Regulatory Nanotoxicology
- Applying the ”Late Lessons from Early Warnings” to Nanotechnology

Steffen Foss Hansen
March 30, 2009
Definitions of Nanotechnology

“Nanotechnology is the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications.”
(The US National Nanotechnology Initiative 2006)

”Nanotechnology cannot be defined in terms of dimensions alone. In fact, it represents a convergence of the traditional disciplines of physics, chemistry and biology at the common research frontier”
(EU-Commissioner Busquin, October 2000)
Why is NT so fantastic?

- Nanotechnology enables us to manipulate with matter at the nanoscale.
- At the nanoscale materials differ in fundamental and valuable ways from the individual atoms, molecules or bulk.

Bulk
3 nm Au
1 nm Au
Copper nanocrystals

Zelens®
Fullerene C-60
Eye Cream

Nanomaterials

Bulk

Surface

Particles

Structured surface, film and structured film

One phase or Multi phase

DTU Environment
Department of Environmental Engineering

Hansen et al. 2007 Nanotoxicology 1:243-250
Nano-ZnO – One Chemistry, Many Shapes

DTU Environment
Department of Environmental Engineering

Courtesy of Prof. Z.L. Wang, Georgia Tech
1- Organic Light Emitting Diodes (OLEDs) for displays
2 - Photovoltaic film that converts light into electricity
3 - Scratch-proof coated windows that clean themselves with UV
4 - Fabrics coated to resist stains and control temperature
5 - Intelligent clothing measures pulse and respiration
6 - Bucky-tubeframe is light but very strong
7 - Hip-joint made from biocompatible materials
8 - Nano-particle paint to prevent corrosion
9 - Thermo-chromic glass to regulate light
10 - Magnetic layers for compact data memory
11 - Carbon nanotube fuel cells to power electronics and vehicles
12 - Nano-engineered cochlear implant

- As pervasive in our society as electricity is today!
Current Applications

Market application focus of nanotechnology companies in Europe 2007

- Healthcare and Life Sciences: 25%
- Consumer Goods: 10%
- Energy: 6%
- Environment: 6%
- Defense and Security: 7%
- Food: 3%
- ITC: 9%
- Personal care: 3%
- Textile: 4%
- Aerospace: 1%
- Automotive and Transportation: 6%
- Chemicals: 9%
- Construction: 6%
Total Products Listed

Number of Products

Mar 8, 2006
Apr 22, 2006
Sep 29, 2006
Nov 26, 2006
May 16, 2007
Oct 2, 2007
Feb 22, 2008
Aug 21, 2008

1) http://www.nanotechproject.org/inventories/consumer/analysis_draft/
W. Wilson Center Product Inventory

**Total** = 580

![Product Categories](http://www.nanotechproject.org/index.php?id=44&action=view)

- **Health and Fitness**: 356 products
- **Home and Garden**: 75 products
- **Electronics and computers**: 50 products
- **Cross-cutting**: 45 products
- **Automotive**: 30 products
- **Goods for children**: 25 products
- **Food and beverages**: 50 products
- **Appliances**: 25 products
W. Wilson Center Product Inventory

Major materials
Analysis: Oct. 2 2007

http://www.nanotechproject.org/index.php?id=44&action=view
Ultrafine Particles vs. Nanoparticles

- Natural sources: Volcanoes, forest fires
- Anthropogenic sources: Cooking, combustion
- Particular matter $\approx 100,000$ premature deaths (EU)
- The smaller the more dangerous
- UFPs $< 0.1 \, \mu m = 100 \, \text{nm}$
- NPs $< 100 \, \text{nm}$
Asbestos fibres vs. CNT

- Asbestos fibres ≥ 250,000-400,000 deaths (EU)
- Fibres = particles with a length at least three times their diameter

- CNT
  - tubes of hexagonal carbon (graphene)
  - diameters as small as 0.4 nm
  - lengths up to micrometers
Concerns about EHS Risk of NMs

Research | Article

Manufac in the Br
Eva Oberdör
Duke University
Dallas, Texas, I

Although nano devices, and peptide derived products are accidental nanoparticle th modified with a such as cel me metals have less and fish. Fule whether a rede. The goal of this impacts on tot peroxidation w nCain GSH wa due to bacteri oxidative dama done to evalua translocation in lipid peroxid (2004). doi:10

Carbon nanotubes introduced into the abdominal cavity of mice show asbestos like pathogenicity in a pilot study

CRAIG A. POLAND1, RODGER DUFFIN1, IAN KINLOCH1, ANDREW MAYNARD2, WILLIAM A. H. WALLACE1, ANTHONY SEATON1, VICKI STONE3, SIMON BROWN1, WILLIAM MacNEE1 AND KEN DONALDSON1,*

*Space and Life Sciences.

1MRC/University of Edinburgh, Centre for Inflammation Research, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, UK
2School of Materials, University of Manchester, Oxford Street, Manchester M1 7HS, UK
3Woodrow Wilson International Center for Scholars, 1390 Pennsylvania Avenue, NW, Washington DC 20004-3027, USA
4Institute of Occupational Medicine, Research Avenue North, Riccarton, Edinburgh EH11 4AP, UK
5School of Life Sciences, Napier University, Colinton Road, Edinburgh EH10 5DT, UK
6e-mail: km.donaldson@ed.ac.uk

Published online: 20 May 2008: doi:10.1038/nuwco.2008.111

Carbon nanotubes have distinctive characteristics, but their needle-like fibre shape has been compared to asbestos, raising concerns that widespread use of carbon nanotubes may lead to mesothelioma, cancer of the lining of the lungs caused by exposure to asbestos. Here we show that exposing the mesothelial lining of the body cavity of mice, as a surrogate for the mesothelial lining of the chest cavity, to long-walled carbon nanotubes results in asbestos-like, length-dependent, pathogenic behaviour. This includes inflammation and the formation of lesions known as granulomas. This is of considerable importance because asbestos and business communities continue to invest heavily in carbon nanotubes for a wide range of products under the assumption that they are no more hazardous than graphite. Our results suggest the need for further research and great caution before introducing such products into the market if long-term harm is to be avoided.

DTU Environment
Department of Environmental Engineering
Late Lessons from Early Warnings

- European Environmental Agency
- 14 case studies where early warnings were ignored incl. asbestos, PCBs, Ozone

How do we avoid that Nanotechnology becomes a future LL?

Conclusions

- Lack of action = Very costly + unpredicted consequences to health and environment
- Decision-makers ignored not only early warnings, but also "severe and late warnings" e.g. asbestos
# Lessons Learned by the EEA

<table>
<thead>
<tr>
<th>Box 1 The 12 lessons outlined by the EEA&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acknowledge and respond to ignorance, uncertainty and risk in technology appraisal.</td>
</tr>
<tr>
<td>2. Provide long-term environmental and health monitoring and research into early warnings.</td>
</tr>
<tr>
<td>3. Identify and work to reduce scientific ‘blind spots’ and knowledge gaps.</td>
</tr>
<tr>
<td>4. Identify and reduce interdisciplinary obstacles to learning.</td>
</tr>
<tr>
<td>5. Account for real-world conditions in regulatory appraisal.</td>
</tr>
<tr>
<td>7. Evaluate alternative options for meeting needs, and promote robust, diverse and adaptable technologies.</td>
</tr>
<tr>
<td>8. Ensure use of ‘lay’ knowledge, as well as specialist expertise.</td>
</tr>
<tr>
<td>9. Account fully for the assumptions and values of different social groups.</td>
</tr>
<tr>
<td>10. Maintain regulatory independence of interested parties while retaining an inclusive approach to information and opinion gathering.</td>
</tr>
<tr>
<td>11. Identify and reduce institutional obstacles to learning and action.</td>
</tr>
<tr>
<td>12. Avoid ‘paralysis by analysis’ by acting to reduce potential harm when there are reasonable grounds for concern.</td>
</tr>
</tbody>
</table>

---

DTU Environment  
Department of Environmental Engineering
Respond to Ignorance and Uncertainty

- Accept that there is bound to be some risk to nanomaterials
- Acknowledge limitations in your knowledge
- Be alert to surprises and act proactively instead of reactively
- Be humble and expect to find evidence of harm even at the beginning

"As we know, there are no knowns. There are things, we know we know. We also know there are known unknowns. That is to say we know there are some things we do not know. But there are also unknown unknowns, the ones we don’t know we don’t know”.

“The absence of evidence is not evidence of absence”

Donald H. Rumsfeld, U.S. Secretary of Defense (on Iraqi weapons of mass destruction)
Regulating "Unknown Unknowns"

EEA experts recommend looking out for warnings e.g.:

- Novelty
- Persistency
- Readily dispersed
- Bioaccumulative
- Potentially irreversible action

How do these compare to NMs?
Novelty by definition?

“Nanotechnology is the understanding and control of matter at dimensions of roughly 1 to 100 nanometers, where unique phenomena enable novel applications.”
(The US National Nanotechnology Initiative 2006)

”Nanotechnology cannot be defined in terms of dimensions alone. In fact, it represents a convergence of the traditional disciplines of physics, chemistry and biology at the common research frontier”
(EU-Commissioner Busquin, October 2000)
Persistency of $C_{60}$

Fullerenes in the 1.85-Billion-Year-Old Sudbury Impact Structure

Luann Becker,* Jeffrey L. Bada, Randall E. Winans, Jerry E. Hunt, Ted E. Bunch, Bevan M. French

Fullerenes ($C_{60}$ and $C_{70}$) have been identified by laser desorption, laser desorption post-ionization, and high-resolution electron-impact mass spectrometry in shock-produced breccias (Onaping Formation) of the Sudbury impact structure in Ontario, Canada. The $C_{60}$ isotope is present at a level of a few parts per million. The fullerenes were likely synthesized within the impact plume from the carbon contained in the bolide. The oxidation of the fullerenes during the 1.85 billion years of exposure was apparently prevented by the presence of sulfur in the form of sulfide-silicate complexes associated with the fullerenes.

SCIENCE • VOL. 265 • 29 JULY 1994
Persistency of CNTs

Chemistry and nanoparticulate compositions of a 10,000 year-old ice core melt water

L.E. Murr\textsuperscript{a,b}, E.V. Esquivel\textsuperscript{a}, J.J. Bang\textsuperscript{a}, G. de la Rosa\textsuperscript{b}, J.L. Gardea-Torresdey\textsuperscript{b}

\textsuperscript{a}Department of Metallurgical and Materials Engineering and Environmental Science and Engineering Ph.D. Program, The University of Texas at El Paso, El Paso, TX 79968-0529, USA

\textsuperscript{b}Department of Chemistry and Environmental Science and Engineering Ph.D. Program, The University of Texas at El Paso, El Paso, TX 79968, USA

Abstract

Particulates extracted from a single section of a 10,000 year-old ice core melt sample exhibited characteristics of contemporary, airborne fine particulates: a majority were microcrystalline particulates and aggregated microcrystals, including some mixtures of microcrystals and carbonaceous matter. Particularly significant were the presence of carbon nanotubes and fullerene nanocrystals composing aggregated particulates reflecting global combustion products similar to contemporary, airborne carbon nanocrystal aggregates. ICP elemental analysis of the melt water showed significant concentrations of Ca, K and especially Na (corresponding to K, NaCl), S, Si, Se, and Zn. Overall, the elemental analysis

“Particularly significant were the presence of carbon nanotubes and fullerene nanocrystals…”
Readily dispersed?

- Are we exposed and do NMs get into the environment?

Hansen et al. 2008 Ecotoxicology 17(5):438-447
Readily dispersed?

- Water soluble vs. insoluble materials
  - Soluble generally move through aqueous environments
  - Insoluble particles have different transport mechanisms
- Lab conditions
  - Hydrophobic particles will aggregate rapidly
  - Hydrophilic particles will disperse evenly
- Unclear what happens in the environment
  - Limited number of nanoparticles
  - Interaction with natural substances
- Solubility can be engineered
  - Depends on surface chemistry and surface charge
Bioaccumulative?

- Dependence on NMs properties

- Example: Carbon nanotubes
  - Non-biodegradable
  - Insoluble in water
  - Lipophilic i.e. preference for entering fatty cell membranes
  - Indicates that carbon nanotubes are likely to bioaccumulate

- Almost nothing is known about other kinds of manufactured nanomaterials
Enhanced bioaccumulation of cadmium in carp in the presence of titanium dioxide nanoparticles

Xuezhi Zhang a, Hongwen Sun a,*, Zhiyan Zhang a, Qian Niu a, Yongsheng Chen b, John C. Crittenden b

a College of Environmental Science and Engineering, Nankai University, Tianjin 300071, China
b Department of Civil and Environmental Engineering, Arizona State University, Tempe, Arizona 85287, USA

Received 1 December 2005; received in revised form 31 July 2006; accepted 3 September 2006
Available online 12 December 2006

Abstract

In this study adsorption of Cd onto TiO2 nanoparticles and natural sediment particles (SP) were studied and the facilitated transports of Cd into carp by TiO2 nanoparticles and SP were assessed by bioaccumulation tests exposing carp (Cyprinus carpio) to Cd contaminated water in the presence of TiO2 and SP respectively. The results show that TiO2 nanoparticles had a significantly stronger adsorption capacity for Cd than SP. The presence of SP did not have significant influence on the accumulation of Cd in carp during the 25 d of exposure. However, the presence of TiO2 nanoparticles greatly enhanced the accumulation of Cd in carp. After 25 d of exposure Cd concentration in carp increased by 146%, and the value was 22.3 and 9.07 μg/g, respectively. And there is a positive correlation between Cd and TiO2 concentration. Considerable Cd and TiO2 accumulated in viscera and gills of the fish.

© 2006 Elsevier Ltd. All rights reserved.

Keywords: TiO2; Facilitated transport; Nanotoxology; Bioaccumulation
Trojan Horse Effect

Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study

CRAIG A. POLAND1, RODGER DUFFIN1, IAN KINLOCH2, ANDREW MAYNARD2, WILLIAM A. H. WALLACE2, ANTHONY SEATON2, VICKI STONE2, SIMON BROWN2, WILLIAM MACKIE1 AND KEN DONALDSON1

1NRIC/University of Edinburgh, Centre for Inflammation Research, Queen’s Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ, UK
2School of Materials, University of Manchester, Greenore Street, Manchester M1 7HS, UK
3Woodrow Wilson International Center for Scholars, 1330 Pennsylvania Avenue, NW, Washington DC 20004-2077, USA
4Institute of Occupational Medicine, Research Avenue North, Riccarton, Edinburgh EH12 9AG, UK
5School of Life Sciences, Napier University, Colinton Road, Edinburgh EH10 5DT, UK
6e-mail: ken.donaldson@ed.ac.uk

Published online: 20 May 2009, doi:10.1038/nature07681

Carbon nanotubes1 have distinctive characteristics, but their needle-like fibre shape has been compared to asbestos2, raising concerns that widespread use of carbon nanotubes may lead to mesothelioma, cancer of the lining of the lungs caused by exposure to asbestos3. Here we show that exposing the mesothelial lining of the body cavity of mice, as a surrogate for the mesothelial lining of the chest cavity, to long, multi-walled carbon nanotubes results in asbestos-like, length-dependent, pathogenic behaviour. This includes inflammation and the formation of lesions known as granulomas. This is of considerable importance, because research and business communities continue to invest heavily in carbon nanotubes for a wide range of products4 under the assumption that they are no more hazardous than graphite. Our results suggest the need for further research and great caution before introducing such products into the market if long-term harm is to be avoided.

combination of properties that are highly desirable in many industrial products5,6. Their high aspect ratio (ratio of length and width) makes them an attractive structural material, but their nanometre-scale diameter and needle-like shape have drawn comparisons with asbestos7-9. Exposure during mining and the industrial use of asbestos led to a global pandemic of lung disease. Study of disease in exposed populations showed that the main body of the lung was a target for asbestos fibres, resulting in both lung cancer and scarring of the lungs (fibrosis). The outside surface lining of the lung and its associated tissue, the pleura, was found also to be a target, with cancer of the pleura (mesothelioma), fluid accumulation in the pleural space (effusion) and scarring of the pleura (pleural thickening and plaque formation), being found in association with asbestos exposure10. A critical factor underlying this pandemic is a prolonged latency period between exposure and the development of mesothelioma, the hallmark cancer of
DTU Environment
Department of Environmental Engineering

Polard et al. 2008 Nature Nanotechnology 3, 423-428
Regulating "Unknown Unknowns"

EEA experts recommend looking out for warnings e.g.:

- Novelty
- Persistency
- Readily dispersed
- Bioaccumulative
- Potentially irreversible action

(EEA, 2001)
## Regulating "Unknown Unknowns"

Comparison for EEA’s "warnings signs" and Nanomaterials

<table>
<thead>
<tr>
<th>Feature</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novelty</td>
<td>✓</td>
</tr>
<tr>
<td>Persistency</td>
<td>✓/÷</td>
</tr>
<tr>
<td>Readily dispersed</td>
<td>✓/÷</td>
</tr>
<tr>
<td>Bioaccumulative</td>
<td>✓/÷</td>
</tr>
<tr>
<td>Potentially irreversible action</td>
<td>✓/÷</td>
</tr>
</tbody>
</table>
# Lessons Learned by the EEA

<table>
<thead>
<tr>
<th>Box 1 The 12 lessons outlined by the EEA²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acknowledge and respond to ignorance, uncertainty and risk in technology appraisal.</td>
</tr>
<tr>
<td>2. Provide long-term environmental and health monitoring and research into early warnings.</td>
</tr>
<tr>
<td>3. Identify and work to reduce scientific ‘blind spots’ and knowledge gaps.</td>
</tr>
<tr>
<td>4. Identify and reduce interdisciplinary obstacles to learning.</td>
</tr>
<tr>
<td>5. Account for real-world conditions in regulatory appraisal.</td>
</tr>
<tr>
<td>7. Evaluate alternative options for meeting needs, and promote robust, diverse and adaptable technologies.</td>
</tr>
<tr>
<td>8. Ensure use of ‘lay’ knowledge, as well as specialist expertise.</td>
</tr>
<tr>
<td>9. Account fully for the assumptions and values of different social groups.</td>
</tr>
<tr>
<td>10. Maintain regulatory independence of interested parties while retaining an inclusive approach to information and opinion gathering.</td>
</tr>
<tr>
<td>11. Identify and reduce institutional obstacles to learning and action.</td>
</tr>
<tr>
<td>12. Avoid ‘paralysis by analysis’ by acting to reduce potential harm when there are reasonable grounds for concern.</td>
</tr>
</tbody>
</table>
Late lessons from early warnings for nanotechnology

STEFFEN FOSS HANSEN†, ANDREW MAYNARD1, ANDERS BAUN† AND JOEL A. TICKNER†

†are in the Department of Environmental Engineering, NanO2 Environment and Health, Technical University of Denmark, Building 111, DK-2800 Kgs. Lyngby, Denmark; 1Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars, 1500 Pennsylvania Avenue, NW, Washington DC 20004-2818, USA; ñDepartment of Community Health and Toxicology, University of Massachusetts, Lowell, Massachusetts 01854, USA.

A new technology will only be successful if those promoting it can show that it is safe, but history is littered with examples of promising technologies that never fulfilled their true potential and/or caused untold damage because early warnings about safety problems were ignored. The nanotechnology community stands to benefit by learning lessons from this history.

Nanotechnology is the latest in a long series of technologies that have been heralded as ushering in a new era or even the next industrial revolution. Since 2001, nanotechnology has grown from little more than a gleam in the eye of researchers to a technology protected to be worth $2.0 trillion in manufactured goods in 2020. So, as new nanomaterials move from the lab to the marketplace, we have learnt the lessons of past technologies, or are we destined to repeat the mistakes made with previous technologies? In 2001 an expert panel commissioned by the European Environment Agency (EEA) published a report, Late Lessons from Early Warnings: The Precautionary Principle 1986–2000, which explored 14 case studies, all of which demonstrated how not heeding early warnings had led to a failure to protect human health and the environment.

Covering topics as diverse as asbestos, chlorofluorocarbons, ionizing radiation and mad cow disease, the EEA report examined the delays between the emergence of scientific evidence of harm and action being taken to reduce risks in each case. The expert group identified 12 “late lessons” (see Box 1) on how to avoid past mistakes as new technologies are developed. These lessons bear an uncanny resemblance to many of the concerns now being raised about various forms of nanotechnology.

A comparison between the EEA recommendations and where we are with nanotechnology shows we are doing some things right, but we are still in danger of repeating old, and potentially costly, mistakes. This commentary explores these 12 lessons in the context of nanotechnology.

LESSONS 5–6: NEED THE WARNINGS:

According to the EEA report “No matter how sophisticated knowledge is, it will always be subject to some degree of ignorance [that is, inevitable surprise or unpredicted effects]. To be alert to — and behave about — the potential gaps in these bodies of knowledge that are included in our decision making is fundamental.”

We are still in danger of repeating old, and potentially costly, mistakes.

Perhaps more than any preceding technology, the early development of nanotechnology has been characterized by discussion of potential risks. Such discussions have always been an integral part of the government-supported National Nanotechnology Initiative (NNI) in the US, for example, while a report published by the Royal Society and Royal Academy of Engineering in the UK in 2004 emphasized the need to address uncertainties regarding the risks of nanomaterials. Currently, most economists investing in nanotechnology pepper discussions about future directions in research with questions concerning potential risks — and how to manage them. However, despite some move to respond to ignorance and uncertainty rather than simply dismissing them, coordinated action seems slow in emerging. The EEA report recommends looking out for “warning signs” such as materials that are novel, expensive, readily dispersed or bioaccumulative, and/or materials that lead to irreversible action (for example, thousands of nanoparticles caused by the inhalation of asbestos dust).

These warning signs are clearly relevant to many nanomaterials, some of which have novel properties, are capable of being incorporated in highly diverse products, may be transported to places in new ways, and may be designed to be persistent. Too little a license to predict the environmental fate of nanomaterials, and feasible documentation of environmental dispersion through monitoring is not expected in the short term. The extent to which specific nanomaterials are bioaccumulative or lead to irreversible impact is largely unknown, but the current state of knowledge suggests that the potential exists for such behaviour under some circumstances.

The global response to these warning signs has been patchy, with governments bringing few if any essential data on production and use patterns and personal protection equipment. Arguably, efforts have been better than those seen with many technologies but they are still far from ideal.