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Good Practice for Safe Handling of Nanomaterials in the Chemical Industry

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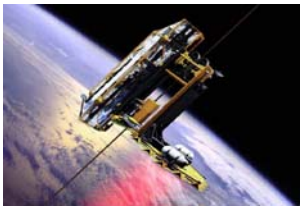
Fachtagung am 16.11.2010 bei der IHK in Karlsruhe

„Nanomaterialien – wie gehen wir damit um?“

Nanotechnology is a Key Enabling Technology

- **Nanotechnology can help to develop new and improved products**



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Emerging Concerns Linked with Nanotechnology

Miniaturisation: End of privacy?

Military: nano-soldiers?

Nano in food: Toxic?

Impact on the environment?

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Current Prevalent Concerns: HSE Issues

- **Only a small minority of media reports on nanotechnology currently deal with concerns***
- **In recent years crystallisation of concerns on HSE issues, particularly on <u>discrete free nanoparticles & nanotubes</u> because of their small size, high surface reactivity and fibre shape**

How to address the emerging concerns?

*Federal Institute for Risk Assessment (BfR, 2008)
Label: Etc group (2007)

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Responsible Development of Nanomaterials

- **Implementation of appropriate safety measures at the workplace is necessary, but not enough.**

→ **Way forward based on a multi-stakeholder approach**

- Get the Safety Facts Right
- Make Sure that we all Follow the Same Approach
- Prevent the Stigmatisation of Nano as „Toxic“
- Support a Responsible Behaviour in the Value-Chain
- Become a Trusted Partner

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Get the Safety Facts Right

- **Review published toxicological findings**
- **Perform (eco)-tox testings and exposure measurements**
- **Implement appropriate safety measures at workplace**
- **Participate in public safety research projects**

Bundesministerium für Bildung und Forschung

nanoCare

TRACER

nanoGEM

Inno.CNT

Ensure funding for safety research
Focus on specific questions relevant for risk assessment

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Toxicological Test Program with Baytubes®

All standard studies performed so far with the MWCNT Baytubes® show no relevant adverse effect at realistic exposure level (GLP studies according to OECD Guidelines). Results continuously presented at scientific meetings and published

- **Acute toxicity, oral (OECD 423)**
  - LD50 rat: >= 5.000 mg/kg
- **Acute toxicity, dermal (OECD 402)**
  - LD50 rat: > 2.000 mg/kg
- **Primary skin irritation (OECD 404)**
  - Non-irritant (rabbit)
- **Primary eye irritation (OECD 405)**
  - Non-irritant (rabbit)
- **Sensitization (OECD 406)**
  - Negative (Guinea pig)
- **Genotoxicity in vitro***
  - Not clastogenic in chromosome aberration test in vitro (OECD 473)
  - Not mutagenic in AMES Test (OECD 471) and HPRT TEST (OECD 476)

*** Wirnitzer et al. (2009) Toxicology Letters 186, 160-165**

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Inhalation Studies in Rats with Baytubes®

- **Goal of testing:** Cover regulatory aspects and gain insight in the principle mode(s) of action
- **Results**
  - **Acute inhalation study (extended OECD 403)[1]**
    - No mortality (LC50 rat: > 241 mg/m³)
    - Effects with Baytubes markedly different from Quarz
    - Conc. >=11 mg/m³ cause a poorly soluble particle effect (essentially reversible)
  - **Subchronic inhalation study (extended OECD 413)[2]**
    - Principal findings correspond with those described for "Poorly Soluble Particle" (PSP effect); a volumetric overload rather than specific structural features seems to be causative for the effects observed
    - 0.1 mg/m³ was tolerated without changes considered to be adverse (NOAEL)
- **Bayer Occupational Exposure Limit (OEL): 0.05 mg/m³ (8h TWA)[3]**

(1) Ellinger-Ziegelbauer and Pauluhn (2009) Toxicology 266, 16–29; Pauluhn (2009) Inhalation toxicology 21 Suppl. 1:40-54
(2) Pauluhn (2010) Toxicol. Sci. 113: 226-242
(3) Pauluhn (2010) Regul. Toxicol. Pharmacol. 57, 1, 78-89

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Make Sure that we all Follow the Same Approach

- **Harmonised definitions (DIN/ISO)**
  - Specification on Terminology (“what is nano?”)
  - Work on Characterisation
- **Global testing guidelines (OECD)**
  - In general the OECD guidelines are applicable, need for guidance for sample preparation and dosimetry (OECD Report ENV/JM/MONO(2009)21)
- **Risk assessment methodology**
  - “*The basic risk assessment paradigm for nanomaterials is essentially the same as for traditional chemicals*.” (OECD Report ENV/CHEM/NANO(2010)12)

Support harmonisation, avoid inconsistent local initiative

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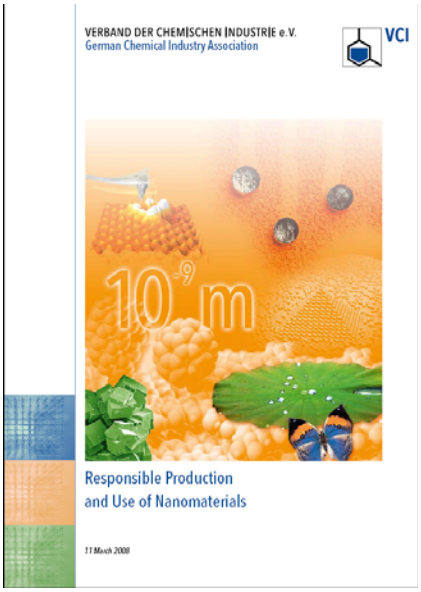
Responsible Production and Use of Nanomaterials (VCI)



- Implementing Responsible Care® for a Responsible Production and Use of Nanomaterials
- Requirements of the REACH Regulation on Substances which are Manufactured or Imported also as Nanomaterials
- Guidance for a Tiered Gathering of Hazard Information for the Risk Assessment of Nanomaterials
- **BAuA/VCI Guidance for Handling and Use of Nanomaterials at the Workplace**
- Guidance for the Passing on of Information along the Supply Chain in the Handling of Nanomaterials via Safety Data
- Strategy Paper of the German Chemical Industry on the Standardisation of Nanomaterials
- Roadmap for Safety Research on Nanomaterials
- Environmental Aspects of Nanoparticles

www.vci.de/Nanomaterialien

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Prevent the Stigmatisation of Nano as „Toxic“

- **„Nano“ is an indication of scale, not a hazardous property**
- **“*Nanomaterials are similar to normal substances in that some may be toxic and some may not*” (*SCENIHR Opinion “Risk Assessment of Products of Nanotechnologies”, 2009*)**
- **„*Die Wirkung von „Nano“ lässt sich daher nicht pauschal beurteilen, sondern hängt von dem jeweiligen Nanomaterial ab*“ (*Conclusion from the project NanoCare, 2009*)**

Reduce unjustified fears
Differentiate between different materials & applications (case by case)

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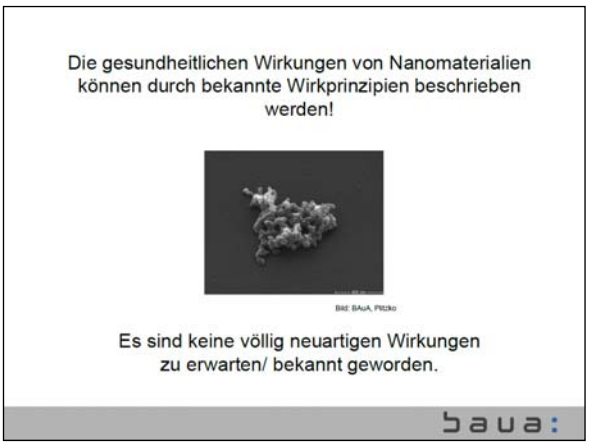
No New Health Effect of Nanomaterials Expected



- **„Gesundheitliche Wirkungen von partikulären Nanomaterialien - derzeitiger Kenntnisstand“ bei Prof. Dr. Tom Gebel (BAuA, 2010)**
- **http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/Nanotechnologie/pdf/Vortrag-Gebel-01.pdf?__blob=publicationFile&v=2**

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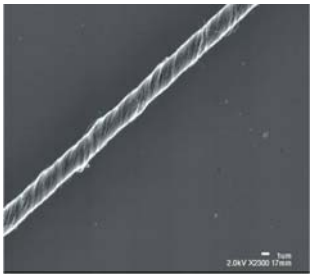
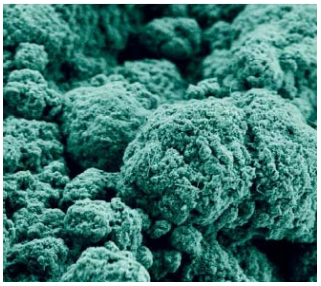
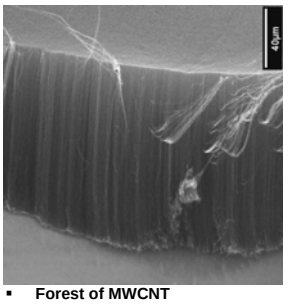
A Great Variety of Different Forms of CNTs Exist



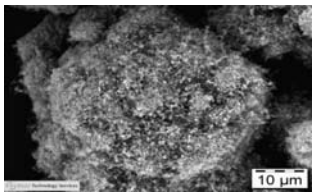
- **DWCNT spun into fibers**
  (www.lanl.gov)



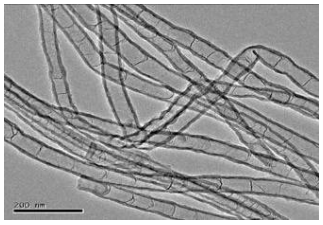
- **MWCNT as agglomerates**
  (www.arkema.com)



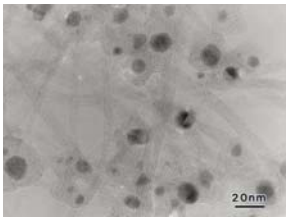
- **Forest of MWCNT**
  (www.me.mtu.edu)



- **Agglomerates of Baytubes®**



- **Bamboo-like CNTs**
  (www.nanotechweb.org/cws/article/tech/33725)



- **SWCNT by arc discharge**
  (www.nano-lab.com)

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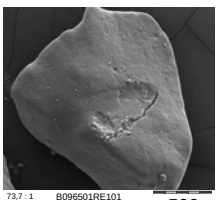
Baytubes® – Characterisation

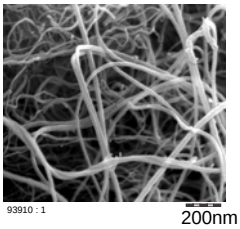
- **Baytubes® are Multi-Walled Carbon Nano Tubes:**
  - Form large and stable agglomerates of high chemical purity
  - Short, thin & entangled tubes (diameter ca. 10-15nm)
  - Display a low respirable dustiness (EN15051-B)
  - Have an low agglomerate density



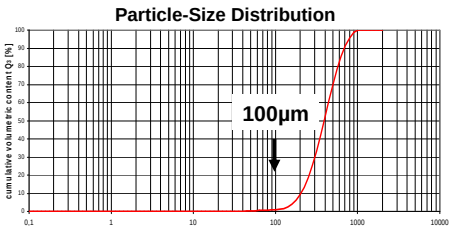
500µm

Magnification

X1300



200nm



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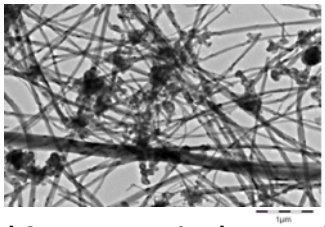
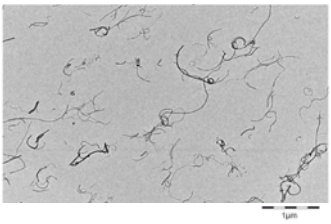
Differentiated Picture for Carbon nanotubes





- **Hazard Assessment: In vivo Toxicity of MWCNT compared to Asbestos?**
  - „Long and thick“ MWCNT
    - fiber-like response in short term assay[1] as well as mesothelioma[2] reported
  - „Short, thin and tangled” MWCNT
    - no fiber effect in short term assay[1] and no carcinogenic response in long term study[3]
- **CarboTox started in Sept. 2010**
  - Project sponsored by BMBF with ca. 1Mil€ budget to develop screening tests for possible carcinogenic potential of CNTs

1. Poland et al., Nature Nanotechnology (2008) 3, 7, 423 – 428
2. Tagaki et al., J. Toxicol. Sci. (2008) 33, 1, 105-116; Sakamoto et al., J. Tox. Sci. 34, 65-76, 2009
3. Muller et al., Tox. Sci. (2009), 110, 442-448

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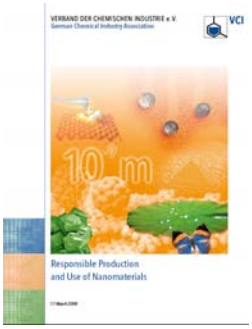
Support Responsible Behaviour in the Value-Chain

- **Recommendations for safety**



- **Projects along the value-chain**

- **Communication**

Safe use of the chemical industry products can only be ensured when the whole value-chain is informed and committed

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Become a Trusted Partner

- **Provide sound information**
  - **Website, scientific symposiums, political forums**
- **Engage with Stakeholders**
  - **Participation in Stakeholder Workshops**
  - **NanoDialog from NanoKommission**
  - **Direct dialogue**
- **Gain credibility**

Build trust and foster long-term cooperations

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Responsible Development of Nanomaterials

- **Nanotechnology can help to develop new and improved products**
- **Emerging concerns linked with nanomaterials focus on HSE issues**
- **Way forward based on a multi-stakeholder approach**
  - Get the Safety Facts Right
  - Make Sure that we all Follow the Same Approach
  - Prevent the Stigmatisation of Nano as „Toxic“
  - Support a Responsible Behaviour in the Value-Chain
  - Become a Trusted Partner

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“The safe and environmentally sound handling is essential for every new technology.”

Bayer Code on Nanomaterials

www.baycareonline.com

Thank You for Your Attention

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BACK-UP

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Hazard Assessment: Evaluation of the literature on CNTs (1/2)

Specific Question: In vivo Toxicity of MWCNT compared to Asbestos after i.p. or intrascrotal application

- **Tagaki et al.[2]: study in mice inadequate**
  - Non standard animal model (p53+/- heterozygous knock out mouse) of unknown relevance in the context of fibre toxicity
    - no historical experience with the test system; no information if the test system is able to differentiate between fibre toxicity and particle or solid state effects
      - very high sensitivity even for unspecific "solid state carcinogenicity" (shown by Tazawa et al., Carcinogenesis 28, 191-198, 2007)
  - Extremely high single dose (3 mg/mouse => very strong local reaction, e.g. peritonitis);
  - References: crocidolite and fullerene
  - **"Long and thick" MWCNT tested**
    - **Induction of mesothelioma**

- **Poland et al.[1]: short-term study in mice (7 days)**
  - Historical experience available with the test system; Single dose 50 µg/mouse;
  - References: short and long fibre amosite, carbon black
  - 2 different types of MWCNTs tested
    - **Fiber-like pathogenic behavior for "long, thick" CNTs***
    - **No fiber effect for "short, thin, tangled" CNTs**

1 Poland et al., Nature Nanotechnology (2008) 3, 7, 423 – 428; 2 Tagaki et al., J. Toxicol. Sci. (2008) 33, 1, 105-116

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Hazard Assessment: Evaluation of the literature on CNTs (2/2)

Specific Question: In vivo Toxicity of MWCNT compared to Asbestos after i.p. or intrascrotal application

- **Muller et al.[3]: long-term study in Wistar rats**
  - Historical experience available with the test system;
    - Two single high doses: 2 and 20 mg/rat;
    - Observation period 2 years
  - Reference: crocidolite
  - **"Short, thin and tangled" MWCNTs tested**
    - **No carcinogenic response**

- **Sakamoto et al.[4]: long term study in F344 rats**
  - Intrascrotal injection; Non standard animal model
  - no historical experience with the test system
    - High single dose (3 mg/kg bw);
    - Observation period 52 weeks
  - Reference: crocidolite
  - **"Long and thick" MWCNT tested (same test substance as Tagaki et al.)**
    - **Induction of Mesothelioma (but no response in the positive control group)**

3 Muller et al., Tox. Sci. (2009), 110, 442-448; 4 Sakamoto et al., J. Tox. Sci. 34, 65-76, 2009

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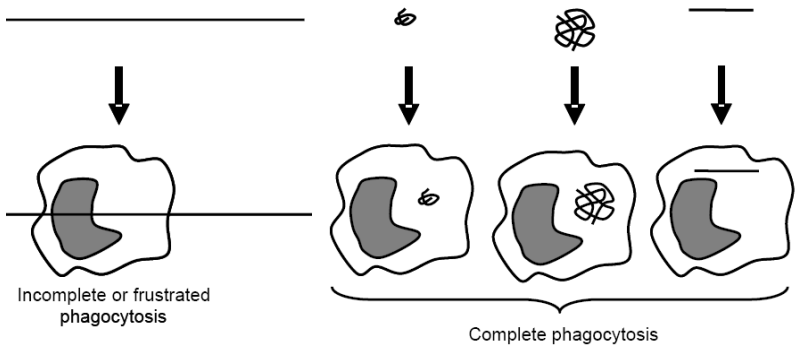
Fiber Pathogenicity Paradigm

- **Frustrated phagocytosis is caused by linear fibers longer than ca. 15µm (longer than macrophage).**



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