron-Spin-Resonance)



less radical formation (OH' radicals) in acellular system by iron-containing NP compared to fine particles

### Electrical activity of neuronal networks

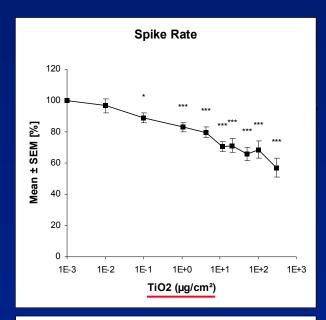


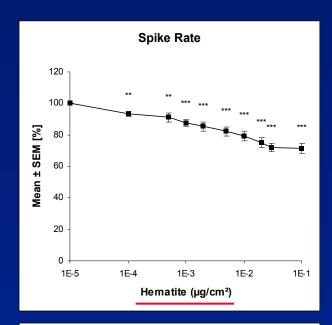


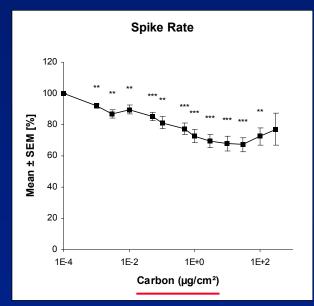
- Measurement of spikes and bursts of neuronal networks
- 250 neuronal cells can be recorded at the same time
- Electrical activity: "Spike rate" = Number of "Spikes" / time interval

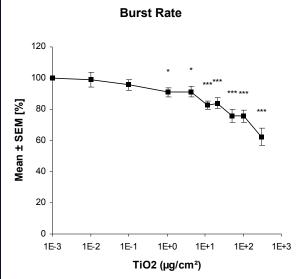
Published in Gramowski et al., Environ Health Perspect. 2010, May 10

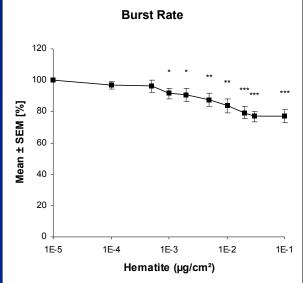
### Electrical activity of neuronal networks

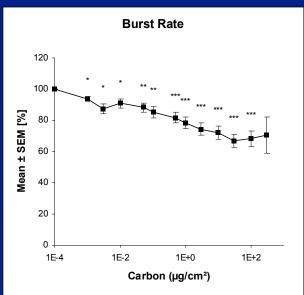












#### Published in:

Bhattacharya K. et al.: Titanium dioxide nanoparticles induce oxidative stress and DNA- adduct formation but not DNA-breakage in human lung cells. Particle and Fibre Toxicology (2009), 6(1):17.

Bhattacharya K. et al.: Cyto- and genotoxic effects of natural and surface-treated ultrafine titanium particles in mammalian cells. J. Toxicol. Environm. Health, Part A 71 (2008) 13-14: 976-980.

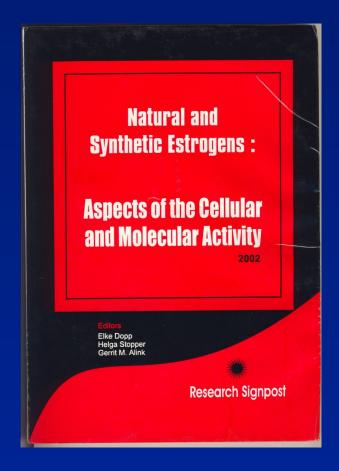
Geh S. et al.: Genotoxic potential of respirable bentonite particles with different quartz contents and crystalline modifications in primary human lung cells. Inhalation Toxicol. 18 (2006) 6, 405-412.

Geh S. et al.: Cellular uptake and cytotoxic potential of respirable bentonite particles with different quartz contents and chemical modifications. Archives of Toxicol. 80 (2006) 2, 98-106.

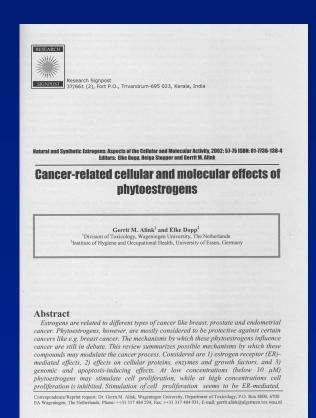
### Fields of interest in food toxicology

- 1.) Phytoestrogens: genomic and non-genomic effects
- 2.) Natural and synthetic estrogens: Aspects of the cellular and molecular activity

### Published books and articles







All the best for the future!