Risk Management & Control of Nanomaterials COR
- A Status Attempt

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Nanosafety at the National Research Centre for the Working Environment

- Government research institute under the Danish Ministry of Employment
- Nanosafety as strategic research area since 2005
- At present 35 persons in nanosafety research
- Past and present partners in 17 EU projects on nanosafety
- Danish Centre for Nanosafety 2012-2019
- Advisors for the Danish Working Environment Authorities, EPA, EU, OECD, WHO

RISK = Hazard x Exposure

Keld A Jensen

The vision

Research →

Mechanism-based understanding of toxicological effect →

Evidence-based risk assessment. Be able to predict hazard on the basis of information on physico-chemcial properties

↓

Grouping and ranking for regulation
Safe-by-design for innovation

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← Safe use of nanomaterials including high volume nanomaterials

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Safe-by-design:

Lung cancer
Fibre-paradigm

Mineralwool

Paint based on organic solvents

Painters syndrome
Organic solvents

Water-based paint
MAL kodes

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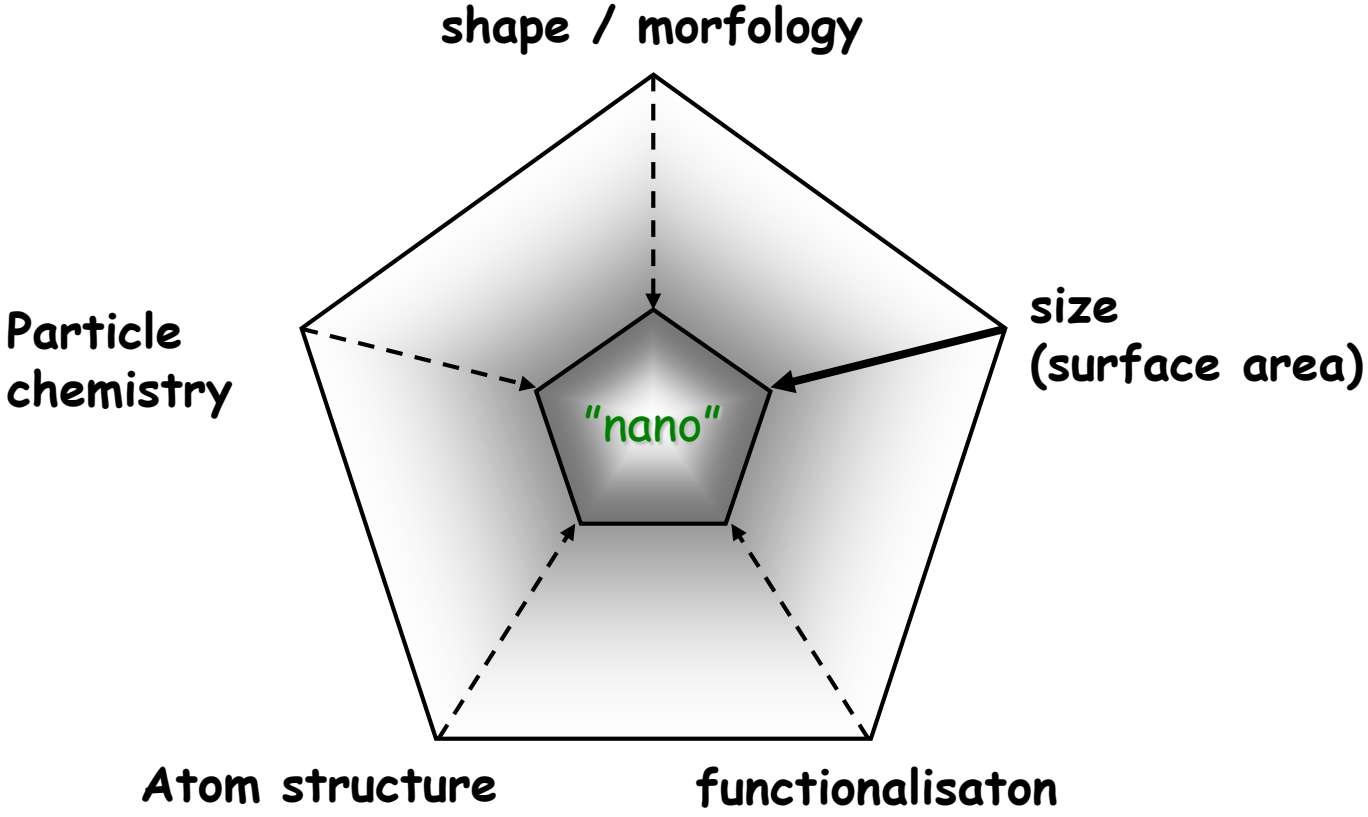
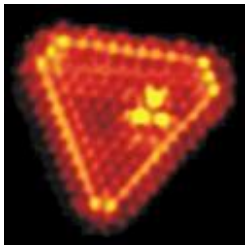
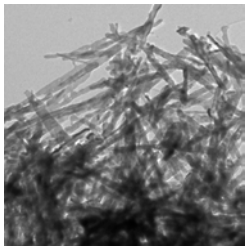
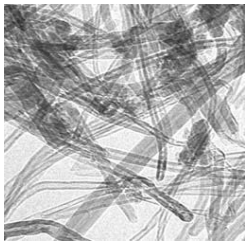
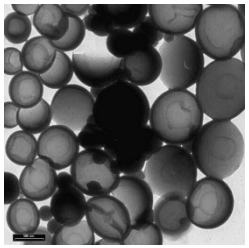
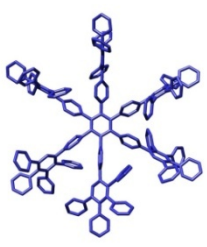
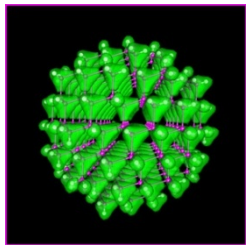
The challenge: the many different nanomaterials



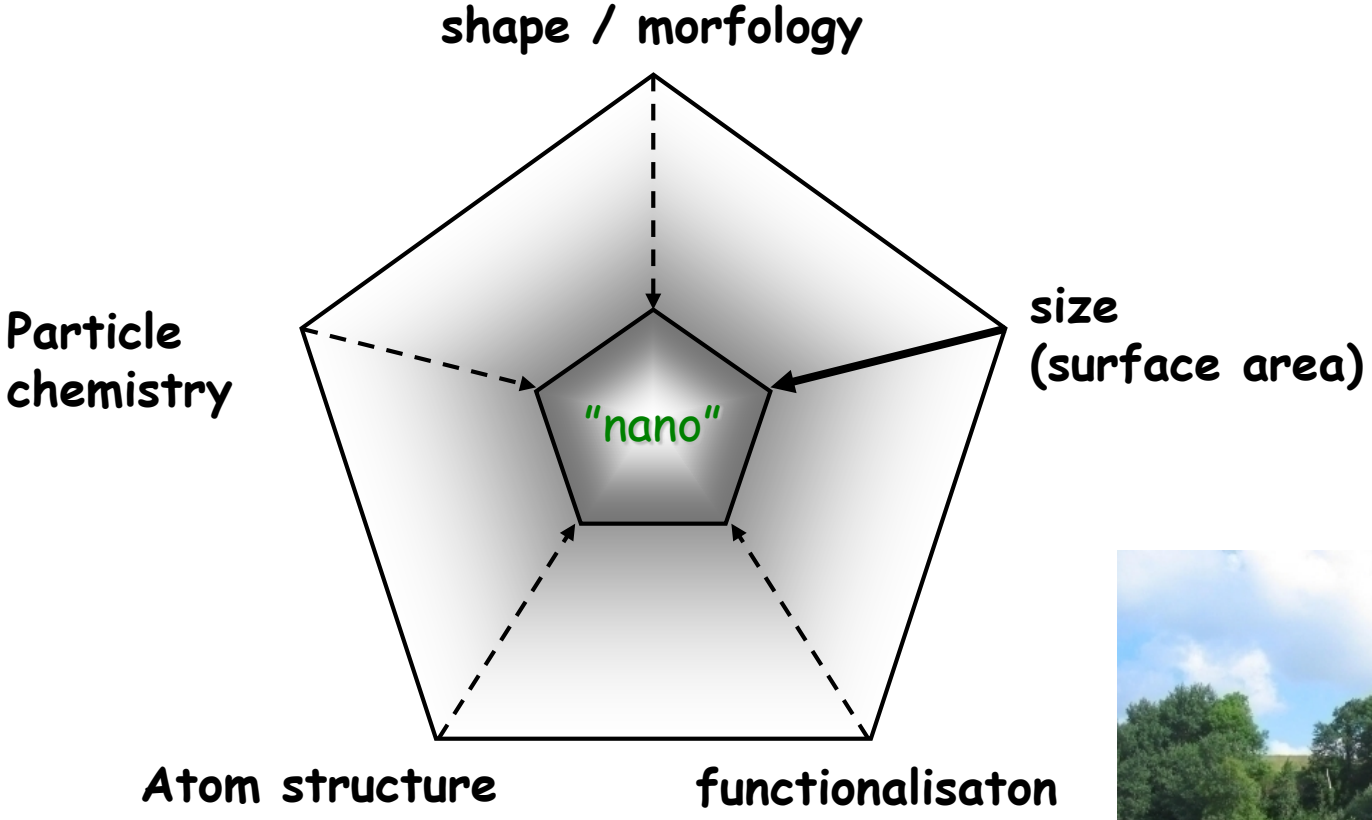



The Nano Issue

10 times smaller particles:
10^3 (1000) more particles pr mass unit
10 times larger surface area pr mass unit

The eco-nanotox challenge: the huge matrix



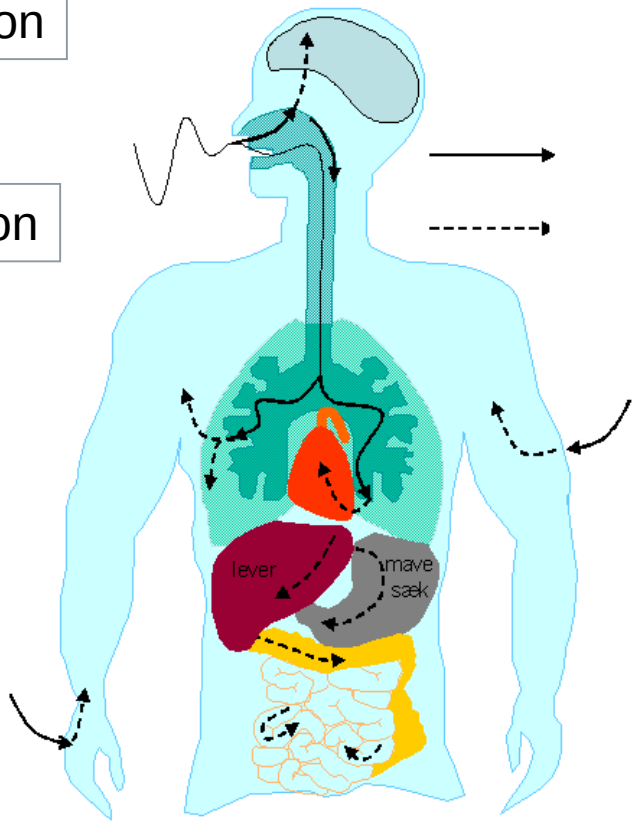
Nanosilver seems to be most hazardous due to dissolution/oxidation to Ag^+

Human hazard

Inhalation

Ingestion

Through the skin

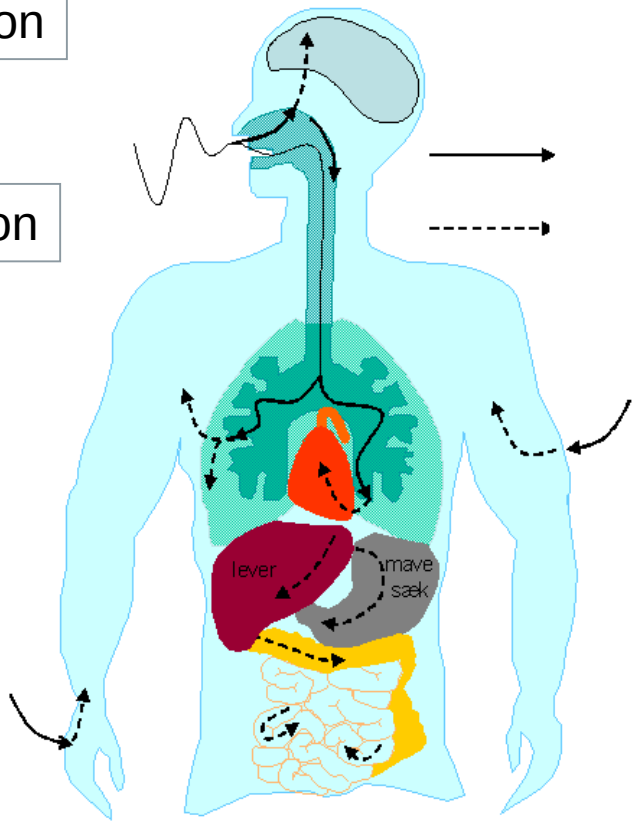


Human hazard

Inhalation

Ingestion

Through the skin



The known

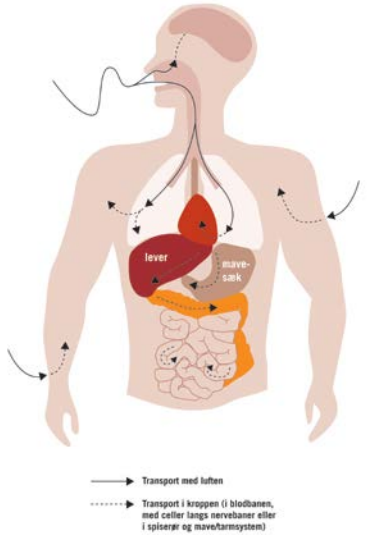
- Inhalation of inert and insoluble nanoparticles is more hazardous by mass than inhalation of larger particles with the same chemical composition
- Soluble nanomaterials may be very toxic (fx Ni particles) or nontoxic (fx $BaSO_4$) by inhalation
- Less clear whether oral or skin exposure is more hazardous than exposure to the corresponding bulk chemical

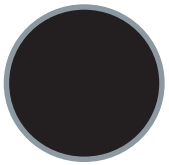
Inhalation – physico chemcical properties that matter

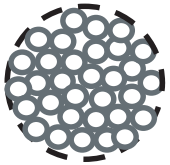
- Size of agglomerate in air
- Specific surface area
- Solubility
- Shape
- Surface reactivity

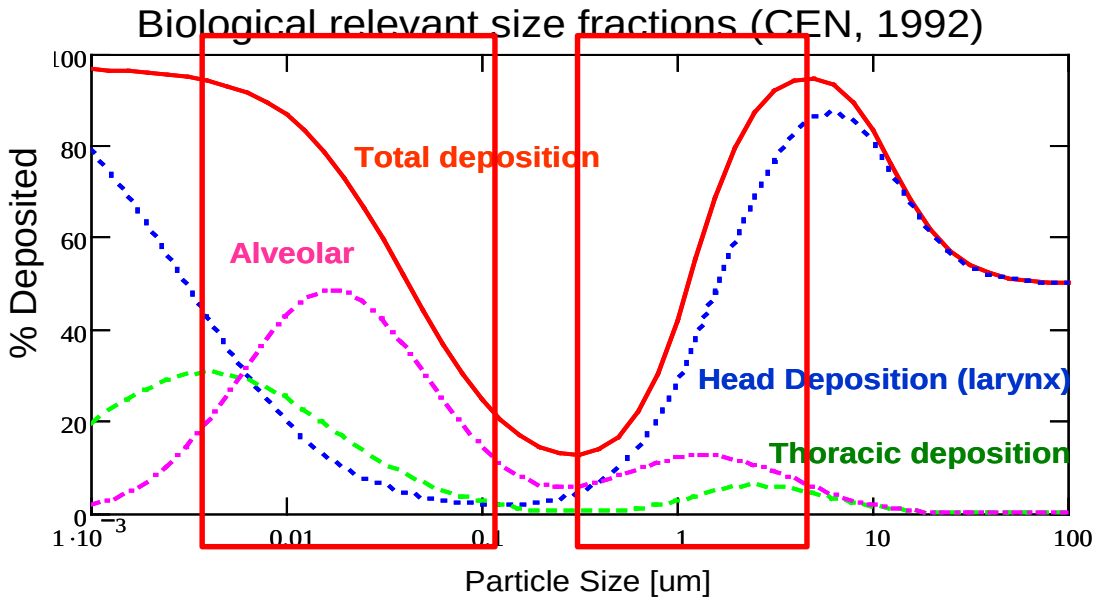
Agglomerate size predicts alveolar deposition/dose

- Size of agglomerate in air
- Deposited surface area
- Solubility
- Shape
- Surface reactivity



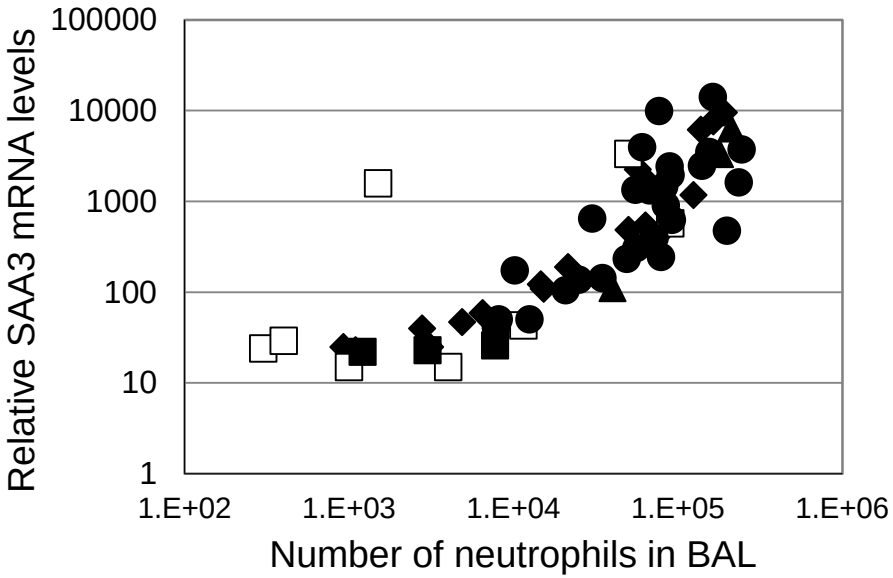


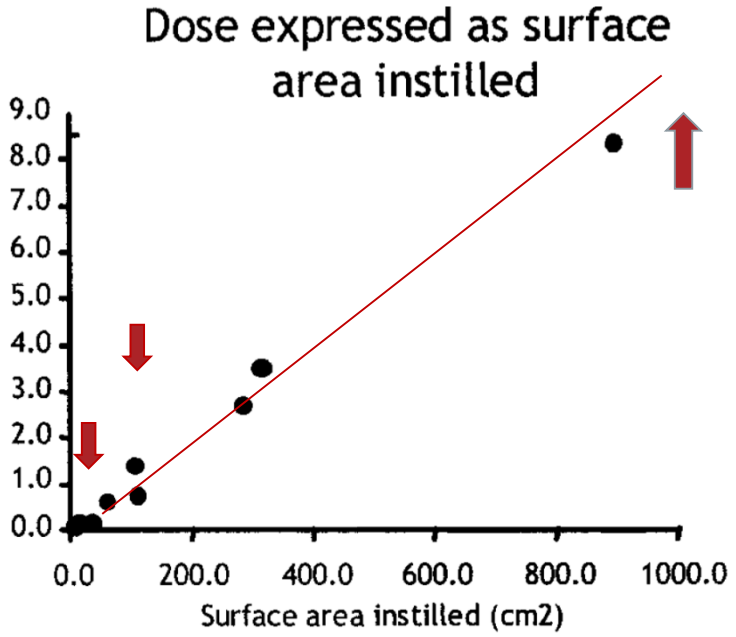




Surface area: inflammation and cardiovascular disease

- Size of agglomerate in air
- Deposited surface area
- Solubility
- Shape
- Surface reactivity





Solubility: efficient delivery of toxic metals

- Size of agglomerate in air
- Deposited surface area
- Solubility
- Shape
- Surface reactivity

Solubility:

- Release of toxic metals (Ni)
- Low toxicity of soluble low toxicity NPs such as $BaSO_4$

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 57:1073–1076 (2014)

Case Report

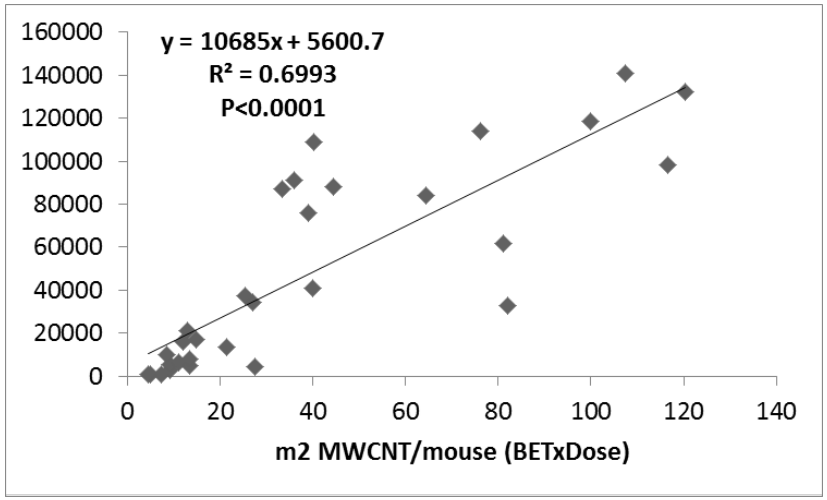
Occupational Handling of Nickel Nanoparticles: A Case Report

W. Shane Journeay, PhD, MD[1]* and Rose H. Goldman, MD, MPH[2,3,4]**

Shape: inflammation, cancer and cardiovascular disease

- Size of agglomerate in air
- Deposited surface area
- Solubility
- Shape
- Surface reactivity

Deposited surface area predicts inflammation



SS Poulsen et al, 2016 Nanotox in press

- CNTs:
- Long, thick, needle-like CNTs cause cancer by inhalation (Mitsui-7, IARC)
- Short and thin CNTs cause persistent inflammation and fibrosis by inhalation with very low NOEL (0.1 mg/m^3)
- Both CNT types cause pulmonary and systemic acute phase response linking to cardiovascular disease

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Surface: ROS generation

- Size of agglomerate in air
- Specific surface area
- Solubility
- Shape
- Surface reactivity

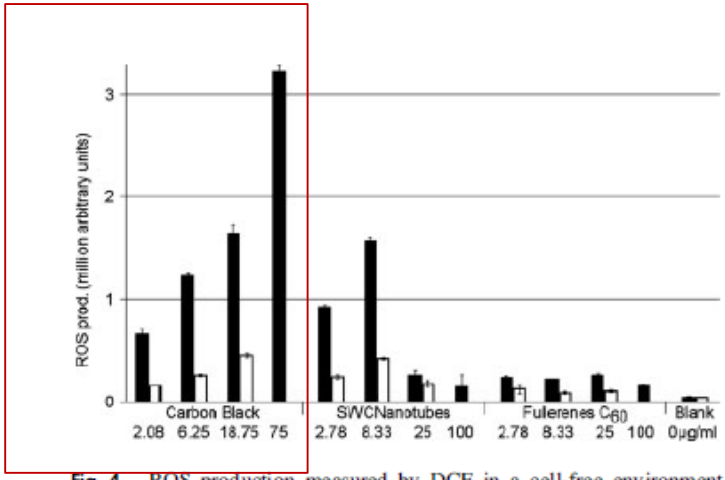

Fig. 4. ROS production measured by DCF in a cell-free environment (filled columns) or within FE1 Muta™Mouse lung epithelial cells (open columns) following 3 hr of incubation. The environment was stimulated with different mass loadings of CB, SWCNT, and C_{60}. Each bar represents the mean and SD of four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

- Carbon black as example:
- Surface dependent generation of reactive oxygen species in cellular and acellular assays
- DNA strand breaks and oxidative DNA damage in vivo and in vitro
- Increased mutation rate in vivo and in vitro
- Mutation spectrum in vitro points to oxidative DNA damage
- IARC: possibly mutagenic for humans

Toxicity in the user phase/the intended use ?

- Most data on pristine NMs
- Little data on toxicity of NMs in the user phase
- The little we know indicates that pristine NMs are most hazardous
- Relevant exposure is primarily in production and handling of NMs, ie in the working environment

Human evidence

- Epidemiology on diesel exhaust particles (Vermeulen et al, EHP 2014):

Table 2. Excess lifetime risk per 10,000 for several exposure levels and settings, United States in 2009.

Exposure setting	Average EC exposure ($\mu g/m^3$)	Excess lifetime risk through age 80 years (per 10,000)
Worker exposed, age 20–65 years	25	689
Worker exposed, age 20–65 years	10	200
Worker exposed, age 20–65 years	1	17
General public, age 5–80 years	0.8	21

Based on linear risk function, lnRR = 0.00098 × exposure, assuming a 5-year lag, using age-specific (5-year categories) all cause and lung cancer mortality rates from the United States in 2009 as referent.

- Increased levels of inflammatory markers in
  - CB exposed workers (high conc) (Zhang et al, 2014 PF&T)
  - CNT exposed workers (low air conc) (Fatkhutdinova LM et al 2016, TAAP)

Challenges & Gaps

- Standardisation
- Paradigms for measurements of NMs in air
- Mapping of nanomaterials
- Regulation of occupational exposure

Risk management

- NIOSH (USA): Proposed OELs for TiO_2 and CNTs
- Holland, Finland, Germany: Reference values as voluntery agreement between the partners on the labour market
- France and others: Register of all products that contain nanomaterials in all phases of the life cycle

Nanosafety; an example of due dilligence ?

- Time line:
  - 1990: The first paper on carbon nanotubes published
  - Ca. 2000: Massive research investments in nanotechnology-driven innovation
  - 2002-: EU funds research in Nanosafety in FP6, FP7 and H2020
  - 2012: NIOSH makes recommendation for OELs for ultrafine TiO_2 and CNTs
  - 2015: Carbon Nanotube Mitsui-7 is classified as possibly carcinogenic to humans (2B)

Nanosafety in Denmark

- 2000: Nanotechnology as innovation research investment
- 2005: Nanosafety as strategic research area at NRCWE
- 2012: Danish Centre for Nanosafety 2012-2016 and 2016-2019
- 2014: Presentation and discussion of nanosafety in the Danish Working Environment Council
- 2015: The Danish Working Environment Council makes 23 recommendations on safe use of nanomaterials in the working enviornment including a recommendation to register all nanomaterials in products in the Danish Product Register
- 2016: NRCWE is asked to make documentation for OELs for CB, TiO_2 NPs, CNTs

Take home

- Nanomaterials are more hazardous to inhale by mass than larger particles with the same chemical composition.
- Pristine nanomaterials are mostly found in production. Thus, nanomaterials are primarily a problem in the working environment.
- Exposure to nanomaterials in the working environment should be regulated.
- It is a challenge to identify nanomaterial exposures in the working environment. The French register of products containing nanomaterials is a valuable source of information.

Implications for process-generated nanoparticle exposure

- Research has shown that inert insoluble engineered nanoparticles are hazardous by inhalation
- The same is true for process- generated nanoparticles such as air pollution, cumbustion particles ect ect.
- Particle counters that count particles by measuring mass-to-charge ratio will detect large nanoparticle agglomerates as smaller single particles thus underestimating the inhaled specific surface area
- Are existing exposure limits for process-generated nanoparticles safe enough ?

Thank you for your attention

Danish Centre for Nanosafety