The needs of industry for techniques for registration

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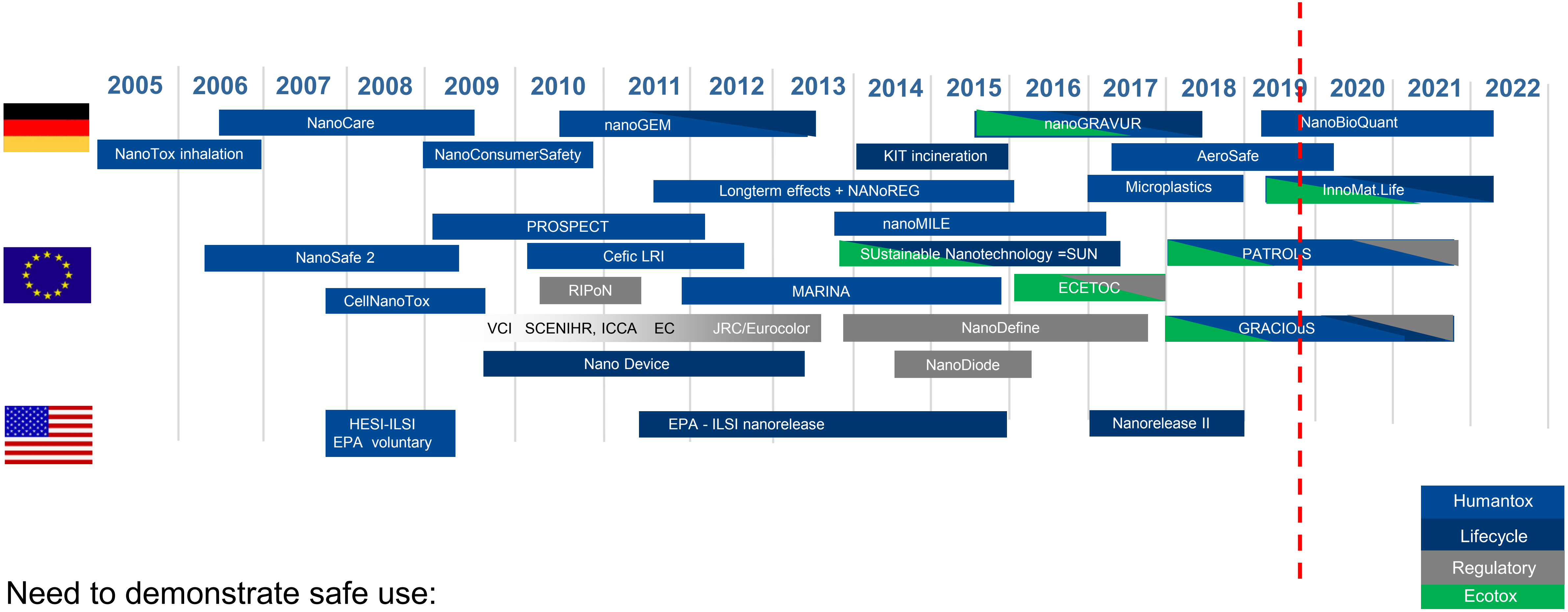
NanoFASE
Concluding Conference
5th - 6th of September 2019, Vienna

Exploring the implications: BASF nanosafety research



Need to demonstrate safe use:

95% for conventional materials, now considered as nanoforms

5% for novel materials, using SbyD processes

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Urgent questions in view of the REACH requirements for 2020

- Which properties are necessary to establish „sets of similar nanoforms“ ?
  - ▶ Manufacturing output ~ nanoform → set (BASF) → set (all producers) → EUCLID
  - ▶ Justification required, must consider human & environmental hazard, and exposure.
- Which properties & (functional) assays are necessary & sufficient to assess similarity for grouping?
  - ▶ Are methods applicable beyond Ag, instead to industrially prioritized materials?
- Which compartments shall be prioritized for environmental RA ?
- If the regulator insists on testing aquatic toxicity – how shall we test hydrophobic / instable materials?

Rules for „sets“ and their grouping or read-across need validation by TG results

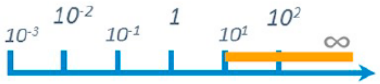
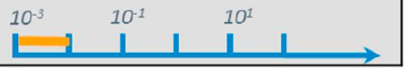
Nanomaterial (type and designation of sub-type)	Ecotoxilogical profile (sensitivity of organisms)	Magnitude of ecotoxicity (most sensitive organism) within the group (range of EC50 [mg/L])
CuPhthalo_nano; CuPhthalo_halogen SiO_2 untreated; _amino; _phosphonate Fe_2O_3_larger CeO_2 NM213	algae = daphnids = FE algae > daphnids, FE algae > daphnids, FE algae > daphnids, FE algae > daphnids, FE	
ZnO NM110; NM111; NM113 Fe_2O_3_nano_A; nano_B CeO_2 NM-211, NM212; Eu doped TiO_2 NM-104; NM-105; Eu doped, Fe doped, undoped	algae > daphnids > FE algae > daphnids, FE algae > daphnids, FE algae > daphnids, FE	
Ag Batch SRM 110525, NM-300K nCu CuO	daphnids > algae > FE algae ≡ daphnids > FE algae ≡ daphnids > FE daphnids > algae > FE	
Ag Batch 1340	daphnids > algae > FE	

Fig. 4. Aquatic hazard scoring of 25 tested NM.

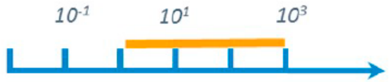
Release of toxic ions	Nanomaterial (type / sub-type)	Magnitude of ecotoxicity (most sensitive organism) within the group (range of EC50 [mg/L])
YES	Ag Batch SRM 110525, Batch 1340, NM-300K nCu ZnO NM110, NM111, NM113 CuO	
	CeO_2 NM-211, NM212, NM213, Eu doped Fe_2O_3_nano_A, nano_B, _larger SiO_2 untreated, _amino, _phosphonate CuPhthalo_nano; _halogen TiO_2 NM-104, NM-105, Eu doped, Fe doped, undoped	

Fig. 6. Terrestrial hazard scoring for 25 tested ENM.

Env. hazard ranks by substance.

Which (functional) assays are required and valid to demonstrate that „environmental hazard assessment can be performed jointly“ for a set of similar NFs ?
NanoFASE??

D. Kuehnel et al. (nanoGRAVUR, May 2019)
NanoImpact: doi: 10.1016/j.impact.2019.100173

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eau 25 : catégories de substances produites et/ou importées en quantités supérieures à 100 t en 2014 (déclarations 2015)

fillers

Nom générique	Bande de tonnage
Carbon black	> 100 000 t
Silicon dioxide	> 100 000 t
Calcium carbonate	10 000 t à 100 000 t
Titanium dioxide	10 000 t à 100 000 t
Boehmite (Al(OH)O)	1000 t à 10 000 t
Copolymère de chlorure de vinylidène	1000 t à 10 000 t
Silicic acid, magnesium salt	1000 t à 10 000 t
Aluminium oxide	1000 t à 10 000 t
Polychlorure de vinyle	1000 t à 10 000 t
Mélange réactionnel de dioxyde de cérium et de dioxyde de zirconium	1000 t à 10 000 t
Calcium 4-[(5-chloro-4-methyl-2-sulphonatophenyl)azo]-3-hydroxy-2-naphthoate	1000 t à 10 000 t
Kaolin	100 t à 1000 t
3,6-bis-biphenyl-4-yl-2,5-dihydropyrrolo[3,4-c]pyrrole-1,4-dione	100 t à 1000 t
Iron hydroxide oxide yellow	100 t à 1000 t
Aluminium hydroxide	100 t à 1000 t
Diiron trioxide	100 t à 1000 t
Iron hydroxide oxide	100 t à 1000 t
3,6-diphenyl-2,5-dihydropyrrolo[3,4-c]pyrrole-1,4-dione	100 t à 1000 t

pigments

Conventional nanomaterials dominate national registers, whereas Ag is not very representative to validate methods or models

Organic pigments

2,2'-[(3,3'-dichloro[1,1'-biphenyl]-4,4'-diyl)bis(azo)]bis[N-(2,4-dimethylphenyl)-3-oxobutyramide]	100 t à 1000 t
3,6-bis(4-chlorophenyl)-1H,2H,4H,5H-pyrrolo[3,4-c]pyrrole-1,4-dione	100 t à 1000 t
3-hydroxy-N-(o-tolyl)-4-[(2,4,5-trichlorophenyl)azo]naphthalene-2-carboxamide	100 t à 1000 t
3,6-Bis(4-tert-butylphenyl)-2,5-dihydropyrrolo[3,4-c]pyrrole-1,4-dione	100 t à 1000 t
2-Propenoic acid, 2-methyl-methyl ester, polymer with 1,3-butadiene, butyl 2-propenoate and ethenylbenzene	100 t à 1000 t

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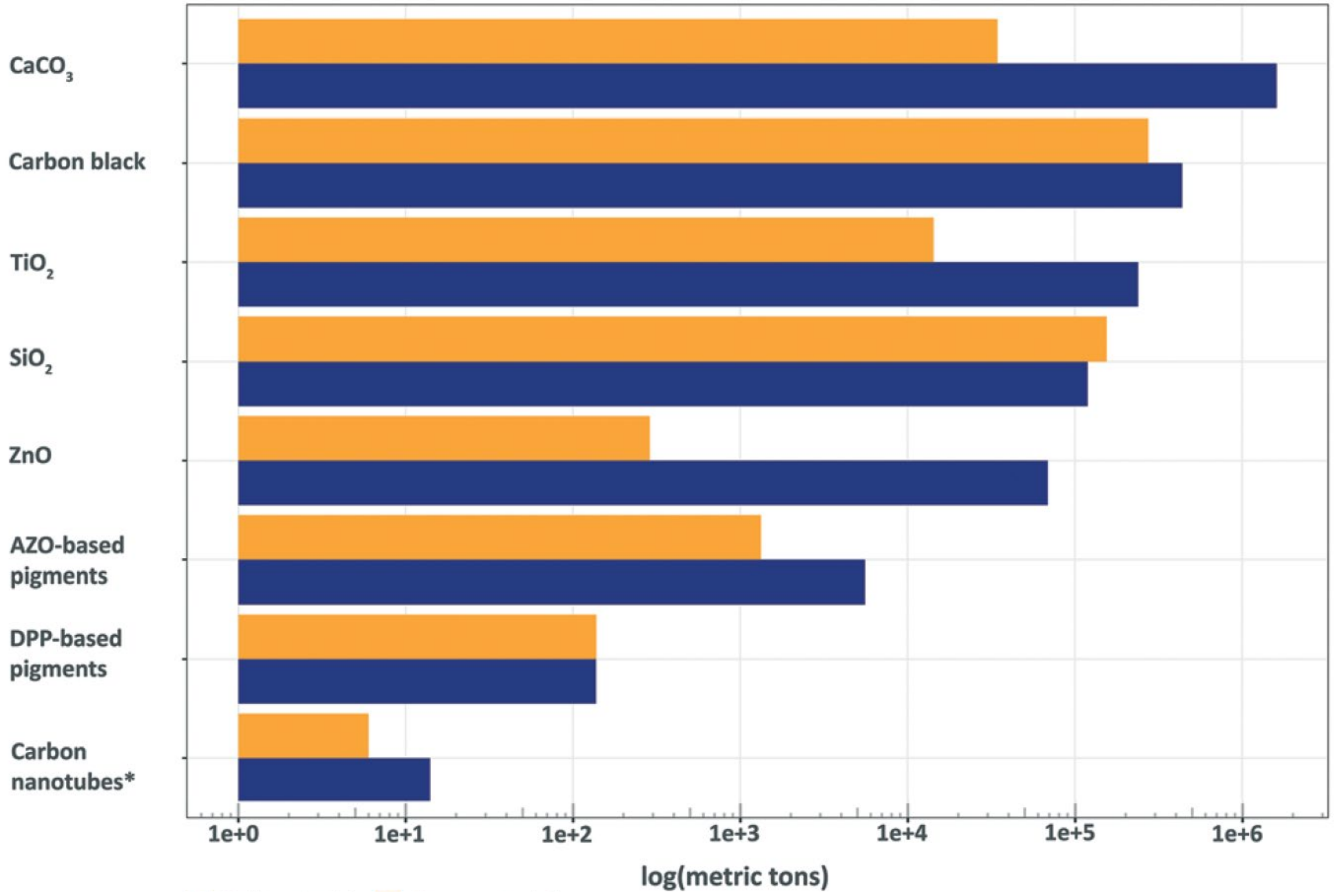
Tonnages reported to the French inventory are plausible



Industry reports to French inventory of nano-form production

Production volumes © Chemical Economics Handbook, scaled to France GDP (= 3.7% GWP) (nano + non-nano forms)

For many fillers and pigments, the entire production is identified as nanomaterial, because the nanostructure is (has always been) required for performance.

For other fillers and pigments, distinct non-nano-forms are required for performance (e.g. $CaCO_3$ in paper or TiO_2 white pigment)

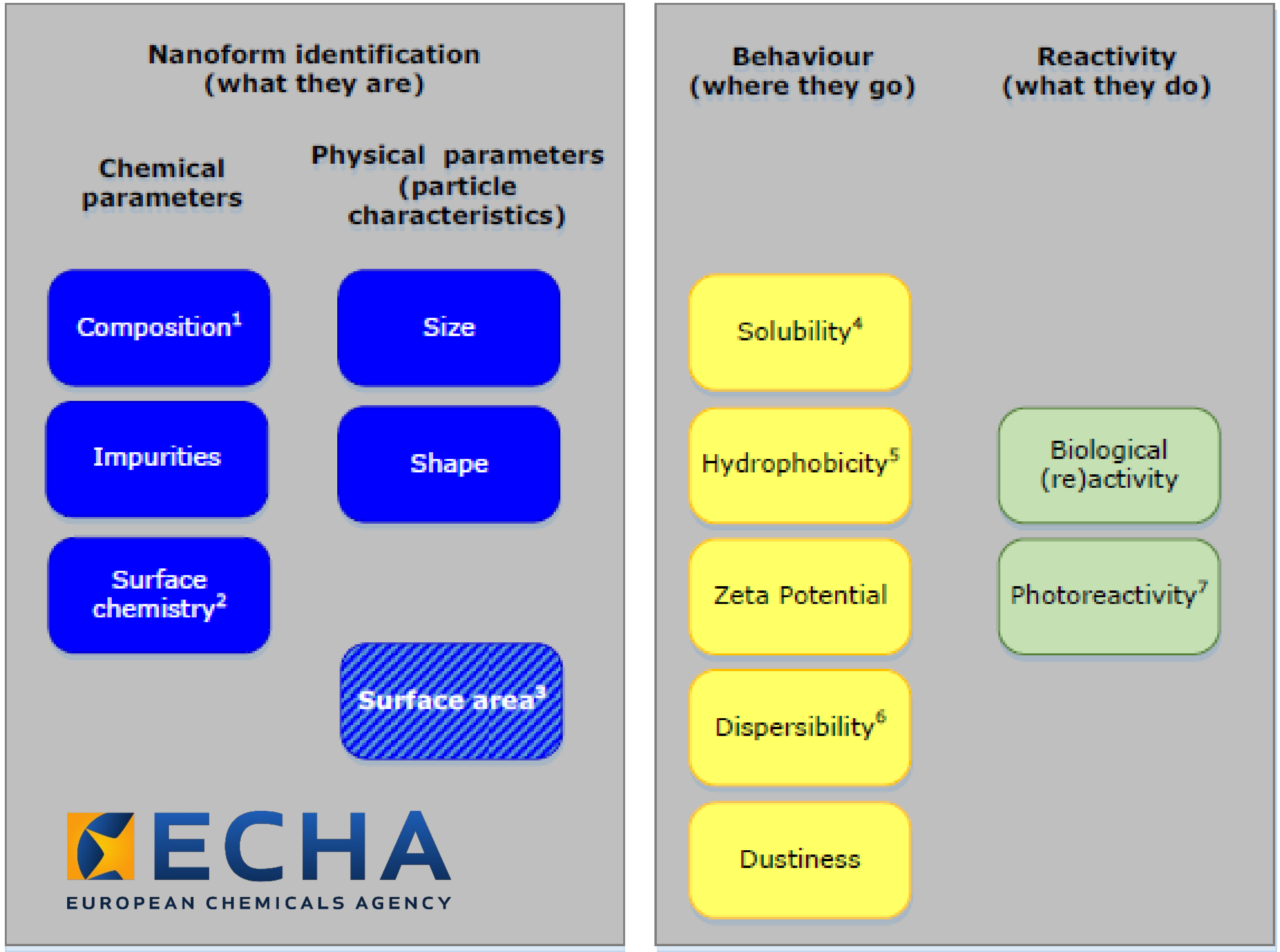
Wigger et al., Env. Sci. Nano (2018), DOI: 10.1039/c8en00137e

Use elements of grouping to demonstrate similarity between nanoforms (NF) to register „sets of similar NFs“

„what they are“: physical structure, chemical composition.

„where they go“: release & fate

„what they do“: hazard screening



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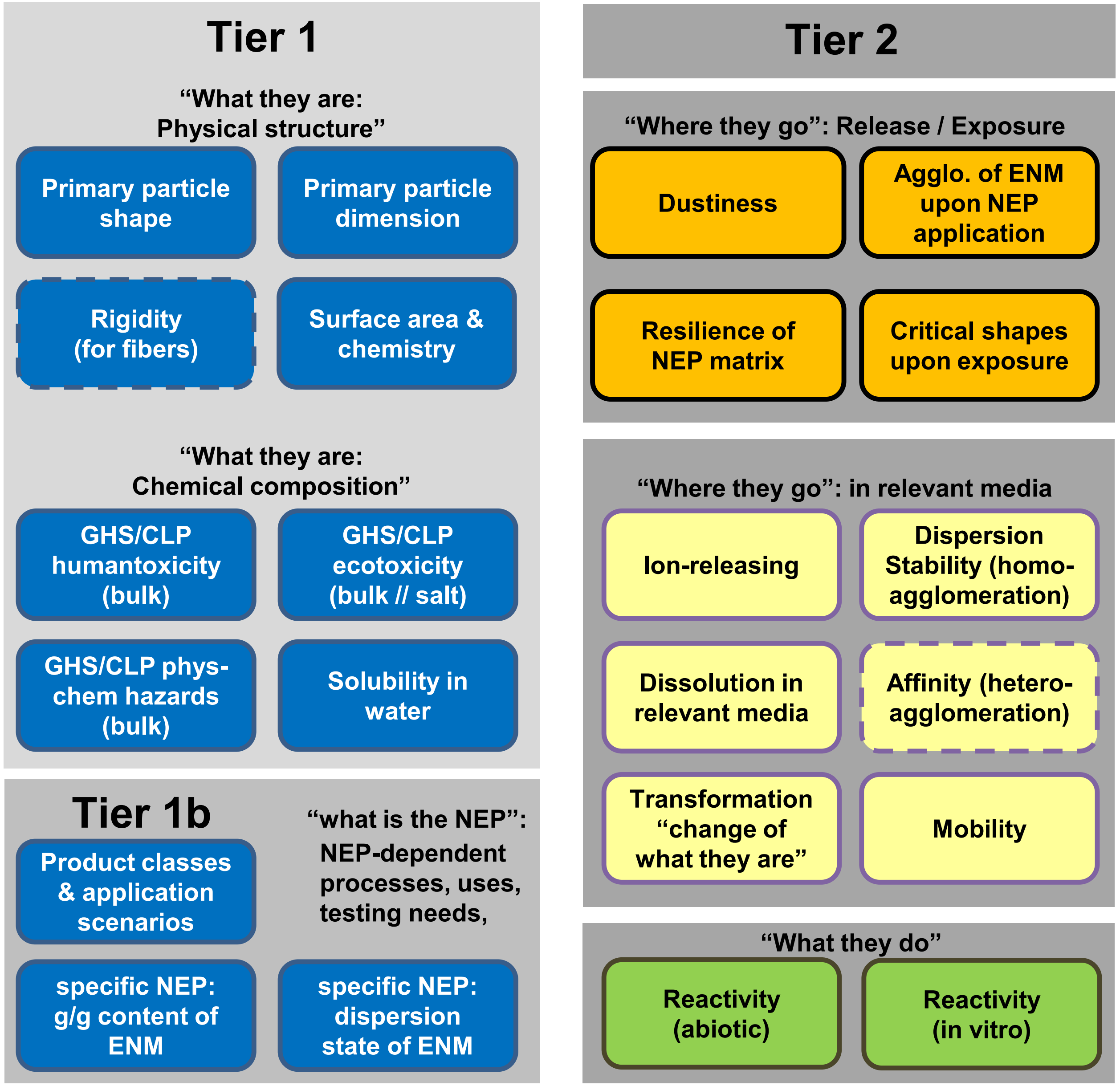
Comprehensive grouping of occup., env., consumer risk: nanoGRAVUR framework

„what they are“: physical structure, chemical composition.

„what is nano-enabled product (NEP)“: system integration / formulation

„where they go“: release & fate

„what they do“: hazard screening



Wohlleben, Kuhlbusch et al, *Nanoscale* **2019**
DOI: 10.1039/c9nr03306h

2 of 34 Case Studies: ZnO uncoated vs coated

different surface chemistry

Properties with numerical values	NM110_ZnO	NM111_ZnO
Composition	1314-13-2	
Primary particle dimension	42	80
Specific surface area (BET/VSSA)	12	14
Surface Chemistry (measured)	30	67.9
	38	24.3
	38	4.3
	3	3.5
Surface charge (zeta-potential)	30	-25
Hydrophobicity	10	152
NEP class & intended use scenarios	sun screen	
Specific NEP: g/g content of ENM	10	10
Dustiness		
Critical shapes upon exposure (for fibres)		
Agglo. of ENM upon NEP application		
Dispersion stability (environ. homoaggl.)	29	36
Solubility in water	0.6	0.1
Ion releasing in relevant environ. media	2.3	2.4
Dissolution rate in relevant human media	204	177
Mobility (in soils)		
Reactivity (abiotic)	3.4	
	2.8	
	43	25
	151	20
Reactivity (in vitro) NR8383 cells	2.8	5.6
Reactivity (in vitro) NR8383 cells	11.3	11.3
Reactivity (in vitro) NR8383 cells	11.3	22.5
Reactivity (in vitro) NR8383 cells	0	0
Reactivity (photo-)	16	

same Tier 2 bands (in dissolution)

data reduction of numerical properties and qualitative descriptors into property ranges	NM110_ZnO	NM111_ZnO
Primary particle shape	1	1
Primary particle dimension	2	2
Composition	410	410
Surface Chemistry (descriptive)	1	3
Hydrophobicity	0	1
NEP class & intended use scenarios	sun screen	
Specific NEP: dispersion state of ENM	2	2
	1	1
	2	2
Specific NEP: g/g content of ENM	1	1
Dustiness		
Dispersion stability (environ. homoaggl.)	1	1
Mobility (in soils)		
Attachment +B68:AP68to algae		
Solubility in water	3	3
Ion releasing in relevant environ. media	1	1
Dissolution (environmental perspective)	0	0
Transformation (environmental perspective)	0	0
Dissolution & Transformation (human perspective)	1	1
Reactivity (abiotic)	4	4
Reactivity (in-vitro), human perspective	3	3

similar ecotoxicity

nanoGRAVUR

	NOAEC (rat, STIS) mg/m³	EC50 (algae) mg/L	EC50 (daphnids) mg/L	EC50 (FET) mg/L	EC50 (soil micro flora) mg/kg
DPP_nano	**>30**	**N.d.**	**N.d.**	**N.d.**	**N.d.**
DPP_non-nano	**>30**	**N.d.**	**N.d.**	**N.d.**	**N.d.**
CuPhtalo_nano	**>30**	**>100**	**>100**	**>100**	**>1000**
CuPhtalo_halogen		**>100**	**>100**	**>100**	**>1000**
Fe2O3_nano_A	**30**	**3.6**	**>100**	**>100**	**>1000**
Fe2O3_nano_B		**2.4**	**>100**	**>100**	**>1000**
Fe2O3_larger	**30**	**111**	**>100**	**>100**	**>1000**
SiO2_untreated	**2.5**	**14**	**>100**	**>100**	**>1000**
SiO2_amino	**>50**	**29**	**>100**	**>100**	**>1000**
SiO2_phosphonate	**>50**	**46**	**>100**	**>100**	**>1000**
NM203_SiO2_hydrophil	**1.0**	**N.d.**	**N.d.**	**N.d.**	**N.d.**
NM211_CeO2	**<0.5**	**8.5**	**>100**	**>100**	**>1000**
NM212_CeO2	**<0.5**	**5.6**	**>100**	**>100**	**>1000**
CuO (PlasmaChem)	**0.6**	**1.4**	**0.3**	**≈30% effect at 100 mg/L**	**~1000**
NM110_ZnO	**N.d.**	**0.1**	**3.4**	**>100**	**118**
NM111_ZnO coated	**0.5**	**0.1**	**8.3**	**>100**	**173**
NM105_TiO2_nano	**<2**	**4.7**	**N.d.**	**N.d.**	**N.d.**
NM104	**N.d.**	**63**	**N.d.**	**N.d.**	**N.d.**
NM400_CNT	**<0.5**	**N.d.**	**N.d.**	**N.d.**	**N.d.**
NM220_BaSO4	**50**	**N.d.**	**N.d.**	**N.d.**	**N.d.**
quartz DQ12	**0.1**	**N.d.**	**N.d.**	**N.d.**	**N.d.**

Human hazards (BASF, RIVM): In vivo inhalation (rat, 28d evaluation)
Ecological toxicity (UFZ, Fraunhofer IME): OECD 201, 202, 236; ISO 15655.

Wohlleben, Kuhlbusch et al, *Nanoscale* **2019;** DOI: 10.1039/c9nr03306h

Interim Summary: nanoform registration of conventional materials

- **NanoDefine identification:** tonnages reported to French inventory are plausible.

- **nanoGRAVUR framework: harmonized methods and benchmark materials**
  - Dissolution and transformation are least modulated by different NFs within one substance,
  - Dustiness, dispersion stability, abiotic and in vitro surface reactivity vary more often between NFs
  - Benchmark materials span the dynamic range, calibrate the significance of dissimilarities

- **nanoGRAVUR 34 case studies.**
  - Within one substance, high similarity of different NFs of SiO_2, $BaSO_4$, kaolin, CeO_2, ZnO, organic pigments, especially when comparing forms that are all untreated on the surface.
  - Different Fe_2O_3 or TiO_2 (nano)forms differ more significantly

- **GRACIOUS draft framework:** Purpose-adjusted level of similarity; floating instead of fixed bands
- **NanoFASE models**: sensitivity of fate & transport against differing NF properties

Nanoscale (2019) c9nr03306h
Env. Sci. Nano 6 (2019) 1443
NanoImpact (2019) 100154

ES&T 52 (2018), 1514
Nanoscale Advances 1 (2019) 781
NanoImpact 12 (2018) 29

Challenges, especially for pigments:

10 mg/l DOC		6h	
$Ca(NO_3)_2$ [mM]	**pH 4**	**pH 7**	**pH 9**
10	9	10	11
1	82	81	87
0	84	80	94

- Establishment of organism-specific most realistic exposure scenario
  - What are the Risk Assessment consequences of the first nano-specific TG (318), if most materials have “intermediate stability” at some ph/Ca/NOM ?
  - Isn’t hetero-agglomeration anyway dominant? → NanoFASE

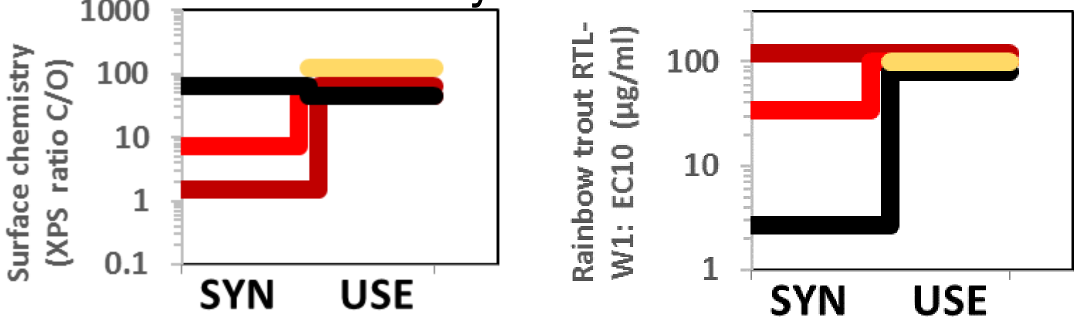
- Testing of dissolved vs. particulate fraction vs. “nano-fraction”
  - Why discard (hetero)agglomerates, if that is the only realistic form of exposure? potential pre-settling time for NM dispersions?
  - exposure stability of NM in different test media (± 20%) for up to 7 days study duration??

- Differentiate intrinsic toxicity vs. physical effects
  - Adapt sample prep for pelagic vs. bentic organisms
  - Testing only stable fractions vs. spiked sediments?

Testing the relevant (nano)form

- ✓ NanoFASE put emphasis on testing the relevant transformation (of ENM that easily transform: Ag)
  - ▶ But only few applications release ENM, instead more often fragments of nano-enabled products
  - ▶ Using the ISO TC229, PG29 „NanoRelease“ categories:

Matrix less durable than nanomaterial (plastics & coatings): Assimilation by matrix & intended use



Amorim et al. ES&T 52 (**2018**) 1514

Nanomaterial less durable than matrix (biocides): Assimilation by dissolution or transformation:

Pantano et al, ES&T 52 (**2018**) 1128

- GRACIOUS will consider the form that is released for grouping of NEPs
  - ▶ Similarity primarily determined by intended use & NEP matrix, least by ENM

Urgent questions in view of the REACH requirements for 2020 with help from nanoFASE

- Which properties are necessary to establish „sets of similar nanoforms“ ?
  - ▶ Manufacturing output ~ nanoform → set (BASF) → set (all producers) → EUCLID
  - ▶ Justification required, must consider human & environmental hazard, and exposure.
- Which properties & (functional) assays are necessary & sufficient to assess similarity for grouping?
  - ▶ Are methods applicable beyond Ag, instead to industrially prioritized materials?
  - ▶ nanoGRAVUR case studies on grouping of ENM and NEP: *Nanoscale*, in print.
- Which compartments shall be prioritized for environmental RA ?
- If the regulator insists on testing aquatic toxicity – how shall we test hydrophobic / instable materials?
- …confronting a deadline of January 2020, but guidance from ECHA is sparse, and many OECD TGs are in development or under revision
  - ▶ Will we have to re-test once the guidance & TGs are available?