Safety Assessment of Nanomaterials

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Nano Innovation
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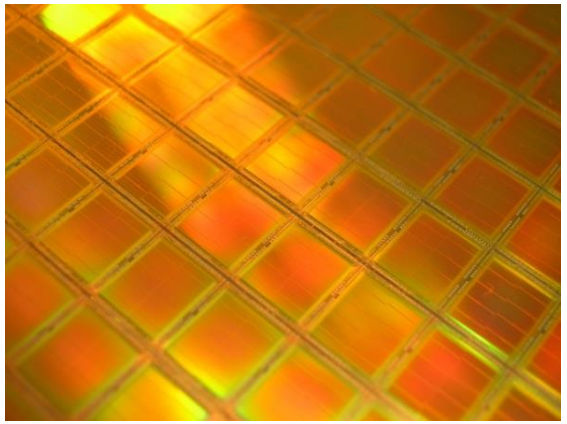
EU COMMISSION RECOMMENDATION
on the definition of nanomaterial

"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.

The smaller group of relevant materials:
Engineered nanoparticles

Resistence

Acceleration



Polishing

Dirt repellent

Flowability

Resistence

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The larger group: conventional products of sub-micron size with a tail of primary particles below 100 nm

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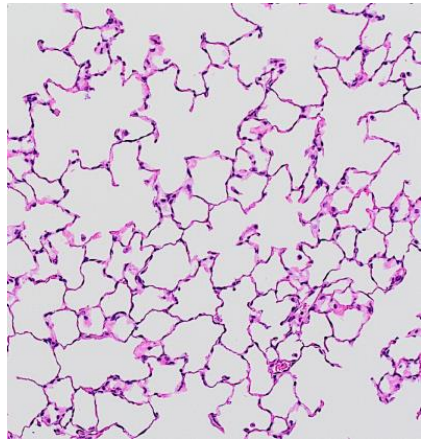
Safety concerns with nanomaterials

Nanoparticles raise questions:

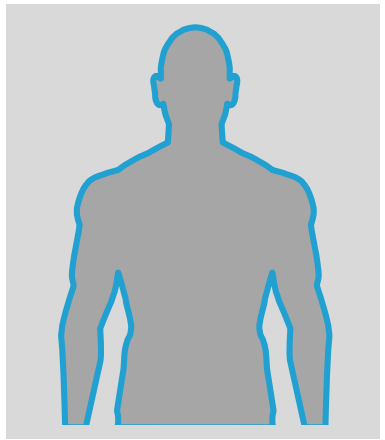
- Large surface → higher reactivity?
- Small size → defeat barriers?
- Life-cycle-dependent nanostructure?
- Unique properties?

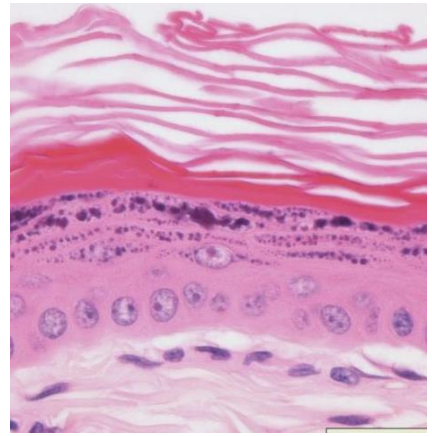
Savolainen, Kai, et al. "Nanosafety in Europe 2015–2025: towards safe and sustainable nanomaterials and nanotechnology innovations.", Helsinki (2013). ISBN 978-952-261-310-3 www.veronananomedicine.it/wordpress/wp-content/uploads/2013/06/nanosafety_2015-2025.pdf



BASF:

- Nano safety research since 2004
- More than 150 studies on nanomaterial toxicity
- More than 25 co-operations and research projects
- More than 50 scientific publications





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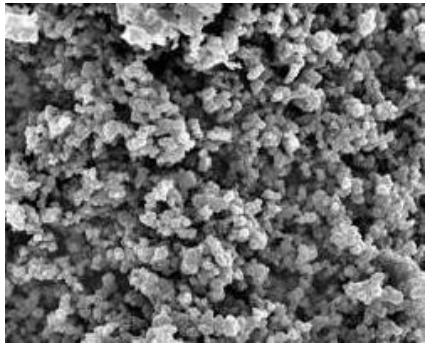
Use of nanomaterials

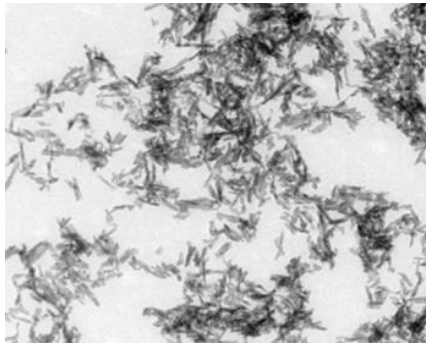
in cosmetic emulsions

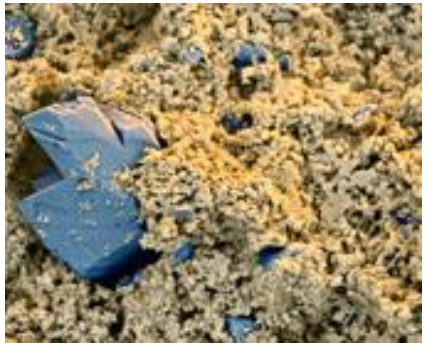
in rubber tires

in car coatings

in concrete







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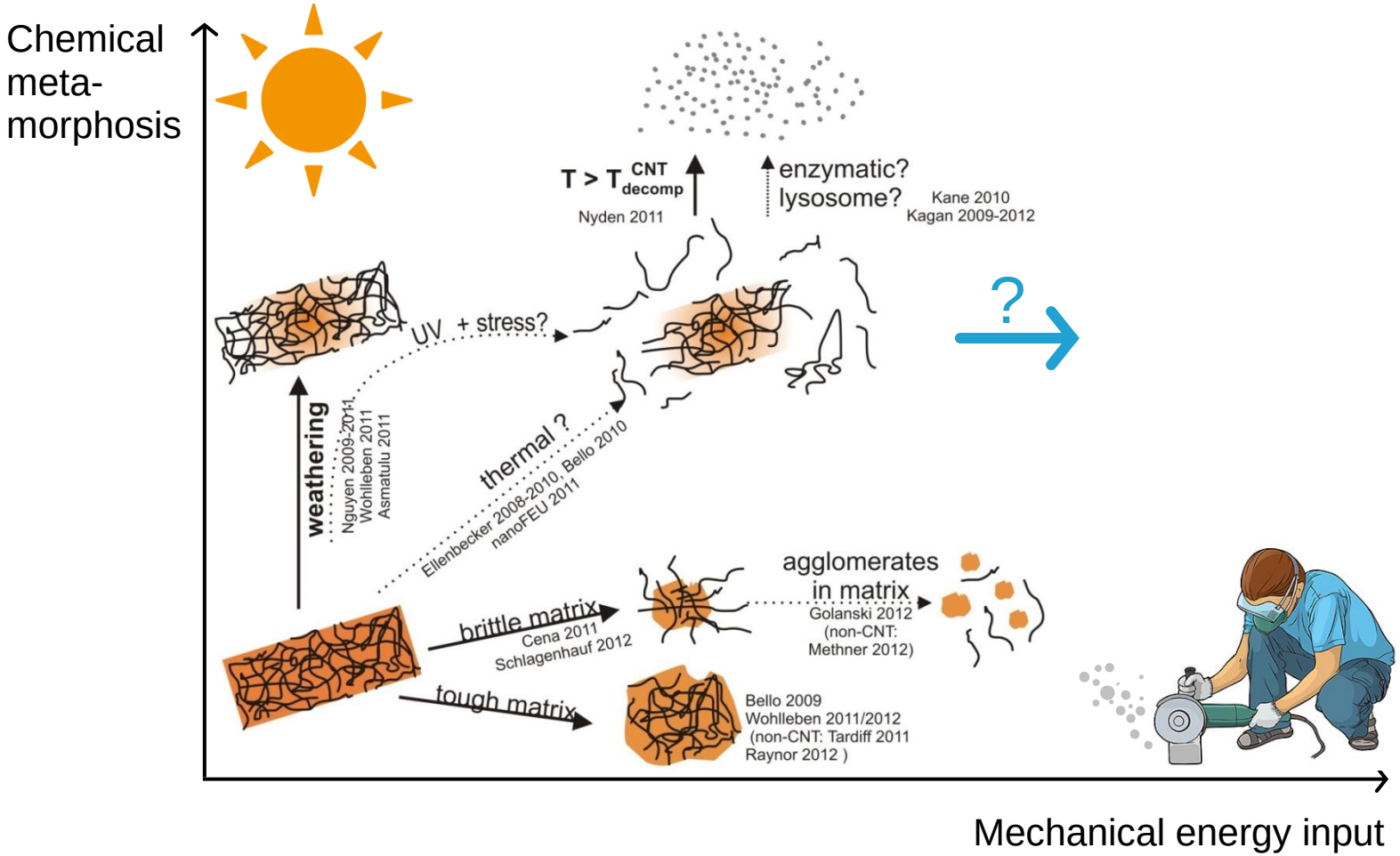
Release of nanomaterials

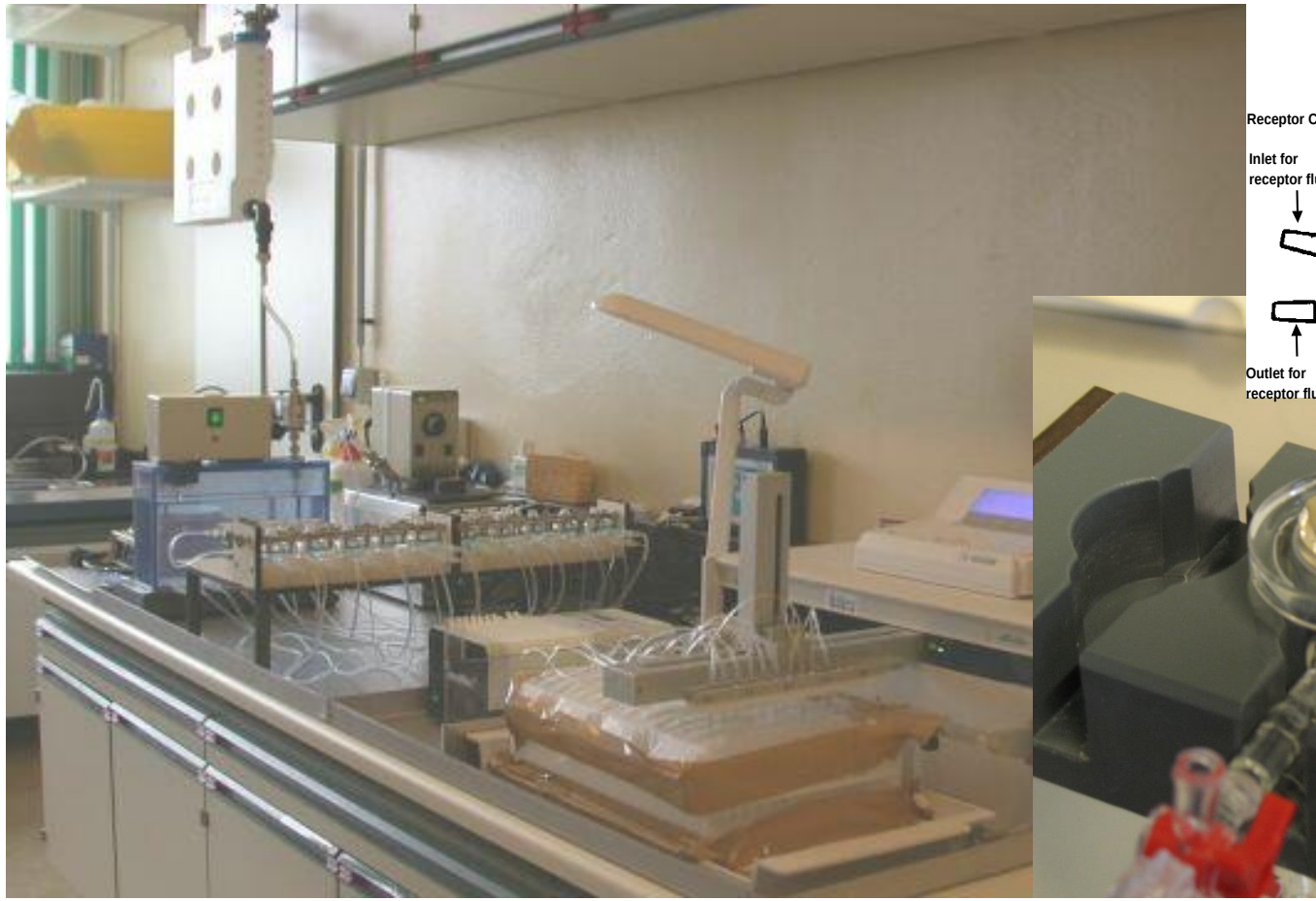


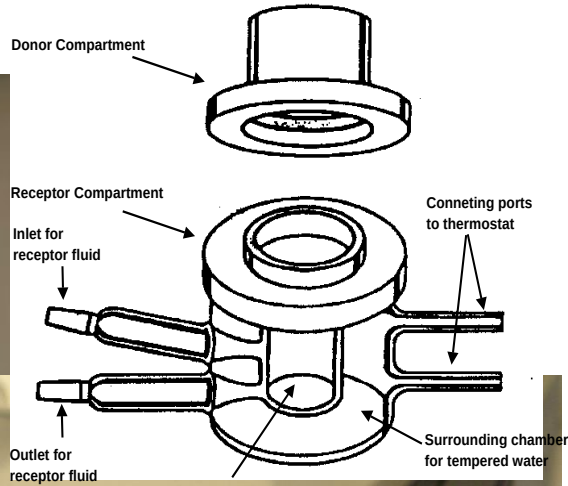
Hirth, Sabine, et al. J Nanopart Res 15.4 (2013): 1-15
Wohlleben, Wendel, et al. Nanoscale 5.1 (2013): 369-380.

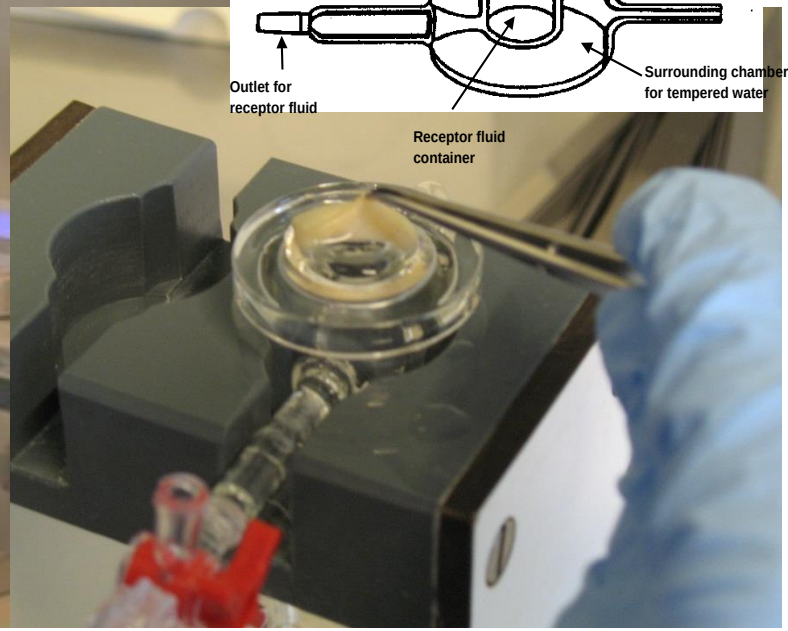
Uptake of nanomaterials

Dermal absorption of nano ZnO

Dermal Penetration Studies *in vitro*







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Sunburned Skin

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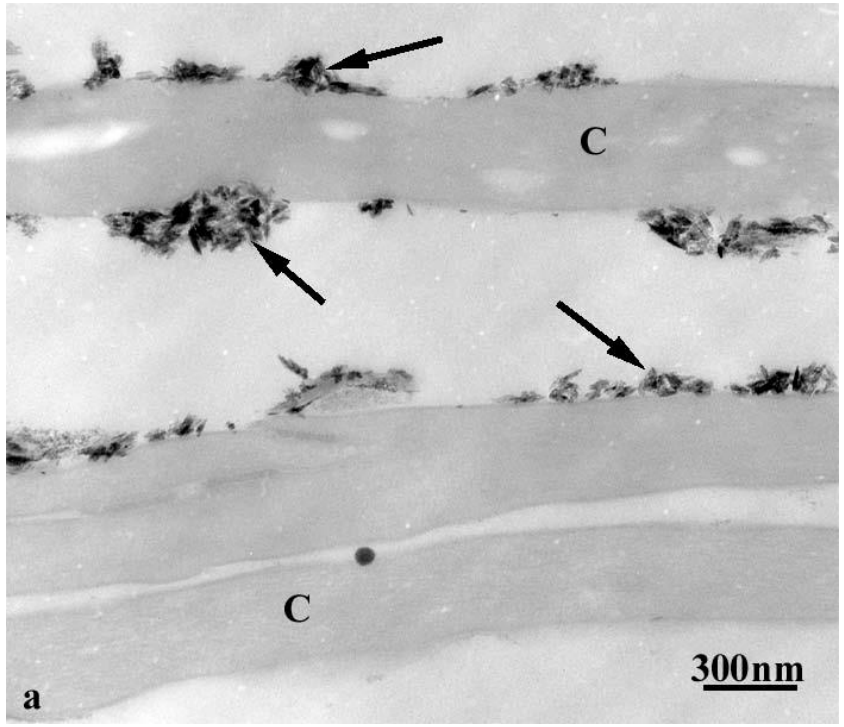
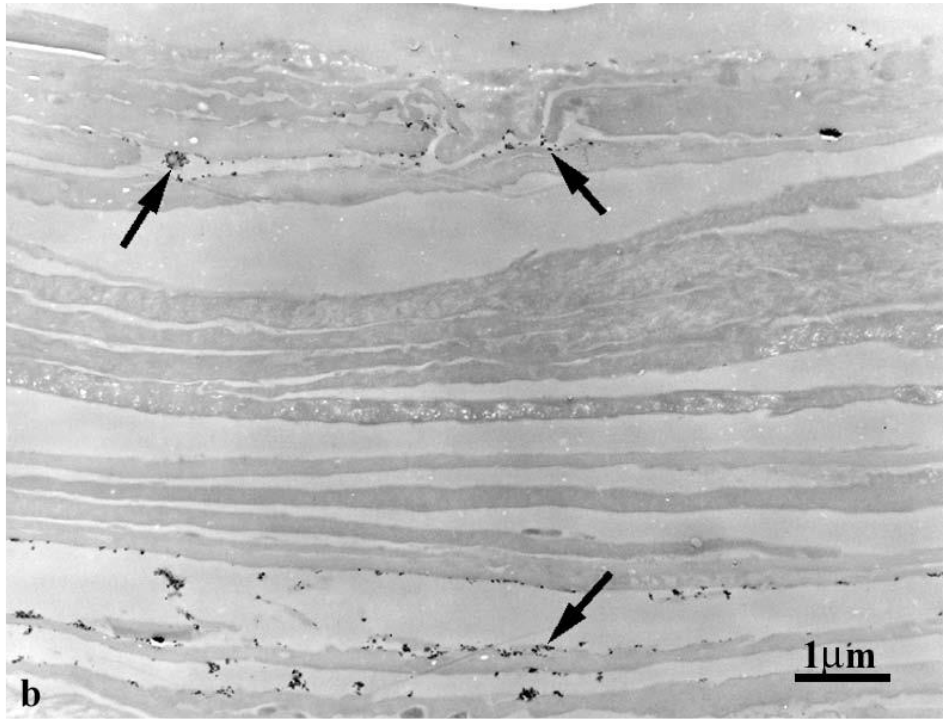
Skin Treated -TiO_2 CM630 - 24 Hrs





(a) Normal skin – 9 layers

(b) UVB - 17 layers

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Effects of Nanomaterials

Inhalation Studies

Short-term inhalation studies (STIS)

Short Term Inhalation Study (STIS)

Male Wistar rats

Study day	1	2	3	4	5	6	7	8	9-27	28
Study phase	x	x	x	x	x	R	R	R	R	R
Examinations					E			L		E+L

X: Head-nose exposure to aerosols for 6 hours per day on 5 consecutive days

R: Recovery period

L: Lavage

E: Examinations

- Organ burden (lung, mediastinal lymph nodes, liver, kidney, spleen and basal brain with olfactory bulb)
- Distribution and translocation
- Particle size distribution within the lung
- Histology of selected organs, cell proliferation / apoptosis
- Cytological and biochemical parameters in the broncho alveolar lavage fluid

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	Target concentration (mg/m^3)	Physico-chemical Data	NOAEC / LOAEC	Clinical Pathology	Pathology
SiO_2	0.5; 2.5; 10	Primary particle size: 15 nm BET surface: 200 m^2/g Morphology: amorphous	NOAEC: 10 mg/m^3	no adverse finding	no adverse finding
SiO_2 coated	0.5; 2; 10	Coating: polycarboxylate	NOAEC: 10 mg/m^3 (local) LOAEC: 0.5 mg/m^3 (sys)	no adverse finding	no adverse finding
TiO_2 P25	2; 10; 50	Primary particle size: 21 nm BET surface: 51.1m^2/g Purity: 99.5 %	NOAEC: < 2 mg/m^3	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑ neutrophil counts	histiocytosis
TiO_2 coated	0.5; 2.5; 10	Purity: 82% TiO_2 Impuity: 10 % $Al(OH)_3$ 1.6 % Si	NOAEC: 0.5 mg/m^3	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑ neutrophil counts	no adverse finding
CeO_2	0.5; 2.5; 10	Primary particle size: 70 nm BET surface: 26.06 m^2/g Morphology: irregular spherical	NOAEC: 0.5 mg/m^3	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑ neutrophil counts	histocytosis, mild inflammation
CeO_2 doted	0.5; 2; 10	Primary particle size: 40 nm BET surface: 46 m^2/g Morphology: cerianite, cubic Purity: 89 %	LOAEC: 0.5 mg/m^3	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑ neutrophil counts	histocytosis, mild inflammation
ZrO_2	0.5; 2.5; 10	Primary particle size: 70 nm BET surface: 25 m^2/g	NOAEC: 10 mg/m^3	no adverse finding	no adverse finding
$BaSO_4$	2; 10; 50	Primary particle size: 37,5 nm BET surface: 41,4 m^2/g Morphology: crystalline, orthorhombic Purity: 93.8 %	NOAEC: 50 mg/m^3	no adverse finding	no adverse finding
ZnO	0.5; 2.5; 12.5	Particle size range: 70-110 nm BET surface: 12 m^2/g Purity: 78.2 %	LOAEC: 0.55 mg/m^3	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑↑ neutrophil counts	minimal to moderate multifocal necrosis of the olfactory epithelium
CB	0.5; 2.5; 10	Particle size range: 11-68 nm BET surface: 40 m^2/g Purity: > 99%	NOAEC: 10 mg/m^3	no adverse finding	no adverse finding
MWCNT 1	2; 8; 32	Diameter: 9.5 nm Length: 1.5 µm Impurities: 10 % (Al, Co, Fe)	NOAEC: < 2.4 mg/m^3	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑↑ neutrophil counts	inflammation/ minimal to mild multifocal granulomatous inflammation
MWCNT 2	0.1; 0.5; 2.5	Diameter: 10-15 nm Length: 0.1-10 µm Impurities: 8.6 % (Al, Fe)	NOAEC: 0.1 mg/m^3 LOAEL: 0.5 mg/m^3	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑↑ neutrophil counts	inflammation
micro-Quarz DQ 12	100	BET surface: 5.9 m^2/g	-	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑↑ neutrophil counts	diffuse histocytosis / significantly increased apoptosis / granulomatous inflammation
micro-TiO_2	250	BET surface: 6 m^2/g	-	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑ neutrophil counts	diffuse histocytosis / increased apoptosis
micro-ZnO	12.5	BET surface: 5.6 m^2/g Purity: > 99.9 %	-	↑ BALF protein conc. ↑ activity of LDH, GGT, NAD, ALT ↑↑ neutrophil counts	minimal to moderate multifocal necrosis of the olfactory epithelium

ADVANCED MATERIALS

pft PARTICLE AND FIBRE TOXICOLOGY

Landsiedel Robert *et al*. (2010)
"Testing Metal-Oxide Nanomaterials for Human Safety"
Advanced Materials, 22:2602-2627.

Landsiedel, Robert, et al. (2014)
"Application of short-term inhalation studies to assess the inhalation toxicity of nanomaterials."
Particle and fibre toxicology 11.1: 16.

Ma-Hock, Lan, et al. (2013)
"Comparative inhalation toxicity of multi-wall carbon nanotubes, graphene, graphite nanoplatelets and low surface carbon black."
Particle and fibre toxicology 10.1: 23.

Ranking of nanomaterials according to their toxic potency in the STIS

No adverse effects observed up to the highest concentration tested, i.e. 10-50 mg/m³

$BaSO_4$, SiO_2.PEG, SiO_2.phosphate , SiO_2.amino, nano.ZrO_2, ZrO_2.TODA, ZrO_2.acrylate, SiO_2.acrylate (no lung effects up to 10 mg/m³; however systemic NOEC at 0.5 mg/m³), **graphite nanoplatelets , low surface area carbon black**

Adverse effects observed at 10 mg/m³

SiO_2.naked, graphene
nanostructured calcium silicate hydrate seeds

Adverse effects observed at approx. 0.5 mg/m³

nano-CeO_2, Al doped nano-CeO_2, coated nano-ZnO, coated nano-TiO_2
uncoated nano-TiO2

NOAEC levels < 0.5 mg/m³ and effects progressive

MWCNT , quartz

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The nanomaterial's life cycle and biological pathway

Life cycle
(manufacture, use, disposal)

Biological pathway
(of nanomaterial in given life cycle stage)

Intrinsic material properties

Use
Release

Exposure

Uptake
Biodistribution

Bio-physical interaction

Cellular effect

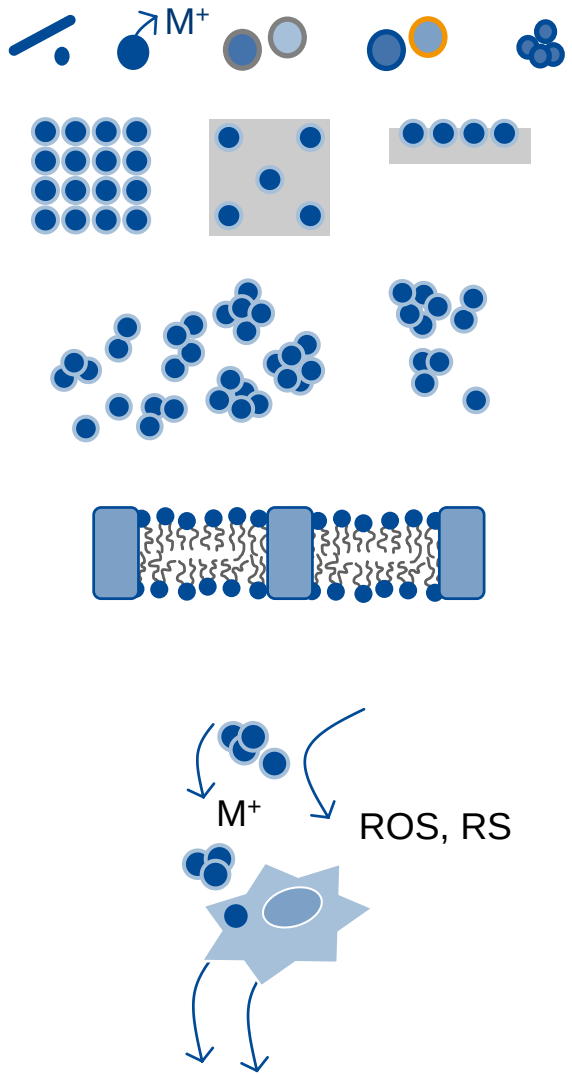
Apical toxic effect

Dispersion
(Aerosol, suspension)

Uptake
Biodistribution
Biopersistence

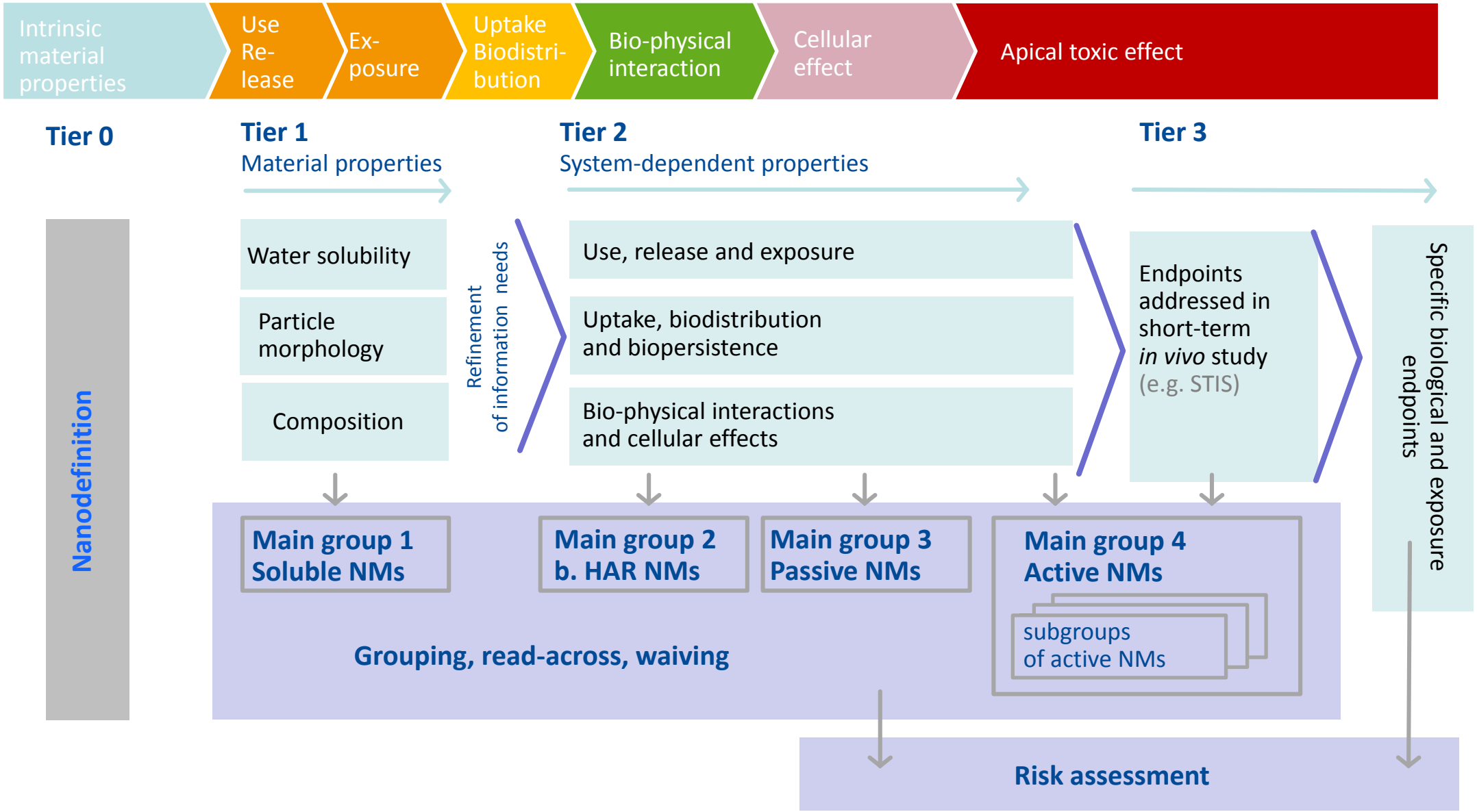
Catalyzing formation of reactive compounds
Ion release by dissolution

Inflammation
Cytotoxicity
…



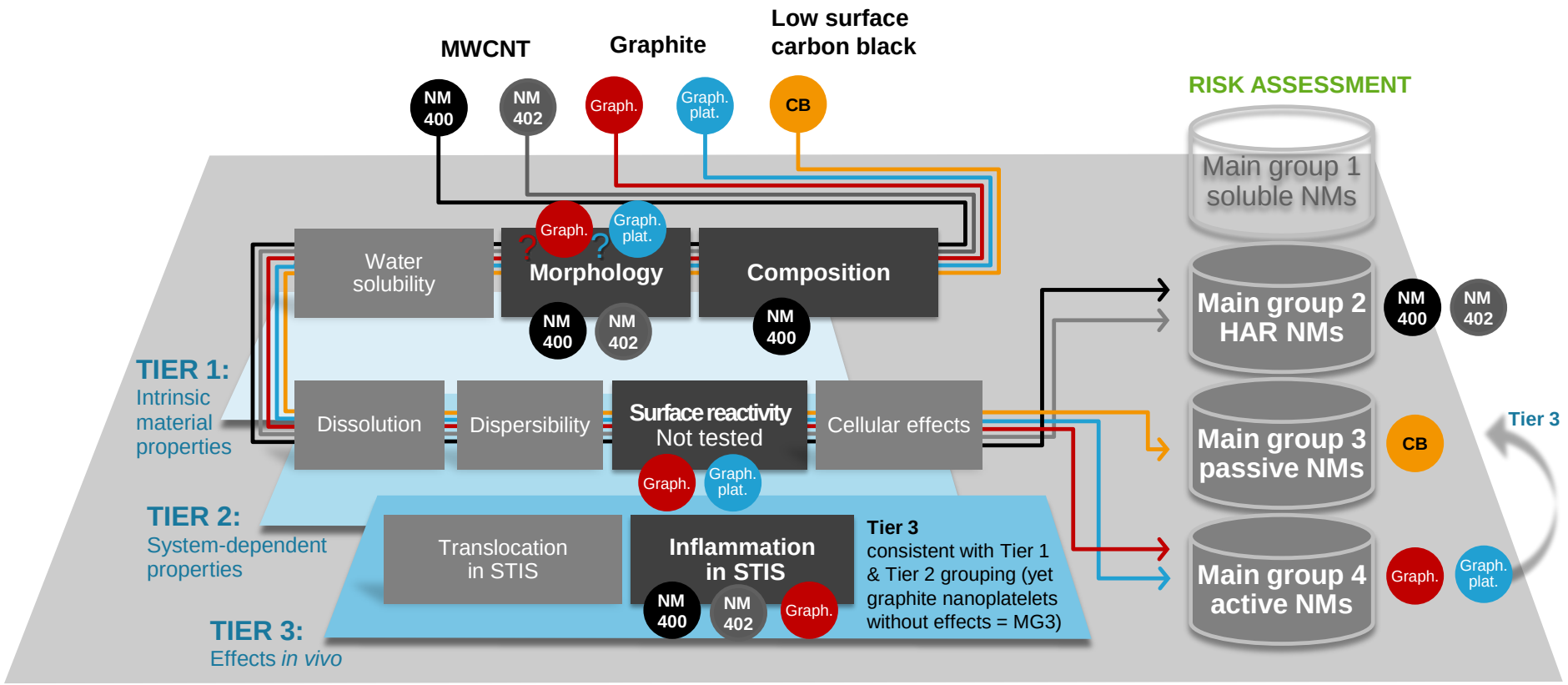
Adapted from: Oomen A et al. 2014. In: Safety of NMs along their lifecycle: Release, exposure & human hazards. Eds. Wohlleben W, Kuhlbusch T, Lehr CM, Schnekenburger J; Taylor & Francis, Boca Raton (USA).

Decision-making framework



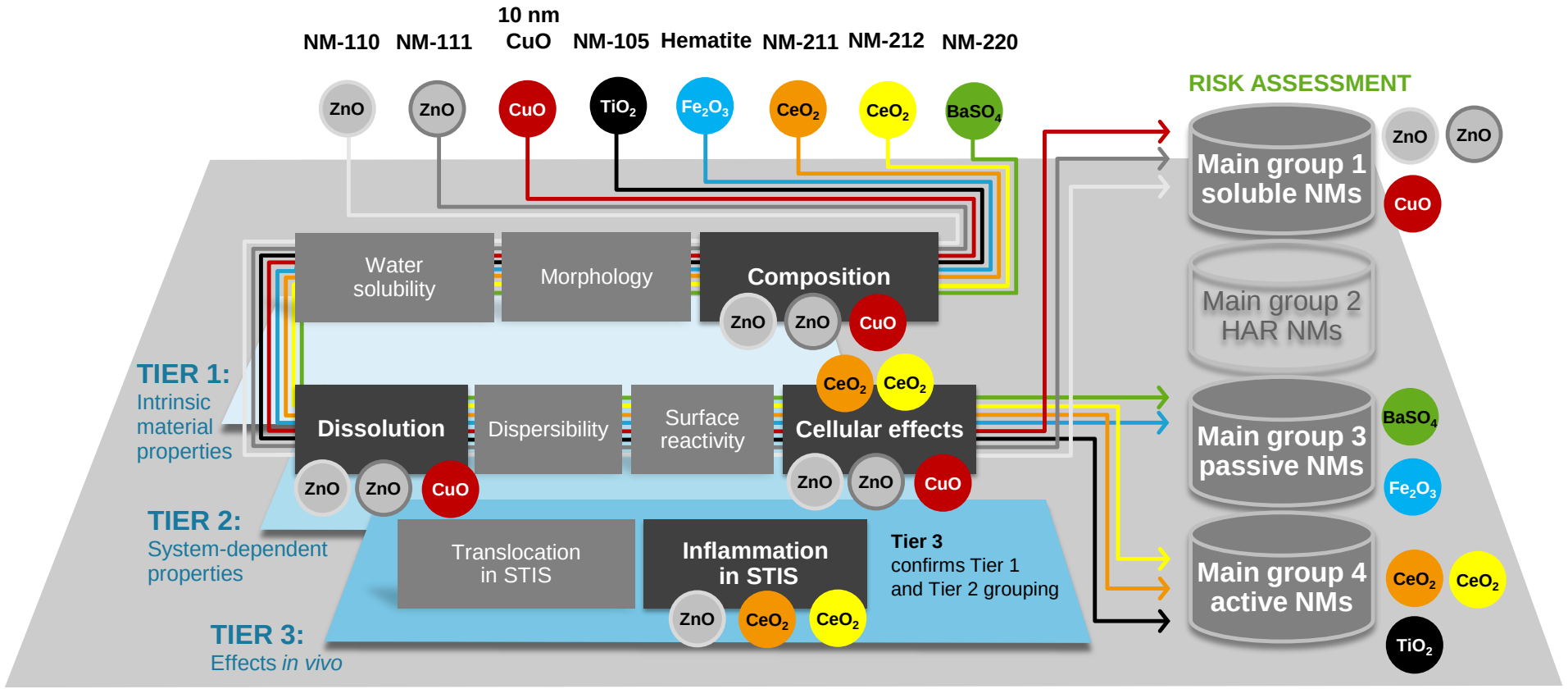
Application of the DF4nanoGrouping: Case study 1 ‘carbonaceous NMs

Arts *et al.* (in preparation)



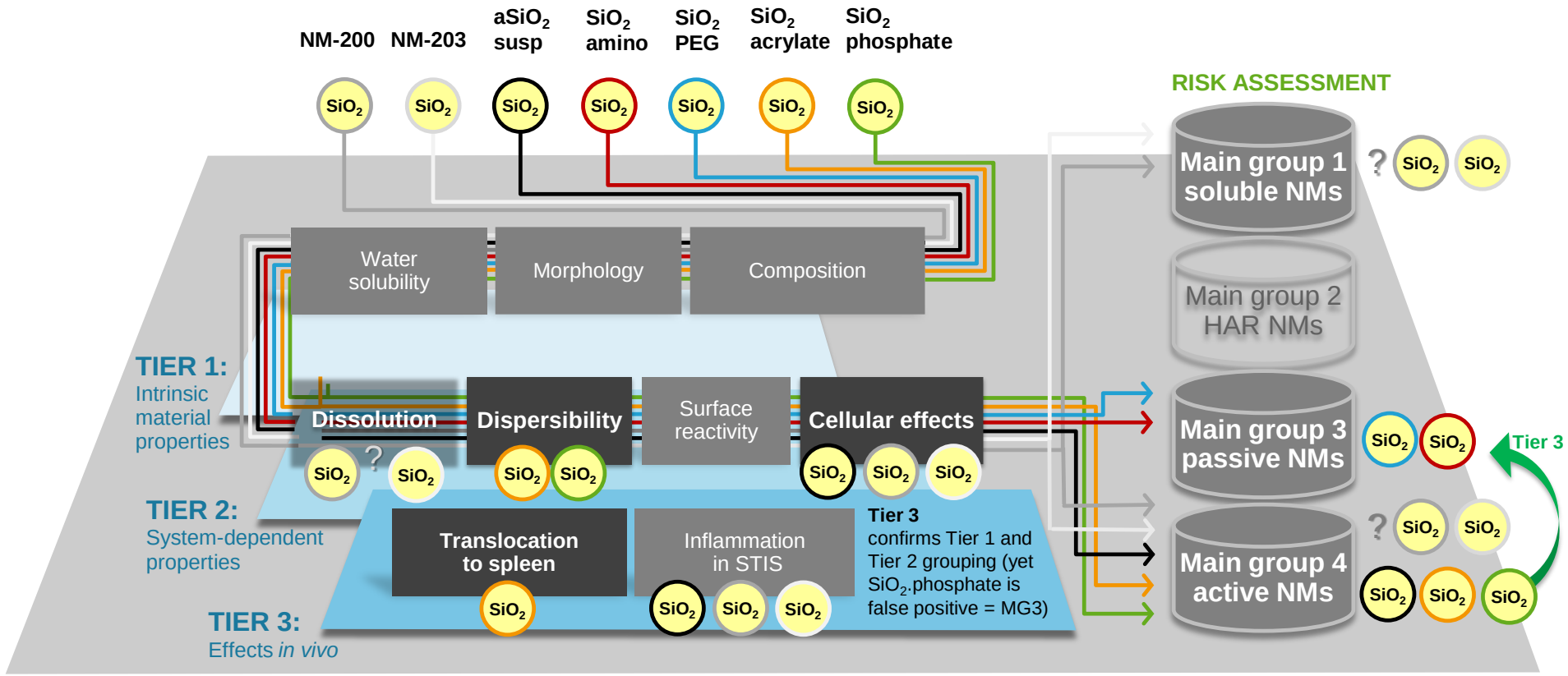
Application of the DF4nanoGrouping: Case study 2 ‘metal oxides and sulphates’

Arts *et al.* (in preparation)



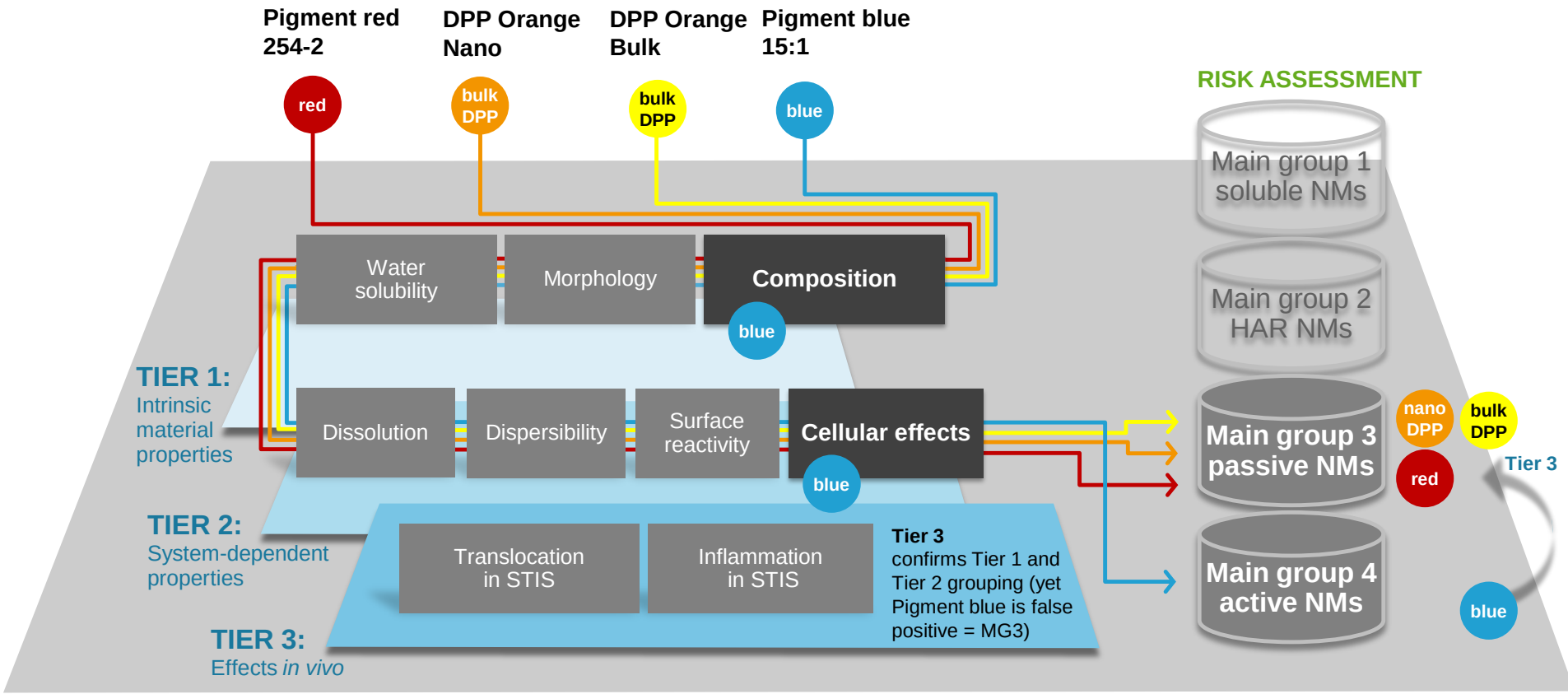
Application of the DF4nanoGrouping: Case study 3 'amorphous silica NMs

Arts *et al.* (in preparation)



Application of the DF4nanoGrouping: Case study 4 ‘organic pigments’

Arts *et al.* (in preparation)

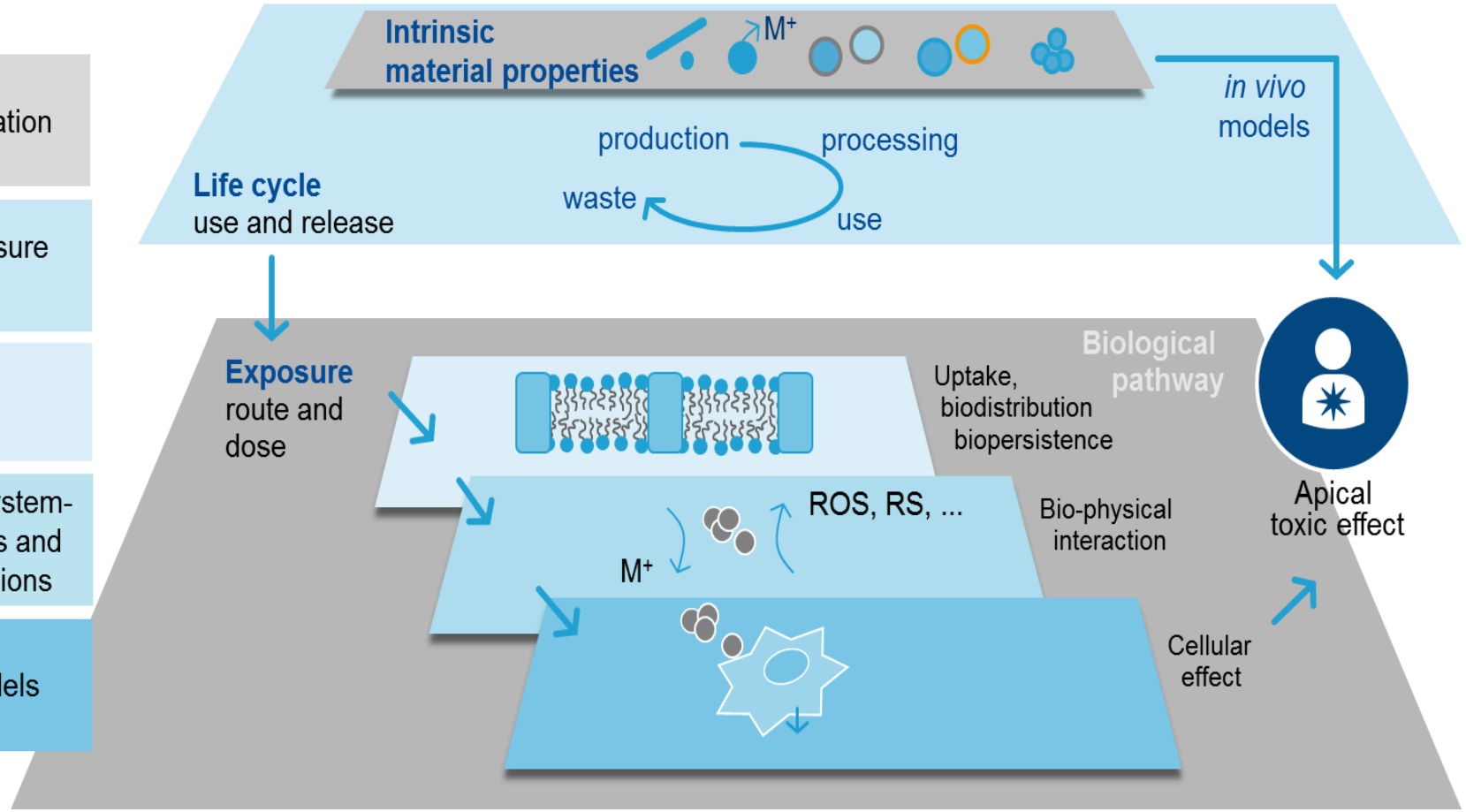


Conclusion

- DF4nano uses a selected, limited number of intrinsic material properties and system-dependent properties for grouping.
- DF4nano proved useful for NM hazard assessment.
- 21 of 24 materials correctly assessed.
- 3 of 24 materials over-predicted (conservative)
- Scientific basis for hazard assessment

Decision-making framework, grouping, read-across and in silico models

- Material characterisation
- Life-cycle and exposure considerations
- Uptake and barrier models
- Characterisation of system-dependent properties and bio-physical interactions
- *In vitro* toxicity models



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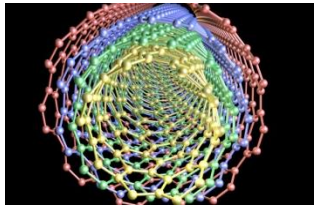
Knowing hazard and exposure enables the safe use of nanomaterials

Hazard potential

High

High hazard, low exposure
*requires appropriate technical measures for containment



*low risk

High hazard, high exposure
→ Not acceptable

high risk

Low hazard, low exposure
Suitable for all consumer products (e.g. nano-composite materials)

Low

low risk

Low hazard, high external exposure
*requires testing of uptake and hazard

*low risk

External exposure

Low

High

Bräu et al. 86 Arch Toxicol (2012) 077 – 1087
Landsiedel, Robert, et al. Advanced Materials 22.24 (2010): 2601 – 2627
Ma-Hock, Lan, et al. 112.2 (2009): 468-481

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