Safety of Nanomaterials

Nano Long-Term Project

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Frankfurt am Main, 15th of January 2013

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20 nm

Background

Only two chronic inhalation studies with dusts of nanomaterials exist:

- **TiO_2 P25** (Degussa):
  Tumors in rats after inhalation of 10 mg/m³ for 24 months
- **Carbon black** (Printex 90):
  Tumors in rats after inhalation of 11.7 mg/m³ for 24 months

No studies according to OECD test guidelines
No studies with low aerosol concentrations

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Safety of Nanomaterials
Focus on Long-term Effects and Cancerogenicity

International Journal of Hygiene and Environmental Health

The carcinogenic potential of nanomaterials, their release from products and options for regulating them

Heidi Becker, Frank Herzberg, Agnes Schulte, Marike Kolossa-Gehring

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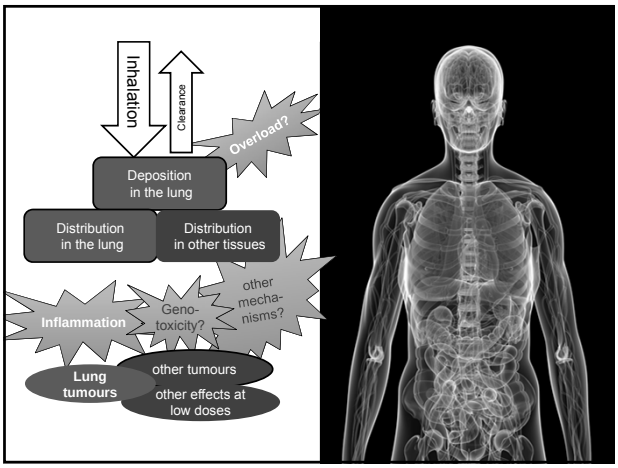

Regulatory Goals

Assess long-term toxicity of granular, biopersistent dusts of nanomaterials

- to aid threshold setting
- same mechanisms as non-nano?
- overload, inflammation or Genotoxicity and other Mechanisms?

Generate data to compare short-term studies' and *in vitro* results

Support

NanoREG (NMP.2012.1.3-3 Regulatory testing of nanomaterials)

OECD sponsorship program

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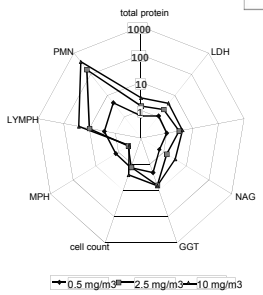
Short-term Inhalation on CeO_2



Increased inflammation markers even at the low concentration

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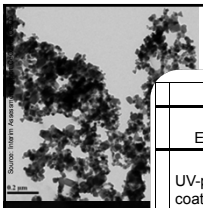
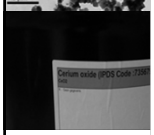
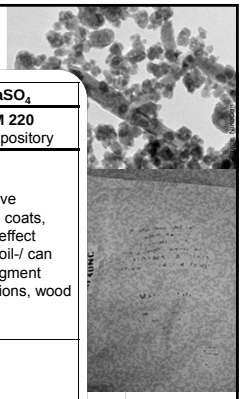
Testmaterials







	CeO_2	$BaSO_4$
	NM 212 EU repository	**NM 220** EU repository
	UV-protection in coating, plastics, cosmetics, novel product: Si-wafer polishing, under evaluation: fuel combustion catalyst	Filler for automotive top/base coats, metallic-effect paints, coil-/ can coats, pigment preparations, wood coatings
Mean particle size:	28 nm	32 nm
BET surface area:	28 m^2/g	39 m^2/g
Crystalline shape:	cubic	cubic, rods

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Toxicological Data on CeO_2

Short-term inhalation (nanoCare, 2009)	0.5 2.5 and 10 mg/m3 Mild inflammation, histocytosis Not completely reversible in 28 days No translocation outside lung (&LN)
Short-term and 28 day inhalation (Cassee et al. 2011, Geraets et al. 2012)	Inflammation Accumulation in pulmonary tissues

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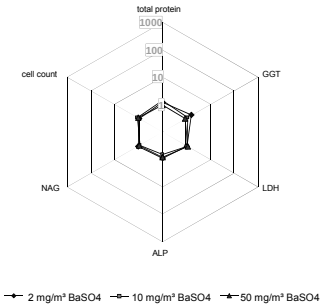
Short-term Inhalation on $BaSO_4$



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Toxicological Data on $BaSO_4$

Short-term inhalation (nanoCare, 2009)	2, 10 and 50 mg/m³ Neither inflammation nor other toxicity No translocation outside lung (&LN)
Subchronic inhalation, non-nano (Cullen et al. 2000, Tran et al. 2000)	75 mg/m³ Mild increase of PMN
2 month inhalation, non-nano (Einbrodt et al. 1972, Holusa et al. 1973)	40 mg/m³ Mild inflammation

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Pre-Studies

- **Technical pre-studies**
  - Set-up of the equipment
  - Aerosol generation and characterization
- **Biokinetic studies**
  - Persistence in biological media
  - Oral uptake
  - Lung burden and clearance
  - Translocation to extrapulmonary tissues
- **Range-finding studies**
  - Short-term inhalation studies (5 and 28 days)

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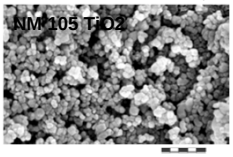
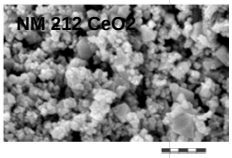
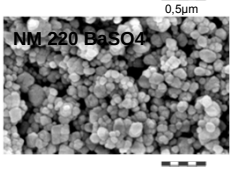
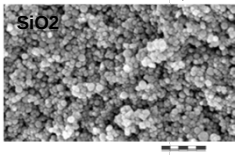
Particle structure after 28 days in PSF

NM105, NM220: spherical. NM212: spherical and rhombic.
SiO2: Dissolution, Ostwald ripening.









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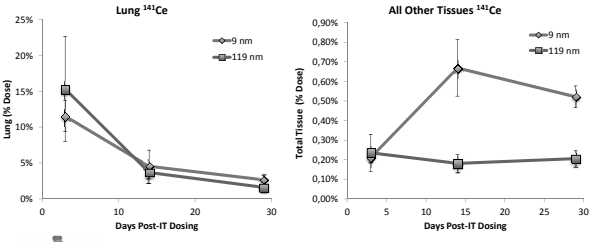
Biokinetics of IT-Instilled $^{141}CeO_2$



13% deposition in lung, cleared in 3 weeks (both sizes)
Translocation up to 0.7%

Study Design

OECD TG 453
Under **GLP**

- **Increased sensitivity:**
  Increased animal number
  Extended histopathology
  Post-exposure observation up to six month (30 month total)
- **Additional examinations** :
  Toxikokinetics (lung burden; organ distribution)
  Genotoxicity
  Bronchoalveolar lavage

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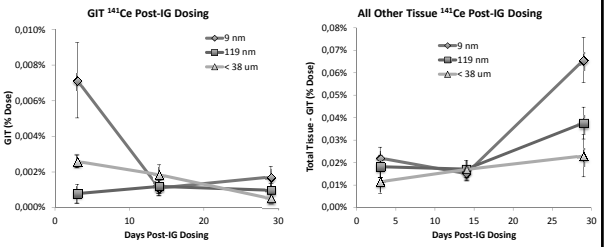
Biokinetics of IG-Instilled $^{141}CeO_2$



Fast clearance from GIT
Slow translocation up to 0.07%

Test Concentrations

Test concentrations will depend on the results of

- 28 days pre-study (BASF)
- Toxicokinetic studies (Havard University)

Animal number	Concentration	Testmaterial	Expected Inflammation	Expected Overload
100	Low	CeO_2	-	-
100	Low	CeO_2	-	-
100	Mid	CeO_2	x	-
100	High	CeO_2	x	x
100	High	$BaSO_4$	-	x
100	0	control	-	-

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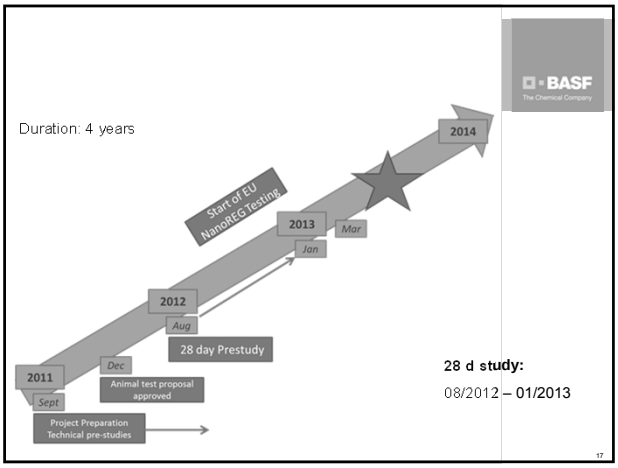

Sehr geehrter Herr Dr. Mellert,

aufgrund des § 8 Abs. 1 des Tierschutzgesetzes in der Fassung der Bekanntmachung vom 18.05.2006 (BGBl. I. S. 1206) zuletzt geändert durch Gesetz vom 15.07.2009 (BGBl I. S. 1950) i. V. m. § 1 der Landesverordnung über Zuständigkeiten auf dem Gebiet des Tierschutzrechts (GVBl 2005 S. 146) erteile ich Ihnen hiermit die

G E N E H M I G U N G

zur Durchführung des Tierversuchsvorhabens

Kombinierte chronische und Kanzerogenitätsstudie mit Nanomaterialien in der Ratte nach inhalativer Exposition

Leiterin des Versuchsvorhabens ist Frau Dr. rer. Lan Ma-Hock, Stellvertreter ist Herr Roland Büsen. Sie erfüllen beide die Voraussetzungen des § 8 Abs. 3 Nr. 2 des Tierschutzgesetzes.

Die Genehmigung gilt bis zum 31.05.2015 und erstreckt sich auf Versuche mit 795 Ratten.

Die von Ihnen aufgezeigte Versuchsplanung einschließlich der Ergänzung vom 03.05.2012 zu den einzusetzenden Materialien ist bindend.

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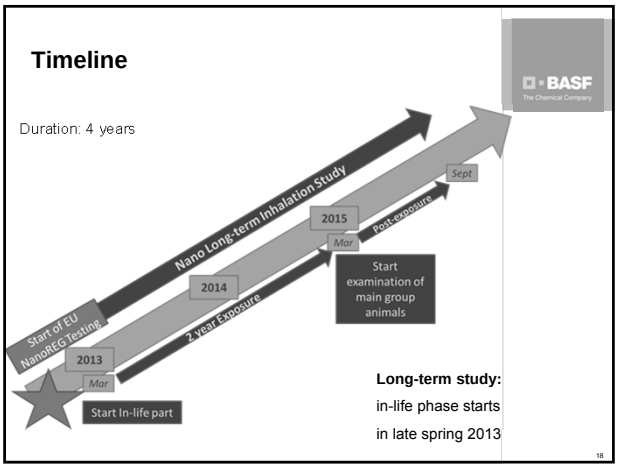

Project Partners

BASF
The Chemical Company

BASF SE, Experimental Toxicology and Ecology
Robert Landsiedel, Lan Ma-Hock, Jana Keller, Sibylle Groeters

BASF SE, Product Safety
Karin Wiench

Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit

Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit
Anke Jesse, Cornelia Leuschner

baua:
Bundesanstalt für Arbeitsschutz und Arbeitsmedizin

Bundesanstalt für Arbeitssicherheit und Arbeitsmedizin
Tom Gebel

BfR
Risiken erkennen – Gesundheit schützen

Bundesinstitut für Risikobewertung
Peter Laux

Umwelt Bundes Amt
Für Mensch und Umwelt

Umweltbundesamt
Petra Apel

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External Advisory Committee

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Thomas Kuhlbusch
(Instituts für Energie- und Umwelttechnik e.V.)

Günter Oberdörster
(University of Rochester, School of Medicine & Dentistry)

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VDI nachrichten
TECHNIK WIRTSCHAFT GESELLSCHAFT
Deutschland plant eine Mission zum Südpol des Mondes
Industrie und Politik wollen Nano sicher machen

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NanoSafety Projects at BASF

Hazard
Exposure
Regulation

2007 2008 2009 2010 2011 2012 2013

NanoCare
NanoGEM
ong-term Tox.
Eco- /EFate
NanoReg
NanoMile
P

>100 toxicological tests with nanomaterials

inhalation tests with more than 30 nanomaterials

>35 publications in scientific peer reviewed journals

www.nanotechnology.basf.com

HESI - ILSI program
EPA voluntary program
ILSI nanorelease

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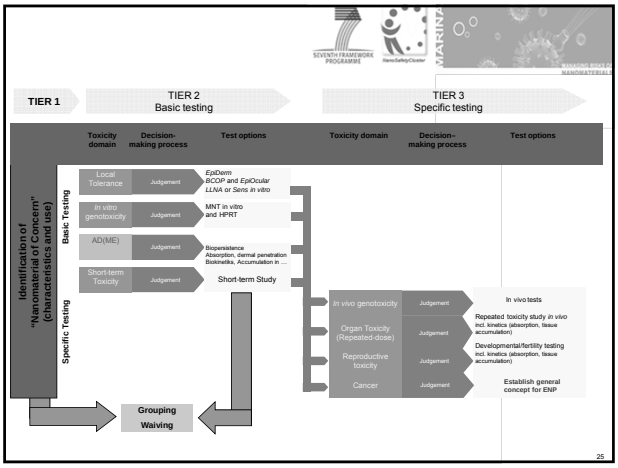

Comparison of Toxic Potency in STIS and Mid- and Long-term Studies

STIS

$BaSO_4$
precipitated SiO_2, Carbon Black (low surface), ZrO_2
TiO_2, pyrogenic SiO_2
MWCNT

NOAEC mg/m³
50
10
1
0.1

Long-term Studies

$BaSO_4$
precipitated SiO_2, Carbon Black (low surface), ZrO_2
TiO_2, pyrogenic SiO_2
MWCNT

NOAEC mg/m³
50
10
1
0.1

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Summary of Effects with different Nanomaterials

Material	Conc. [mg/m³]	NOAEC [mg/m³]	BAL	Pathology	Reversibiliyt	Translocation
Quarz	100	-	pronounced inflammation	diffuse histocytosis increased apoptosis granulomatous inflammation	not complete	no indication
SiO_2	0.5; 2.5; 10	**10**	no effects	no effects	-	no indication
SiO_2 coated	0.5; 2.5; 10	**10**	no effects	no effects	-	Yes in Spleen
p TiO_2	250	-	inflammation	diffuse histocytosis / increased apoptosis	not complete	no indication
TiO_2	2, 10, 50	**2**	inflammation	histocytosis	not complete	no indication
p ZnO	12.5	-	inflammation	mild diffuse histiocytosis nose: necrosis	yes	Yes (Zn ions?)
ZnO	0.5; 2.5; 12.5	**≤ 0.5**	inflammation	lung: inflammation / cell death; nose: necrosis	yes	Yes (Zn ions?)
CeO_2	0.5; 2.5; 10	**< 0.5**	inflammation	histocytosis, mild inflammation	not complete	n.d.
CeO_2 dotiert	0.5; 2; 10	**< 0.5**	inflammation	histocytosis, mild inflammation	not complete	n.d.
$BaSO_4$	2; 10; 50	**50**	no adverse finding	no adverse finding	-	n.d.
Carbon-black	0.5; 2.5; 10	**10**	no effects	no effects	-	n.d.
MWCNT	0.1; 0.5; 2.5	**≤ 0.1**	inflammation	inflammation	no	no indication

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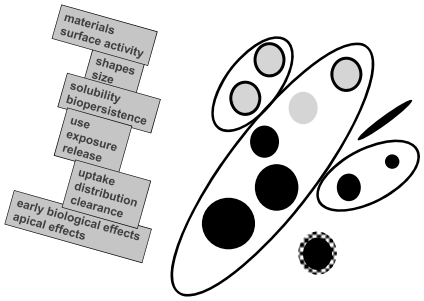
Grouping of Nanomaterials by various criteria



Grouping
Testing Program

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