Nanodefinition and Nanoanalytics: The NanoDefine Project

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Outline

- EC definition of nanomaterial: measurement requirements
- Regulatory implementation:
  the need for an integrated approach
- The NanoDefine project and its decision making framework

Nanomaterials and EU legislation

- Recently adopted or discussed EU legislation specifically addresses nanomaterials
- Current EU legislation on chemicals applies to nanomaterials, even if it does not specifically address them

EC definition of nanomaterial (2011/696/EU) - October 2011

- A definition is necessary for legal clarity

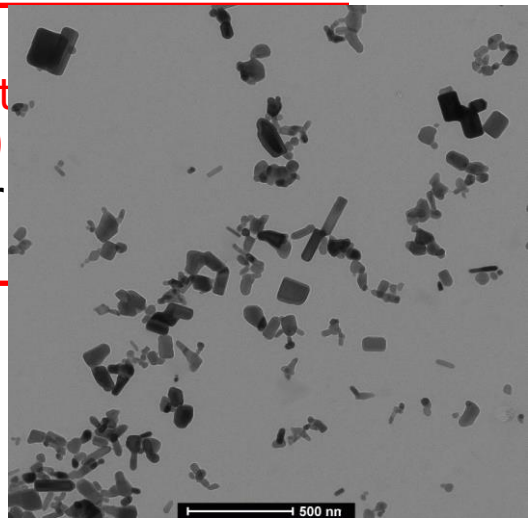
> "Nanomaterial" means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.
>
> In specific cases…[the] threshold of 50% may be replaced by a threshold between 1 and 50%.
>
> …fullerenes, graphene flakes and single wall CNTs…should be considered as NMs.

- Recommendation (legally not binding), developed for regulatory purposes
- No relation to hazard or risk intended
- Important for:
  - REACH - working definition, future annexes
  - Biocidal Products Regulation 258/2012
  - Medical Devices Regulation – proposal
  - Future amendments of Regulations: Cosmetic Products, Food information, Novel food

Some resulting measurement requirements

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

- Determination of the constituent particles of the material
  The constituent particles are often aggregated or agglomerated
- Determination of the external dimensions of the (constituent) particles
- Address particle size distribution (by number)
  e.g., "Determination whether 50% or more of the particles have an external dimension in the size range 1-100 nm"



Analysis of widely available techniques for measurement of particle size

- Working principle
- Measurement range
- Which materials can be characterized?
- Results in terms of particle numbers available?
- Distinction between aggregates/agglomerates and constituent particles?
- Availability of instruments
- Availability of standards
- Availability of reference materials
- Development perspectives

EUR 25404 EN
July 2012

Implementation of the EC nanomaterial definition: The need for an integrated and coherent approach

Situation

- Methods have to meet certain *requirements* – nanospecific aspects
- Available methods cover requirements to varying degree
  - Material type / size range / agglomerates, aggregates / size distributions /…
- No single method covers all requirements for all materials
- Combination of methods is promising
- Validated nanospecific methods & reference materials needed

The way forward

- Nanoanalytical potential is there, but scattered
- Coherent and integrated approach to combine it and translate it into practical guidance is lacking
- Readily available methods may have the potential for further development with a view to the EC NM definition

Robust, broadly applicable and widely accepted implementation approach needed

The NanoDefine project

The strategic objective of NanoDefine is to provide the affected industries and regulatory agencies with the tools that support the implementation of **the EC definition of nanomaterial** in all relevant regulatory contexts.

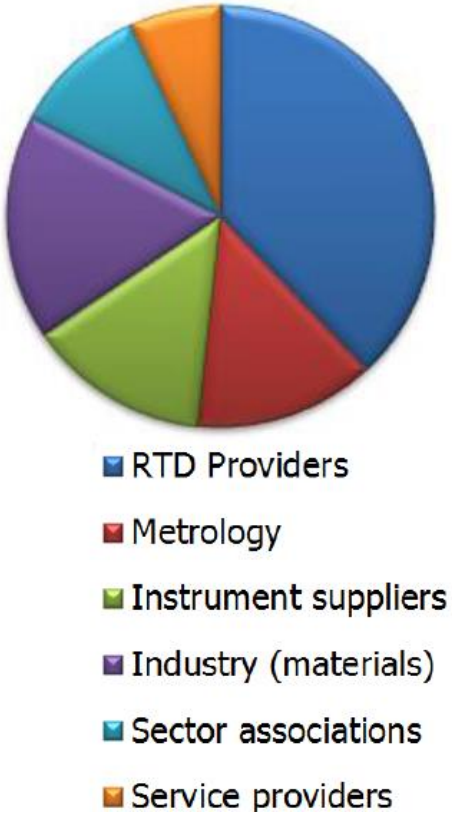
- EU FP7 contract no: 604347
- Starting date: 1st November 2013
- Ending Date: 1st November 2017
- Total budget: 9,3 million €
- EC contribution: 6.9 million €
- Project coordinator: RIKILT (NL)

Definition issues addressed

- size range 1 – 100 nm
- agglomerates, aggregates
- complex materials
- number based size distribution, conversion from other metrics
- cost-efficiency

NanoDefine Consortium

29 Partners form a consortium of European RTD performers, metrology institutes and nanomaterials and instrument manufacturers.



Development of a decision making framework

Entry pathway

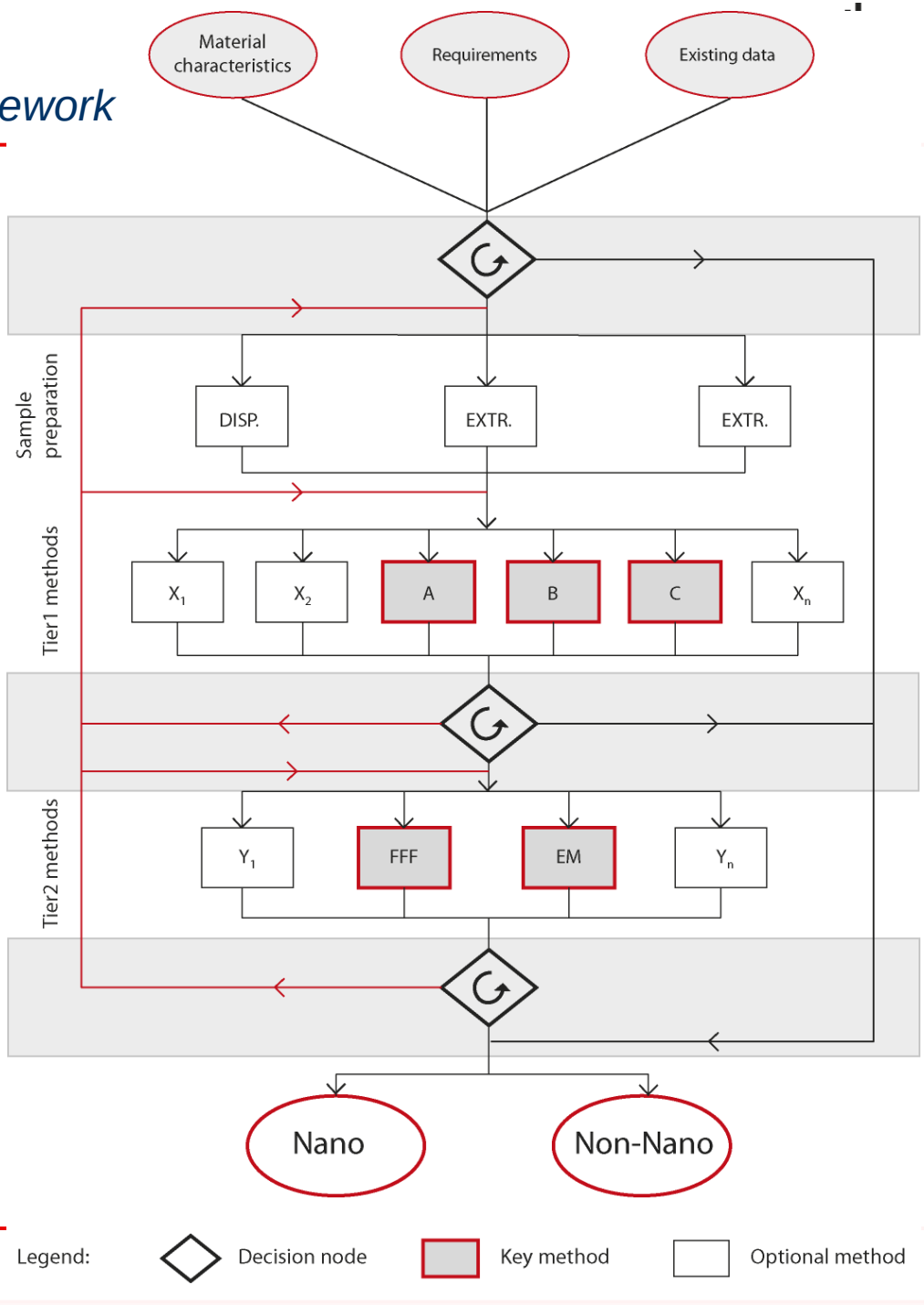
- Material classification system
- Requirements
- Existing data

Sample preparation

Tiered approach

- Tier 1: "screening methods"
- Tier 2: "confirmatory methods"
- Performance criteria
- Method evaluation
- Method development (selected techniques)

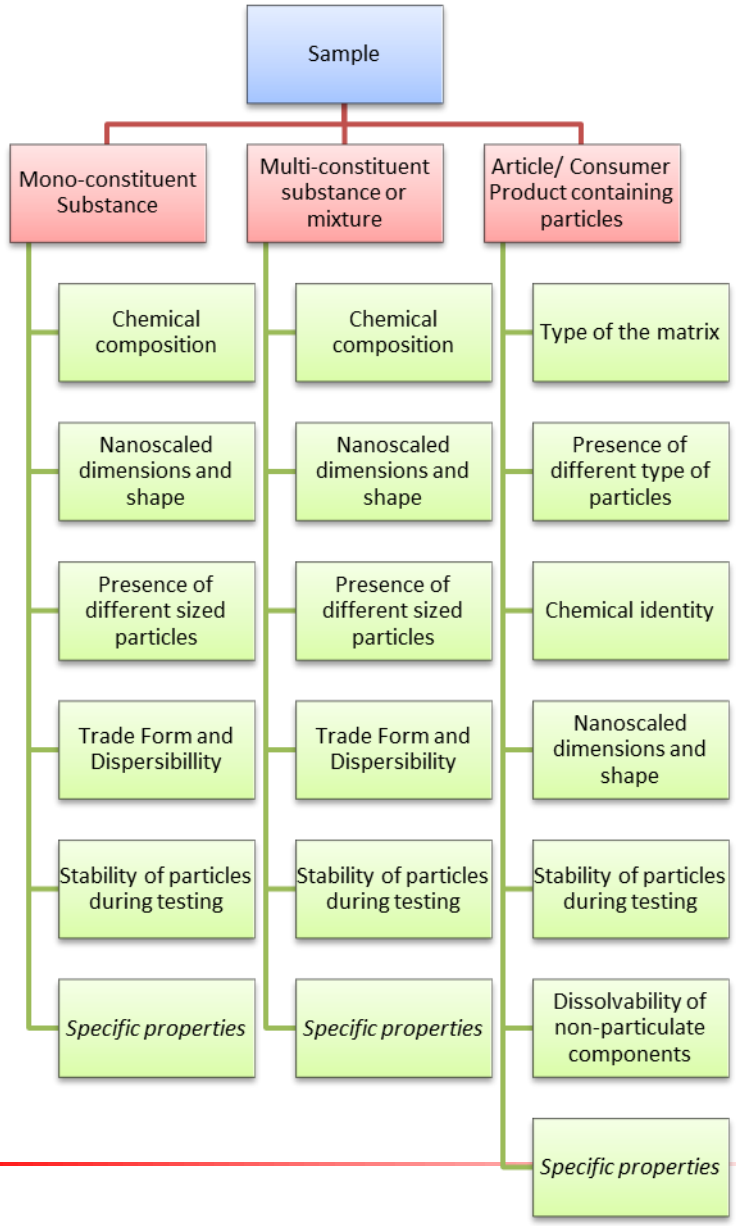
Output/products



Material classification system

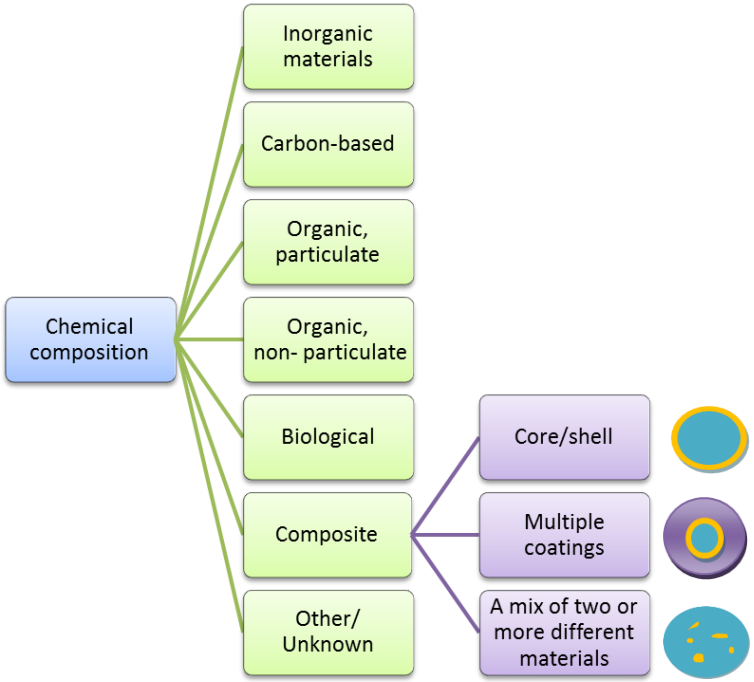
- Starting point: material type
  - Monoconstituent substance
  - multiconstituent substance, mixture
  - article, consumer product
- Depending on the type, the material is classified

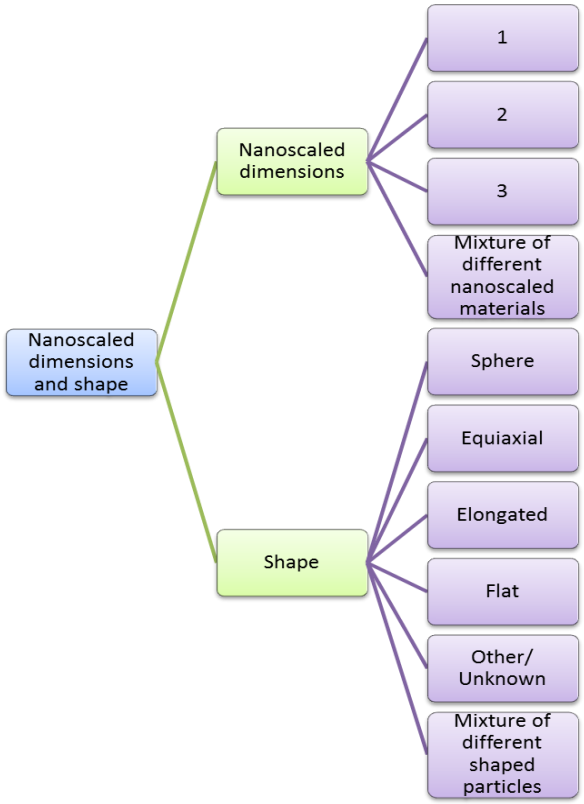
  according to several parameters
- Will link to recommendations for
  - sample preparation
  - Measurement methods



Material classification system

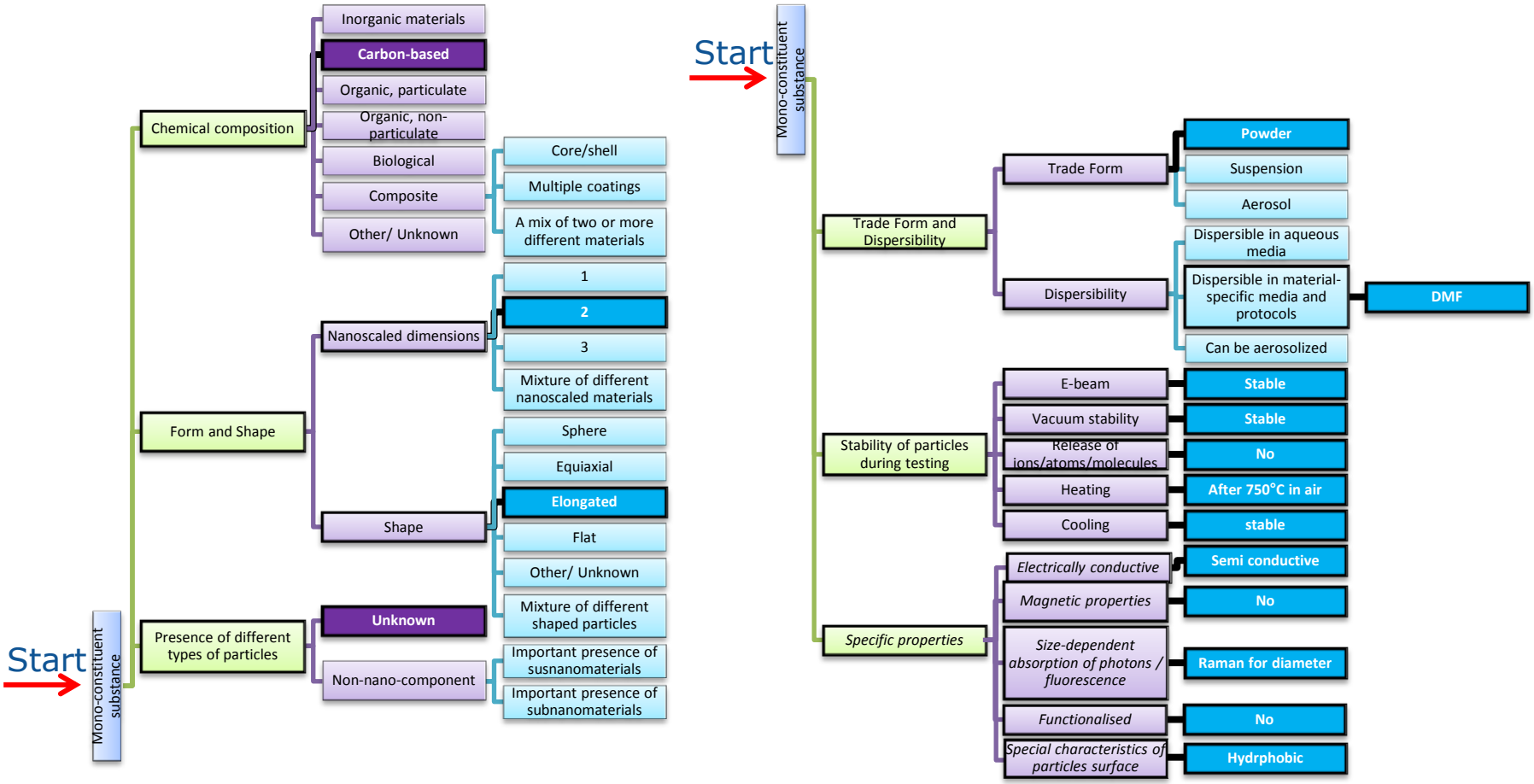
Main criteria – example details





Material classification system

Example: Multiwall carbon nanotubes



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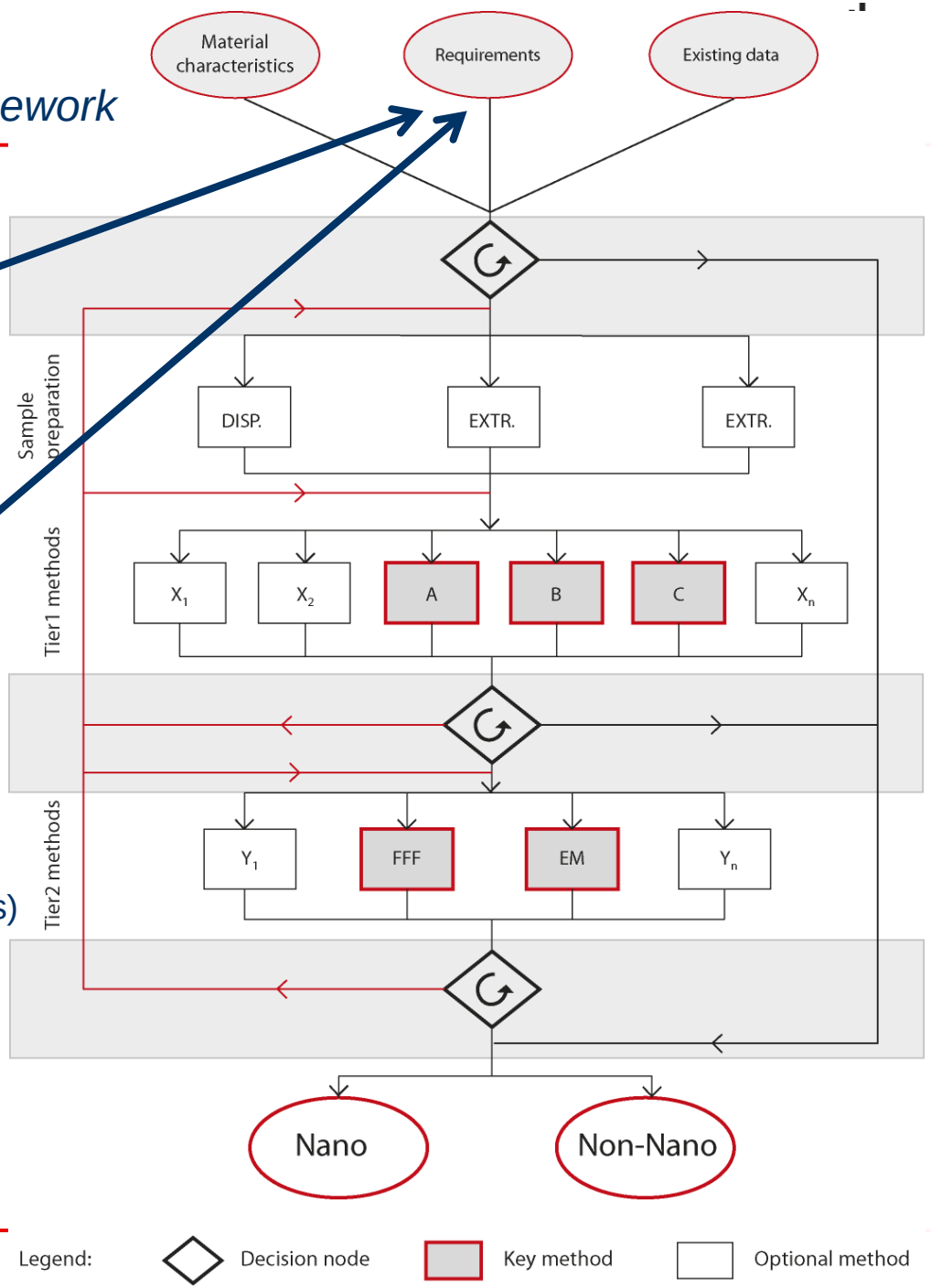
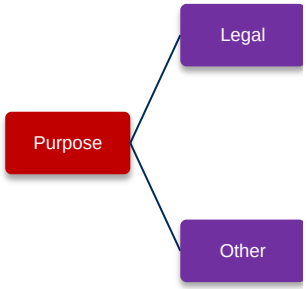


Purpose (of the analysis)

The requirements depend on the purpose



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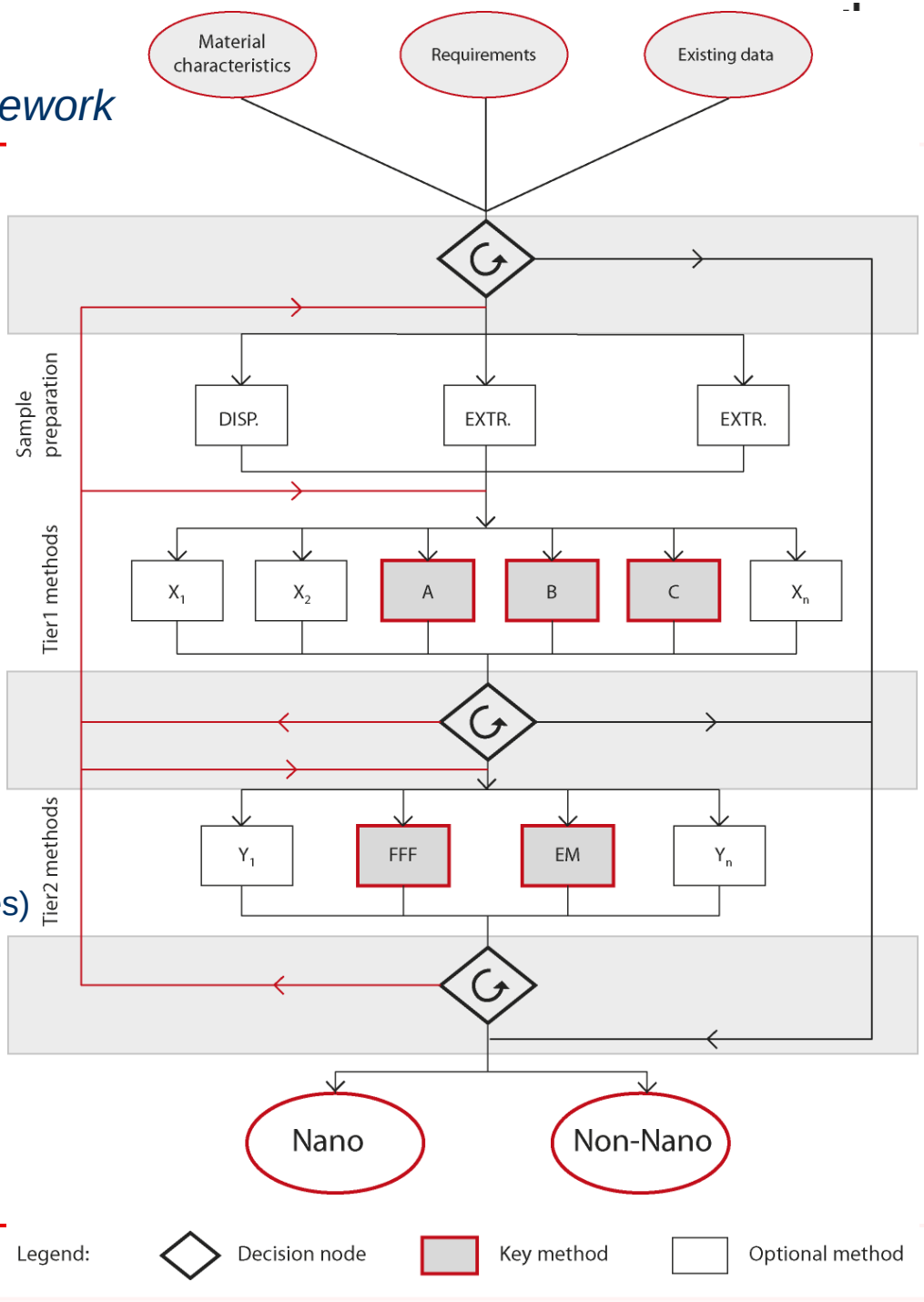


Methods performance criteria

Performance criteria of each measurement method have to include:

- Applicability to different groups of substances (chemical scope of the method)
- Applicability to polydisperse samples
- Measurement in terms of size and in terms of test medium for different groups of substances
- Capacity to measure aggregates, agglomerates, primary particles and/or non -spherical particles
- Accuracy of the results determined with the CM
- Standardization status (traceability of the measured values / availability of CRMs)

Methods performance criteria

Method-related criteria

- Counting, separative or ensemble techniques
- Working range
- Limits of detection/quantification
- Trueness
- Robustness
- Precision
- Resolution
- Selectivity
- Measures aggregation/individual particles
- Counting constituent particles in aggregations
- Composition
- Specification of the type of size (diameter)
- Destructive method or not

Substance-related criteria

- Nanoparticles in powder, or liquid suspensions or embedded in a matrix
- Dispersibility according to dispersion protocols
- Substance Nature
- Particle shape, number of dimensions in the nanoscale
- Thermal, cooling and e – beam degradation sensitivity
- Sample dispersity and modality
- Conductive and magnetic properties
- Functionalisation particles
- Agglomeration/ aggregation state

Evaluation of the methods

- counting techniques (measuring particle properties at individual particles)
- fractionating techniques (measuring the amount or concentration of size/property classes after fractionating the particle system)
- ensemble techniques (all particles in the sample are measured in the same time and the size distribution is extracted from a combined signal for all particles)
- integral methods (solely measure an integral (effective/mean) property of the particle systems such as the specific surface area)

Evaluated methods

Counting Methods

- Imaging Methods (electron and atomic force microscopy)
- Particle tracking analysis / Dynamic ultramicroscopy
- Tunable Resistive Pulse Sensing
- Single particle ICP-MS

Fractionating methods

- Field-Flow-Fractionation
- Analytical centrifugation / Centrifugation analysis - including Centrifugal Liquid Sedimentation, Analytical Ultra Centrifugation
- Differential electrical mobility analysis

Ensemble methods

- Dynamic light scattering
- Small-angle X-ray scattering
- Ultrasonic spectroscopy
- X-ray diffraction

- Integral sizing methods

- BET (specific surface area)

The NanoDefine Methods Manual

- Substance-related criteria (applicability to different substance groups)
- Method-related criteria
- All characterisation methods are evaluated against these criteria

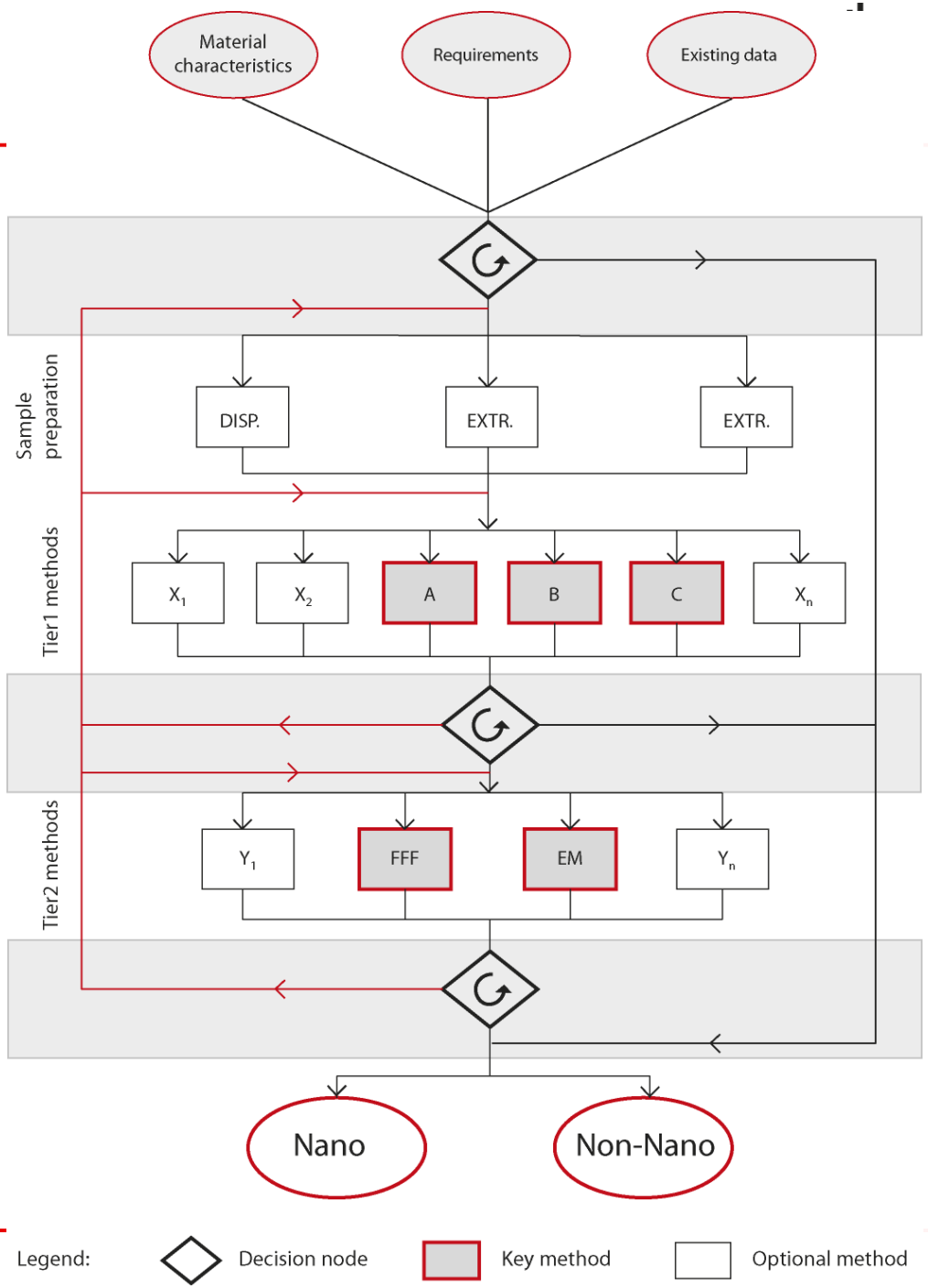
Example: electron microscopy – selected fields (SEM, TEM and STEM)

Criteria	Criteria - detail	Caracterization (yes/no)	Notes
Substance Nature	Inorganic	yes	
	Carbon based	Yes	
	Organic, particulate	Yes	
	Organic, non-particulate	Yes	
	Composite	Yes	
	Other	yes	
Shape of nanoparticles	Sphere or assimilated	yes	
	Equiaxial	Yes	
	Tubes, fibres, rods	Yes	
	Flakes and discs	No	
	Other	Yes	
Thermal degradation sensitivity	Above 0°	No	Yes with cryo stage
	Sensitivity above 25°C	Yes	
	Sensitivity above 37°C	Yes	
	Sensitivity above 50°C	Yes	
	…		
Sample dispersity and modality	Monodisperse sample	Yes	
	Polydisperse sample	Yes	
…	…		

Criteria	Criteria - detail	Caracterization (yes/no)	Notes
counting, separative or ensemble techniques	Single particle counting	Yes	
	Calculate number or concentration from ensemble methods	No	
	Method combination (hyphenated methods)	Yes	
Working range	Size range	> 1 nm	Lower range varies in dependence on instrument type, sample type and preparation
	Concentration range	“mono layer”	EM measures accurately only “dry” particles deposited on a substrate. Droplet of 0.1-1 µL at 0.1%-vol. conc. typically sufficient.
	Minimum needed sample	0.1 µL	Minimum 500 NPs for a monodisperse/ monomodal sample (Motzkus et al., 2013)
	Limits of detection/quantification	1 nm to 10 nm	Depending on instrument, sample type and preparation, etc.
…	…		

Tier 1: (validated) rapid screening methods

Tier 2: (validated) in depth confirmatory methods



Tier 1 and tier 2 methods

TIER 1 Recommended to WP4 (Screening methods)	TIER 2 Recommended to WP5 (Confirmatory methods)	Recommended to WP6 (Methods ready for direct validation or standardisation)
PTA/DUM sp ICP-MS AC DMAS DLS TRPS SAXS USSp	EM AFM (or SFM) FFF	EM AFM PTA/DUM sp ICP-MS FFF AC

NanoDefine products to be delivered

Product	Planned release
The NanoDefiner e-tool: Standardised semi-automated procedure for method selection and NM classification for the most economic implementation of the definition	Project end
The NanoDefine Method Manual: Technical guidance on the use of available methodologies	first edition ca within 3-4 months (summer 2015)
Standard operation procedures (SOPs) for analysis of materials and products	first versions to be included in the Methods Manual
CEN/ISO work items for key methods	at project end
Calibration standards and reference materials (potentially to be certified later)	at project end
Technology transfer of developed methods to end users	at project end and via workshops

Conclusions

- The NanoDefine project supports the implementation of the EC definition of nanomaterial for regulatory purposes
- Applicable in all regulatory relevant contexts
- Development of a broadly applicable decision flow scheme
- Integrated, tiered approach
- Current results include
  - Materials classification scheme
  - Methods performance criteria
  - Preliminary methods evaluation: screening/confirmatory
  - Methods manual, first edition (soon)
- Final products
  - NanoDefiner e-tool (intelligent decision support software incl. manual)
  - Improved (and new) methods
  - Recommendations for use cases
  - Reference materials, progress towards standards

NanoDefine consortium

Thank you!

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