Bundesanstalt für Arbeitsschutz und Arbeitsmedizin

How to address health hazards of nanomaterials?

Tom Gebel
Toxicologist DGPT, Senior Scientist, Scientific Director, Prof. Dr.
Federal Institute for Occupational Safety and Health
Division 4 "*Safety and Health with Chemical and Biological Agents*"
D-44149 Dortmund

Which nanomaterials pose particular concern?

- particulate nanomaterial dusts:

  relevance of inhalation exposure

- and: high persistence in biological systems

- *not covered here : medical applications:*

  - materials are generally different due to design (e.g. solid lipids)

  - different definition (primary particle diameter up to 1000 nm)

Systemic distribution and toxicity of persistent nanomaterials

https://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/AGS/AGS-zu-Nanomaterialien_content.html

not covered here:

Distribution in(to) the body (kinetics)

generally low distribution rate

Data gap: systemic accumulation after long term exposure

Systemic toxicity (dynamics) : generally low (AGS 2011)

Data gap: systemic toxicity after long term exposure

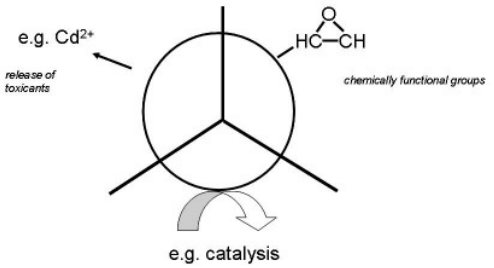
Particles may be systemically distributed – if nano or not

Example: spleen tissue, coal workers

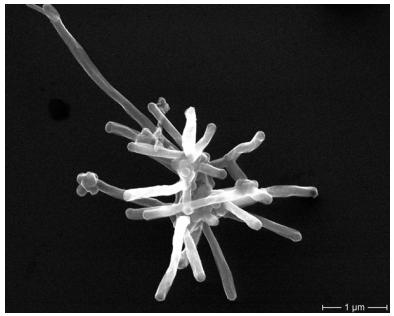
LeFevre et al. Hum Pathol. 1982;13(12):1121-6.

Nanomaterials: grouping according to mode of action

i) Is there a specific ‚chemical' toxicity?



ii) Does the fibre principle apply?

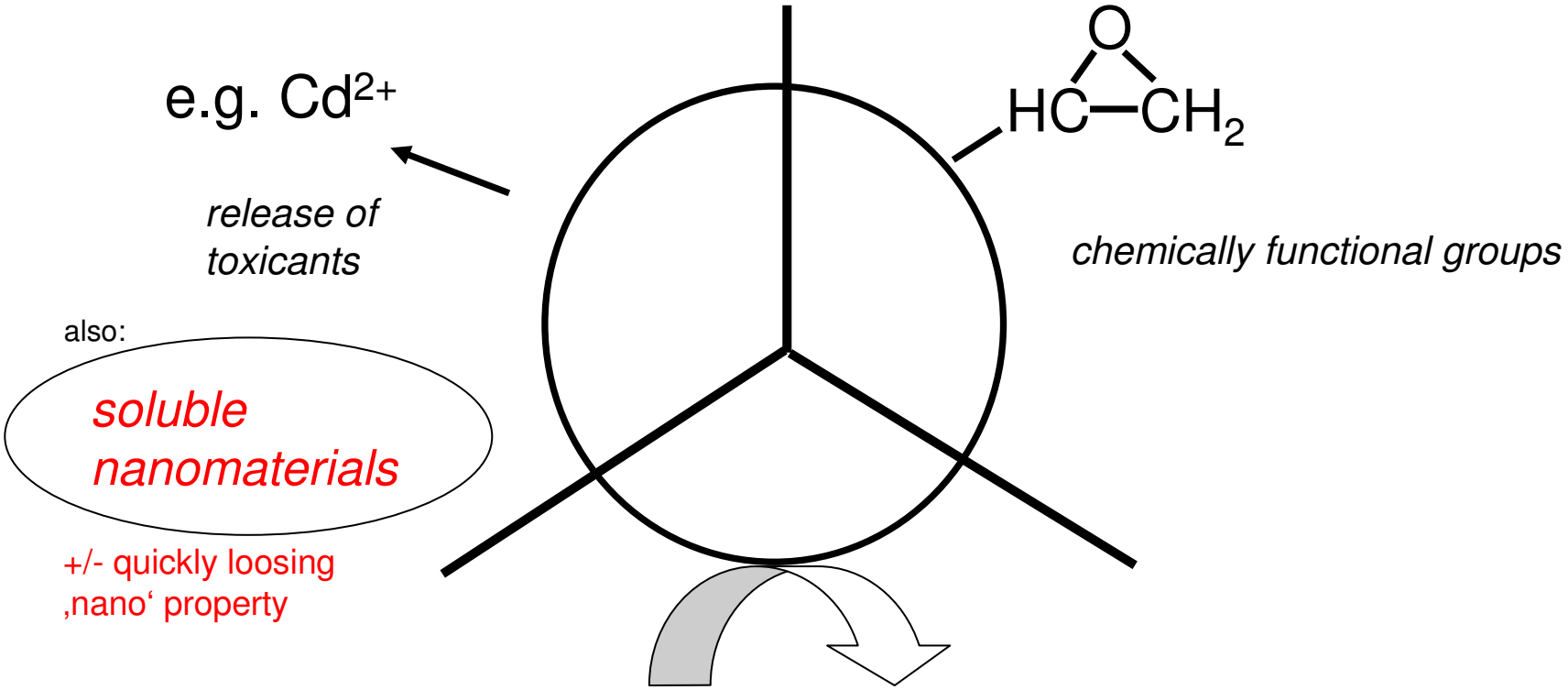


iii) Are the particles granular, biopersistent & not specifically toxic?

Pics: BAuA, Plitzko

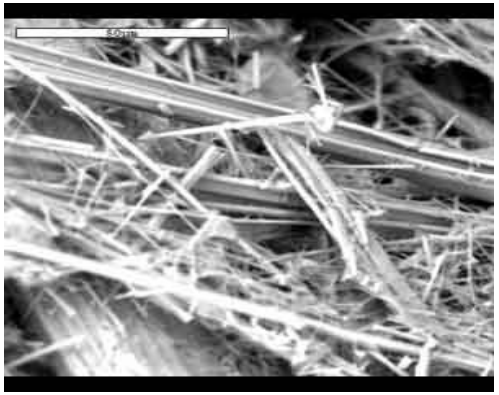
nanomaterials: possible modes of action – I-

i) Evaluation case by case, if:

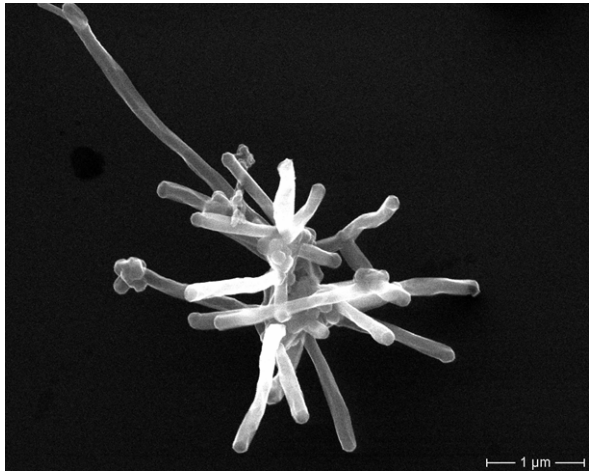


nanomaterials: possible modes of action – II-

ii) Does the fibre principle apply?

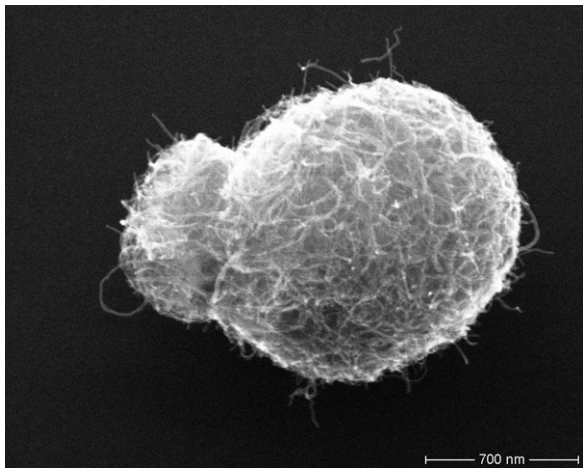


asbestos



carbon nanotubes

3-D-principle:
dose,
dimension,
durability



Pics: BAuA, Plitzko

Can nanomaterials be described as…..?

GBP
respirable granular biodurable particles without known significant specific toxicity *(Roller & Pott, 2006)*

PSP
poorly soluble particles of low cytotoxicity
(Oberdörster et al., 2002)

PSLT
poorly soluble, low toxicity particles *(Dankovic et al., 2007)*

…and there are more terms….

GBP nanomaterials

respirable granular biodurable low toxicity particles:
same mode of toxicological action
relevant group of nanomaterials

e.g.

titanium dioxide,
carbon black,
cerium oxide,
barium sulphate

Status of discussion

- IARC 2006: titanium dioxide & carbon black:
  sufficient evidence in experimental animals *(rat)* for *(inhalation)* carcinogenicity *(Baan et al., 2007)*

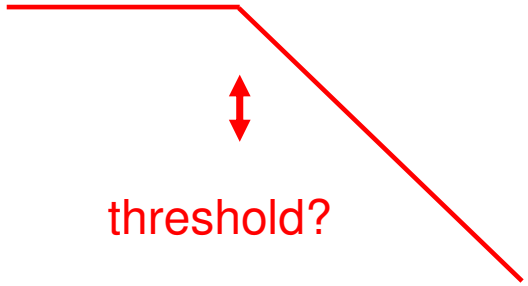
- there are people that say….
  rat is no adequate species to study GBP carcinogenicity
  threshold for carcinogenicity
  lung tumours only due to lung overload

What do the data tell us….

rat is relevant: hazard & risk assessment

evidence for inflammation at non-‘overload‘ exposures

no clear evidence for threshold *(clearance with increasing dust load)*

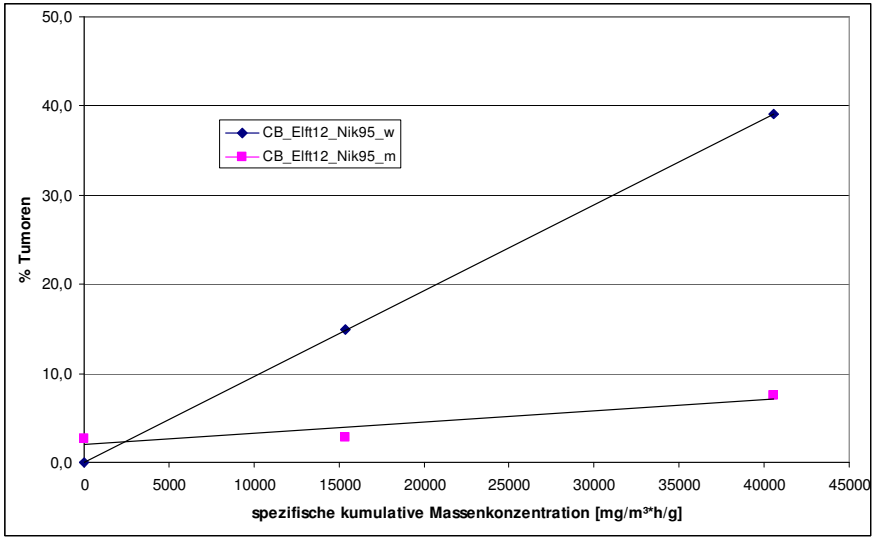


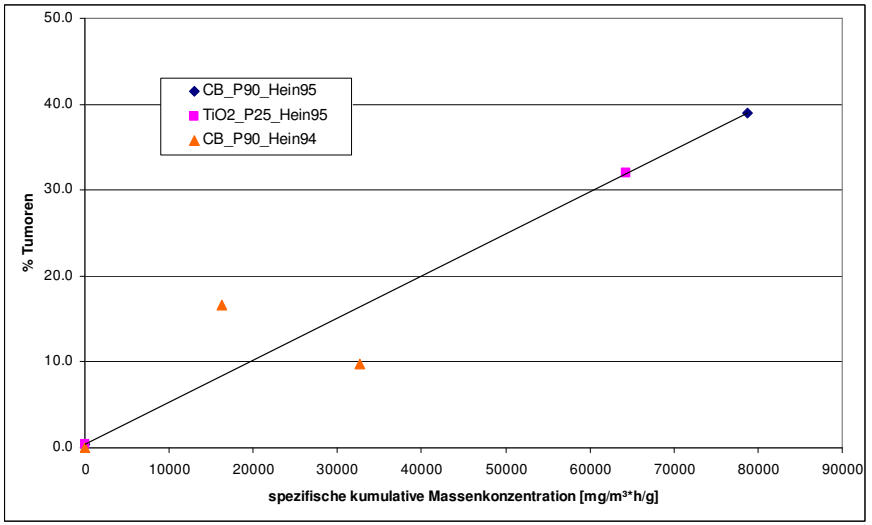
semi-logarithmic

linear

What do the data tell us….

Linear rat lung carcinogenicity TiO_2, carbon black looks linear !





GBP nanomaterials

Open question

comparative carcinogenic potency

of GBP nanomaterials

vs GBP micromaterials

(PPD > 100 nm in all dimensions)

selected endpoint: carcinogenicity in rat inhalation studies

➔ meta-analysis was performed

Gebel (2012) Arch Toxicol. 2012; 86(7):995-1007.

PPD, primary particle diameter

baua:

Survey on the available rat carcinogenicity studies

substance	form	study	abbreviation	rat strain	$t_{exposed}$ (mth)	$t_{section}$ (mth)	sex	MMAD (µm)	PPD (µm)	BET (m^2/g)
coal dust		Martin et al. 1977	Coal_Mart77	SD	24	24	f	-	-	-
titanium dioxide	rutile	Lee et al. 1985; 1986	TiO2_Lee85	SD	24	24	f/m	1.6	230	8
	P25 (80% anatase / 20% rutile)	Heinrich et al. 1995	TiO2_P25_Hein95	Wistar	24	30	f	0.8	21	48
carbon black	Printex 90	Heinrich et al. 1994	CB_P90_Hein94	Wistar	10/20	30	f	1.1	14	227
	Elftex-12	Nikula et al., 1995	CB_Elft12_Nik95	F344/N	24	25.5	f/m	1.95/0.1	37	43
	Printex 90	Heinrich et al. 1995	CB_P90_Hein95	Wistar	24	30	f	0.64	14	227
diesel engine emissions		Heinrich et al. 1995	DME_Hein95	Wistar	24	30	f	0.25	15	~20
		Mauderly et al., 1987; Cheng et al., 1984	DME_Maud87	F344/ Crl	24	30	f/m	0.25	-	
		Nikula et al., 1995	DME_Nik95	F344/N	24	25,5	f/m	2.00/0.1	-	
		Iwai et al., 2000	DME_Iwai00	F344	3/6/9/12	30	f	-	-	
		Heinrich et al. 1986	DME_Hein86	Wistar	32	32	f	0.35	-	
		Brightwell et al. 1989	DME_Bright89	F344	24	30	f/m	-	-	
		Iwai et al., 1986	DME_Iwai86	F344	24	30	f	-	-	
		Ishinishi et al., 1986	DME_Ishi86	F344/Jcl	30	30	f/m	-	-	
talc		NTP 1993	Talc_NTP93	F344/N	28/26	28/26	f/m	2.95	-	11
toner		Muhle et al., 1991; Bellmann et al., 1991	Ton_Muhle91	F344	24	26	f/m	4	-	3,6

MMAD, mass median aerodyn. diameter; PPD, primary particle diameter, BET: spec. surface area, t, time

red: GBP micromaterial studies; black: studies with nanostructered particles

Meta-analysis procedure

Carcinogenicity studies with different protocols:

Several adjustments needed before comparison:

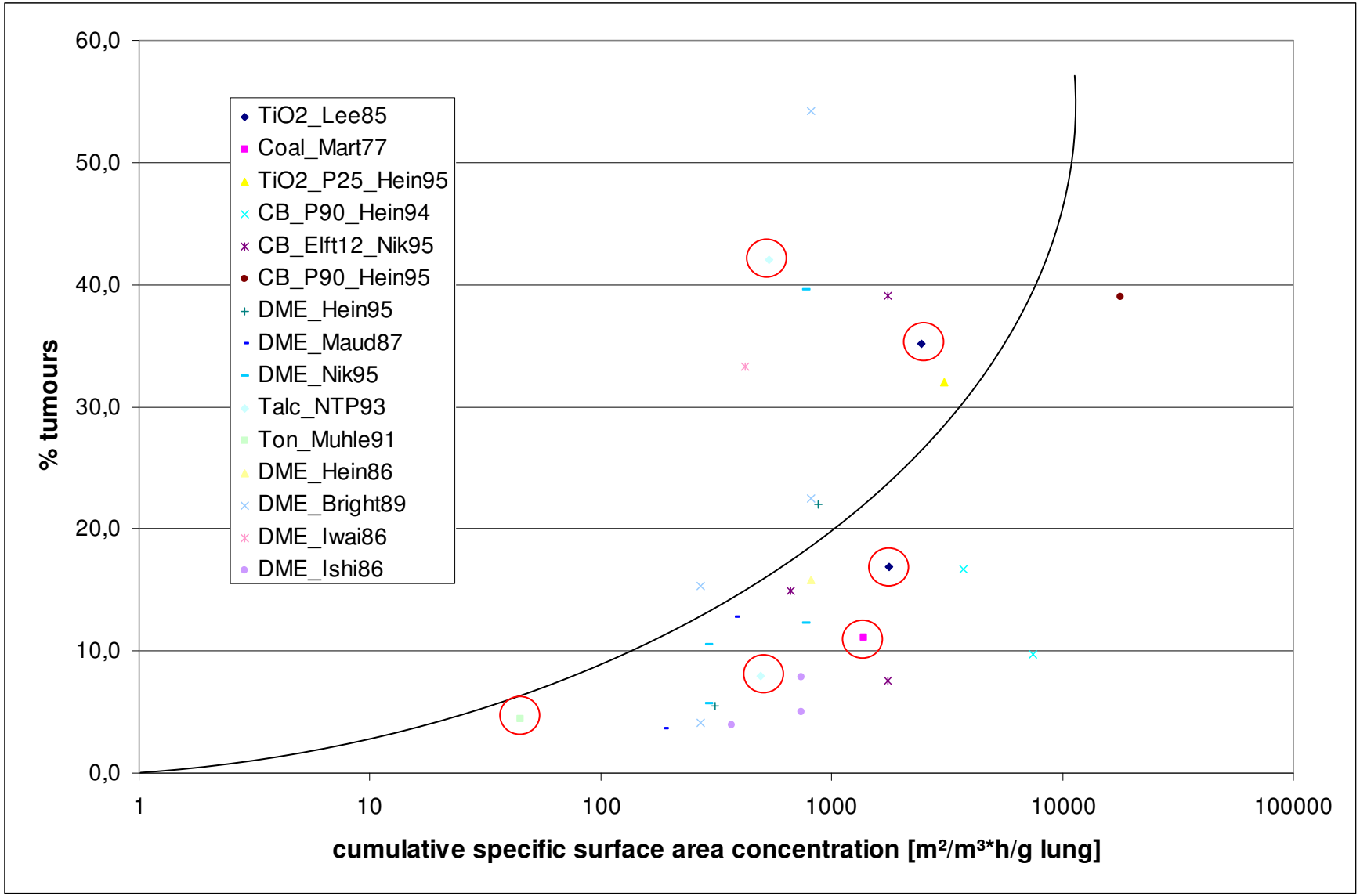
e.g.

- exposure duration (h/d; d/week, total months)

- total study duration (tumour incudtion age-dependent)

Mauderly et al. 1987

Tumour rate & cumulative surface area concentration – all studies



indicates GBP micromaterials

Gebel (2012) Arch Toxicol. 2012; 86(7):995-1007.

Comparative carcinogenic potency

- rat carcinogenicity studies: GBP nanomaterials are maximally ~ 5 times more potent cf. GBP micromaterials.

- studies with GBP nanomaterials longer than those with GBP micromaterials (median value 4 mths):
  real potency difference is ~ 2-3

- no relevant difference +/- diesel data: particle is toxic principle

conclusion: potency difference between GBP nanomaterials and GBP micromaterials for OEL derivation is small when using the rat carcinogenicity studies

Summary I

The relevant toxic effects of the major nanomaterials are covered by the current knowledge in dust toxicology

target organ: lung (inhalation)

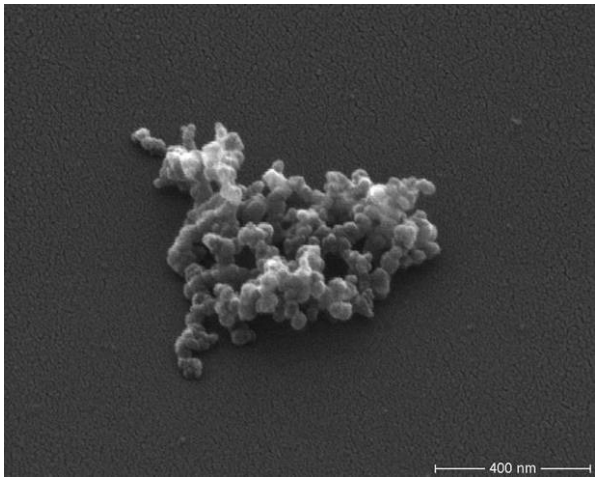
→ effects are known:

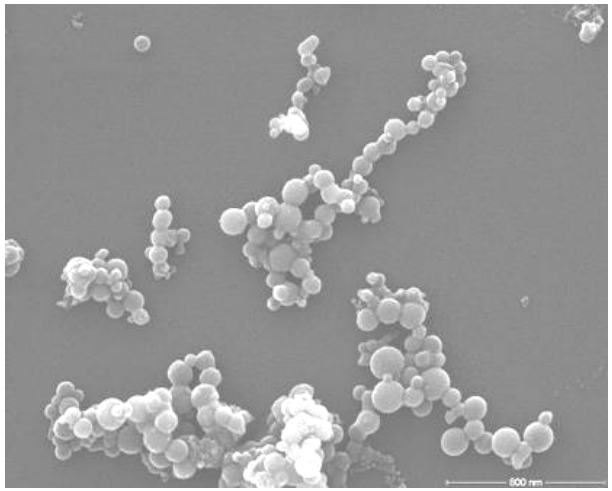
chronic inhalation of respirable dust (work place!):
inflammation and putative carcinogenicity

Summary II

nanomaterial health hazards
can be described by known modes of toxic action

⇒ methods for the evaluation of possible
effects of nanomaterials are available





There is currently no evidence for
a new & specific nanomaterial toxicology.

Pics: BAuA, Plitzko

baua: