nanoGRAVUR - Gruppierung hinsichtlich Arbeits-, Verbraucher- und Umweltschutz und Risikominimierung

nanoGRAVUR

Nanostructured materials – Grouping in view of worker, consumer and environmental safety and risk minimization

Thomas Kuhlbusch, Wendel Wohlleben and the nanoGRAVUR Team

Scientific Workshop - Grouping of Nanomaterials
12th -13th September 2018, Paris

Why nanoGRAVUR?

- Optimal **use of the potential** of nanomaterials along with **responsible and safe handling**.

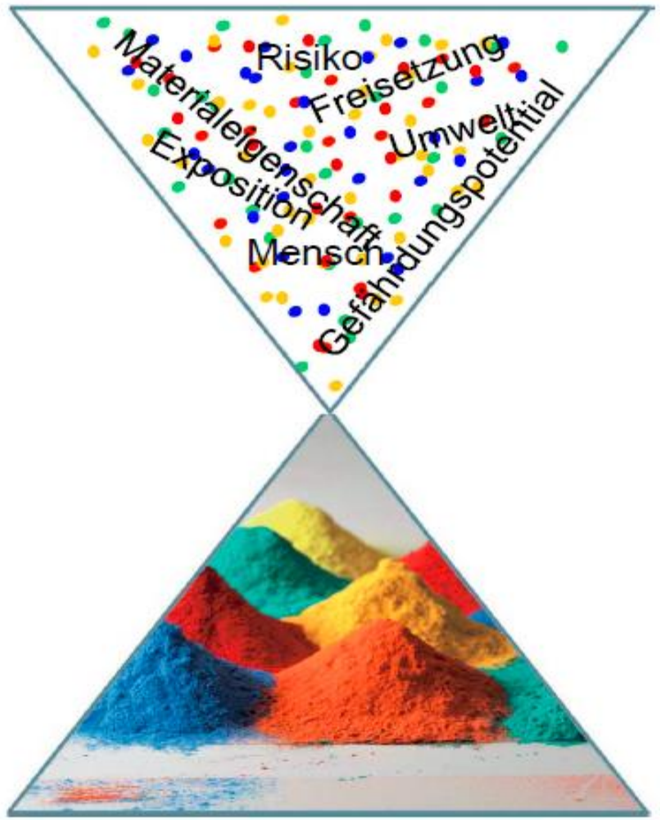
But
the **efforts to study the effects and behaviour** in the regulatory and economic framework can be **enormous**.

- **Development of criteria catalogues** for the **grouping** of nanomaterials with regard to **release, exposure, transformation, hazard and risk potentials**.

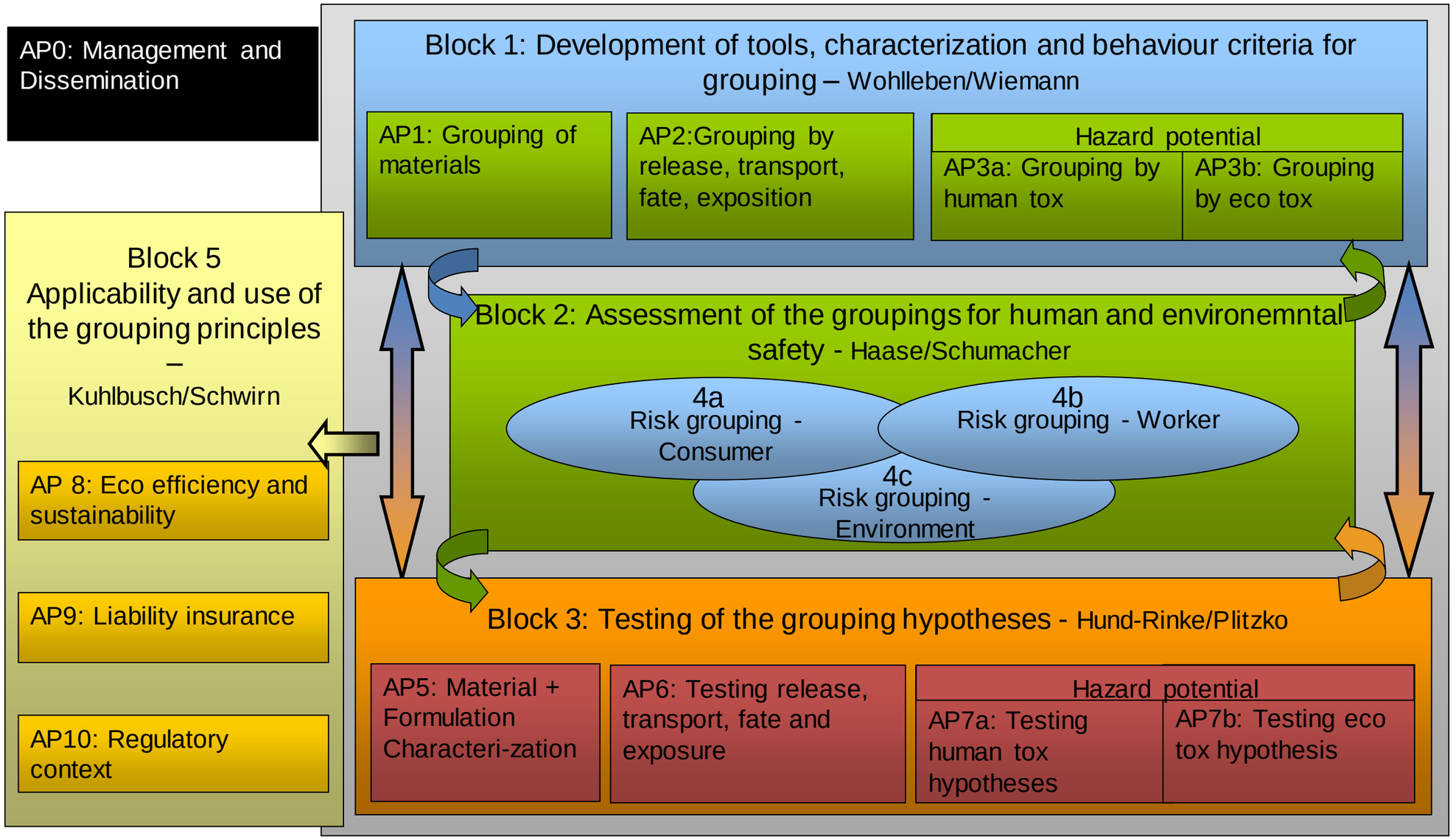
Grouping

Grouping for
Risk assessment
Hazard assessment
Release assessment
Defining risk management measures
Screening
……

for facilitating safe use of nanomaterials



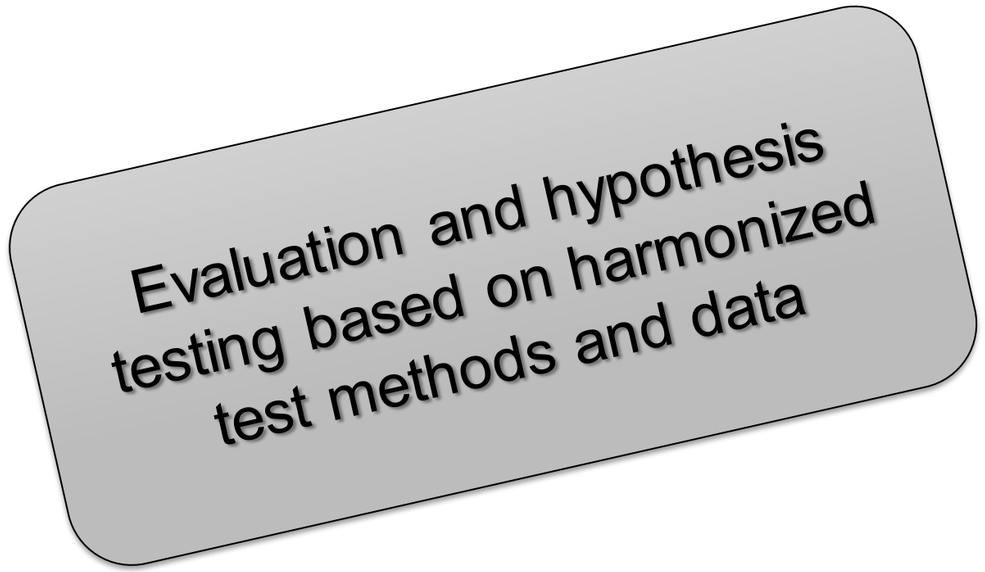
Structure nanoGRAVUR



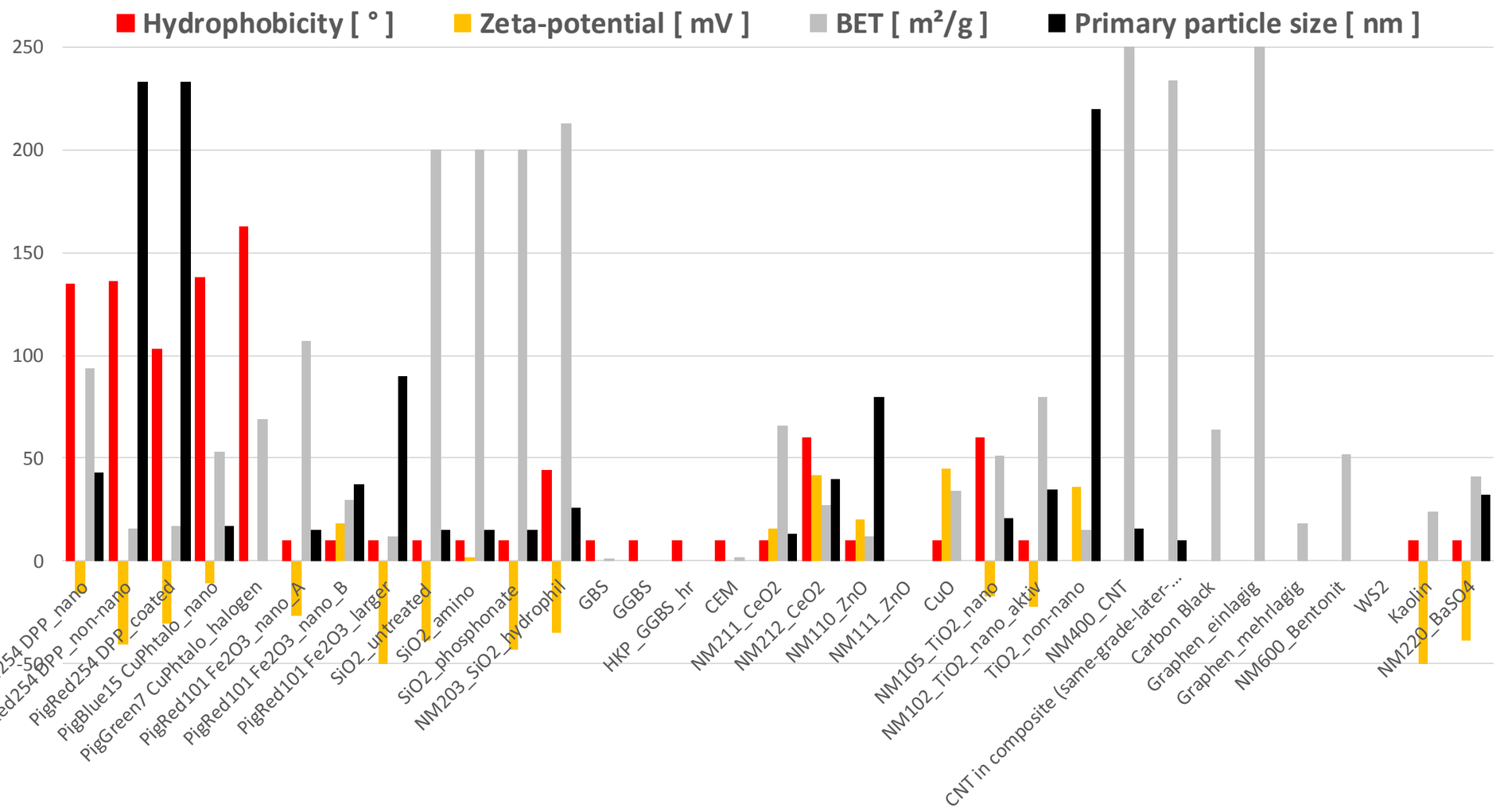
Results of nanoGRAVUR

Grouping schemes for

- Release
- Physico-chemical properties
- Ecotoxicity
- Environmental safety
- Consumer safety
- Worker safety

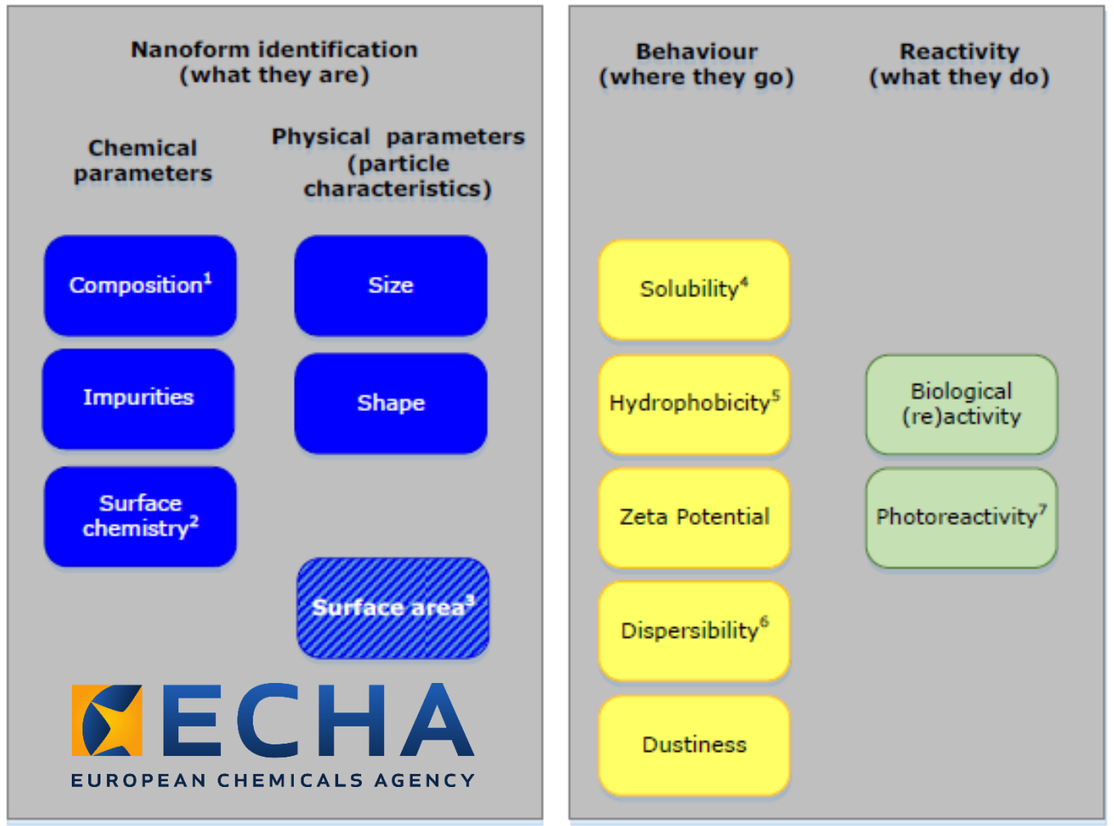


Case studies cover wide ranges of intrinsic material properties



Systematic variation of properties within and across substance families

Properties	NanoGRAVUR data ?	ECHA guidance 2017
Primary particle shape	✓	Proposed
Primary particle dimension	✓	Proposed
Composition + GHS (incl. Impurities)	✓	Proposed
Specific surface area (BET/VSSA)	✓	Proposed
Surface Chemistry (descriptive)	✓	Proposed
Surface Charge (zeta-potential)	✓	Proposed
Hydrophobicity	✓	Proposed
Rigidity (for fibers)		
NEP classes & intended use scenarios	(✓)	
Specific NEP: g/g content of ENM	✓	
Specific NEP: dispersion state of ENM	(✓)	
Dustiness	✓	Proposed
Critical shapes upon exposure	(✓)	
Agglo. of ENM upon NEP application	(✓)	
Resilience of NEP Matrix	✓	
Dispersability (dispersion stability: TG318)	✓	Proposed
Solubility in water (screening test)	✓	Proposed
Dissolution rate in relevant media	✓	Proposed
Ion releasing	(✓)	
Transformation „change of what they are“	✓	
Mobility (in soils)	✓	
Mobility (systemic) by altern. Method		
Affinity (heteroagglomeration)		
Reactivity (abiotic)	✓	Proposed
Reactivity (in vitro)	✓	
Reactivity (photo-)		Proposed



nanoGRAVUR color code avoids red/yellow/green traffic lights for properties:

- WHAT THEY ARE
- WHERE THEY GO (release & exposure)
- WHERE THEY GO (in relevant media)
- WHAT THEY DO

Properties	NanoGRAVUR data ?	ECHA guidance 2017	DF4nano-grouping 2015	NanoGRAVUR occupation	NanoGRAVUR consumer	Envrionmental hazard 2018	NanoGRAVUR environment	Method TRL
Primary particle shape	✓	Proposed	**Criterion**	**Criterion**	**Criterion**	**Criterion**	**Criterion**	+
Primary particle dimension	✓	Proposed		**Criterion**	**Criterion**	**Criterion**	**Criterion**	+
Composition + GHS (incl. Impurities)	✓	Proposed	**Criterion**	**Criterion**	**Criterion**	**Criterion**	**Criterion**	+
Specific surface area (BET/VSSA)	✓	Proposed	Supplementary					+
Surface Chemistry (descriptive)	✓	Proposed	Supplementary					O
Surface Charge (zeta-potential)	✓	Proposed	Supplementary					+
Hydrophobicity	✓	Proposed	Supplementary					-
Rigidity (for fibers)				Proposed				-
NEP classes & intended use scenarios	(✓)			**Criterion (NEP)**	**Criterion (NEP)**			
Specific NEP: g/g content of ENM	✓			**Criterion (NEP)**				+
Specific NEP: dispersion state of ENM	(✓)			**Criterion (NEP)**	**Criterion (NEP)**			O
Dustiness	✓	Proposed	Qualifier	**Criterion**				+
Critical shapes upon exposure	(✓)			**Criterion**	**Criterion (NEP)**			O
Agglo. of ENM upon NEP application	(✓)			**Criterion (NEP)**	**Criterion (NEP)**			O
Resilience of NEP Matrix	✓			**Criterion (NEP)**	**Criterion (NEP)**			+
Dispersability (dispersion stability: TG318)	✓	Proposed	**Criterion**		**Criterion**		**Criterion**	+O
Solubility in water (screening test)	✓	Proposed	**Criterion**	**Criterion**	**Criterion**		**Criterion**	+
Dissolution rate in relevant media	✓	Proposed	**Criterion**	**Criterion**	**Criterion**		**Criterion**	O
Ion releasing	(✓)					**Criterion**	**Criterion**	+O
Transformation „change of what they are“	✓						**Criterion**	O-
Mobility (in soils)	✓						**Criterion**	+
Mobility (systemic) by altern. Method					Proposed			-
Affinity (heteroagglomeration)							**Criterion**	O
Reactivity (abiotic)	✓	Proposed	**Criterion**	**Criterion**	**Criterion**	**Criterion**	**Criterion**	+O
Reactivity (in vitro)	✓		**Criterion**	**Criterion**	**Criterion**			+O
Reactivity (photo-)		Proposed						-

nanoGRAVUR

Properties	NanoGRAVUR data ?	ECHA guidance 2017	DF4nano-grouping 2015	NanoGRAVUR occupation	NanoGRAVUR consumer	Envrionmental hazard 2018	NanoGRAVUR environment	Method TRL
Primary particle shape	✓	Proposed	Criterion	Criterion	Criterion	Criterion	Criterion	+
Primary particle dimension	✓	Proposed		Criterion	Criterion	Criterion	Criterion	+
Composition + GHS (incl. Impurities)	✓	Proposed	Criterion	Criterion	Criterion	Criterion	Criterion	+
Specific surface area (BET/VSSA)	✓	Proposed	Supplementary					+
Surface Chemistry (descriptive)	✓	Proposed	Supplementary					O
Surface Charge (zeta-potential)	✓	Proposed	Supplementary					+
Hydrophobicity	✓	Proposed	Supplementary					-
Rigidity (for fibers)				Proposed				-
NEP classes & intended use scenarios	(✓)			Criterion (NEP)	Criterion (NEP)			
Specific NEP: g/g content of ENM	✓			Criterion (NEP)				+
Specific NEP: dispersion state of ENM	(✓)			Criterion (NEP)	Criterion (NEP)			O
Dustiness	✓	Proposed	Qualifier	Criterion				+
Critical shapes upon exposure	(✓)			Criterion	Criterion (NEP)			O
Agglo. of ENM upon NEP application	(✓)			Criterion (NEP)	Criterion (NEP)			O
Resilience of NEP Matrix	✓			Criterion (NEP)	Criterion (NEP)			+
Dispersability (dispersion stability: TG318)	✓	Proposed	Criterion		Criterion		Criterion	+O
Solubility in water (screening test)	✓	Proposed	Criterion	Criterion	Criterion		Criterion	+
Dissolution rate in relevant media	✓	Proposed	Criterion	Criterion	Criterion		Criterion	O
Ion releasing	(✓)					Criterion	Criterion	+O
Transformation „change of what they are“	✓						Criterion	O-
Mobility (in soils)	✓						Criterion	+
Mobility (systemic) by altern. Method					Proposed			-
Affinity (heteroagglomeration)							Criterion	O
Reactivity (abiotic)	✓	Proposed	Criterion	Criterion	Criterion	Criterion	Criterion	+O
Reactivity (in vitro)	✓		Criterion	Criterion	Criterion			+O
Reactivity (photo-)		Proposed						-

Properties with methods of low TRL: not ripe for grouping

Significant TRL improvement by nanoGRAVUR

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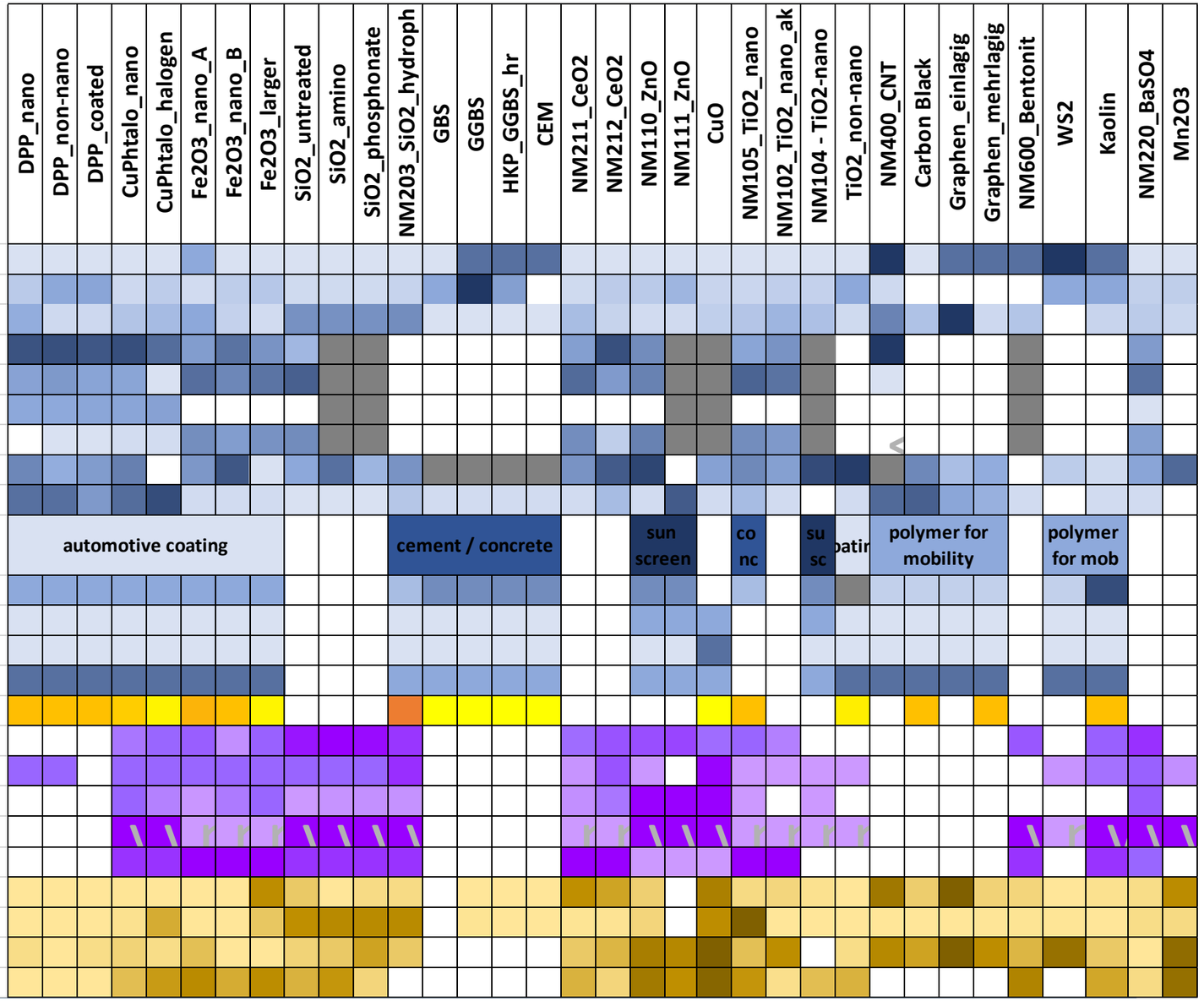
Case studies

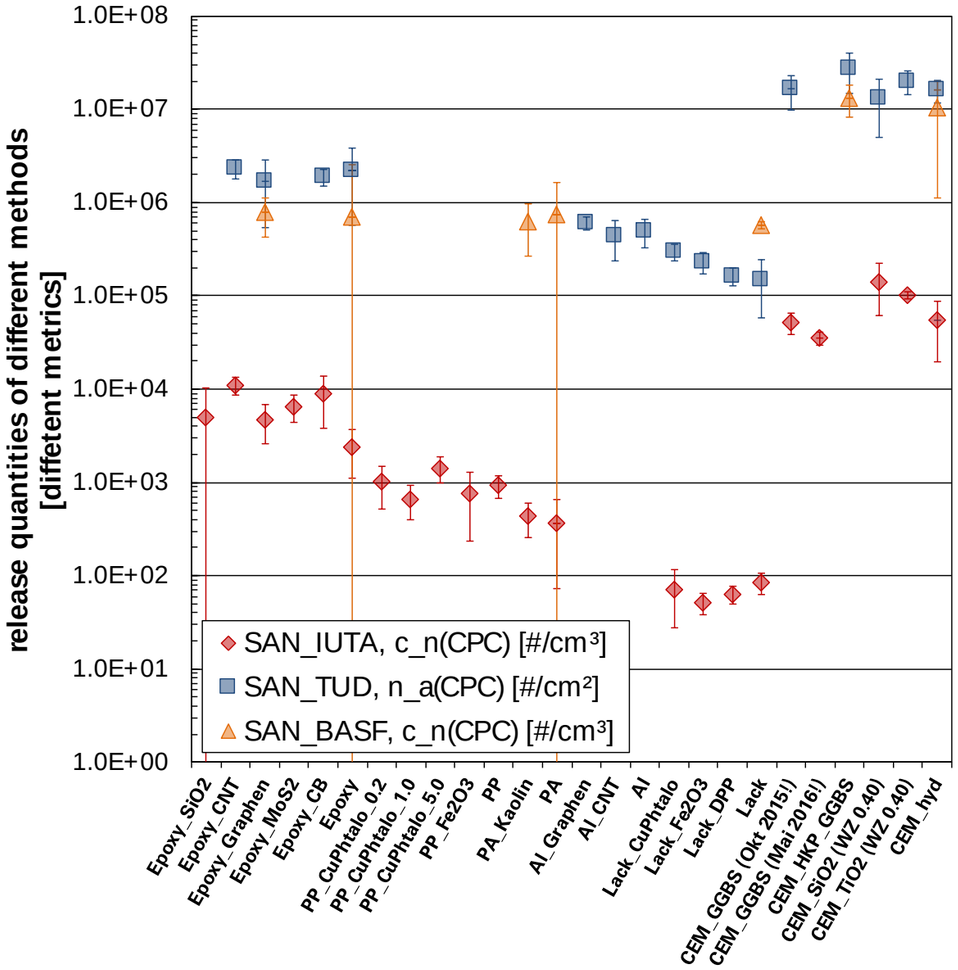
challenge relevance of ECHA proposed properties and of alternatives.

Properties	ECHA	nanoGRAVUR	descriptors
Primary particle shape	X	X	sphere 1, rod 2,
Primary particle dimension	X	X	nm
Specific surface area (BET/VSSA)	X		m^2/g
Surface Chemistry (measured)	X		% C
			% O
			% N
			% metals
Surface charge (zeta-potential) in	X		mV
Hydrophobicity	X		°
NEP class & intended use scenarios		X	lifecycle tested:
Specific NEP: g/g content of ENM		X	% g/g
Specific NEP: dispersion state of ENM		X	dispersed system 1:
			integration into
			agglomeration in
Dustiness	X	X	mg/kg respirable
Dispersion stability	X	X	% stable after 6 hours
Solubility in water (screening test)	X	X	ppm
Dissolution rate in relevant media	X	X	dissolution rate k
Ion releasing in relevant media		X	
Transformation „change of what		X	1: non persistent high
Reactivity (abiotic)	X	X	x-fold of D2O control
			x-fold of D2O control
			nmolTEU/m²ENM
			nmolTEU/m²ENM

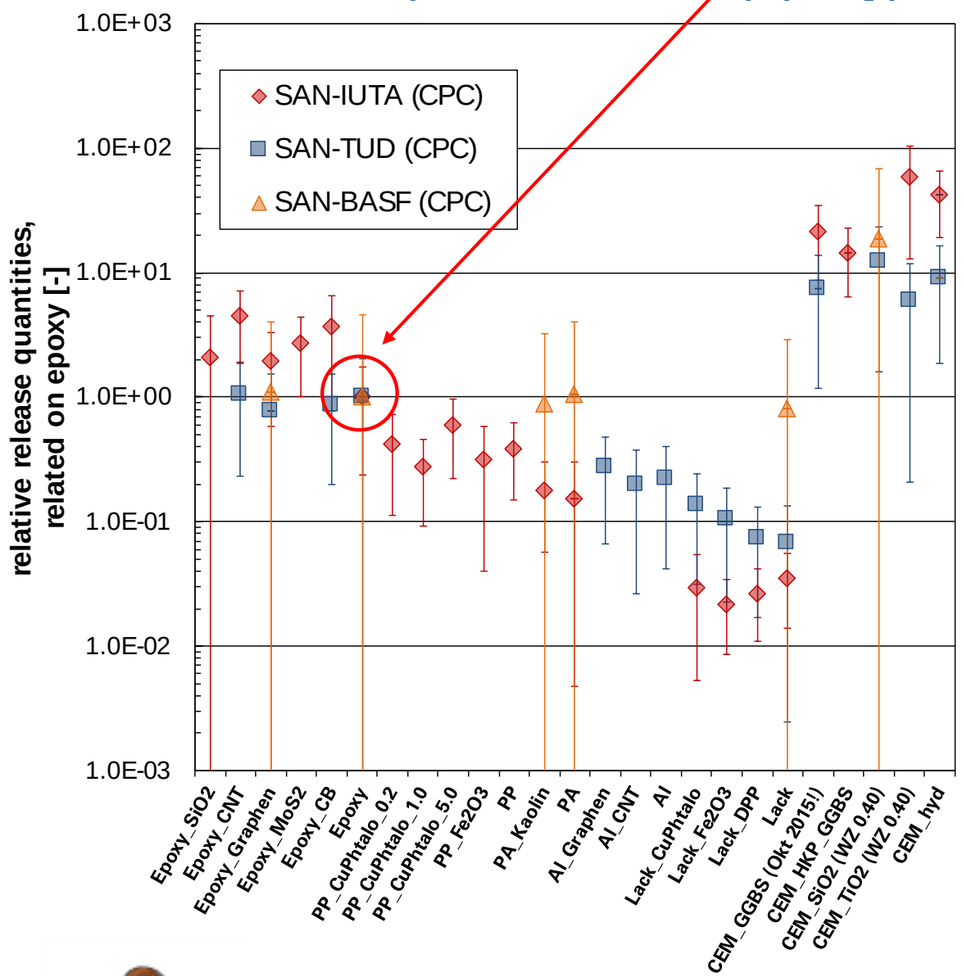


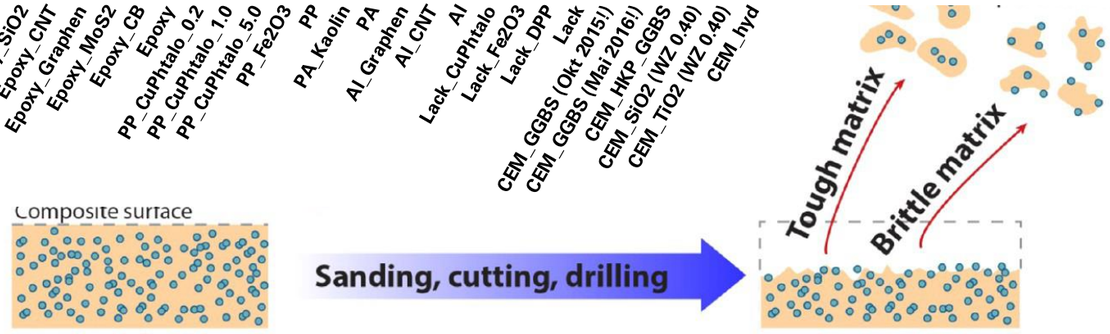
Lifecycle releases (selected results):
Consistent groupings by 3 different institutes after benchmarking

to one specific matrix (epoxy)



benchmark





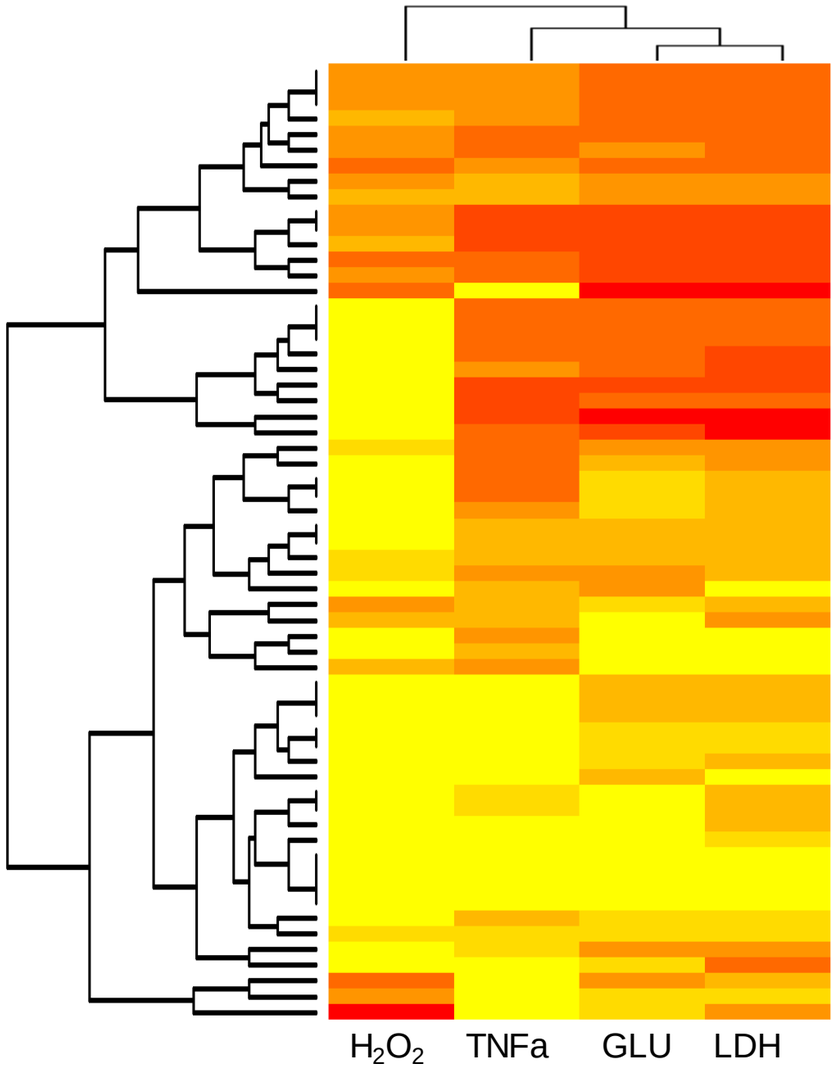
Mechanical energy input ⟶ Degradation

What they do (selected results):

Cluster Analysis from Alveolar Macrophage Assay & Abiotic Assays

based on LOAECs

Macrophages vs. ESR, FRAS, carbonylation of NRK cells (ISO 18227)



SiO_2, Bentonite, Kaolin: similarity

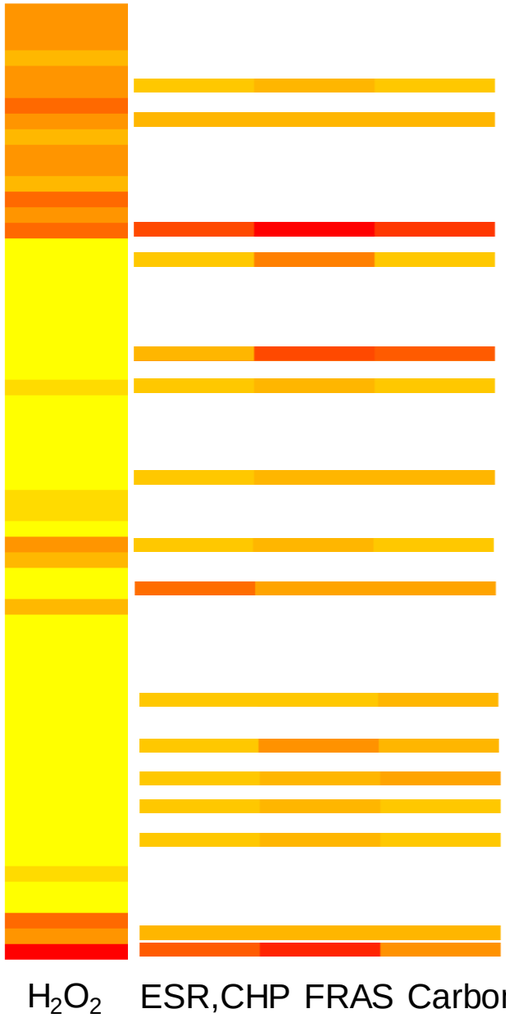
ZnO: similarity

CeO_2 similarity

TiO_2 variability

$BaSO_4$, corundum, pigments: similarity

Mn_20_3, Fe_2O_3, WS_2



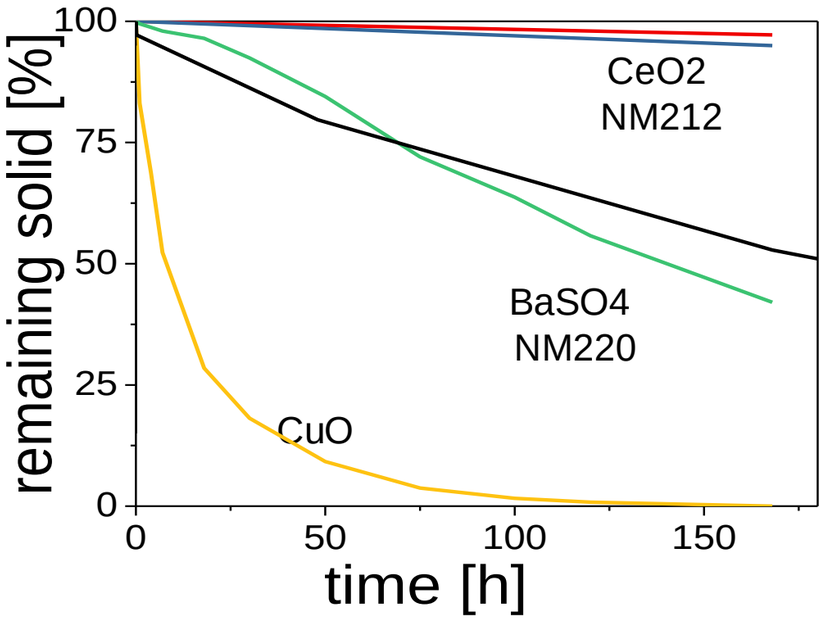
CuO

Mn_2O_3

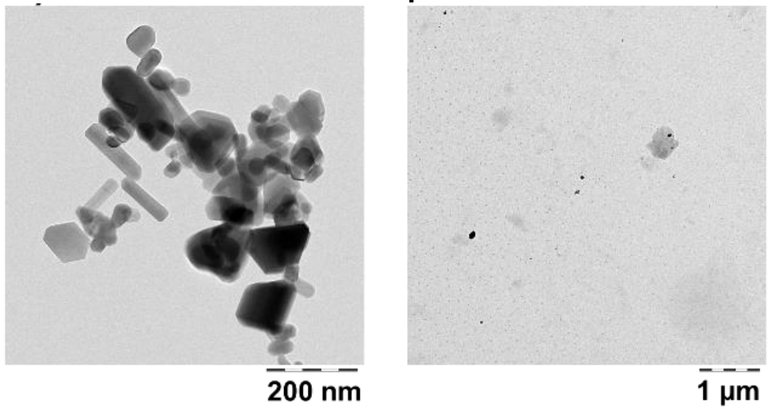
Wiemann *et al. J Nanobiotechnol* (***2016***) *14:16* DOI 10.1186/s12951-016-0164-2

Where they go (selected results)
Dynamic dissolution testing with assessment of transformation (ISO 19057:2017)

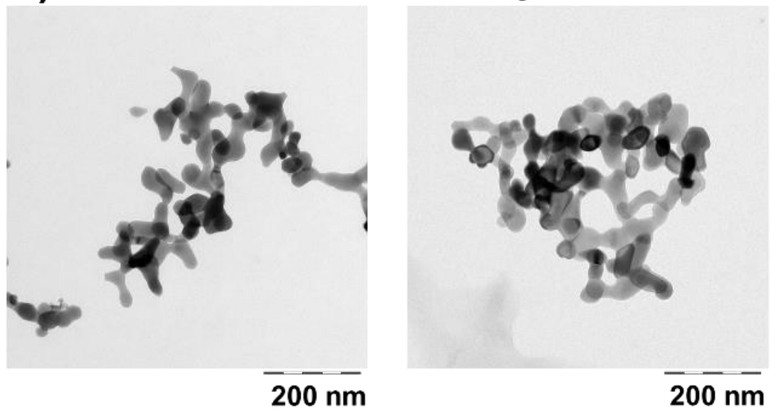
Comparison abiotic vs. invivo



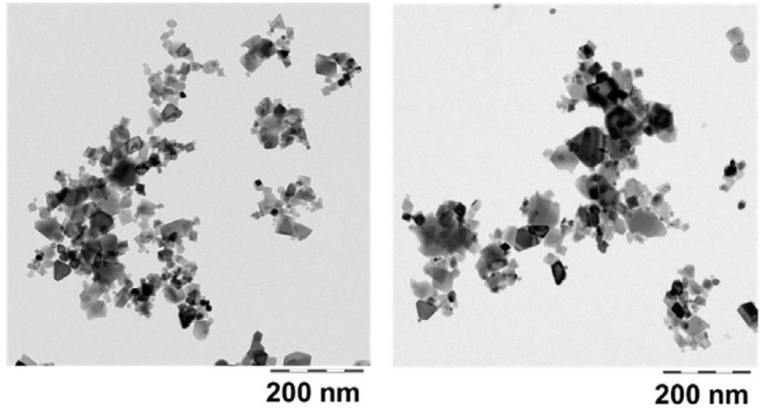
ZnO NM111: complete dissolution



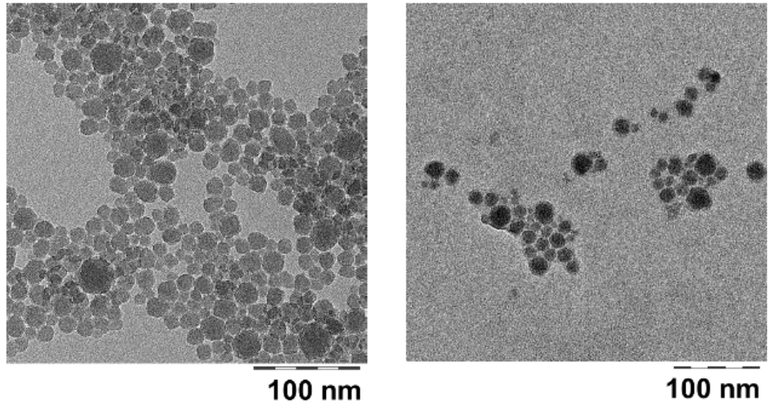
Fe2O3: no changes



CeO2 NM212: no changes



Colloidal SiO2: reprecipitation

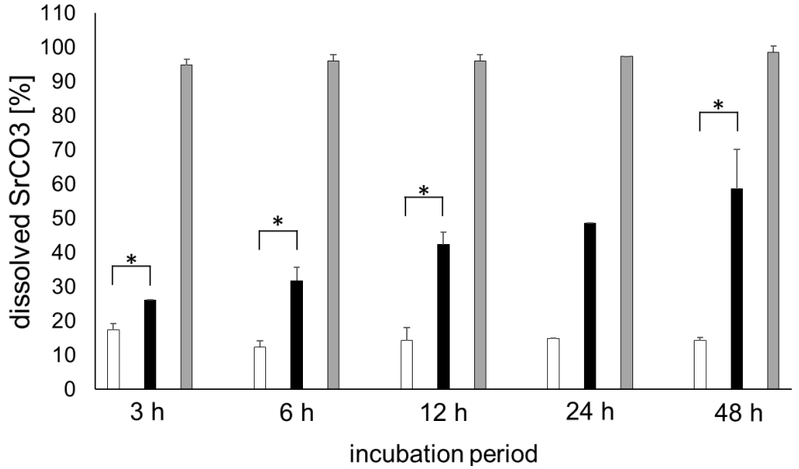


NanoImpact **12** (2018) :29-41.

Where they go: Comparison of dissolution rates: abiotic flowcell vs macrophages vs inhalation on 8 of 24 tested materials

	Dissolution rate macrophage -assisted (24h) [ng/cm²/h]	Dissolution rate Abiotic flow-through, pH4.5 [ng/cm²/h]	Half-time calculated from k [days]	Dissolution rate Abiotic flow-through, pH4.5 [% per 7 days]	In vivo pulmonary clearance in STIS recovery [% per 21 days]
$BaSO_4$_NM-220	4.2	10	7	58 %	52 %
ZnO_NM-111	117	177	1.2	100 %	93 %
$SrCO_3$	61	108	1.9	100 %	
CeO_2_NM-211		< 0.28 (LoD)	> 156	<3 % (LoD)	7 %
CeO_2_NM-212		< 0.73 (LoD)	> 146	<3 % (LoD)	5 %
CuO		283	0.7	100 %	>85 % (LoD)
SiO_2_amino		0.216	66	7 %	34 %
SiO_2_untreated		0.044	328	1.2 %	39 %
TiO_2_NM-105		< 0.013 (LoD)	> 4356	< 0.1% (LoD)	26%

NR8383 macrophages:
Only for one material with steep pH dependence (SrCO3) the macrophage acceleration was significant. Also observed for BaSO4, ZnO, but never faster than flowcell.



NanoImpact **12** (2018) :29-41.

Where they go: Grouping by biodissolution & transformation
(despite differences in size, shape, crystallinity)

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1. **non-persistent materials with high dissolution rate k>100ng/cm²/h** and no remaining original particles in TEM; <u>invivo validation</u>: Cleared completely (down to LoD) during a STIS inhalation recovery period.
   → CuO, $Cu(OH)_2CO_3$, ZnO NM110 and coated ZnO NM111 (initial retardation by coating)

2. **non-persistent materials with k ranging from 1ng/cm²/h to 100ng/cm²/h** and also **significant transformation** or reprecipitation. <u>Invivo validation</u>: Chemical clearance (dissolution) dominates, but physical clearance (tranport) and reprecipitation contribute in a relatively complex "invivo processing".
   → nano-$BaSO_4$ NM220 and non-nano $BaSO_4$ IRMM381.

3. **Very low dissolution** (**k<1ng/cm²/h or below LoD**) but a **significant transformation** during the test period. Physical clearance from the lung (transport) is accompanied by aggregation and/or reprecipitation .
   → CuPhthalocyanines and silica (significant modulation by functionalizations)

4. **materials very low or no dissolution (k<1ng/cm²/h or below LoD) and no significant transformation.** Physical clearance (transport) dominates the pulmonary clearance.
   → All tested (nano)forms of Fe_2O_3 (A, B, larger),
   → both CeO_2 (NM211, NM212) and both TiO_2 NM104 and NM105

NanoImpact **12** (2018) :29-41.

Properties	NanoGRAVUR data ?	ECHA guidance 2017
Primary particle shape	✓	Proposed
Primary particle dimension	✓	Proposed
Composition + GHS (incl. Impurities)	✓	Proposed
Specific surface area (BET/VSSA)	✓	Proposed
Surface Chemistry (descriptive)	✓	Proposed
Surface Charge (zeta-potential)	✓	Proposed
Hydrophobicity	✓	Proposed
Rigidity (for fibers)		
NEP classes & intended use scenarios	(✓)	
Specific NEP: g/g content of ENM	✓	
Specific NEP: dispersion state of ENM	(✓)	
Dustiness	✓	Proposed
Critical shapes upon exposure	(✓)	
Agglo. of ENM upon NEP application	(✓)	
Resilience of NEP Matrix	✓	
Dispersability (dispersion stability: TG318)	✓	Proposed
Solubility in water (screening test)	✓	Proposed
Dissolution rate in relevant media	✓	Proposed
Ion releasing	(✓)	
Transformation „change of what they are“	✓	
Mobility (in soils)	✓	
Mobility (systemic) by altern. Method		
Affinity (heteroagglomeration)		
Reactivity (abiotic)	✓	Proposed
Reactivity (in vitro)	✓	
Reactivity (photo-)		Proposed

Tier 1

“What they are: Physical structure”

- Primary particle shape * #
- Primary particle dimension *#
- Rigidity (for fibers)

“What they are: Chemical composition”

- GHS/CLP humantoxicity (bulk)
- GHS/CLP ecotoxicity (bulk // salt)
- GHS/CLP phys-chem hazards (bulk)
- Solubility in water

Tier 2

“what is the NEP”: NEP-dependent processes, uses, testing needs,

- Product classes & application scenarios
- specific NEP: g/g content of ENM
- specific NEP: dispersion state of ENM

Tier 2

“Where they go”: Release / Exposure

- Dustiness
- Agglo. of ENM upon NEP application
- Resilience of NEP matrix
- Critical shapes upon exposure

“Where they go”: in relevant media

- Ion-releasing
- Dispersion Stability (homo-agglomeration) #
- Dissolution in relevant media
- Affinity (hetero-agglomeration)
- Transformation “change of what they are”
- Mobility

“What they do”

- Reactivity (abiotic) #
- Reactiviy (in vitro)

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future property: No method yet established

* = descriptor of nanoform ranges (ECHA) # = descriptor of discrete forms (EPA)

NEP = nano-enabled product

Methods to implement ECHA or other frameworks
Additional methods for additional purposes

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nanoGRAVUR serves three purposes of grouping: occupational / environmental / consumer

- the overarching scheme guides the assessment
  a) By purpose (properties are selected for each purpose)
  b) By tiers with increasing specificity of testing
  c) By specific methods & SOPs, descriptor metric, representative materials (OECD NMs)

Additional properties decrease uncertainty at limited additional efforts, as they:

- are descriptive (e.g. NEP categories / intended uses)
- rely on simple methods (e.g. ion-releasing based on OECD draft TG „screening“),
- assess the similarity of nano-enabled products (value chain relevance, consumer relevance)

If grouping is performed only for occupational handling of powders, our choice of properties is a *selection* of the ECHA proposed properties, now with specific methodology:

- We do not group by *intrinsic* properties that are only a proxy of biological interactions (surface chemistry incl. hydrophobicity, charge),
- Instead, we group by *extrinsic* properties (dispersability, biologial reactivity, dissolution), that assess the interactions more directly, and correlate to in vivo results.

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