Implementation of the risk-neutral, wide scope EC nanodefinition: Practical concepts and test cases

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COMMISSION RECOMMENDATION on the definition of nanomaterial

Need to know how to consider aggregate/agglomerates

EC does not consider 'intention' or 'novel properties' (cf Canada)

Refers to primary (constituent) particles

"Nanomaterial" means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.

Median in number metrics !
No method indicated !!?!

Few methods can detect 1nm

… [or] where the specific surface area by volume of the material is greater than 60 m² / cm³.

Alternative metrics

Impact vs. scope

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- BiPRO study expects alone in Belgium
  - about 2,000 – 5,000 substances
  - 80,000 – 160,000 preparations
  - 800,000 – 1,300,000 articles.*

- The actual numbers that industry faces are much higher, since BiPRO focused on engineered nanomaterials and excluded non-engineered particulates (often referred to as incidental)

*A unique article is here a product anywhere along the supply chain, placed on the Belgian market, and that has its own product identifier (e.g. different coloured paints are unique products)


Federal Public Service Health, Food Chain Safety and Environment, Brussels, Belgium

STUDY OF THE SCOPE OF A BELGIAN NATIONAL REGISTER FOR NANOMATERIALS AND PRODUCTS CONTAINING NANOMATERIALS

REFERENCE: DG5/MR/JP/12026

FINAL REPORT

2013

BiPRO
Beratungsgesellschaft für integrierte Problemlösungen

In cooperation with

Öko-Institut e.V.
Institut für angewandte Ökologie
Institute for Applied Ecology

…dy to Assess the Impact
…f Possible Legislation to
…crease Transparency on
…naterials on the Market

Evaluation Report
prepared for
DG Enterprise and Industry

June 2014

bipro RPA Risk & Policy Analysts

Nanotechnology is a cross-sectional enabler for BASF and its customers

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Resources, Environment & Climate	Food & Nutrition	Quality of life

Chemistry as enabler

Customer industries

Growth fields*

Transportation	Construction	Consumer Goods	Health & Nutrition	Electronics	Agriculture	Energy & Resources
Batteries	Heat management	Enzymes	Medical	Organic Electronics	Plant biotechnology	Energy management
Leightweight composites					Functional crop care	Rare earth metals recycling
Heat management						Wind energy
						Water solutions

Technology fields

- Raw material change
- Materials, systems & nanotechnology
- White biotechnology

*including growth fields still under evaluation

Need to screen all „particulate“ materials
in the absence of guidance or validated methods.

→ Indicative ranking of conceptual & metrological challenge

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1. Pigments, fillers, anticaking agents are clearly particulate, and product performance is linked to their relatively well-defined morphology
   - Datasheets often specify size in volume metrics or specific surface area
   - No technical relevance of size in number metrics

2. Solidified waxes, dried salts, mortars, polymer granulates are particulate, but product performance is after melting or dissolution
   - Size and shape are not engineered, not specified (µm // mm // cm)
   - Can be indispersible (soluble, reactive), polydisperse, complex shaped

3. Formulations, liquids with particulate traces, porous materials
   - Conceptually very vague in the present EC definition

Conclusions from round robin on 8 pigments with LD, CLS, DLS, VSSA, TEM and standardized sonication protocols

Eurocolour + JRC-IHCP

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- **From results of this project it has not been possible to recommend any single, simple and commonly available method which can reliably identify, according to the EU definition, a nanomaterial after re-dispersion in liquid.**

- Interim proposal of a pragmatic approach, which uses accessible and cost-effective methods, requires tiered approach
- **Sample state (especially dispersions) is critical** to achieve a valid and representative determination of a particle size distribution: wetting – disintegration – stabilisation
- Expertise and knowledge of the substances in question is needed to obtain meaningful results.

A route to solution?

Compare classifications by measurement of „smallest dispersible unit“

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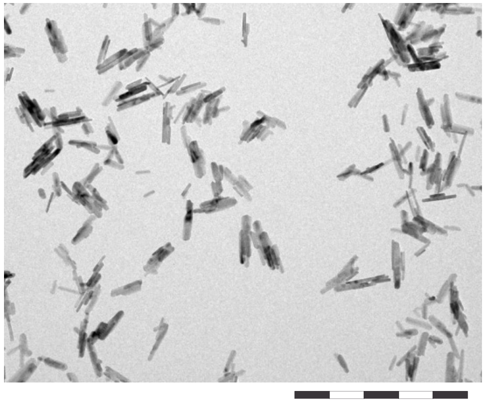
Sonication in water often assumed as «smallest dispersable». Even better dispersion is known from performance testing:

- DIN 53238-13 Dispersion in low-vicosity media by a shaker
- ISO 8781-1:1990 Pigments and extenders -- Methods of assessm. of dispersion characteristics



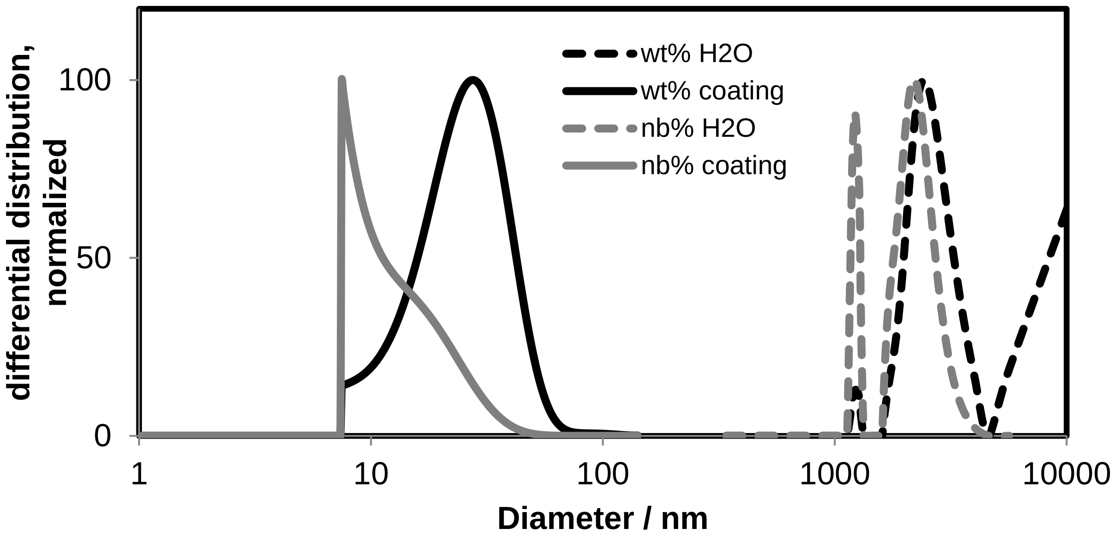
Pigment Yellow 42

✓ Much enhanced dispersion in organic coating than in water

✓ Dispersed D50 by CLS matches **TEM (15nm)** and BET (80m²/g) expectations

❖ Size distribution screwed by detection limit, not credible.

❖ Number metrics conversion amplifies errors



A route to solution?

Compare classifications by measurement of „smallest dispersible unit“

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The „smallest dispersible unit“ classifies 60% of those pigments as non-nano that are nano by EM and BET/VSSA.

However, it achieves the same ranking of materials.

Color index	Baseline EM: Shape	Smallest external dimension (EM, BET): D50 / nm	Smallest dispersable unit (CLS): D50 / nm
Pigment Yellow 42	Rod, agglom.	10	14
Pigment Red 101	Rod, agglom.	9	20
Pigment Yellow 139	Irregular particle	150	448
Pigment Red 254 opaq	Irregular particle	233	976
Pigment Red 254 trans	Irregular particle	36	250
Pigment Blue 15:4	Irregular rod	30	162
Pigment Blue 15	Irregular rod	75	114
Pigment Yellow 184	Irregular particle	107	240

If number metrics is a key paradigm, classify by „smallest dispersible unit“

PRO

- Measurement of „smallest dispersible units“ is technically feasable
  - sonication in water, then classifying & counting methods (CLS, spICPMS, NTA, SMPS, …)
  - delivers a size distribution in number metrics

- Integrates an element of risk assessment (dispersability)

CONTRA

- In general no agreement with „smallest external dimension“ (EM, BET)
  - BASF pigments, many more test cases in NanoDefine project
    - even some materials with product performance directly linked to structures (pigments, fillers) would be non-nano
- JRC report #2 advises against universal dispersion protocol, making the concept irreproducible between manufacturers.

Expected improvements with view to the implementation of the definition

- some reference materials available
- agglomerates can be measured (aggregates?)
- validity of conversion algorithms rated
- more methods available for range < 30 nm and complex materials
- largely increased cost-efficiency
- standardised methods available
- guidance on use of methods

NanoDefine Deliverable 3.1 preview

Resulted from subjective opinions of NanoDefine experts.
The table will be revised at a later stage and is not final.

			Costs per sample	Widely used/ Availability	Potential for improvement in NanoDefine within 2014-2017?	Measurement of the material as it is
Counting	EM	SEM	-	++	+	--
		TSEM	-	+	+	--
		TEM	--	o	o	--
	SFM		-	+	o	-
	PTA		+	o	+	-
	TRPS		+	-	-	-
	sp ICP-MS		+	-	+	-
Fractionating	FFF		o	-	+	-
	AC		+	+	+	-
	DMAS		+	o	o	-
	SEC		o	o	-	-
Ensemble	DLS		++	++	o	-
	SAXS		+	o	o	+
	USSp		+	-	-	-
	XRD		+	++	-	+
	ALS		+	o	o	-
	OS		+	+	-	-
	FCS		N/A	--	--	--
Integral	BET		+	++	-	o

Costs per sample very different between methods.

Expect techniques to improve only incrementally.

Very few methods measure „as is“

NanoDefine Deliverable 3.1 preview

Resulted from subjective opinions of NanoDefine experts.
The table will be revised at a later stage and is not final.

		Size range						Access to primary particles?	Access to the smallest dimension of each particle
		nm			µm				
		1-10	10-30	30-100	0.1–1	1–10	>10		
Counting	EM SEM	-	(+)	++	++	++	++	+	+
	EM TSEM	(+)	+	++	++	++	++	+	+
	EM TEM	++	++	++	++	++	+	++	+
	SFM	+	++	++	+	o	-	o	++
	PTA	--	o	+	++	-	--	--	--
	TRPS	--	--	o	+	+	--	--	--
	sp ICP-MS	-	o	+	++	-	--	-	--
Fractionating	FFF	+	++	++	++	o	--	-	-
	AC	o	+	++	++	+	-	--	--
	DMAS	+	++	++	++	–	--	-	-
	SEC	o	+	+	+	o	--	--	--
Ensemble	DLS	+	++	++	++	o	-	-	-
	SAXS	+	+	+	-	–	--	+	o
	USSp	-	+	++	+	o	o	--	-
	XRD	+	+	+	-	–	--	+	-
	ALS	-	o	+	++	++	++	-	-
	OS	+	+	+	o	-	--	--	-
	FCS	--	--	--	--	–	--	--	--
Integral	BET	+	+	+	+	+	o	o	-

Only EM and BET/VSSA cover the entire size range 1nm – 10µm.

Only EM and ALS measure large particles >10µm.

Few techniques access „primary particles“.
Most techniques access „smallest dispersible unit“.

PROPOSAL 1: Counting requires validation

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Counting result (CLS preferred*)	Classification
D50 < 100nm	Nano
D50 > 100nm	Non-nano If dispersion quality is validated**

*** Validation of *technique* by nano and non-nano reference materials**

**** Validation of *dispersion* vs „smallest dispersable unit" by standardized dispersion protocol**

**** Validation of *dispersion* vs „smallest external dimension" by baseline XRD, SAXS, EM, VSSA**

Methods other than counting or EM required:

solubles, reactives,

platelet morphologies non-engineered particulates

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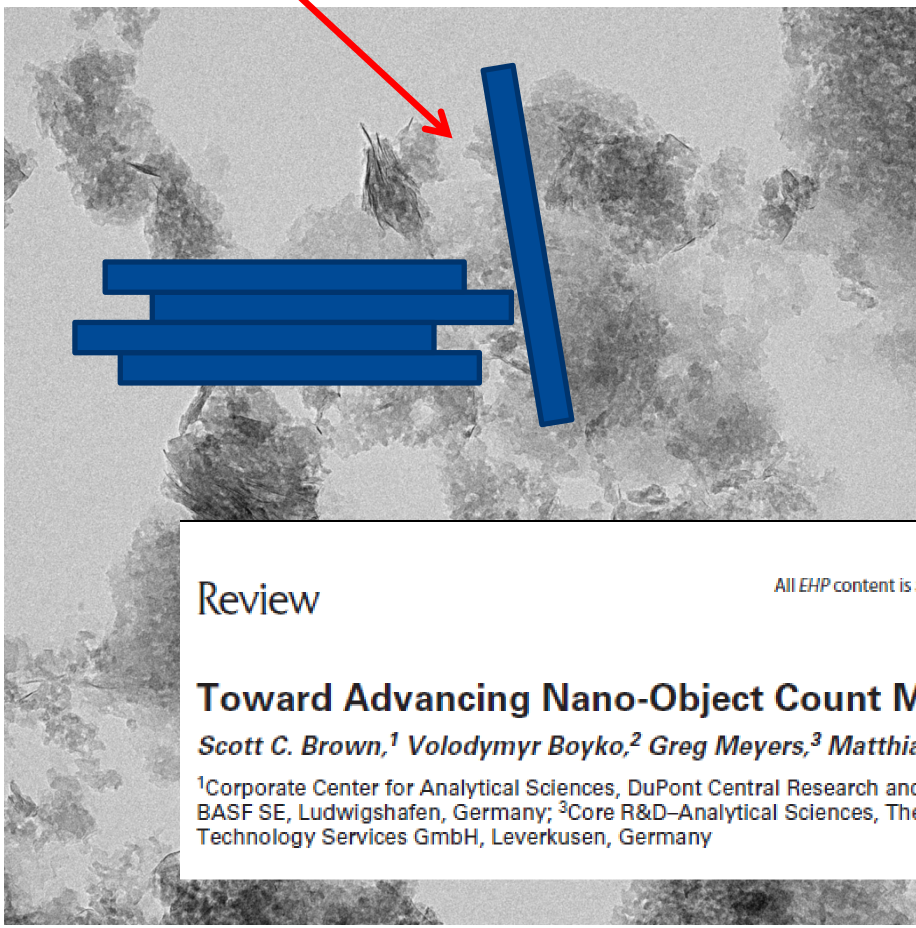

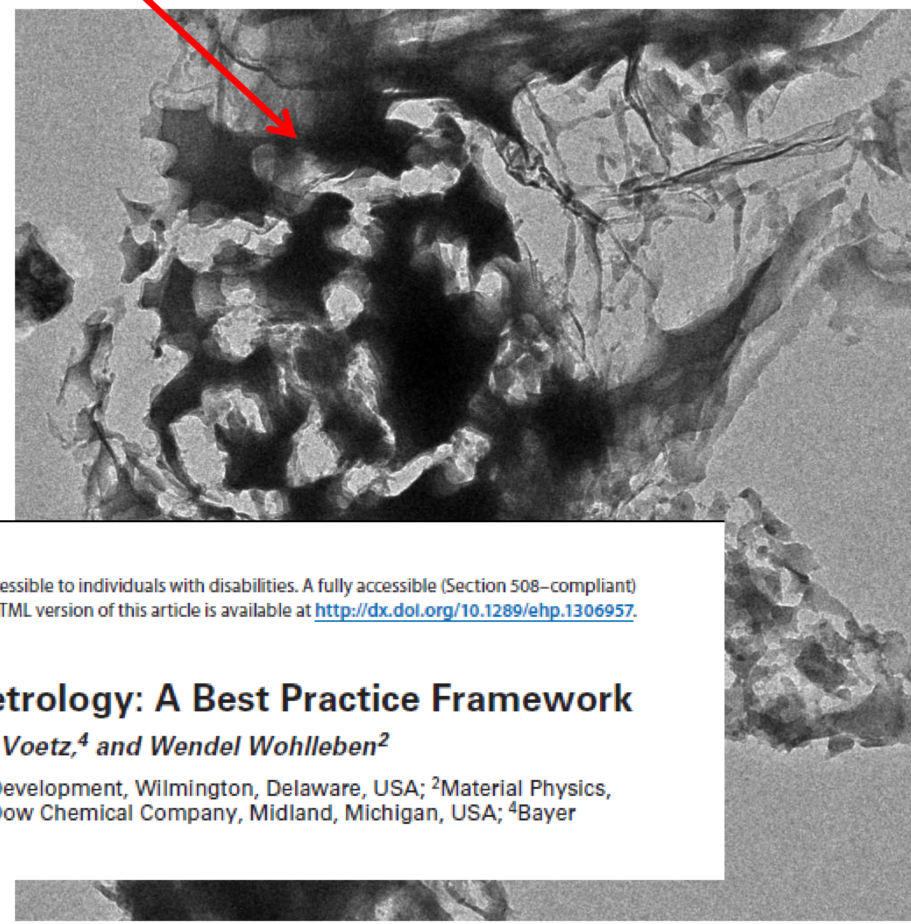

Review

All *EHP* content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1306957.

Toward Advancing Nano-Object Count Metrology: A Best Practice Framework

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200 nm

500 nm

Interim summary on methods and policy options in the revision process

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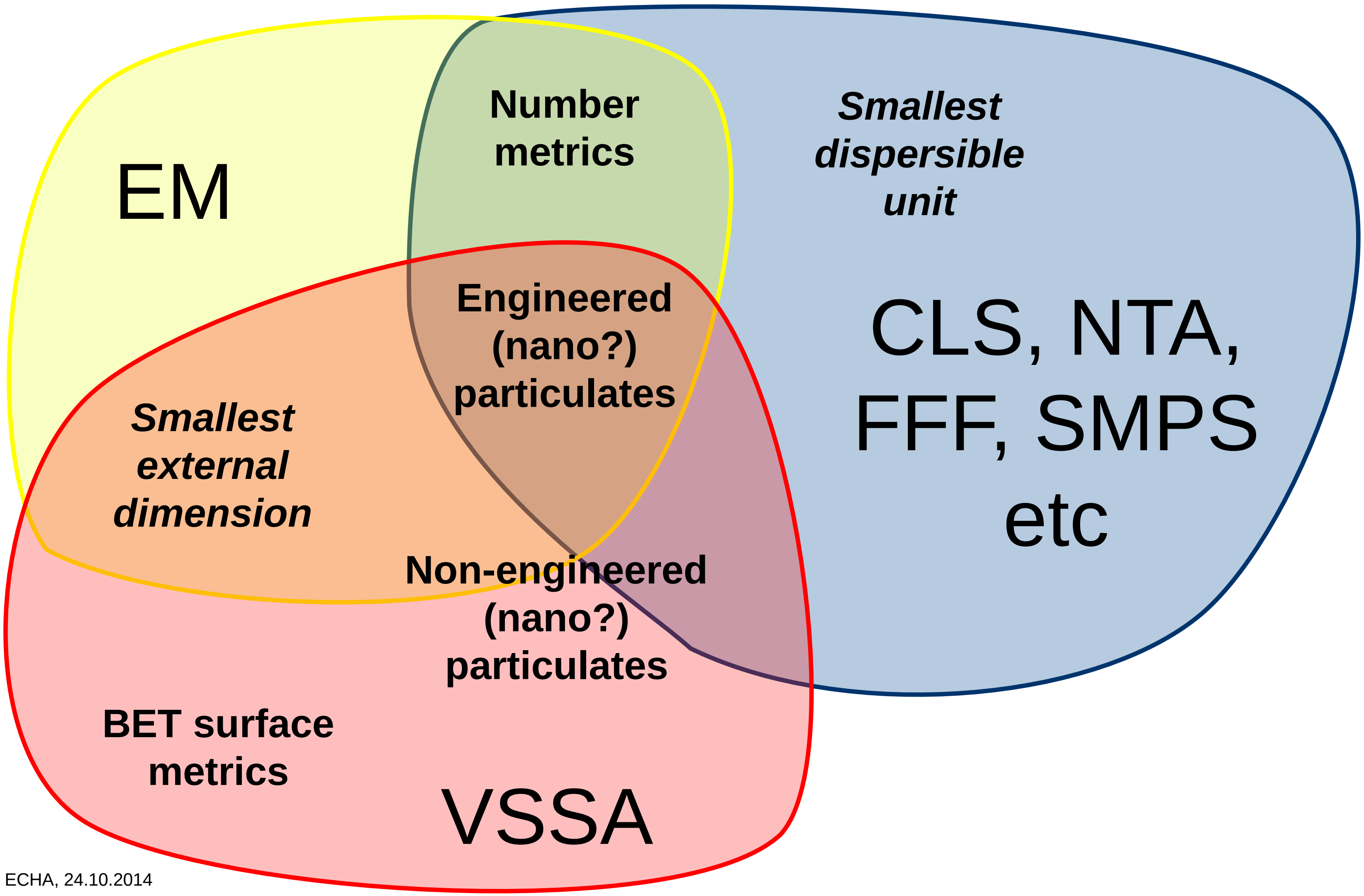

VSSA is unique for screening

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VSSA = Volume-Specific Surface Area
= BET x density

Nanomaterial, if VSSA > 60 m^2/cm^3

- ☑ BET and density data are already available and specified
- ☑ 1nm – 10µm size range
- ☑ Minimal sample preparation, works on agglomerates
- ☑ Works on soluble materials !
- ☑ 2 % of TEM costs / material
- ☑ Excellent reproducibility between producers, excellent enforceability

JRC report #2 explores VSSA validity and safety margins

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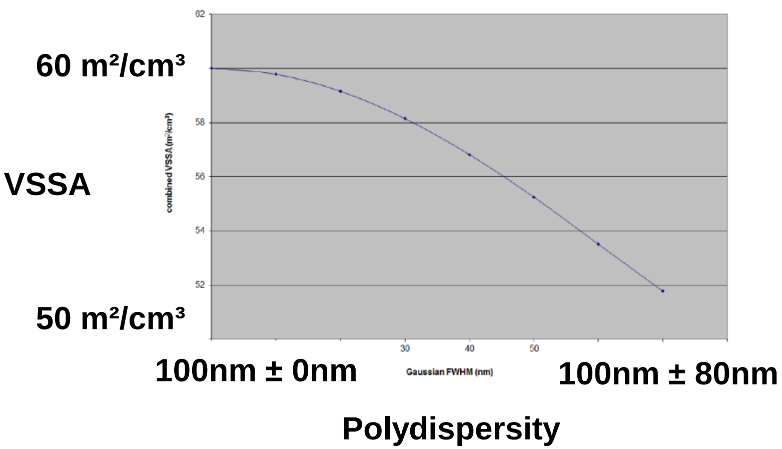
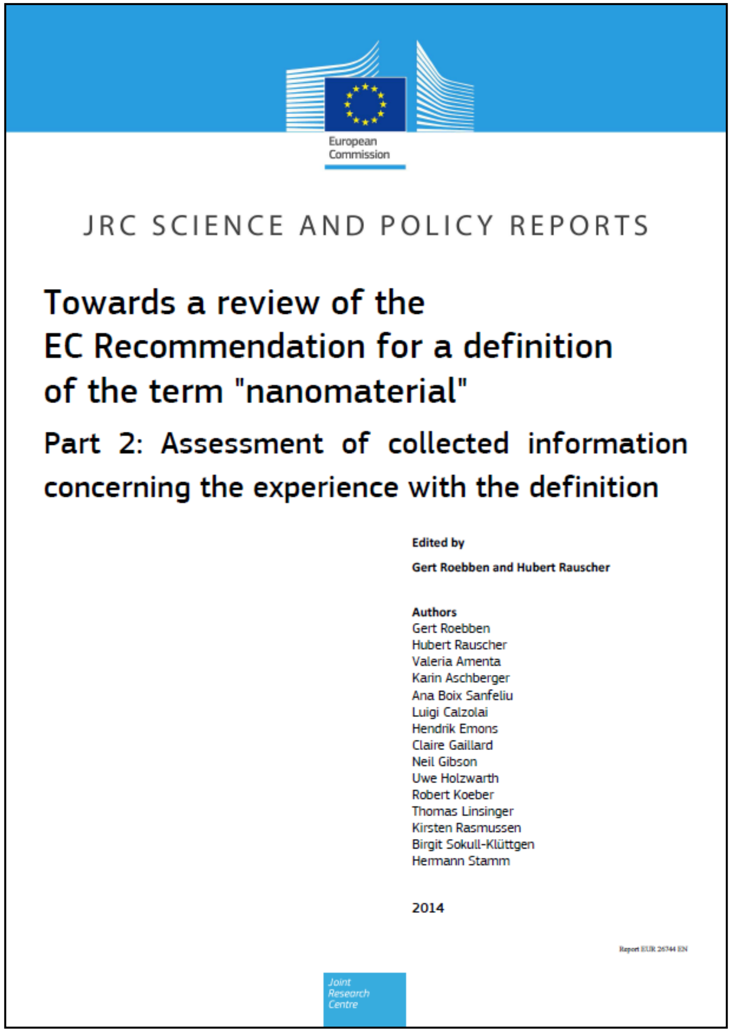
- [VSSA] could be a reliable method of classification both as nanomaterial and non-nanomaterial.
- … verification with appropriate baseline EM studies.
    - For **needle-shaped** particles, against a threshold value of **40 m²/cm³**
    - For **platelet/flake** shaped particles against a threshold value of **20 m²/cm³**
    - For non-porous particles with non-complex shapes a large "safety margin" would have to be used




European Commission

JRC SCIENCE AND POLICY REPORTS

Towards a review of the
EC Recommendation for a definition
of the term "nanomaterial"

Part 2: Assessment of collected information concerning the experience with the definition

Edited by
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2014

Joint Research Centre

PROPOSAL 2: Screening by VSSA (powder substances)

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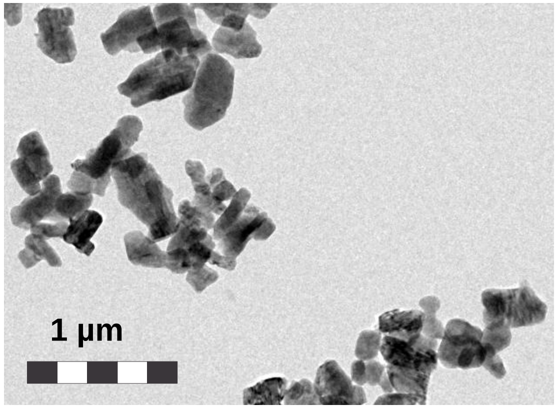
Units of m²/cm³	Classification
VSSA > 60	Nano, unless „baseline EM“ shows inner or coating porosity
60 > VSSA > M	Cannot decide by VSSA, need EM or validated counting on this specific product
M > VSSA > X	Non-nano, if „baseline EM“ on similar products shows no extraordinary shape or bimodality
X > VSSA	Non-nano without any further evidence

JRC report #2: M= 20 (platelets) and 40 (fibers)
BASF proposal X = 6 (uncertainty factor 10, easy to measure)
BASF proposal X = 0.6 (uncertainty factor 100, equivalent to PM_{10} , but challenges measurement range of BET)

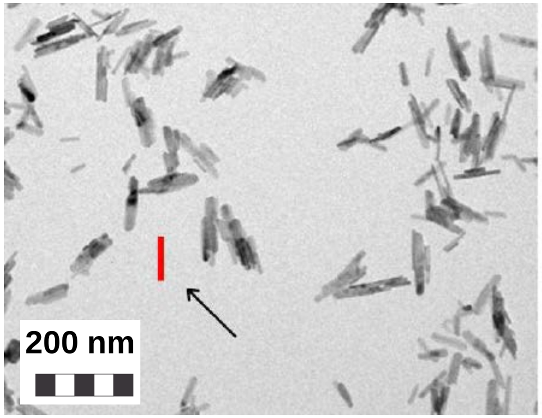
PROPOSAL 2: Screening by VSSA

VSSA + baseline EM

Color index	Baseline EM: Shape	VSSA / m^2/cm^3
Pigment Yellow 42	Rod, agglom.	324
Pigment Red 101	Rod, agglom.	419
Pigment Yellow 139	Irregular particle	43
Pigment Red 254 opaq	Irregular particle	24
Pigment Red 254 trans	Irregular particle	153
Pigment Blue 15:4	Irregular rod	103
Pigment Orange 73	Platelet	30



Pigment Yellow 139
Baseline EM → irregular, agglom. particles



Pigment Yellow 42
Baseline EM → agglomerated rods
(from JRC-report #2)

PROPOSAL 2: Screening by VSSA

VSSA + baseline EM + counting EM validation
M = 40 m²/cm³ also for agglomerated irregular shapes

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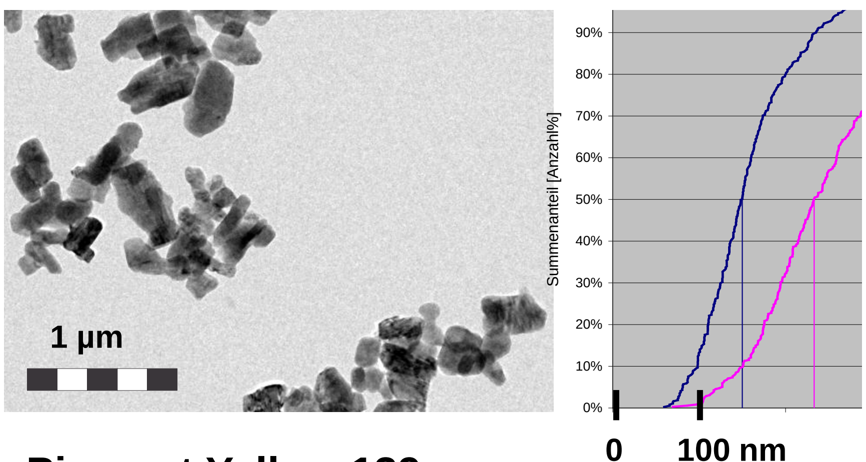
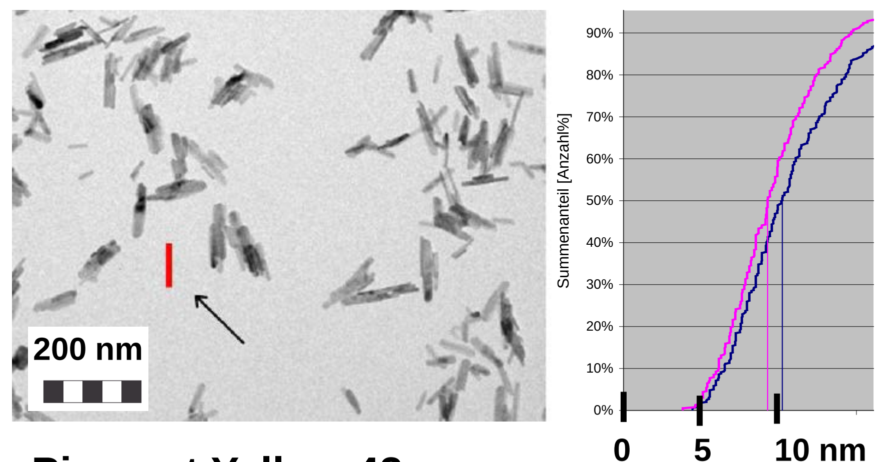
Color index	Baseline EM: Shape	VSSA / m²/cm³	Counting EM: D50 / nm
Pigment Yellow 42	Rod, agglom.	324	10
Pigment Red 101	Rod, agglom.	419	9
Pigment Yellow 139	Irregular particle	43	150
Pigment Red 254 opaq	Irregular particle	24	233
Pigment Red 254 trans	Irregular particle	153	36
Pigment Blue 15:4	Irregular rod	103	30
Pigment Orange 73	Platelet	30	

EM and VSSA provide same classification on engineered solid particulates



Pigment Yellow 139
Baseline EM → <u>irregular, agglom. particles</u>



Pigment Yellow 42
Baseline EM → <u>agglomerated rods</u>
(from JRC-report #2)

PROPOSAL 2: Screening by VSSA

Macroscopic substances that are „usually <u>not</u> considered a nanomaterial” (JRC report #2) are classified <u>non-nano</u>

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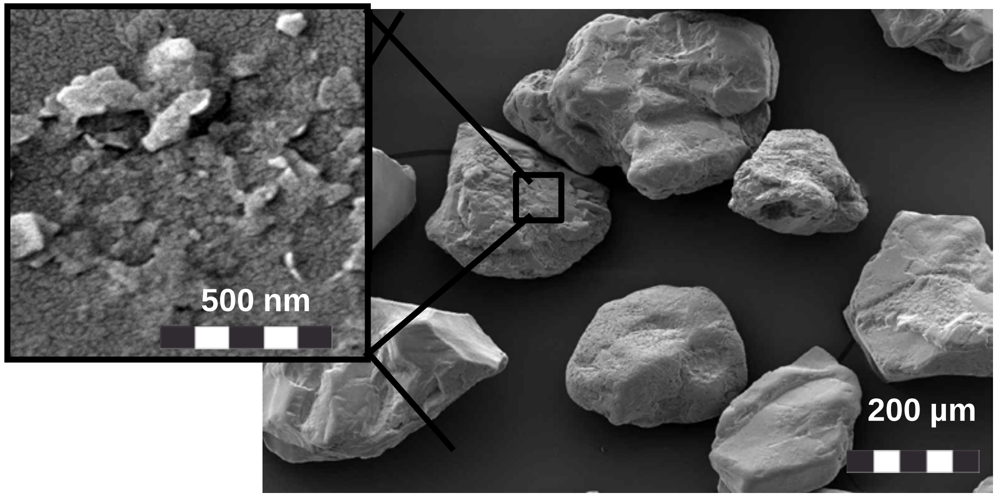
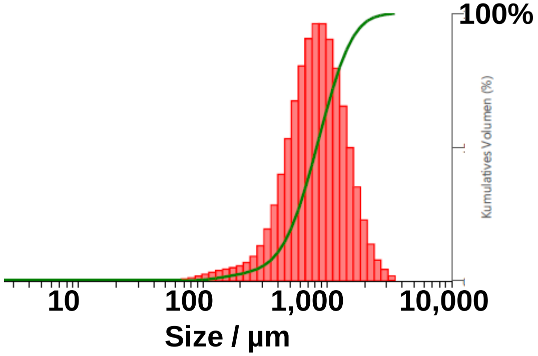
Sea-sand: large particulate
removed by VSSA < X screening





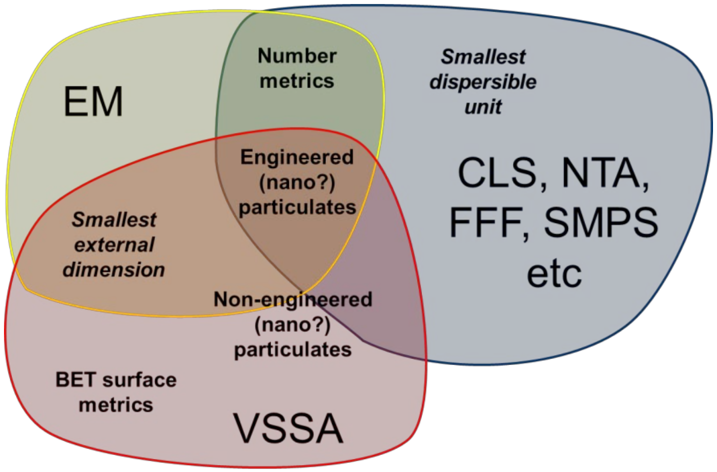
mm-size polymer granulates:
removed by VSSA < X screening

	BET [m²/g]	VSSA [m²/cm³]
ULTRAMID B3M6 LS SCHWARZ 23213	<0.01	<0.012
ULTRAMID B3S UNGEFÄRBT	<0.01	<0.012
ULTRAMID B3WG10 SCHWARZ 564	<0.01	<0.012
ULTRABATCH 422	<0.01	<0.012

1,000s engineered vs. 10,000s non-engineered

pigments, fillers, anticaking agents

waxes, polymer granulates, mortars, organics, dried salts, …



EM and VSSA provide same classification on engineered particulates (pigment test cases)

VSSA screening reduces by-catch of large particulates, where nano-specific risk assessment does not work anyway (engineered or non-engineered)

Four guidance PROPOSALS, priority on:

→ Screening must allow simple & definite non-nano classification, e.g. VSSA with safety margins

→ Reproducibility of counting metrics requires either a standardised dispersion protocol or a validation against smallest dimensions.

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Nano-specific risk assessment? Some consensus on relevant properties, even if definitions differ in properties, metrics, cut-offs

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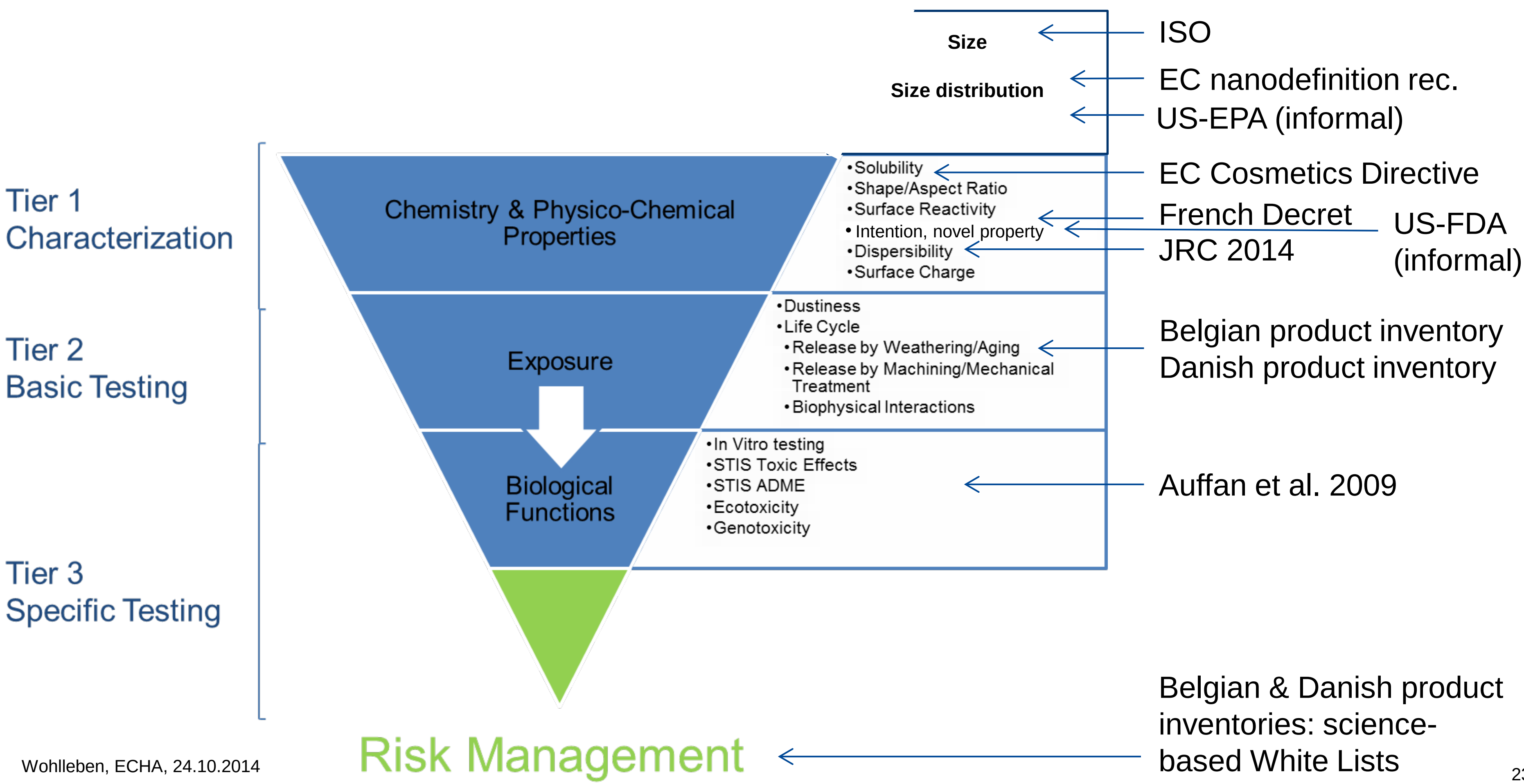
Testing strategy for risk assessment

Definitions



Dispersibility, Solubility are no intrinsic properties, but procedural phenomena related to specific scenarios of exposure

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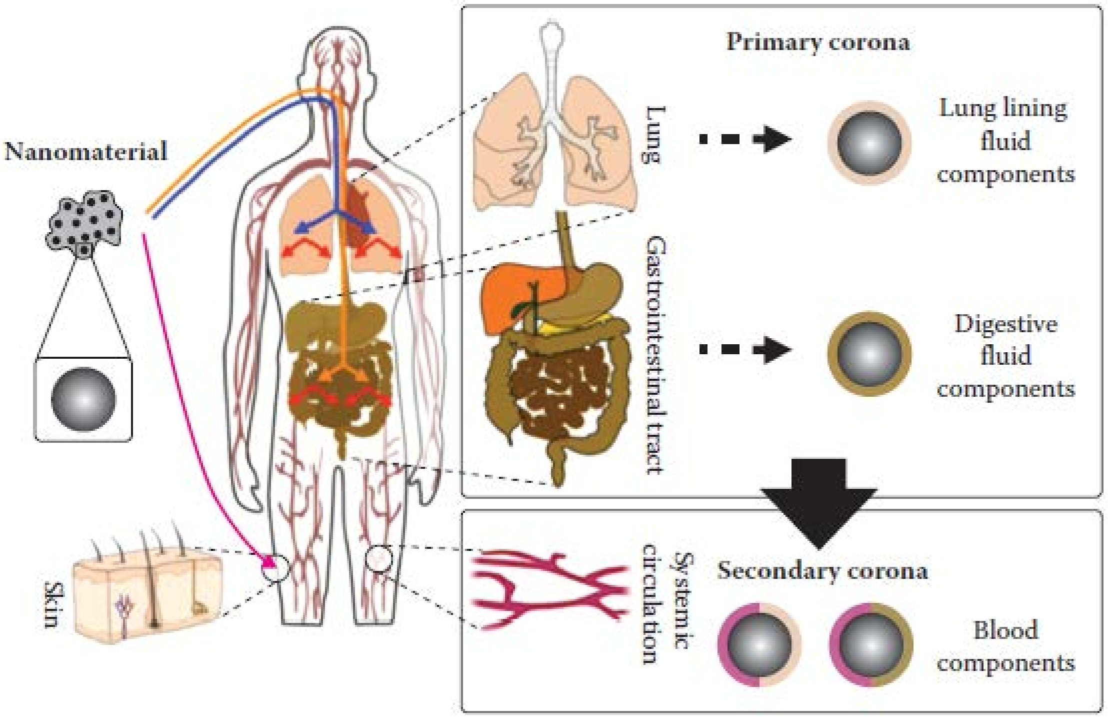

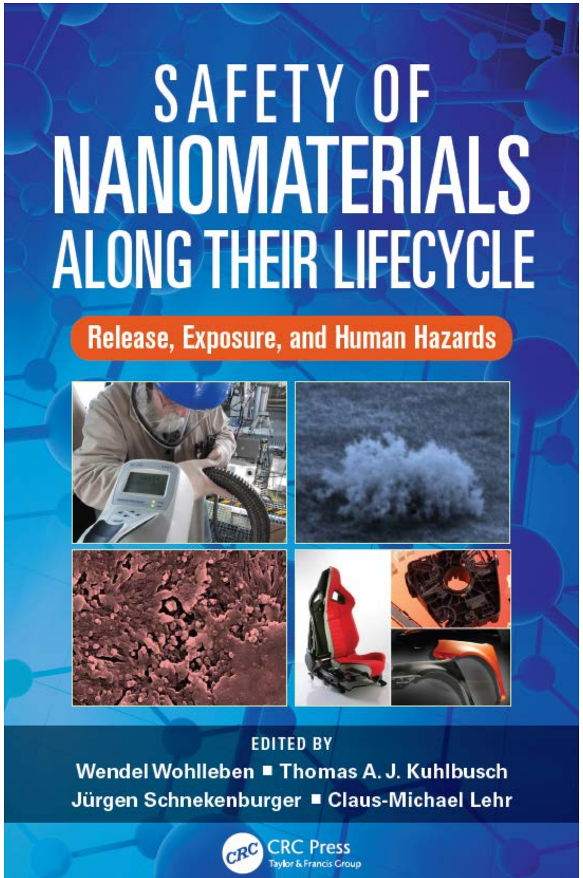

435 pages, ISBN 978-1-46-656786-3

Christian A. Ruge, Marc Driessen, Andrea Haase, Ulrich F. Schaefer, Andreas Luch, and Claus-Michael Lehr
pp 59 – 95 in ISBN 978-1-46-656786-3, **2014**.

Release is measurable (→ NanoRelease round robins), but depends more on polymer matrix and scenario than on nanomaterial

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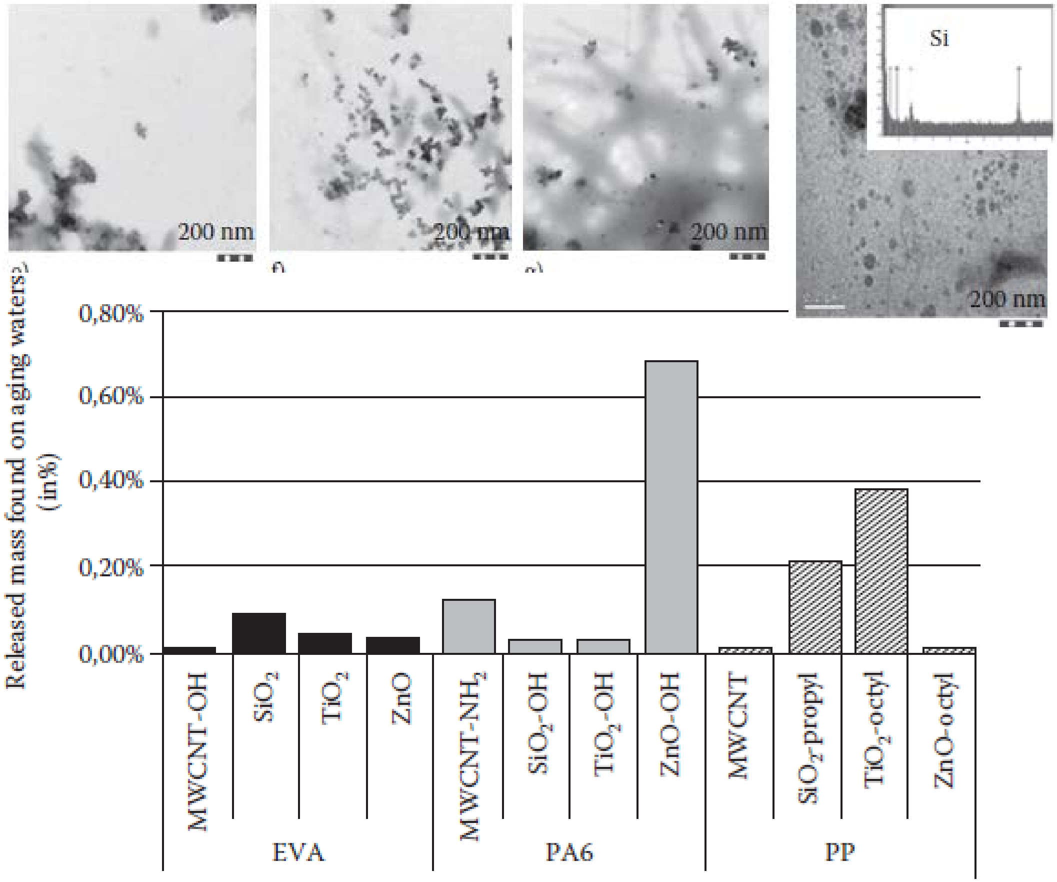
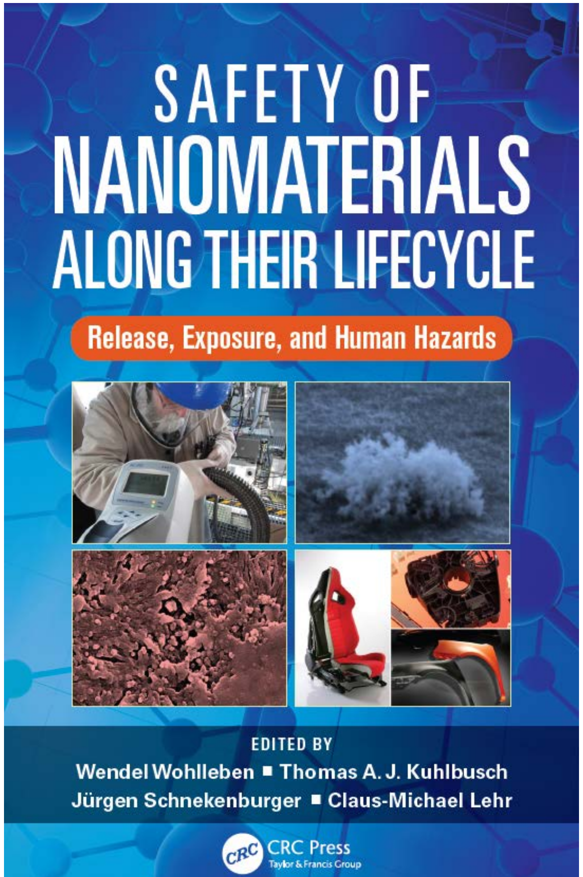


Tinh Nguyen, Wendel Wohlleben and Lipiin Sung, pp 315 – 334 in ISBN 978-1-46-656786-3, **2014**.



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Release, Dispersibility, Solubility require a combined assessment as part of a testing strategy

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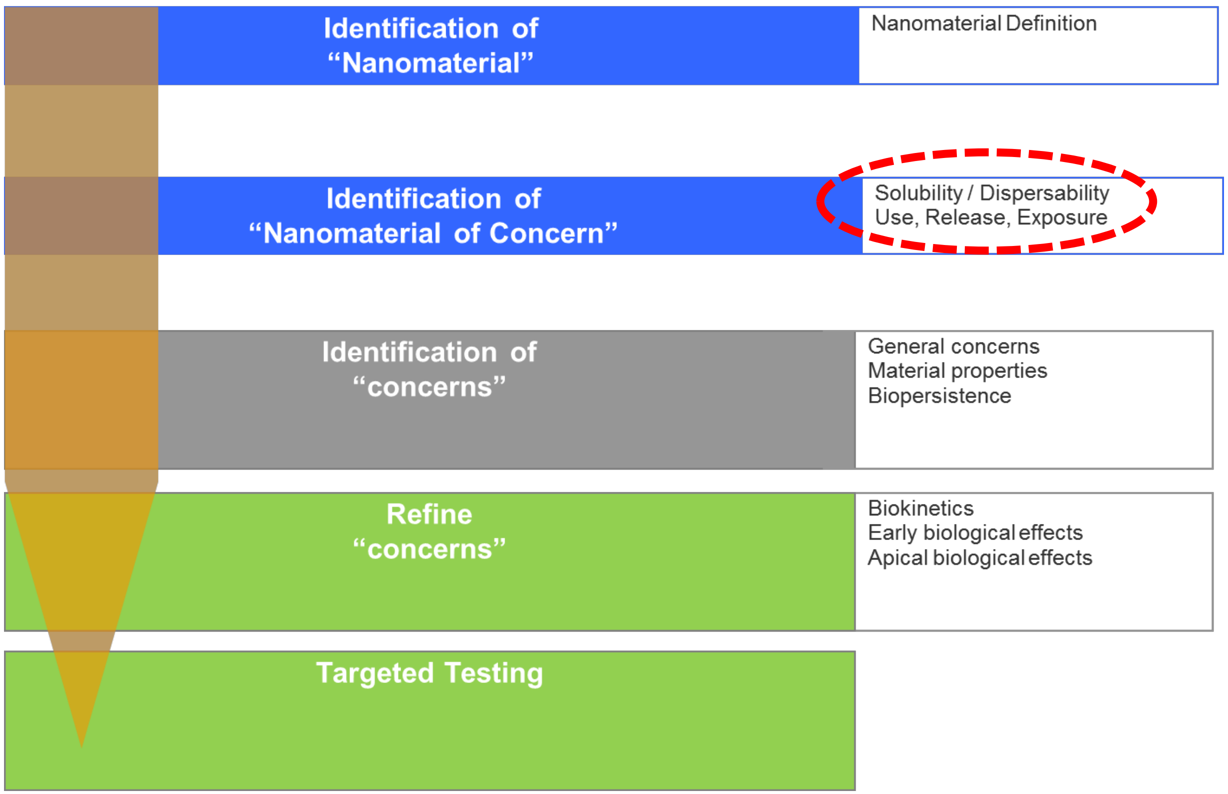

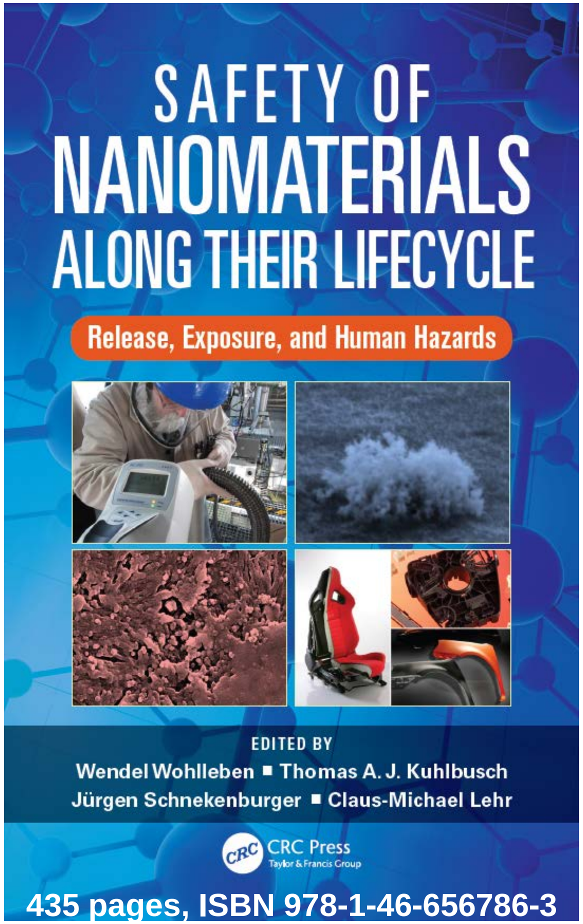

Agnes Oomen, Peter Bos, and Robert Landsiedel → **talk Friday**
pp 358 – 379 in ISBN 978-1-46-656786-3, **2014**.

Ackowledgements

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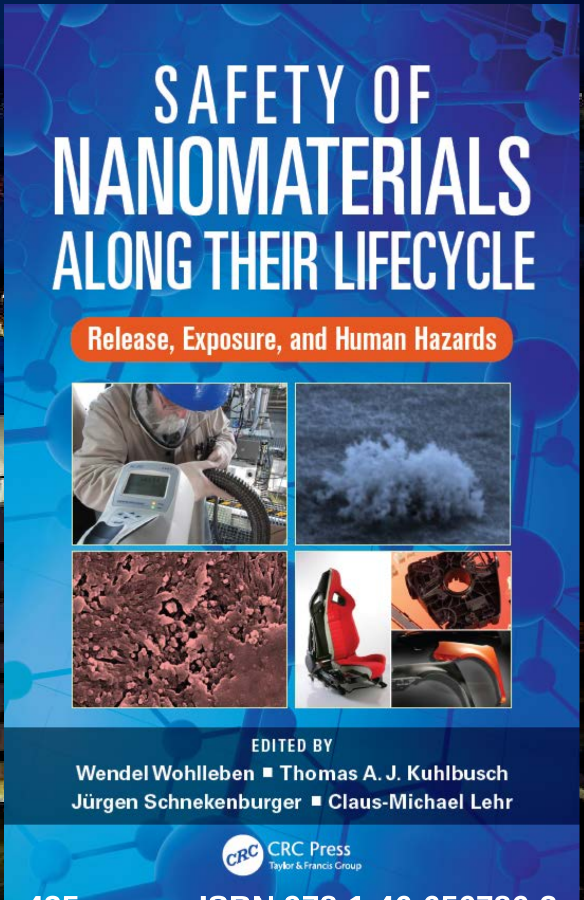
S.D. Brown, DuPont; M. Voetz, Bayer



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Clarifications required for materials that are no mono-constituent powders.

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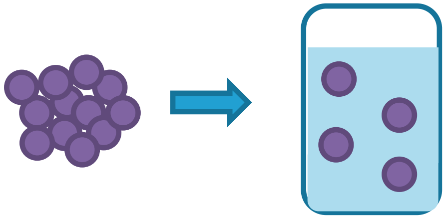
- JRC report #2 considers revision from “material containing particles” to “material consisting of particles”.
  - PRO: a liquid chemical containing 1 nanoparticle is non-nano
  - CONTRA: new uncertainty created by “functionality”: If nanoparticles are suspended in water + additives, is this product non-nano?
- BASF: In formulations, non-particulate components ruin image evaluation

→ *PROPOSAL 3: Assess mixtures and formulations by ingredients.*

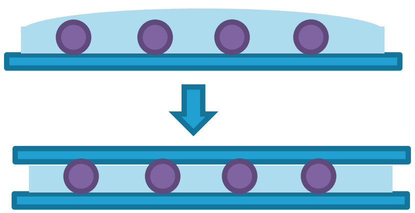
→ *PROPOSAL 4: Mixtures, suspensions and formulations are nanomaterials, if one or more ingredient is a nanomaterial, and if these ingredients constitute more than N% of the solids mass.*

(CLP: N = 1% or 0.1%)

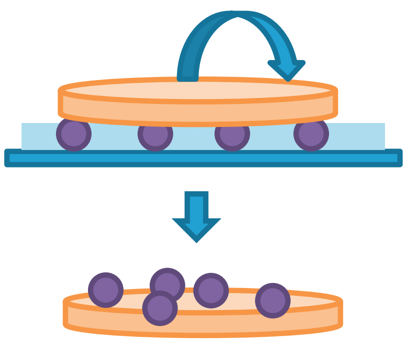
TEM Sample preparation also requires dispersion, has in general uncertain representativeness



1. dispersion of powder (e.g. water, ethanol)



2. wetting of glass microscope slide



3. transfer to ultra-thin TEM grid + evaporation of water/ethanol

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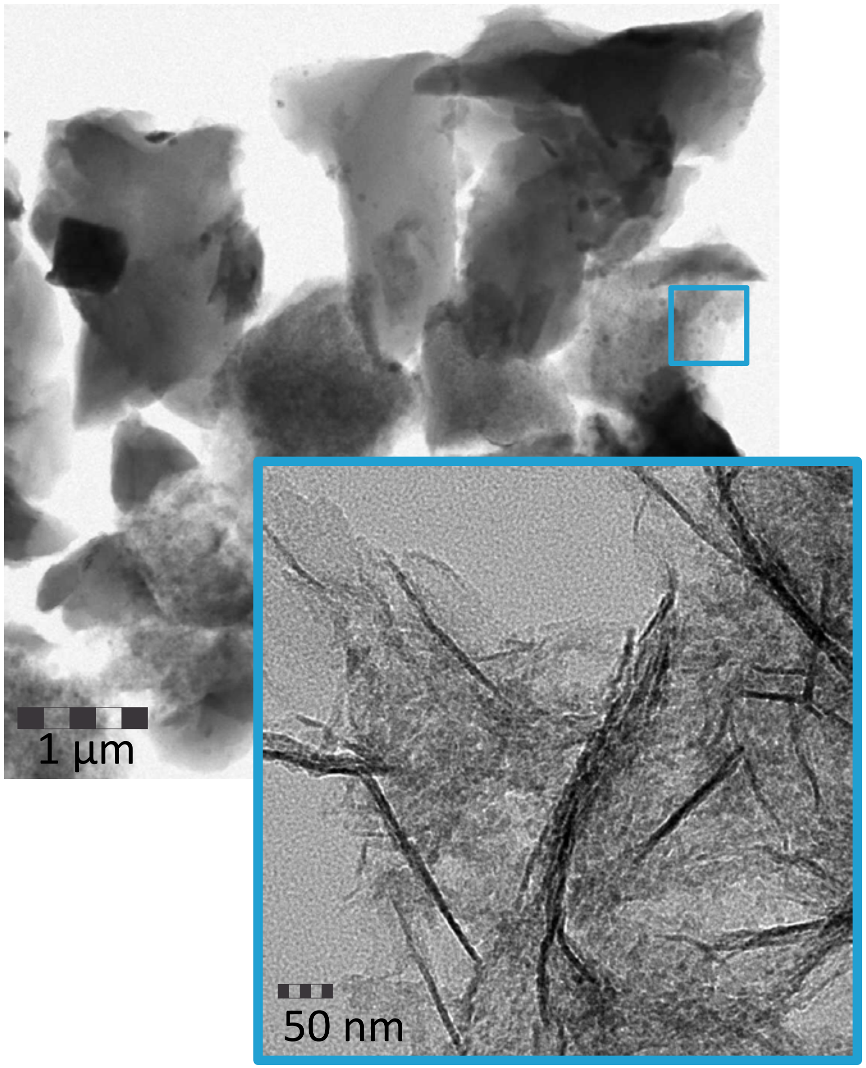
TEM Image evaluation strategy



! automation e.g. by Olympus/SIS iTEM software impossible (common case) !

→ manual evaluation by trained lab-team

1. detection of different phases/ size categories
2. large fraction might be negligible for number-based evaluation
3. screening of sample for representative position
4. complete evaluation of distinct area
5. **remaining operator bias on choice of „smallest external dimension“**
6. number of evaluated particles depending on result: unambiguous results ~ 200 particles; borderline cases ~1000 particles