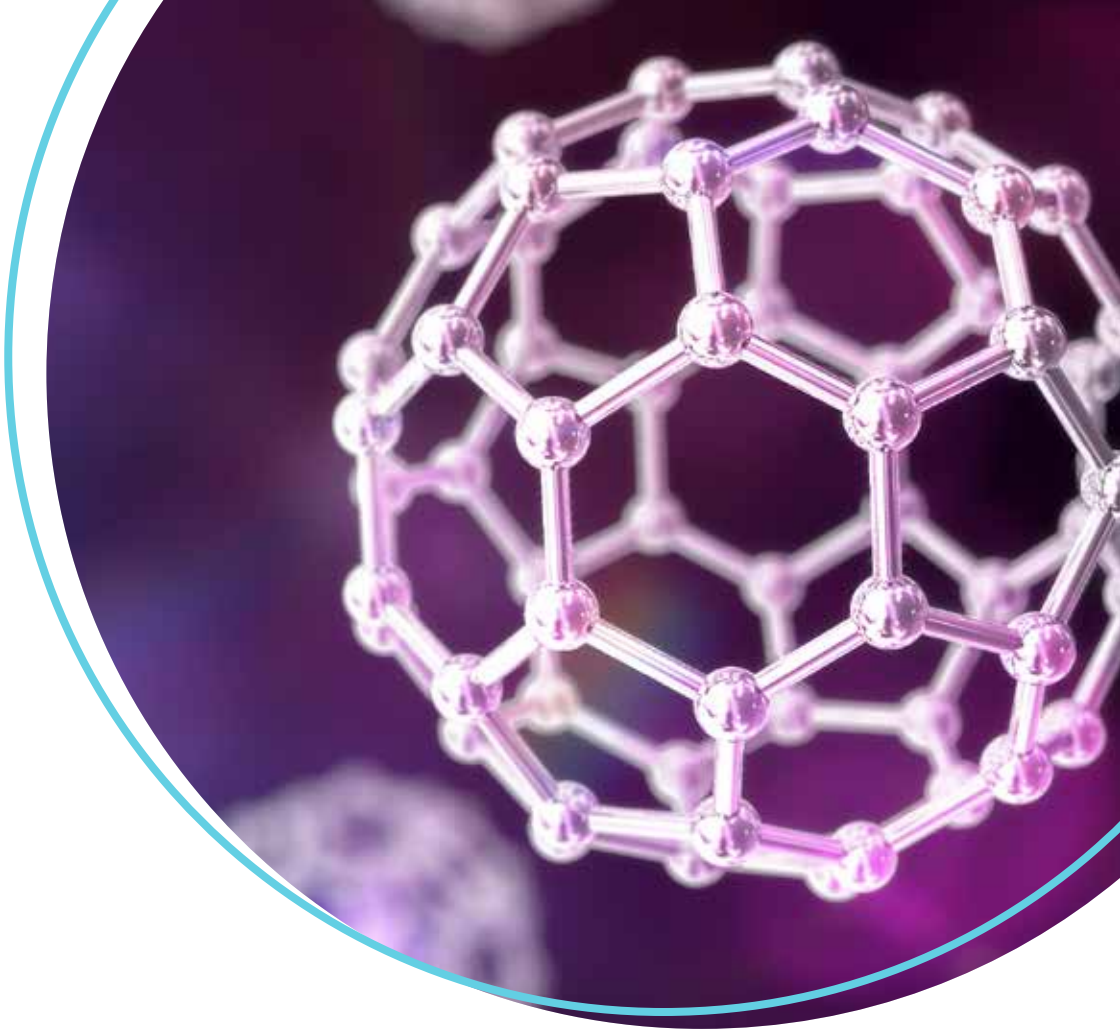

Nanomaterials:

How to Overcome REACH Regulatory Challenges

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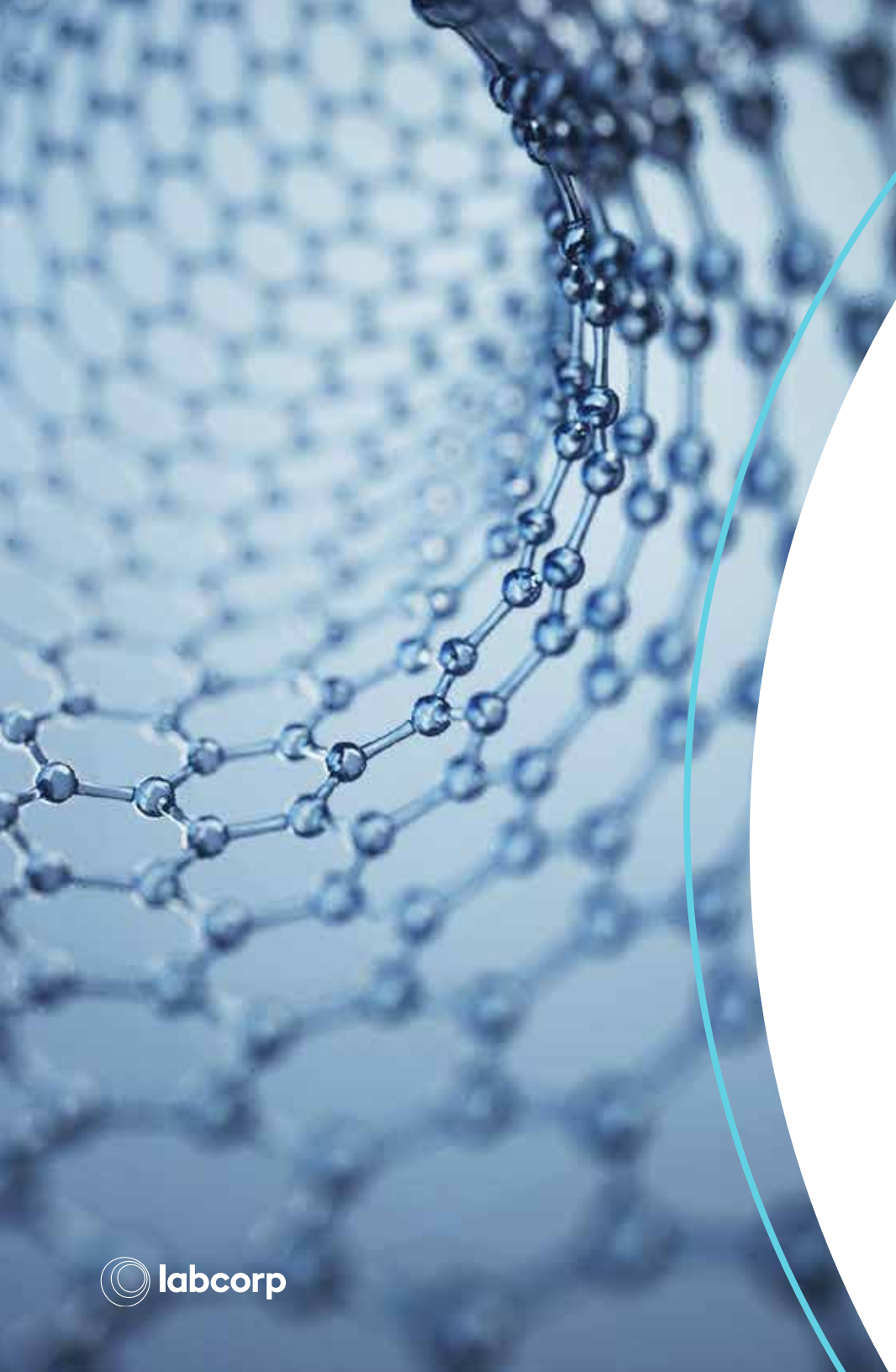

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Introduction

Nanomaterials are chemical substances that have a particle size between 1 and 100 nanometers (nm) in at least one dimension.[1] What is special about nanomaterials is that the properties of a substance change when it is scaled down to nanosize – such changes can include improvements in optical, electrical and magnetic properties.

The unique characteristics of nanomaterials have been exploited for hundreds of years to produce a range of diverse items. For example, the corrosion-resistant blue pigment, Maya Blue, first used by the Mayans in 800 AD is a complex nanomaterial that combines a dye with nanoporous clay.

Similarly, Damascus steel swords, forged between 300 and 1700 AD, contain wire-and-tube-like nanostructures arranged in such a way as to confer great strength to the blades.[2] It is unlikely, however, that any of the people involved in the creation of these items understood that it was the minute structure of the material that conveyed their special properties.

In more recent times, scientists have come to understand the value of nanomaterials and exploit them to deliver technological advances in a wide range of industries; however, as the use of nanomaterials has increased, so have questions about their safety to human health and the environment, and, therefore, how best to regulate them.

Regulations vary worldwide and they are evolving in line with the revolution of nanotechnology. In 2018, the European Commission (EC) adopted regulation 2018/188[1,3] which amended the existing Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation, to address nanomaterials directly. The regulation mandates effective characterization of a substance and contains new data requirements relevant to both new and registered nanomaterials. Importantly, the amendment also applies to any substance that might contain nanomaterials (e.g., powder), whether or not it has been manufactured as a nanomaterial. The European Union Observatory for Nanomaterials (EUON), which provides information about nanomaterials on the EU market, had identified 81 pigments that could be classed as nanomaterials, as of June 28, 2018.

This e-book reviews the REACH amendment and some of the key concepts it contains in order to meet Regulation 2018/1881.

Characteristics of Nanomaterials

The feature that all nanomaterials have in common is their minute size – in all other aspects of physiochemistry, nanomaterials are a diverse and heterogeneous group. It is not necessarily the minute size that determines if a nanomaterial is hazardous or not, but the size does mark out nanomaterials as substances that need specific regulatory consideration.[4]

Many nanomaterials also exist at the micro- and macroscopic level, but it is impossible to predict if the physiochemical behavior observed at this scale changes when the material is nanosized. This is one of the main challenges in understanding and regulating nanomaterials, especially when there is no clear size threshold at which properties may change.

Nanomaterials have applications in a range of industries

For example, they can be used for pathogen detection in food packaging, to aid the refinement of crude oil, in the medical sector to improve targeted drug delivery, and in electronics to enable wearable technology in phones and clothes.

Definition of a Nanomaterial

In general, nanomaterials are defined as chemical substances or materials with particle sizes between 1 and 100 nm in at least one dimension;[1,4] however, the detailed definition from a regulatory perspective varies across the globe, with the EU definition being one of the most specific.

Within the EU, there is currently no single specific regulation for nanomaterials. Instead, nanomaterials are governed by different legislations; for example, nanomaterials in cosmetic products are addressed under Regulation 1223/2009 and those in medical devices under Regulation 2017/745.

The EC first recommended a definition for a nanomaterial in 2011 (2011/696).[1] In 2018, the EC adopted Regulation 2018/1881,[3] which amended existing REACH regulation, to address nanomaterials. Regulation 2018/1881 provided a definition of a nanoform, as it specifically applied to REACH legislation.

There are some differences between the definitions of nanomaterials and nanoforms, as shown in Figure 1.

Figure 1. Definitions of a Nanomaterial and Nanoform[1,4]

Nanomaterial (2011/696)

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

In specific cases and where warranted by concerns for the environment, health, safety or competitiveness, the number size distribution threshold of **50%** may be replaced by a threshold between and %.

By derogation, fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below nm should be considered as nanomaterials.

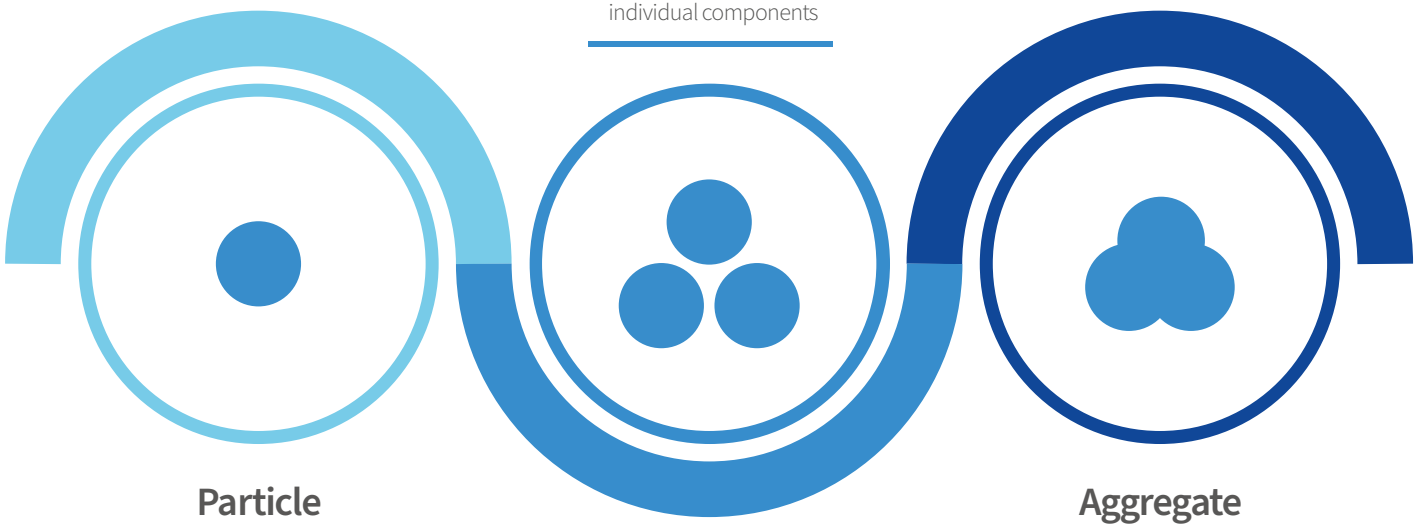
There is no flexibility of the ≥ % threshold criteria in REACH

Nanoform (2018/1881)

A nanoform is a form of a natural or manufactured **substance**, containing particles in an unbound state or as an aggregate or agglomerate, where, for % or more of the particles in the number size distribution, one or more external dimensions is in the size range – nm, including also, by derogation, fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below nm.

The term substance, rather than material, is used in REACH and there is no incidental substance in REACH

Figure 1. Definitions of a Nanomaterial and Nanoform[1,4]



Agglomerate

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

Particle

A minute piece of matter with defined physical boundaries

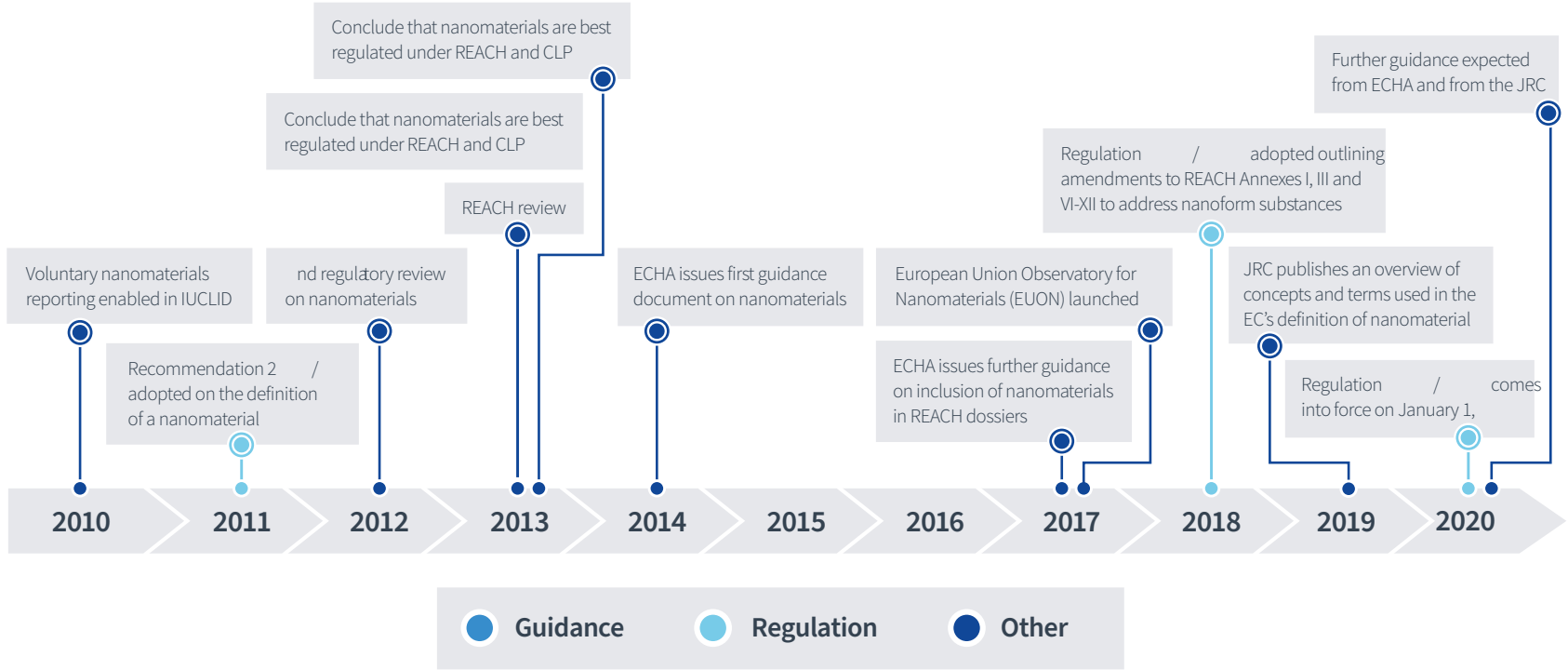
Aggregate

A particle comprising of strongly bound or fused particles

Regulation 2018/1881: Updating REACH to Address Nanoforms

The EC has been considering the appropriate way to regulate nanomaterials for some time (Figure 2), culminating in the adoption of Regulation 2018/1881 on December 3, 2018. Although not explicitly stated in Regulation 2018/1881, it is clearly implied that all registrants of active substances must confirm if their substance contains nanoforms. Most importantly, this applies to substances that are intentionally created as nanomaterials, as well as substances that may contain nanoforms. This may be especially relevant to registrants of powders, in which nanoforms may unintentionally exist. The EC NM definition of a nanomaterial covers only particles that are solid at normal temperature and pressure (NTP).[5] The regulation mandated that, by January 1, 2020, dossiers for both previously registered substances and new substance registrations should include information on nanoforms.

Figure 2. A Recent History of Nanomaterial Regulation in the EU Relevant to REACH



Important Concepts Relevant to REACH Nanoform Submissions

The production of nanomaterials can result in the creation of a number of different nanoforms of the substance, which can vary in terms of size distribution, shape and surface chemistry. This means that various nanoforms may be present in one nanomaterial or that the production process may need to be adjusted to produce only one nanoform.

It is important to understand how these different characteristics may impact the behavior and reactivity of a nanoform. The behavior encompasses factors like solubility, hydrophobicity or the ease of dispersal – all of which can affect where the nanoform ultimately ends up in biological systems.

Under REACH Regulation, the Three Features That Are Required in Dossiers Are:

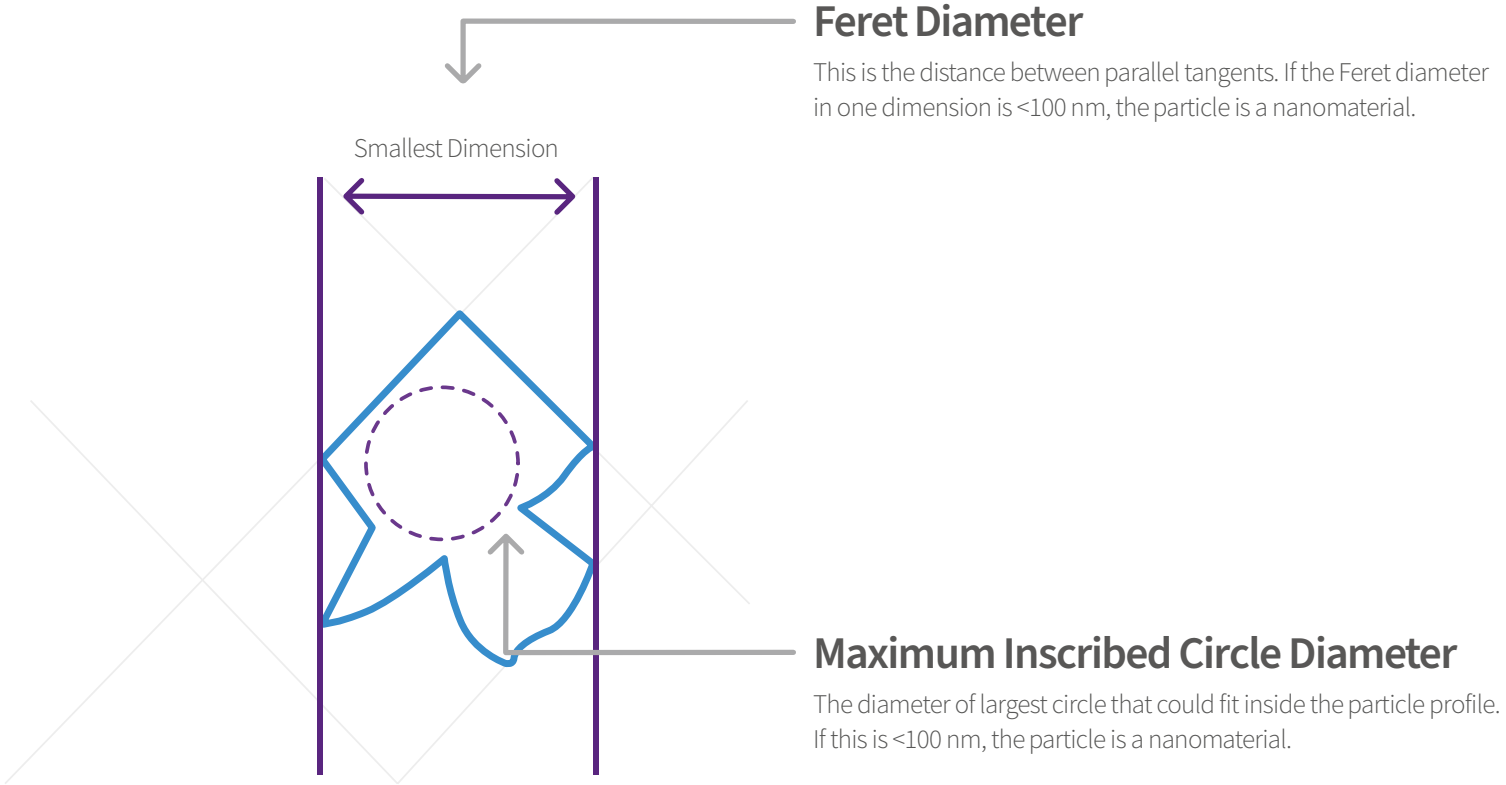
- Particle size/number size distribution
- Particle shape
- Surface chemistry

Reactivity determines what the nanoforms do and their subsequent toxicologic or ecotoxicologic impact

Particle Size

For particles that are spherical, it is easy to establish size using a single descriptor – the spherical diameter. Not all particles are spherical, however, and although many techniques used to analyze particle size can identify an equivalent spherical diameter, results vary with technique and there is a tendency to overestimate size. To overcome this issue, EU regulations use external dimensions as a means of defining particle size; two approaches of assessing external dimensions are summarized in Figure 3.

Figure 3. Two Commonly Used Approaches of Assessing External Dimensions of Irregular-Shaped Particles



Number Size Distribution

The definition of a nanoform specifies that more than half of the particles in the number size distribution should have at least one external dimension between 1 nm and 100 nm. For most situations, this essentially means that if the median size of particles in the substance is between 1 nm and 100 nm, then the substance is a nanomaterial.[5]

Although conceptually it is easy to visualize number size distribution as a histogram plotting particle size (grouped into size bands) against the number of particles in each band, in reality, the number of particles is measured in an alternative way (the total surface area for each size band provides a surface area size distribution). The total surface area for each size band provides a surface area size distribution.

Additional Information: Volume-Specific Surface Area (VSSA)

The recommended definition of a nanomaterial in Regulation 2011/696 includes a criterion based on VSSA; however, this is not defined for nanoforms in Regulation 2018/1881.

Using the VSSA criterion, a nanomaterial can be defined as a material in which the specific surface area by volume is >60 m^2/cm^3. VSSA is likely to be a reliable indicator in most cases, unless the constituent particles have rough surfaces or are porous. However, the VSSA criterion only allows you to demonstrate that a material is a nanomaterial, but not that it is not one. Materials that have specific surface areas <60 m^2/cm^3 but comply with the definition based on particle number size are still classed as nanomaterials.

VSSA may still be a helpful tool in assessing particle size distribution in REACH, even if it is not inherent in that regulation.

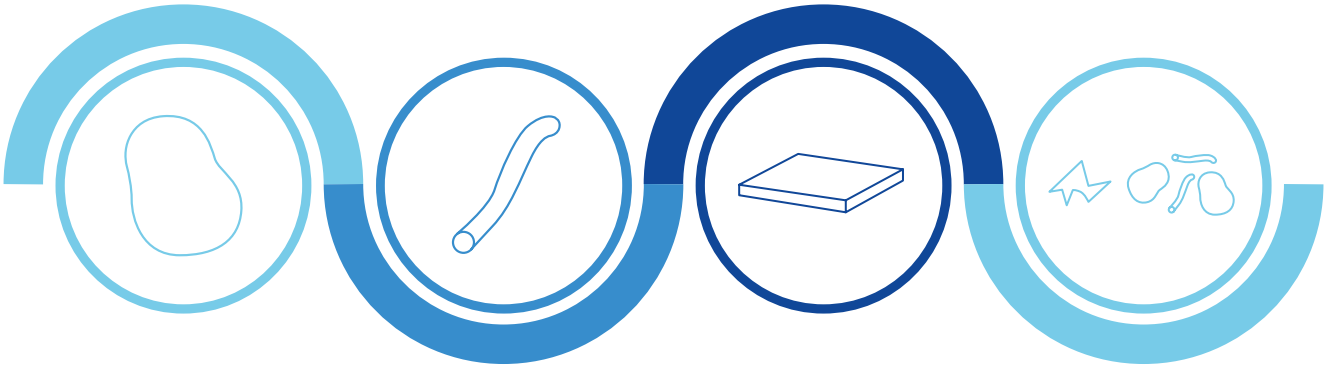
Particle Shape

The shape of a nanoform can dictate its behavior and, therefore, its potential (eco)toxicity – for example, it may impact how easily a nanomaterial can enter a cell. Shape may also differentiate one nanoform from another; therefore, characterizing and reporting nanoform shape is important. For the purpose of REACH submissions, there are four main categories, as shown in Figure 4, with the nanoform category determined as the shape represented by >50% of the particles.

Figure 4. Shape Categories For Nanoforms

The Shape of the Nanomaterial Has a Direct Effect on Particular Cellular Effects:

- Needle-shaped or "wire-shaped" particles can cause physical cell damage Spherical nanoparticles can easily cross cell membranes by endocytosis
- Single-walled carbon nanotubes have the potential to block calcium channels
- The toxicological effects of nanomaterials are numerous but could cause asthma, lung cancer heart problems, autoimmune disease, etc.



Spheroidal-like Particles	High-Aspect-Ratio Shapes	2-D Shapes	Other
These have three similar external dimensions in all projections. They include shapes that can be approximated as spheres, cubes, prisms, etc. They exclude shapes with an aspect ratio ≥5:1.	Particles with two similar external dimensions and a significantly larger 3rd dimension (aspect ratio ≥5:1) and parallel sides. **Include:** Hollow structures: nanotubes Solid structures: nanorods	One external dimension significantly smaller than the other two external dimensions. The smaller dimension is the thickness of the particle (e.g., flakes or platelets).	**These could include:** Particles with any other irregular shape Mixtures of particles with different shapes

Surface Chemistry

As nanomaterials have a very large surface area, the chemistry of the surface of the particles can have a huge influence on the particles' properties.
In fact, surface chemistry is often adjusted in the manufacturing process to alter properties such as reactivity, solubility and dispersibility. This can be achieved by adjusting the processes and conditions used to create the nanomaterial or by using surface-specific treatments.

The surface characteristics, and indeed the nanoform composition, can be highly dynamic and change depending on use or as the material passes through the supply chain. Tracking this can be difficult.

From a regulatory standpoint, it is therefore essential to characterize the surface chemistry, in order to predict the potential hazard posed by a nanoform. Recording this or the surface treatment methodology is required for REACH submission.

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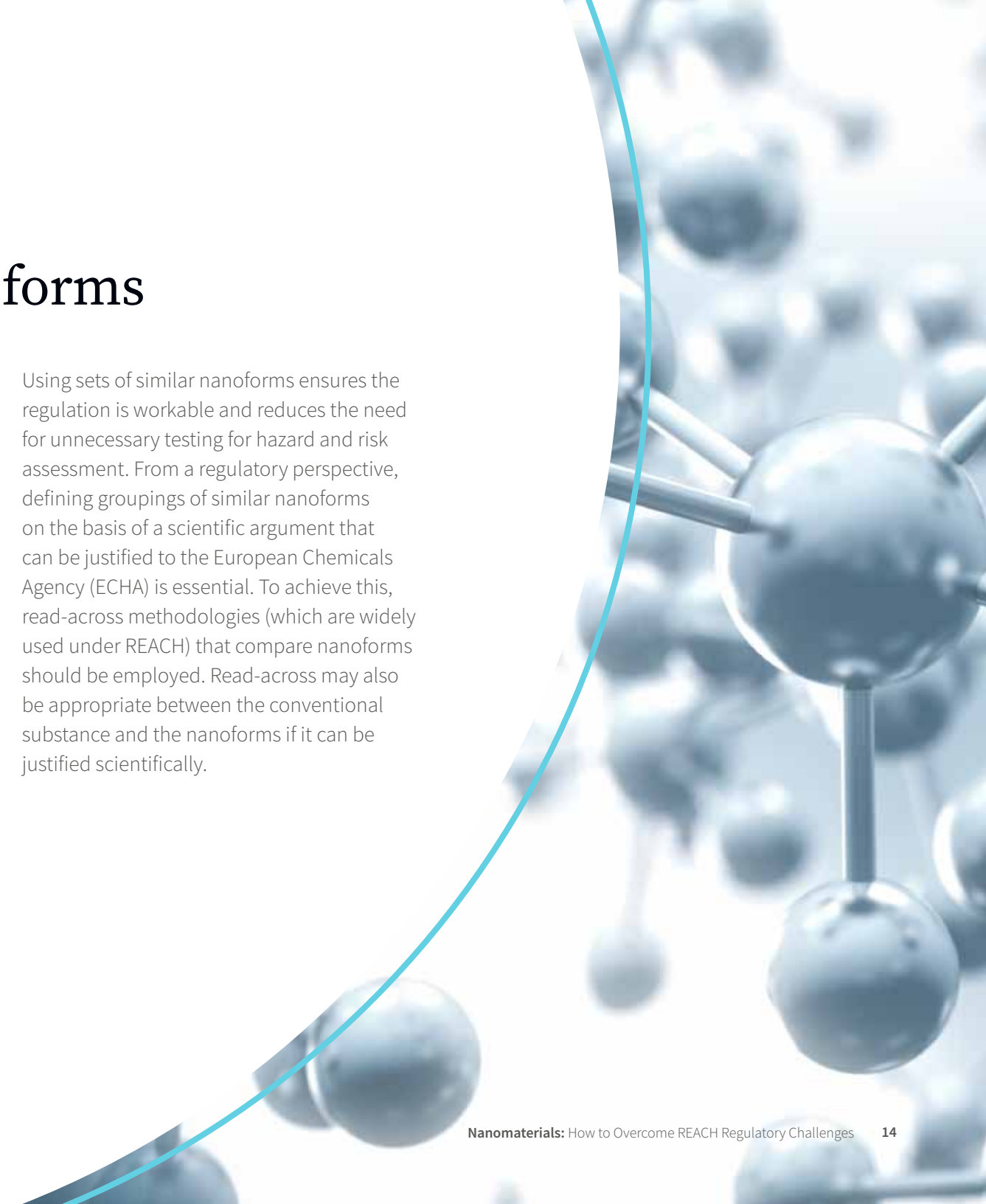
Sets of Similar Nanoforms

Regulation 2018/1881 sets out provision for grouping together nanoforms with similar characteristics into 'sets of similar nanoforms'. The grouping should define the boundaries for the set of similar nanoforms and provide a clear justification that any variation within these boundaries does not affect the hazard assessment, exposure assessment and risk assessment of the individual nanoforms within the set of similar nanoforms. Nanoforms can only belong to one set of similar nanoforms.

Using sets of similar nanoforms ensures the regulation is workable and reduces the need for unnecessary testing for hazard and risk assessment. From a regulatory perspective, defining groupings of similar nanoforms on the basis of a scientific argument that can be justified to the European Chemicals Agency (ECHA) is essential. To achieve this, read-across methodologies (which are widely used under REACH) that compare nanoforms should be employed. Read-across may also be appropriate between the conventional substance and the nanoforms if it can be justified scientifically.



An Overview of the Regulatory Changes

As Well As Defining a Nanoform, Regulation 2018/1881 Amended the Following Annexes:[7]

- **Annex I:** general provisions for assessing substances and preparing chemical safety reports. Extensive and effective identification and characterization of nanoforms and sets of similar nanoforms within a substance are required; this may pose technical challenges.
- **Annex III and VI-XI:** registration requirements for tonnage bands. Specific data requirements applicable to nanoforms have been identified (e.g., dispersion stability instead of octanol/water partition coefficient) and those not relevant have been highlighted. Most of these are straightforward and simple, based on application of the appropriate science. Note that the requirements vary by tonnage band, based on the total annual tonnage for the bulk substance and not the nanoforms.
- **Annex XII:** general provisions for downstream users to assess substances and prepare chemical safety reports. Risk analysis is required for all nanoforms, so simplification of nanoforms into groups will be essential. What may prove challenging is that downstream users may apply specific treatments to substances that may alter the nanoform composition and characteristics; however, because these treatments are usually protected under intellectual property rights, users may be reluctant to communicate the changes to the registrant.

Many of the approaches and tests required for assessing nanomaterials are evolving, and harmonized test guidelines appropriate for regulatory use are in development. A recent Organization for Economic Co-operation and Development (OECD) publication provides a comprehensive review of the current status,[6] and further guidance on measurements related to the EU regulatory environment was published on December 2019 by the Joint Research Centre (JRC).

There is an ongoing review as to whether Annex of the REACH Regulation, relating to the compilation of safety data sheets, requires amendment.

Particle Characterization

The usual methods employed for substance characterization, such as spectral analysis and chromatography, may be insufficient for complete characterization of nanoforms. You may, therefore, have to employ a new range of techniques to fully characterize all nanoforms and sets of similar nanoforms. Zeta potential, for example, which assesses the electrical charge on a particle, may be a good indicator of the likelihood of agglomerate formation.

Physiochemical Endpoints Overview

The regulation identifies the partition coefficient (Kow) as being inappropriate for nanomaterials, as, given their small size, they can easily cross biological membranes, regardless of their water solubility. Instead, dispersion stability and rate of dissolution are key characteristics that should be assessed. For the latter, it is important to consider this in terms of dissolution in water and relevant aqueous environments such as bodily fluids.

Toxicological Endpoints Overview

For conventional substances, the Ames test for mutagenicity (Annex VII) is a standard endpoint. As nanoforms are too large to cross bacterial cell walls, however, exposure is not possible using this test, so mammalian cell studies are required instead. Inhalation studies are especially relevant for nanomaterials, as the main route of exposure is likely to be through inhalation.

Environmental Fate and Behavior Endpoints Overview

The dispersal stability and dissolution rate will determine many of the tests you will need to conduct for environmental fate studies. Consider also how nanoforms may be altered by the environment and what the implications of this are for environmental fate and behavior. Although waivers are available for conventional substances with low water solubility, these will not apply to nanoforms.

The Next Steps for Joint Registrants

The 'one substance, one submission' approach mandated under REACH still applies.

However, the situation for nanoforms can be complex because of confidentiality requirements. Individual registrants will often use specific surface treatments to alter particle characteristics and these may be confidential, so sharing this information may infringe intellectual property rights. It is still necessary to work with other registrants to enable dossier update/creation, so all registrants need to explore this carefully.

Requirements and Timings

If you have a substance that is registered under REACH and you suspect it may contain nanoforms, you will need to confirm this. A useful approach is to ask these questions:

- Is the substance a solid or a liquid?
- Does the substance consist of particles or aggregates/agglomerates of particles that have an external dimension between 1 nm and 100 nm?
- Does the particle size distribution data indicate the possibility of nanoparticles (>50% having a diameter below 100 nm?
- What is the particle shape (e.g., sphere, cube, tube, wire, plate)?

If the substance is confirmed to be nanomaterial you will need to fully identify and characterize it and update your dossier in line with the new regulatory requirements.

For many registrants, the biggest challenge will be the correct characterization of nanoforms. Fortunately, ECHA have published a best practice guide for the characterization of nanomaterials for REACH. This helpful document suggests the use electron microscopy, dynamic light scattering and X-ray scattering methods to determine particle size. For surface area it is recommended to measure the gas adsorption isotherm of the substance microscopy to determine particle shape.

When carrying the latter measurements, it is noted that sample preparation is very important because the method used can affect results significantly (e.g., sonication versus dispersion) and because size is method dependent, no single method is perfect and the use of multiple methods is preferable. Finding a laboratory that understands the relevance from a regulatory perspective and has the scientific capability to run the particle characterization tests and interpret the results is crucial.

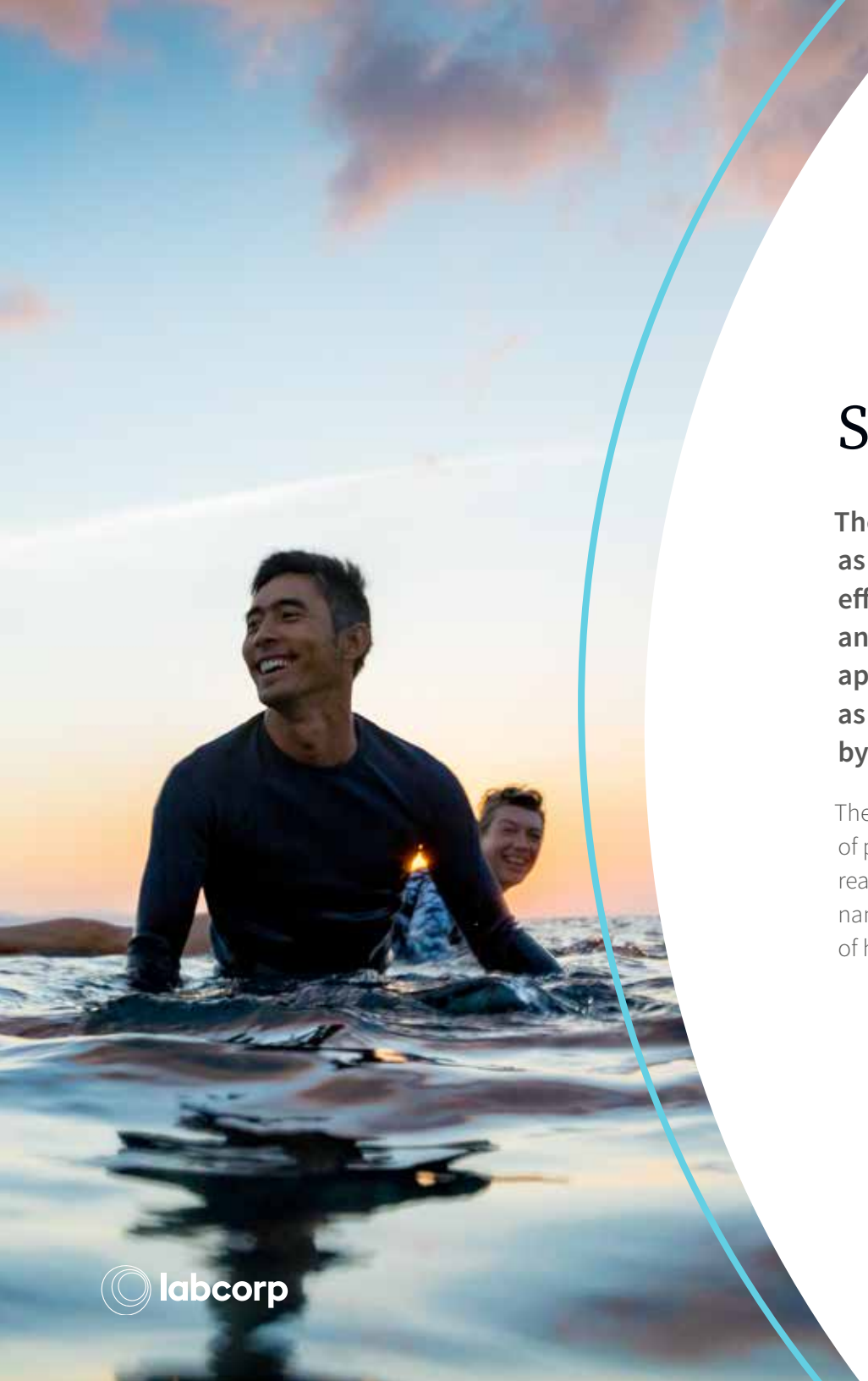
If you have many nanoforms, you need to group them into sets of similar nanoforms on the basis of scientific arguments that can be justified to ECHA. The ECHA guidance document on quantitative structure–activity relationships (QSAR) and grouping has good information on how best to tackle this.[8] Optimizing the grouping means that you can then also use read-across to address endpoints required for hazard assessment, which could obviously reduce the need for costly additional studies.

Finally, Regulation 2018/1881 requires manufacturers and importers to assess, and where relevant, generate the necessary information and document in the chemical safety report that the risks, arising from the identified uses of the substance with nanoforms they manufacture or import, are adequately controlled.

Main Considerations:

- Determine rate of dissolution in addition to water solubility testing
- Determine dispersion stability in octanol and water where determination of the octanol-water partition coefficient is not possible
- Review any QSAR determinations that use as input experimental values for water solubility and octanol-water partition coefficient and consider using dissolution rate instead
- Provide information on dustiness
- Consider one or more in vitro mutagenicity study(ies) for substances registered at 1-10tpa, in addition to the standard data requirement for bacterial mutagenicity
- Bear in mind that for low volume substances (1-10tpa), the inhalation exposure route may be more important than the standard requirement for oral exposure in acute toxicity
- Make sure sub chronic repeated dose tests carried out on nanomaterials via inhalation exposure include histopathological determination of brain and lung tissues as well as examination of bronchoalveolar lavage (BAL) fluid, kinetics and an appropriate recovery period
- Unless the nanoform dissolves quickly on entering the organism, the toxicokinetic assessment should be carried out on the nanoform in addition to the bulk substance
- For substance registered above 10tpa, specific relevant physicochemical properties may provide useful information on a case-by-case basis (e.g., agglomeration/aggregation state, surface morphology/topography, crystallinity)
- Waivers should be reviewed to make sure nanoforms are addressed separately from bulk substance
- Ecotoxiological test and environmental tests for nanoforms may not be waived on the basis of high insolubility in water alone.

Annexes VII to X of the REACH Regulation (EC) No 1907/2006 will be amended to include these changes.



Summary

The regulatory framework for nanomaterials is evolving, as the technology expands. New REACH regulations came into effect on January 1, 2020 for both currently registered substances and new substances. Most importantly, these requirements apply to substances intentionally developed as nanomaterials, as well as those that may unintentionally contain nanomaterials by virtue of their formulation.

The identification and characterization of specific nanoforms requires assessment of particle size distribution, particle shape and surface chemistry. By employing read-across and robust scientific arguments, it will be possible to categorize nanoforms into sets of similar nanoforms in order to simplify the assessment of hazard and risk.

Useful Reading and Source Material

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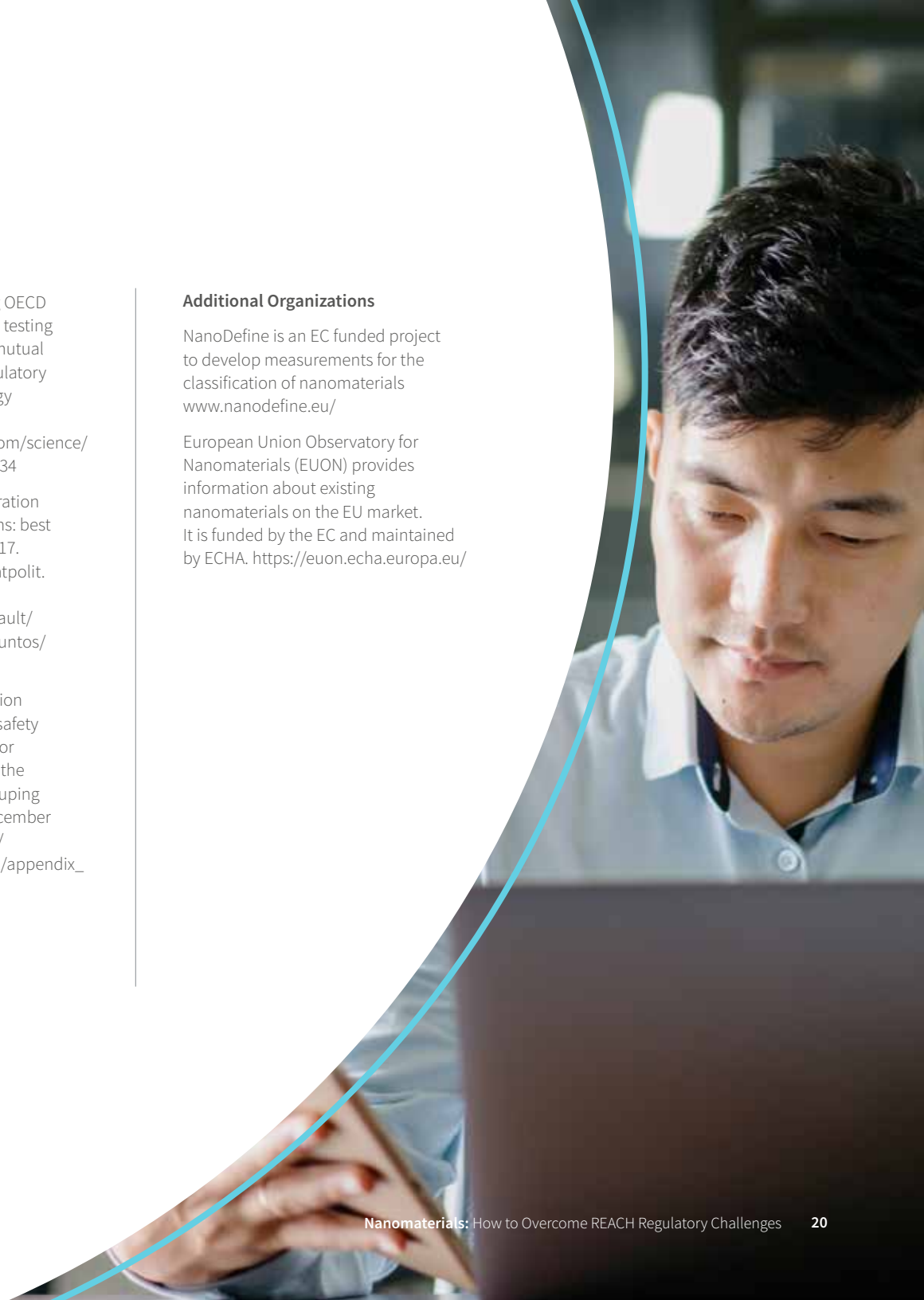
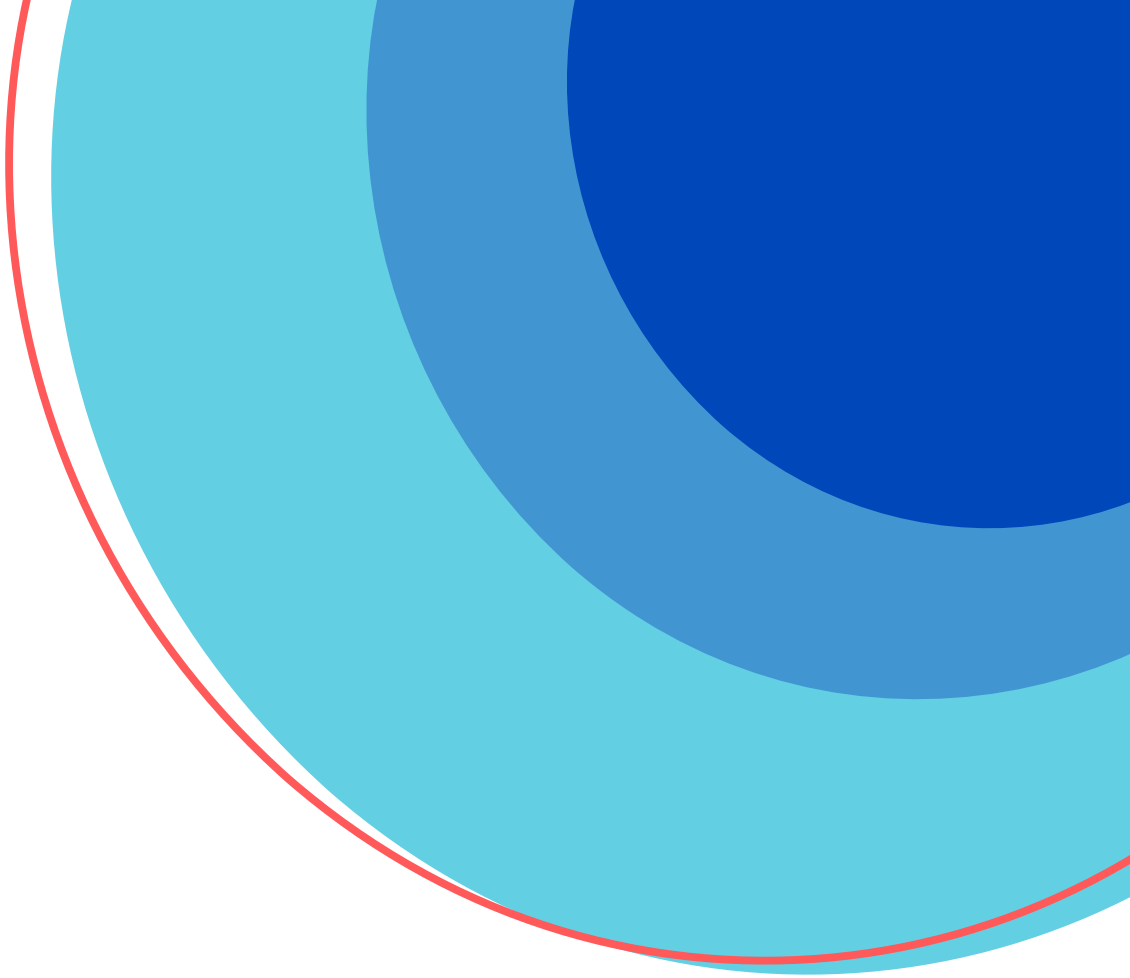
8. ECHA. Guidance on information requirements and chemical safety assessment Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals. Version 2.0 December 2019 https://echa.europa.eu/documents/10162/23036412/appendix_r6_nanomaterials_en.pdf

Additional Organizations

NanoDefine is an EC funded project to develop measurements for the classification of nanomaterials www.nanodefine.eu/

European Union Observatory for Nanomaterials (EUON) provides information about existing nanomaterials on the EU market. It is funded by the EC and maintained by ECHA. https://euon.echa.europa.eu/





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