Nanomaterials in Europe: Navigating Regulatory Obligations and Compliance Challenges

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What is a nanomaterial according to the EU chemical Regulations

Definition of Nanomaterials

Nanomaterial means a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50% or more of these particles in the number-based size distribution fulfils at least on of the following conditions:

- One or more external dimensions of the particles are in the size range 1nm to 100nm
- The particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller that 1nm and the other dimension is larger than 100nm
- The particle has a plate-like shape, where one external dimension is smaller than 1nm and the other dimensions are larger than 100nm

COMMISSION RECOMMENDATION of 10.6.2022 on the definition of nanomaterial

Definition of Nanomaterials

Particle: a minute piece of matter with defined physical boundaries; single molecules are not considered ‘particles’

Aggregate: a particle comprising of strongly bound or fused particles;

Agglomerate: means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components.

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Commission Recommendation of 10th June 2022

Definition of Nanomaterials

A recommendation has been published by the European Commission on 10th June 2022.

It is a useful toll to give a proper interpretation of nanomaterial definition.

EUROPEAN
COMMISSION

Brussels, 10.6.2022
C(2022) 3689 final

COMMISSION RECOMMENDATION

of 10.6.2022

on the definition of nanomaterial

(Text with EEA relevance)

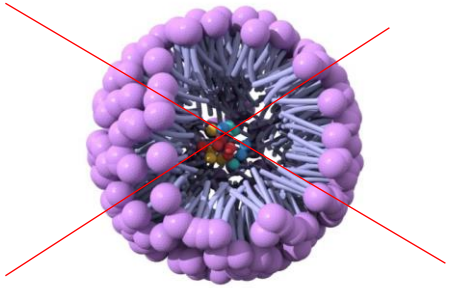
{SWD(2022) 150 final}

Definition of Nanomaterials

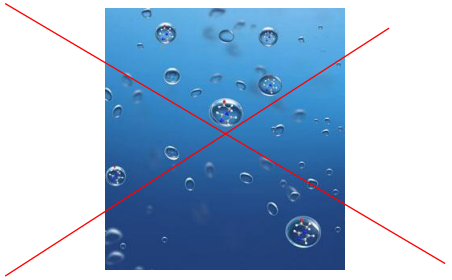
Other non-particulate components such as additives necessary for material stability and/or solvents should not be considered when assessing whether a material is a nanomaterial.

The term Nanomaterial should refer only to particles in solid state, present on their own or bound as constituent parts of aggregates or agglomerates.

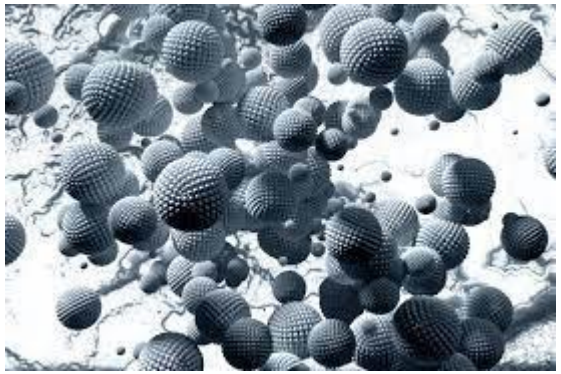
Definition of Nanomaterials



Micelles



Nanoscale droplets



Solid Nanoparticles

Definition of Nanomaterials

Specific Surface Area

Based on a large set of different industrial materials, that there were no inconsistencies in classification of non-nanomaterials, based on the median value determined from the particle number-based size distributions and on the volume specific surface area being less than 6 m2/cm3 (even if particle shape is unknown), respectively. Therefore, a material with a volume specific surface area less than 6 m2/cm3 should not be considered a nanomaterial.

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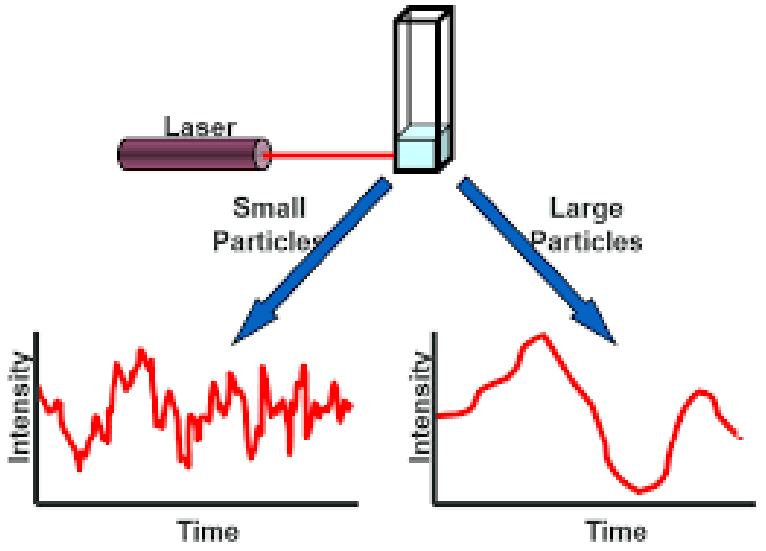
Characterization of a Nanomaterial

Particle size distribution

The particle size distribution is the main value to understand if a material can be considered as nanomaterial or not.

For materials suspected to be nanomaterial, this value can be properly measured thought the dynamic light scattering technique.



Particle size distribution

- **Number Size Distribution**: The number distribution is the number of particles counted of each size, shown as a differential across the total number of counts
- Volume Size Distribution: the contribution of each particle in the distribution relates to the volume of the particle
- Weight Size Distribution: the contribution of each particle in the distribution relates to the weight of the particle

Particle size distribution

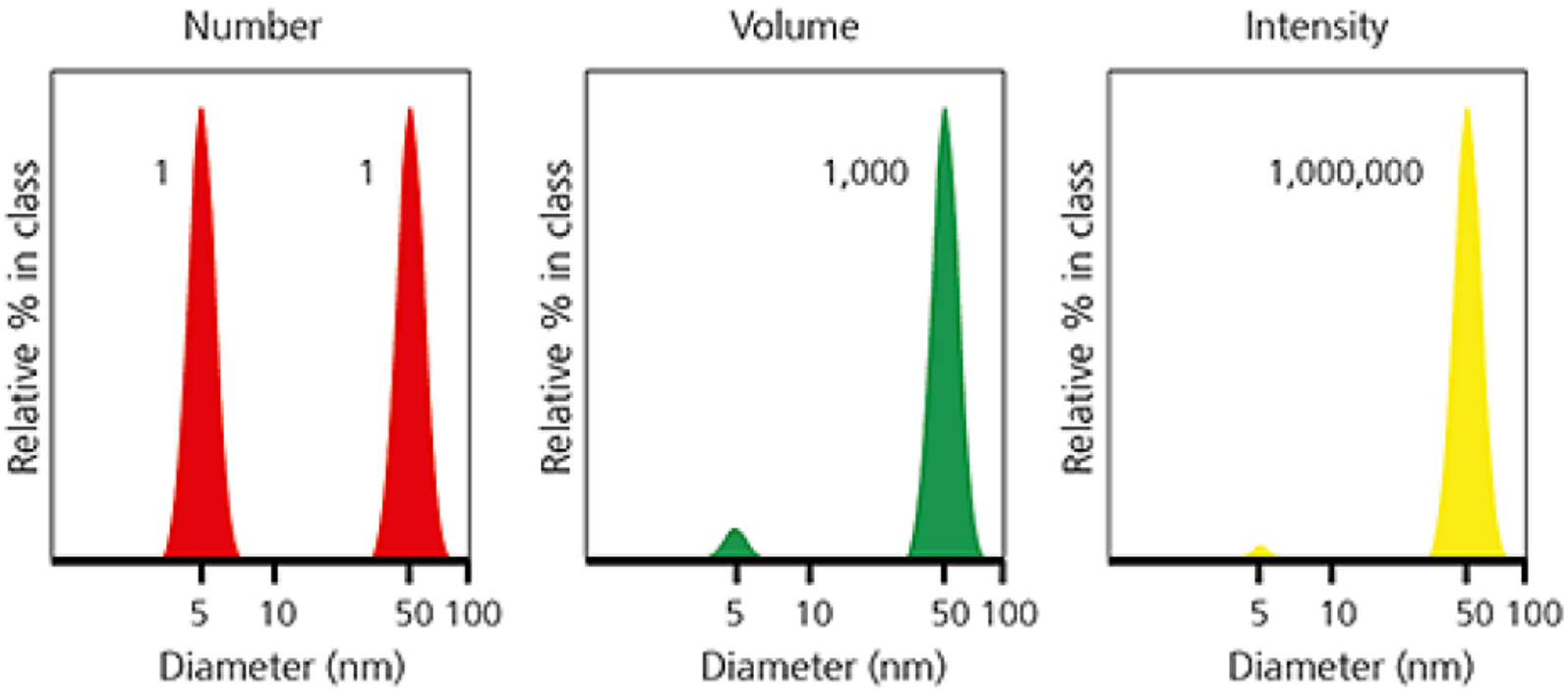
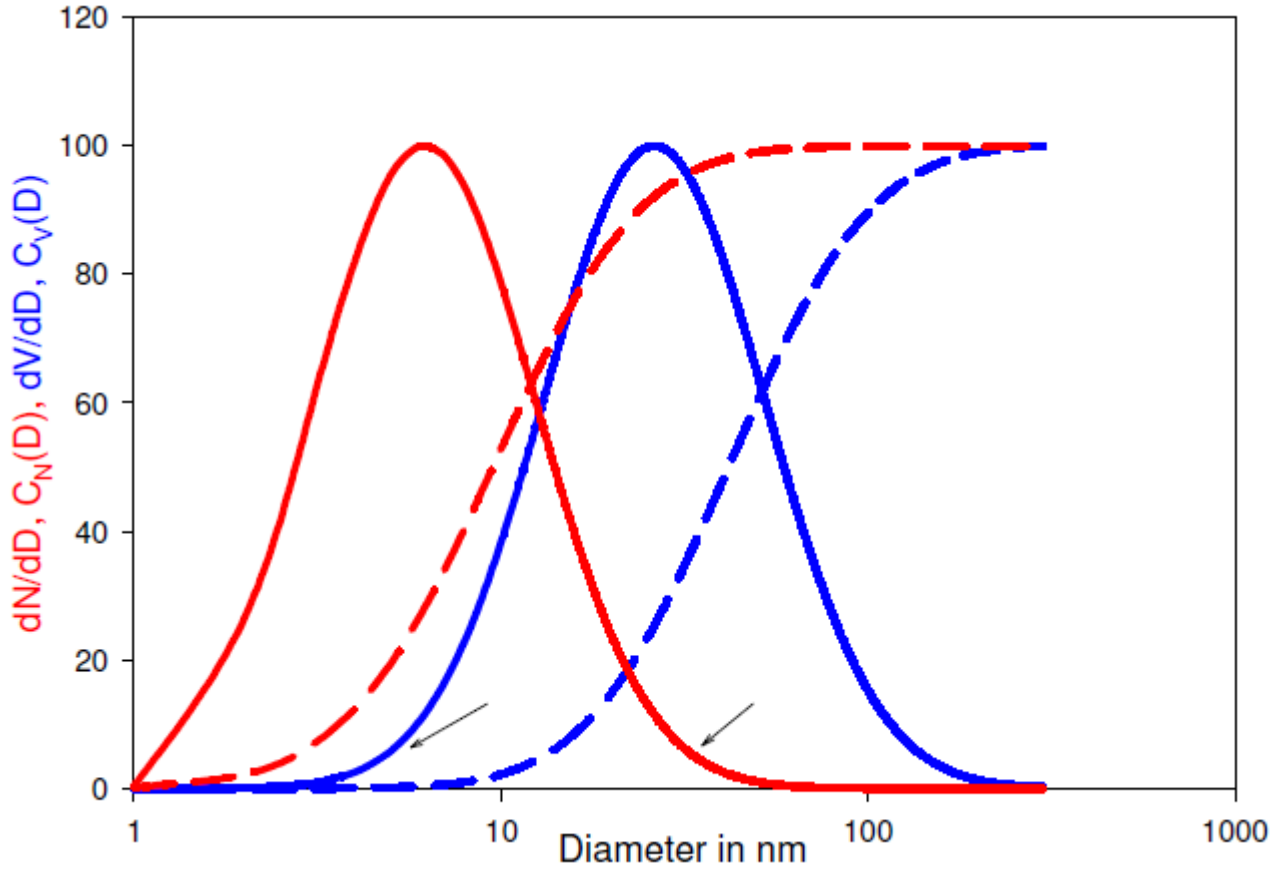


Figure 3: Example of number, volume and intensity weighted particle size distributions for the same sample.

Particle size distribution

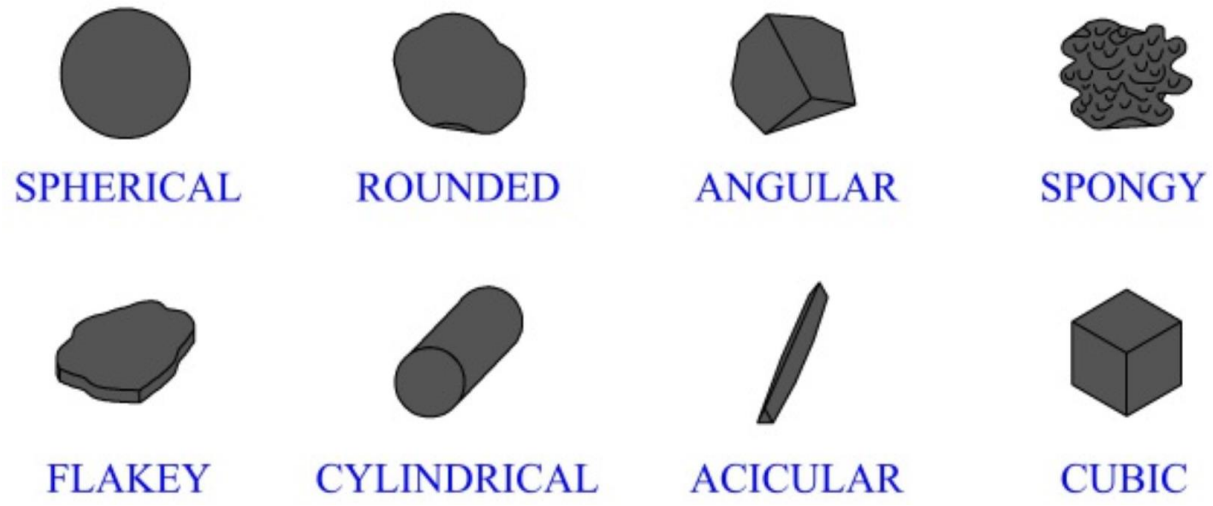
Number VS Volume Distribution



Particle Shape

Particle shape is the relative dimension of the long, intermediate and short axes of the particle. It is often related to the preparation method.

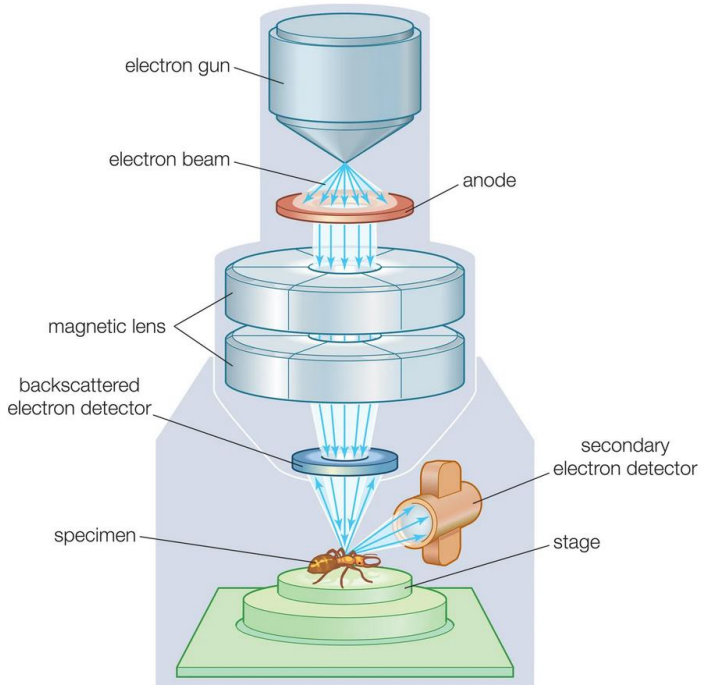
Particle shape can affect the technical behaviour of a powder, as well as its dangerousness



Particle Shape

There is not a quantitative technique to measure particle shape. The Scanning Electron Microscope (SEM) is the most common instrument to perform this measurement.

It is based on a focused beam of high energy electron projected on the sample's surface. The interaction of electrons of the beam and the sample produces various signals that can be used to obtain information about the surface's topography.



Particle Shape – Scanning Electron Microscopy

The result is a high magnification 2D picture of the sample.

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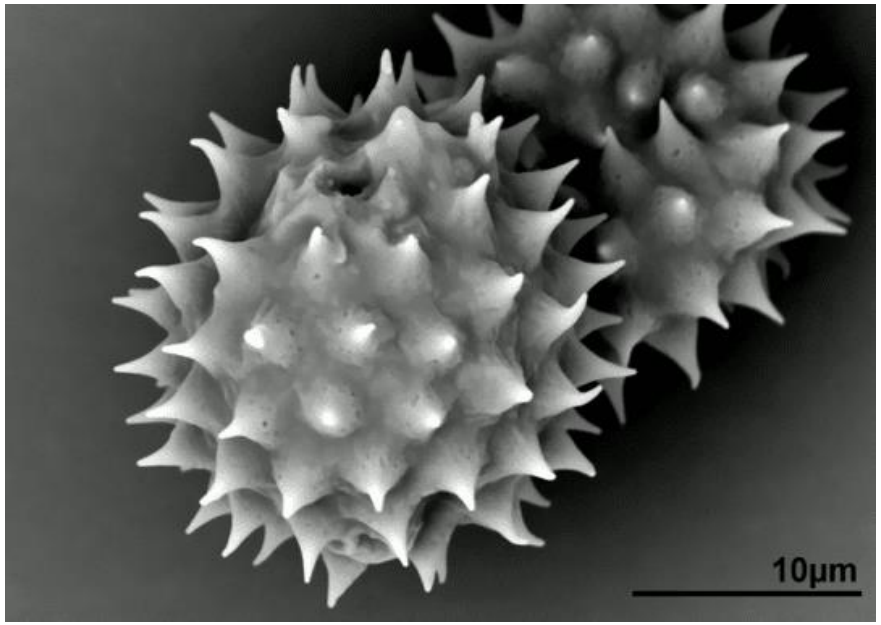
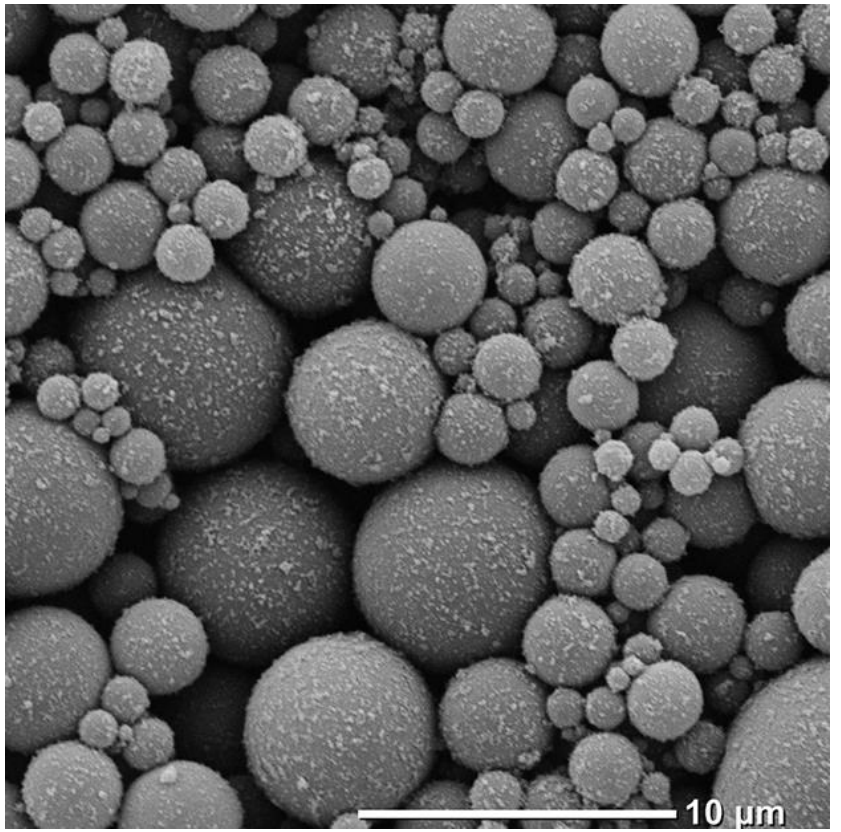




Particle Shape – Scanning Electron Microscopy

SPHEROIDAL

- Spherical
- Pyramidal
- Cubic
- Star Shaped
- Orthorhombic
- Polyhedral

ELONGATED

- Tube
- Rod
- Wire

PLATELET

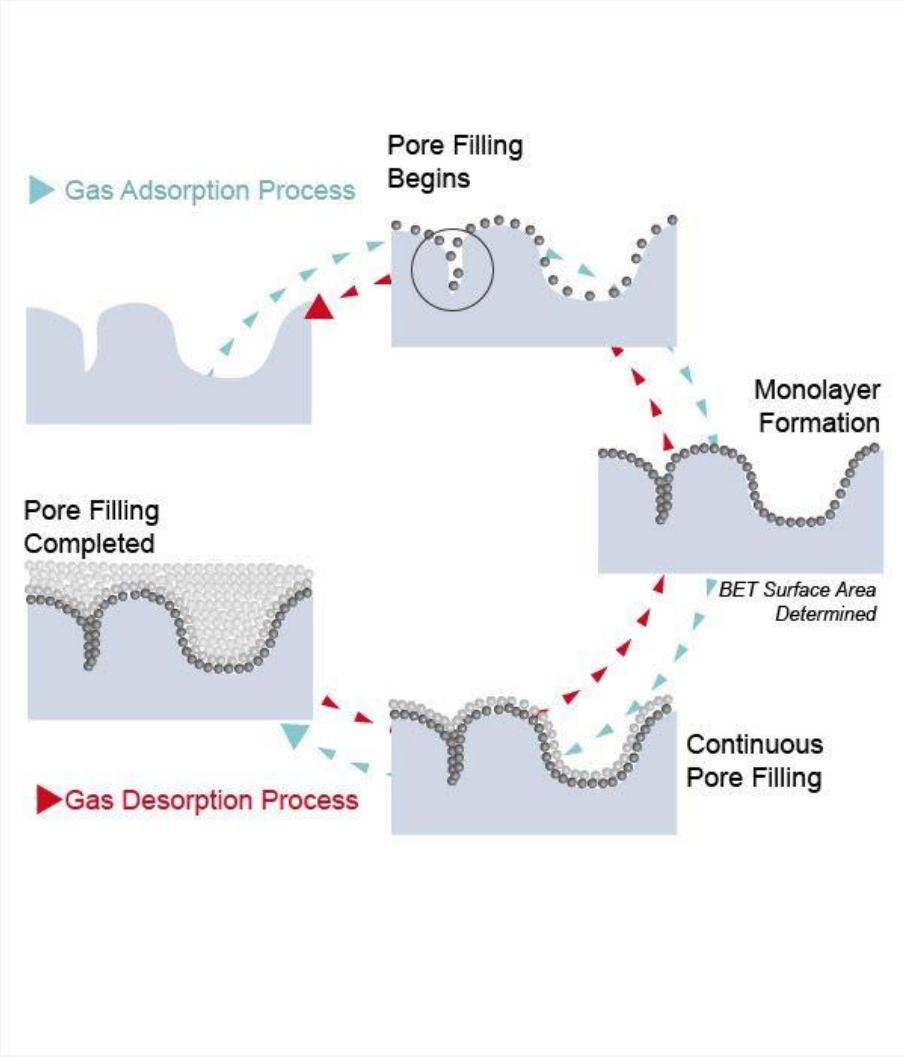
- Plate
- Disk

Specific Surface Area

The Specific Surface Area (SSA) is defined as the surface area of particles divided by their mass.

It has an impact on dissolution rate, toxicokinetic behaviour,

Fate, bioavailability and toxicity



Specific Surface Area

The BET (Brunauer, Emmett and Teller) theory is commonly used to evaluate the gas adsorption data and generate a specific surface area result expressed in units of area per mass of sample (m^2/g). The technique is referenced by several standard organizations such as ISO, USP and ASTM.

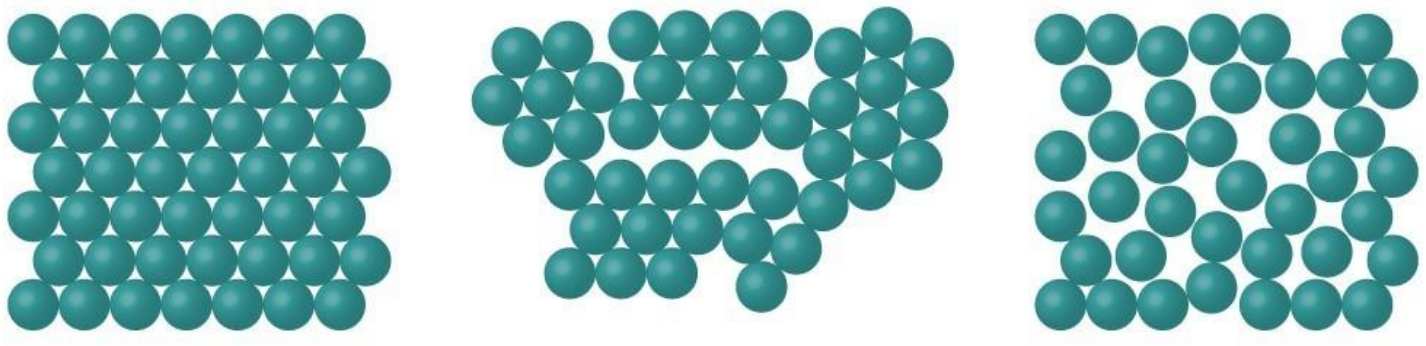
This technique is based on the physical adsorption of a gas (typically nitrogen, krypton, or argon) onto the surface of the sample at cryogenic temperatures (typically liquid nitrogen or liquid argon temperatures).

Crystallinity

The crystallinity of the powder must be reported and taken into account to properly characterize a nanomaterial.

Crystallinity has an impact on dissolution rate, toxicokinetic behaviour,

Fate, bioavailability and toxicity.



Crystallinity

Electron diffraction or X-ray powder diffraction are the most common techniques used to characterize particle crystallinity.

Nanomaterials with different crystallinity cannot be assessed in the same nanoset.

Particle Characterization

- Particle Size Distribution
- Particle Shape
- Specific Surface Area
- Crystallinity

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The Registration of Nanomaterials Under REACH Regulation

Information Requirements

Under the REACH regulation, registrants have the responsibility to generate data and obtain information on the substances they manufacture or import.

On this matter, REACH Annexes have been amended to address nanoforms of substances. Therefore, registrants have now the obligation to characterise each nanoform of the substance they manufacture or import and submit this information in the registration dossier.

Information Requirements

REACH Annexes VII – XI now include specific information requirements for Nanoforms and amendment to the existing one in the form of adaptation possibilities.

These amendments bring the obligation to report additional information when the concerned substance is a nanomaterial.

Set of Different Nanoforms

According to Annex VI of REACH: A 'set of similar nanoforms' is a group of nanoforms characterised in accordance with section 2.4 where the clearly defined boundaries in the parameters in the points 2.4.2 to 2.4.5 of the individual nanoforms within the set still allow to conclude that the hazard assessment, exposure assessment and risk assessment of these nanoforms can be performed jointly. A justification shall be provided to demonstrate that a variation within these boundaries does not affect the hazard assessment, exposure assessment and risk assessment of the similar nanoforms in the set. A nanoform can only belong to one set of similar nanoforms.

Set of Different Nanoforms

Boundaries for the parameters in 2.4.2-2.4.5 must be clearly defined. The variations will in this case arise from merging of information on different nanoforms (i.e. parameters such as shape, particle size distribution, surface treatment, surface area, are different, see section 3).

The registrant shall provide a proper justification explaining why the hazard profile of all the nanoforms within the set is the same. Some small variability is allowed as long as the hazard assessment is conservative and a single hazard conclusion can be reached for the whole set. For instance, when considering particle size distribution: gradual changes in hazard when reducing particle size may be covered within the same set. This may be justified by an adequate choice of testing material.

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From Bulk chemical to Nanomaterial

From Bulk to Nanomaterial

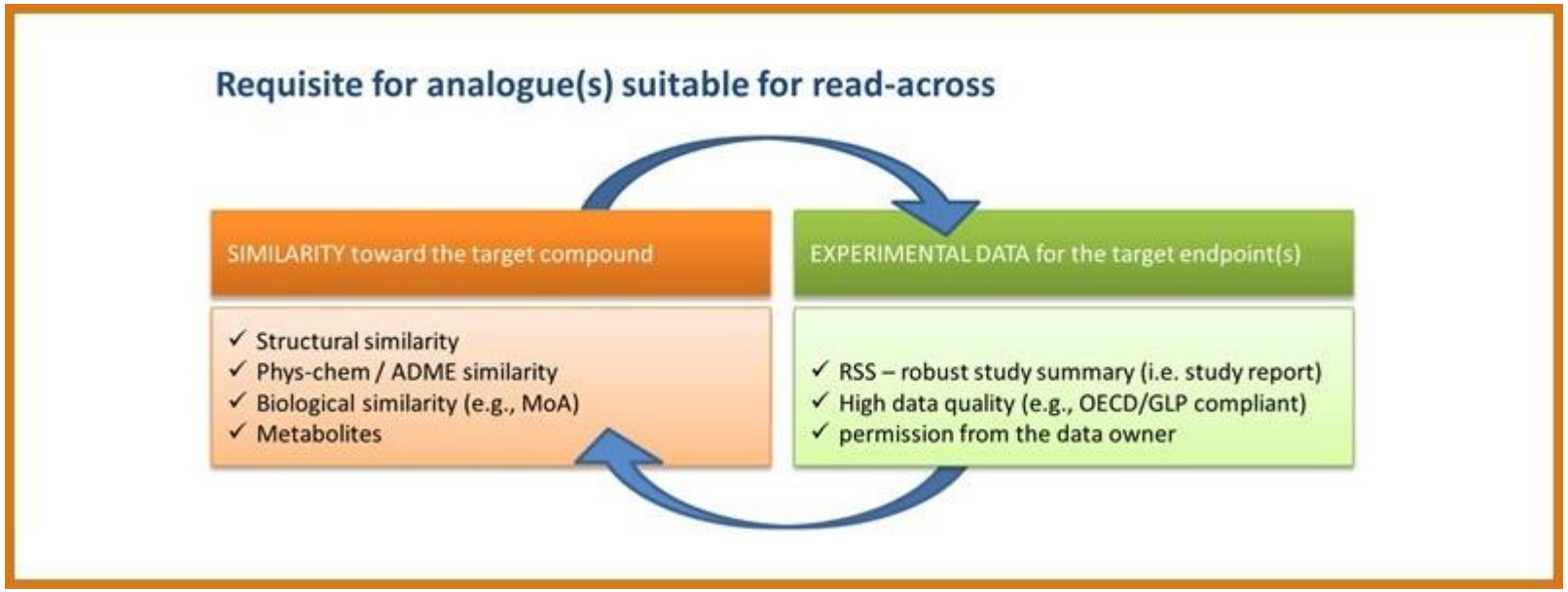
Many registrants have been impacted by the changes in information requirements for Nanomaterials. They have already provided all study requirements on a non-nanoform.

- Read-Across Approach
- QSAR Approach

From Bulk to Nanomaterial

Read-Across Approach

Through the read-across approach information requirements for physicochemical, human health and/or environmental properties may be predicted from information from tests conducted on reference substance (analogue - source substance)



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Read-Across Approach

The term ‘analogue approach’ is used when read-across is employed between a small number of structurally- similar substances; there is no trend or regular pattern on the properties. As a result of the structural similarity, a given (eco)toxicological or fate property of one substance (the source) is used to predict the same property for another substance (the target) to fulfil a REACH information requirement. The outcome of a study conducted with the source substance is read-across for all investigated parameters to the target substance. A worst-case approach may also be used.

In the context of read-across, a worst-case approach means that the strength of effect(s) in the target substance is actually expected to be lower than the strength of effect(s) observed for the source substance. Using the value obtained from the source substance, the prediction constitutes a worst case that will not lead to an underestimation of the effect(s) that would be observed in a study with the target substance if it were to be conducted

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Read-Across Approach

Under REACH, any read-across approach must be based on structural similarity between the source and target substances. However, structural similarity alone is not sufficient to justify the possibility to predict property(ies) of the target substance by read-across. A read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological, ecotoxicological or environmental fate property is possible and should be based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and target substances.

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Read-Across Approach

Key physicochemical parameters to take into account when a read-across approach is applied

- Chemical Composition
- Impurities
- Surface treatment
- Particle size
- Surface Area
- Zeta potential
- Dispersibility
- Dustiness
- Solubility
- Hydrophobicity

From Bulk to Nanomaterial

QSAR Approach

Quantitative structure-activity relationship (QSAR) is a computation modelling method for assessing the relationship between the chemical structure of a chemical compound and its biological activity.

It can be used to easily predict the physicochemical, toxicological and environmental fate properties of compounds

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QSAR Approach

Results obtained by a QSAR approach can be used instead of testing only when all the following conditions are met:

- The substance falls within the applicability domain of the QSAR model
- Results are derived from a QSAR model whose scientific validity has been established
- Results are adequate for the purpose of classification and labelling and/or risk assessment
- Adequate and reliable documentation of the applied method is provided

From Bulk to Nanomaterial

QSAR Approach

It can be used for the following purposes:

- Provide information for use in priority setting procedures
- Guide the experimental design of an experimental test or testing strategy
- Improve the evaluation of existing test data
- Provide mechanistic information (which could be used, for example, to support the grouping of chemicals into categories)
- Fill a data gap needed for hazard and risk assessment
- Fill a data gap needed for classification and labelling
- Fill a data gap needed for PBT or vPvB assessment

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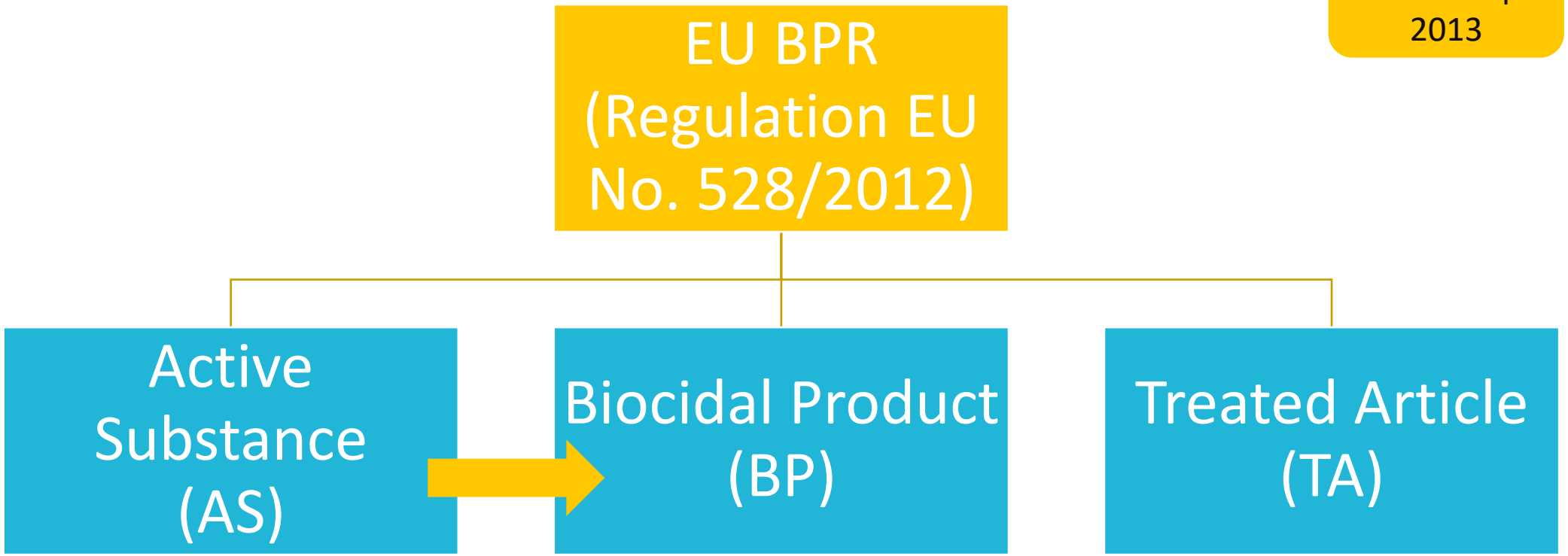
Nanomaterials in the Biocidal Product Regulation

Nanomaterials in the Biocidal Product Regulation

Art 2, Regulation (EU) 528/2012

- This Regulation concern the placing on the market and use of biocides and shall apply to biocidal products (and treated articles)

In force since 1 sept 2013



Nanomaterials in the Biocidal Product Regulation

- Biocidal products containing nanomaterials must meet additional requirements under Regulation (EU) 528/2012.
- Testing obligations: Ecotoxicological and toxicological assessments for nanoforms.
- Risk mitigation measures for environmental and human exposure.
- Target: Registration of a nanomaterial-based disinfectant.
- Challenges in ensuring safety and efficacy.

Nanomaterials in the Biocidal Product Regulation

Bulk Active Substance

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Nano Active Substance

Nanomaterials in the Cosmetic Regulation

Nanomaterials in the Cosmetic Regulation

Notification Requirements

- Notification must be made via the Cosmetic Product Notification Portal (CPNP).
- Key information required: Identification and characterization of the nanomaterial.
- Particle size, distribution, and functional properties.
- Toxicological data and exposure conditions.
- Submission is required six months before market placement.

Nanomaterials in the Cosmetic Regulation

Safety Assessment of Nanomaterials

- Comprehensive toxicological evaluation includes:
  - Skin penetration studies.
  - Systemic effects and long-term exposure.

- Risk assessment focuses on:
  - Inhalation risks for aerosolized products.
  - Combined exposure from multiple products.
  - Regulatory authorities may request additional testing data.

Conclusions

Conclusion

Challenges:

- Complex and evolving regulatory landscape for nanomaterials in Europe.
- High costs and technical challenges in compliance (e.g., testing and characterization).
- Specific requirements under REACH, BPR, Cosmetic Regulation, and CLP.

Targets:

- Driving innovation in product safety and functionality.
- Leveraging tools like Read-Across and QSAR to reduce testing burdens.
- Collaboration with regulatory bodies to streamline compliance

Thank You!

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