ECHA
EUROPEAN CHEMICALS AGENCY

GUIDANCE

Appendix for nanoforms applicable to the Guidance on Registration and Substance Identification

Version 2.0
January 2022

This document aims to assist users in complying with their obligations under the REACH Regulation. However, users are reminded that the text of the REACH Regulation is the only authentic legal reference and that the information in this document does not constitute legal advice. Usage of the information remains under the sole responsibility of the user. The European Chemicals Agency does not accept any liability with regard to the use that may be made of the information contained in this document.

Appendix for nanoforms applicable to the Guidance on Registration and Substance Identification

Reference: ECHA-21-G-06-EN
Cat. Number: ED-08-21-370-EN-N
ISBN: 978-92-9468-030-3
DOI: 10.2823/40
Publ. Date: January 2022
Language: EN

If you have questions or comments in relation to this document, please send them (quote the reference and issue date) using the information request form. The information request form can be accessed via the Contact ECHA page at:
http://echa.europa.eu/contact

European Chemicals Agency

Mailing address: P.O. Box 400, FI-00121 Helsinki, Finland
Visiting address: Telakkakatu 6, 00150, Helsinki, Finland

Version	Changes	Date
Version 1.0	First edition	December 2019
Version 2.0	Revision of the document addressing the content and structure. Main changes include the following: additional guidance on joint submission of data as well as clarifications regarding the need for one dataset per nanoform/set of nanoforms, considering changes in the Guidance on Registration Sections 3 and 4 were out of the scope of this update and they remain as in version 1.	January 2021

PREFACE

This appendix for nanomaterials has been developed in order to provide guidance to registrants preparing registration dossiers that cover “nanoforms”. The advice provided covers nano-specific issues related with registration and characterisation of nanoforms.

This appendix does not preclude the applicability of the general principles given in the *Guidance on Registration* [1] and the *Guidance on Substance Identification* [2]. The parent guidance documents apply when no specific information for nanoforms has been given in this appendix.

The aim of this document is to provide guidance on how to interpret the term “nanoform” for registration purposes and provide advice on how to create “sets of nanoforms” for the purpose of registration. It also outlines what is expected in terms of characterisation of the nanoforms and sets of nanoforms in the registration dossier. Finally, it gives important information related to the joint submission of data on nanoforms as well as on confidentiality aspects.

This guidance does not aim to give potential registrants advice on how to fulfil their information requirements for the substances they are registering. This is addressed in other guidance material (See [3], [4], [5], [6]).

Table of Contents

Table of Figures

1. Introduction

This guidance has been developed to provide advice to registrants for substances that cover “nanoforms”.

Section 2 of the guidance explains general requirements regarding the registration of nanoforms.

Section 3 explains the concept of nanoform, how to distinguish one nanoform from another and the characterisation requirements when registering individual nanoforms.

Section 4 focuses on how to create and justify sets of similar nanoforms and details the characterisation and reporting requirements when registering sets of nanoforms instead of individual nanoforms.

Section 5 describes the registration process and illustrates the concepts of nanoforms and sets of nanoforms in the context of a joint submission. It also explains important principles related to the joint vs. separate submission of REACH Annex VII-X information.

2. General considerations

The Guidance on Registration [1] outlines the steps that potential registrants should follow when preparing to register a substance. These include:

- determining their registration obligations, including establishing the identity of the substance and considering joint submissions with other registrants where relevant;
- collecting/generating relevant Annex VII-XI data;
- ultimately submitting this information in technical dossiers to ECHA.

In addition, the Guidance for identification and naming of substances under REACH and CLP [2], provides guidance on reporting the identity of a substance, including:

- how to name a substance;
- substance sameness;
- how to apply substance identification principles when collectively defining the identity and scope of the substance covered by a registration.

This Appendix will not repeat the above information, as far as it is applicable to registrations that cover nanoforms. It gives some specific advice applicable only for the registration of nanoforms. The focus of this Appendix is on the nano-specific concepts of the REACH Annex VI requirements, i.e. requirements applicable to each registrant of a nanoform/nanoforms of a substance. Nano-specific guidance on fulfilling the information requirements under REACH Annexes VII-IX are provided with the nano-specific appendices to the relevant Guidance on information requirements and chemical safety assessment. This Appendix does however cover the particular nanoform aspects of joint data submission. The guidance aims to ensure unambiguous linking of the relevant data fulfilling information requirements in the joint submission with the registered nanoform.

2.1. Registration obligations

The Commission Regulation ((EU) 2018/1881) of 3 December 2018 amending REACH to address nanoforms of substances makes it explicit that the registration dossier must include the characteristics of the manufactured or imported nanoform(s) of the substance and information on specific hazards and risks of the nanoform(s). Further details on the concept are provided in section 3.1 of this document.

Once the registration obligation is triggered for a substance, in addition to any non-nanoform (if applicable) each of its nanoforms manufactured or imported must be reported in the registration dossier of the substance. Otherwise, a registrant manufacturing or importing such a nanoform is in breach of the legal obligations of the REACH regulation.

2.1.1. Actors with registration obligations

The actors with registration obligations under REACH are described in the Guidance on Registration [1]. The principles set out in that Guidance are also applicable for registration of substances with nanoforms. These actors are manufacturers and importers of substances on their own or in mixtures located in the EU; producers and importers of articles located in the EU in case the substance is intended to be released under normal or reasonably foreseeable conditions of use; and Only Representatives established in the EU and appointed by a manufacturer, formulator or article producer established outside the EU.

Given that nanoforms can be produced from, or modified from, nanoforms or non-nanoforms of the same substance, certain clarifications are necessary regarding the actors with registration obligations. Registration obligations only apply to the above-mentioned actors at the level of a substance, regardless of whether the substance is a nanoform or non-nanoform. When an actor in the supply chain purchases the substance and converts it from a non-nanoform into a nanoform, or modifies it from one nanoform to another nanoform, this actor is considered a downstream user.

Commission Regulation ((EU) 2018/1881) of 3 December 2018, makes explicit that downstream users do not have the obligation to register a new nanoforms of the substance. A downstream user must, however, check that their use of the nanoform is covered, e.g. via the safety data sheet they are supplied with when a safety data sheet is required. When the nanoform is not covered, the downstream user has the option to communicate the new nanoforms (and its uses) upstream to get it covered by the supplier. If the supplier refuses to cover the nanoform or the downstream user does not want to disclose the nanoforms and its uses to the supplier, the downstream user must prepare their own chemical safety report to demonstrate the safe use of this nanoform. Whether the use is covered in a registration, by a downstream user's own assessment or if the downstream user is relying on an exemption, the downstream user must ensure that the risks that the nanoform may present are controlled. For further information please see the ECHA Guidance for Downstream Users and the section I (on downstream user obligations) of ECHA Q&As for nanoforms of substances [7]. When a registration is covering a nanoform generated in the supply chain, the required information is the same as for the manufactured/imported nanoform.

There are a number of exemptions under Article 37(4) of REACH, where a downstream user is not required to prepare a chemical safety report. These relate to tonnage, concentration, or use of the substance for the purposes of product and process-oriented research and development (PPORD) among others. Details are given in section 4.4.2 of the *Guidance for downstream users*. Note that if you rely on the exemptions in Article 37(4)(c) or (f) of REACH related to tonnage and PPORD use respectively, then you still have to report to ECHA that you are relying on an exemption, indicating which exemption(s) applies.

2.1.2. Overview of registration scope

The generic registration obligation explained in the Guidance on Registration [1] also holds for substances covering nanoforms. In other words, registration is required for all substances manufactured or imported in a total quantity of one tonne or more per year, per manufacturer or importer, irrespective of the form, unless they are exempted from the scope of registration.

For a registrant of a substance covering nanoforms, it is therefore the total volume of all forms of the manufactured or imported substance, including all nanoforms and non-nanoforms, that will determine the need for registration and the information requirements for the registered

substance. Once the registration obligation is triggered, all nanoforms covered by registration must be reported in the registration dossier. The dossier must contain associated data covering all information requirements for all the forms of the registered substance'

Below you can find some examples of tonnage calculations.

Example 1:

Registrant 1 manufactures substance A with the tonnage of the nanoforms being 10 tonnes per year, and the tonnage of the non-nanoform being 50 tonnes per year. The total tonnage of the registration for this registrant is 50+10 = 60 tonnes per year. The registrant should provide the information requirements to cover the 10 to 100 tonnage band.

Example 2:

Registrant 1 manufactures substance B only as nanoforms, with a tonnage of 9 tonnes per year. Registrant 2 manufactures the same substance B as non-nanoform, with a tonnage of 50 tonnes per year. Manufacturers 1 and 2 submit each their registration as part of the joint submission for substance B. The tonnage of the joint submission is not the addition of the tonnage of all the members. The requirements of the information submitted jointly should cover the higher tonnage band of the registrants, which in this case is 10 to 100 tonnes. The jointly submitted data should cover the information requirements of the 10 to 100 tonnage band. Each registrant is responsible for fulfilling the information requirements corresponding to their own tonnage band (1-10 tonnes for registrant 1 and 10-100 for registrant 2).

Example 3:

Registrant 1 manufactures substance C only as nanoforms, with a tonnage of 10 tonnes per year. Registrant 2 manufactures 50 tonnes per year of the same substance C as nanoforms and 45 tonnes per year as non-nanoforms. The tonnage of manufacturer 1 is 10 tonnes per year, and the tonnage of manufacturer 2 is 95 tonnes per year. Manufacturers 1 and 2 submit each their registration as part of the joint submission for substance C. The tonnage of the joint submission is not the addition of the tonnage of all the members. The requirements of the information submitted jointly should cover the higher tonnage band of the registrants which in this case is 10 to 100.

The obligation to register nanoform(s) of a substance applies to all nanoforms meeting the definition set out in REACH, irrespective of whether the manufacture of a nanoform was intentional or not. Nanoforms manufactured as a dispersion must also be registered.

Each manufacturer and/or importer is responsible for determining whether or not the substance meets the criteria of a nanoform. If a form of the manufactured substance qualifies as a nanoform, this nanoform must be characterised and reported in the registration dossier.

2.1.3. Exemptions from registration obligation

All the registration exemptions outlined in the parent Guidance on Registration also apply to substances with nanoforms. Examples of substances that may cover nanoforms and that are exempt from the registration obligation are naturally occurring substances, such as minerals, ores, etc. described in REACH Annex V.7.

3. Nanoforms

The revised Annex VI of REACH introduces the concept of “nanoform” into the Regulation. It establishes the principles that all the nanoforms of the substance that are covered by the registration have to be reported in the registration dossier. By derogation to this principle, the revised Annex VI enables registrants to report several nanoforms together if certain conditions are met. The following sections will explain the criteria and conditions to report nanoforms (section 3.1) and sets of nanoforms[1] (section 4).

3.1. Nanoform concept

According to Annex VI of the REACH Regulation, a “nanoform” is a form of a natural or manufactured substance[2] 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, including also by derogation fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm. The concepts and terms used for nanoform in this guidance follow the concepts and terms used in the European Commission’s recommendation on definition of nanomaterial [8] as outlined and explained in the Joint Research Centre (JRC) Report ‘An overview of concepts and terms used in the European Commission’s definition of nanomaterial’ [8]. A second JRC report (Identification of nanomaterials through measurements) aims to support the implementation of the nanomaterials definition [9].

A nanoform must be characterised in accordance with Annex VI section 2.4 of REACH. A substance may have one or more different nanoforms, based on differences in the parameters in points 2.4.2 to 2.4.5 (size distribution, shape and other morphological characterisation, surface treatment and functionalisation and specific surface area of the particles).

Variation of one or several of the characterisers defined in section 2.4.2-2.4.5 results in a different nanoform, unless such variation results from a batch-to-batch variability. A batch-to-batch variability only results from the variation of parameters inherent to a manufacturing process that is defined by a series of process parameters (e.g. starting materials, solvents, temperature, order of manufacturing steps, purification steps, etc.). In this context, the process parameters can be modified only to minimise the batch-to-batch variations. Any other modification in process parameters results in a different nanoform.

Different manufacturing processes may result in almost identical characterisers. These different nanoforms can be registered as part of a set of nanoforms. In such cases, the creation of a set of nanoforms will be simple as the variation of the different characterisers will be small (see section 4). The smaller the variation the easier the justification to cover different nanoforms in the same set.

Sections 3.1.1 to 3.1.4 below provide explanations on the determination of nanoforms in practice for each parameter set out in section 2.4.2-2.4.5 of the revised Annex VI of REACH. Each of the sections explaining how nanoforms are identified includes a subsection on the characterisation requirements for an individual nanoform for the parameter described. For the sake of clarity, the explanations are given for each specific parameter. However, when considering what constitutes a different nanoform, the four parameters must be considered jointly.

[1] In this document often the term “set of nanoforms” is used instead of “set of similar nanoforms”, for simplicity, but it should be always interpreted the “set of similar nanoforms” as defined in REACH Annex VI.

[2] Please note that some substances may not require a registration. For further information on substances exempted from the REACH Regulation, exempted from registration or regarded as already registered see sections 2.2.2, 2.2.3 and 2.2.4 of the *Guidance on registration*.

3.1.1. Particle size distribution and number fraction of constituent particles

REACH Annex VI section 2.4.2 requires the reporting of the number based particle size distribution with indication of the number fraction of constituent particles in the size range 1 nm to 100 nm. When the Guidance refers to 'particle size distribution', it refers to the number based particle size distribution in line with the JRC Report [9]. When the Guidance refers to number fraction (of constituent particles or of nanoparticles), it refers to the number fraction of constituent particles in the size range 1 nm to 100 nm.

3.1.1.1. Distinguishing one nanoform from another

Each single nanoform has a specific particle size distribution where the variability in the distribution is within the batch-to-batch variability. Any variability in the particle size distribution beyond batch-to-batch variability creates another nanoform. The range of the values to be reported as described in the section 3.1.1.2.1 reflects the batch-to-batch variability.

3.1.1.2. Requirements for measurement or calculation method

The measurement or calculation method to determine the particle size distribution and the number fraction of constituent particles needs to be scientifically sound. When selecting the most suitable measurement or calculation method(s), the registrant needs to keep in mind that not all methods are suitable for nanoforms, and some methods are suitable only for certain nanoforms. For example, shape, size range as well as the chemical and physical nature of the particles must be taken into consideration when the method is selected [10], [11], [12]. The registrant is recommended to use at least one electron microscopy technique to measure the particle size distribution and the number fraction of constituent particles. The electron microscopy techniques can also provide essential information for reporting the length of the elongated particles and the two lateral dimensions (orthogonal external dimensions other than thickness) of the platelets.

The particle size distribution should be measured on the nanoform as manufactured. Where the particles are surface-treated or functionalised, the method(s) to measure the particle size distribution should be selected in such way that results provide information on the external size of the particles in accordance with the nanomaterial definition [8], [9]. This may require use of more than one method providing complementary results.

3.1.1.2.1. Reporting in the dossier

The registrant needs to provide in the dossier the particle size distribution of the external dimension of the particles of the nanoform following the concepts defined in the JRC Report [9] as a histogram with a table showing values on which the histogram is based. In addition, the registrant needs to provide the number fraction of constituent particles with at least one of the external dimensions in the size range 1 nm to 100 nm as a value between 50 % and 100 %[3]. In the case of elongated particles and platelets, the external dimensions are the width and the thickness, respectively. In the context of reporting the particle size distribution, a d_{10}[4], d_{50}[5] and d_{90}[6] value each with a range reflecting the batch-to-batch variability must be reported. For the determination of the number fraction of the constituent particles, all the measured particles of the nanoform must be taken into consideration.

[3] For a nanoform, the value for the number fraction needs to be 50 % or more. If a registrant manufactures or imports a form were the number fraction is below 50 %, the registrant should still maintain the information on the particle size distribution of those forms as an evidence for any possible enforcement actions.
[4] Size for which 10 % of the particles have size less than this value
[5] Median size of the particles
[6] Size for which 90 % of the particles have size less than this value

The registrant must describe the method(s) used and provide all the relevant bibliographical references in the dossier. The description of the method(s) needs to include the description of sample preparation, instrument parameters, functions and calculations applied, as appropriate, as well as the measurand or precise name of the external dimension of the particles used in the measurement (e.g. minimum Feret diameter or maximum inscribed circle diameter) and the corresponding measurement uncertainty. The measurement uncertainty needs to be expressed in line with principles outlined in the document JCGM 100:2008 [13].

3.1.2. Shape, aspect ratio and other morphological characterisation

According to section 2.4.4 of Annex VI of the REACH Regulation information on "Shape, aspect ratio and other morphological characterisation: crystallinity, information on assembly structure including e.g. shell-like structures or hollow structures, if appropriate", must be assigned to each nanoform.

Morphological characterisation of a nanoform requires information on the shape of the particles (including information on the aspect ratio and assembly structure), and information on crystallinity of the constituent(s) of the nanoform. In this document, shape (including aspect ratio and assembly structure) is discussed in a separate section (Section 3.1.2.1) from crystallinity (see section 3.1.2.2).

While shape and crystallinity are in different sections in this document, a registrant must take into account both parameters when deciding whether to distinguish between nanoforms.

3.1.2.1. Shape, including aspect ratio and assembly structure

3.1.2.1.1. Distinguishing one nanoform from another

Solid particles can exist in a wide variety of shapes, such as spheres, cubes, tubes, wires, plates, etc. Each nanoform, as a result of a defined manufacturing process, can consist of particles of the same shape (e.g. cubic) or particles with different shapes can be present simultaneously (e.g. 30% spheres and 70% cubes). Any variability in the shape of the particles beyond batch-to-batch variability defines a different nanoform. When assessing batch-to-batch variability for shape, several descriptors/parameters must be considered, e.g. aspect ratio and assembly structure.

When defining a particular nanoform, registrants should first see if any variability beyond the batch-to-batch variability occurs in size distribution (e.g. variation in the width for high-aspect ratio nanoforms). If no variations occur in width but changes in length occur (and consequently a different aspect ratio value is obtained), a different nanoform is defined.

Regarding assembly structure (e.g. multi-walled carbon nanotubes or nano-onions), variations in the characteristics of the assembly structure (e.g. number of walls or of concentric layers formed), will likely be captured by other parameters such as size distribution, and the result will in that case be the creation of a different nanoform. If such variations in assembly structure that go beyond the batch-to-batch variability are not already captured by the parameter size, the registrant must consider these variations separately.

The batch-to-batch variability is reflected by the range of values to be reported as described in the section 3.1.2.1.3.

3.1.2.1.2. Requirements for measurement or calculation method

In support to the description of the shape of the particles that constitute a nanoform, the registrant must always provide representative electron microscopy image(s) with a scale bar and the size in pixels (e.g. 2000 px x 3000 px) and the resolution in nm/px (e.g. 2 nm/px) of

the image, accompanied by a description of the sample preparation method (e.g. dispersion medium and energy, temperature, etc.) and a reference to the standards and reference materials used. Electron microscopy techniques that can be typically applied for the analysis of the morphology of the particles are Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Atomic force microscopy (AFM) is a microscopic technique that can be used for obtaining topological pictures of the surface of nanoparticles fixed on a flat substrate. The registrant must select, based on the material properties, the most appropriate technique for determining the morphology of the particles. The representativeness of the sample used for the measurements is fundamental. The issue of sample preparation and representativeness is extensively discussed in the documents ISO/TR 16196:2016 [14], OECD/ENV/JM/MONO(2012)40 [15] and ISO 14488:2007 [16]. Specific protocols for preparation of nanoparticles-containing products for microscopy methods are available in a technical report of the Nanodefine project [17].

3.1.2.1.3. Reporting in the dossier

In order to characterise the shape (including aspect ratio and assembly structure) of the particles that constitute a nanoform, registrants must provide in the dossier, at first instance, an electron microscopy image that allows visualising the shape of a representative number of the particles that constitute the nanoform. A qualitative description of the shape of the particles must also be provided.

As the number of possible particle shapes for nanoforms is very large, for organisation purposes, four broad *categories of shapes* are defined and reported below:

- **Spheroidal:** this category includes particles with aspect ratio up to 3:1 and thus this is a category for approximately “equiaxial” particles. Examples of shapes included in this category are spherical, pyramidal, cubic, 3D star-shaped particles orthorhombic, polyhedral, etc.

- **Elongated**: this category includes particles with two similar external dimensions and a significantly larger third dimension (aspect ratio larger than or equal to 3:1). Examples of shapes included under the elongated category are tubes (particles with hollow structures), rods (solid, non-hollow particles), wires (electrically conducting or semi-conducting particles), etc.

- **Platelets**: this category includes particles with one external dimension significantly smaller than the other two external dimensions. The smaller external dimension is the thickness of the particle. Examples of shapes covered under this category are discs, plates, etc.

- **Multimodal shapes**: this fourth category includes particles whose shapes belong to different shape categories (e.g. 60% spheroidal and 40% elongated). A nanoform consisting of particles with multimodal shapes is the outcome of a manufacturing process and it is therefore by definition not obtained by mixing particles of different shapes.

Particles with irregular shapes are covered under the categories reported above and must be assigned to one of those categories based on their aspect ratio and on having one, two or three similar external dimensions.

These four categories of shape are illustrated in Figure 1.

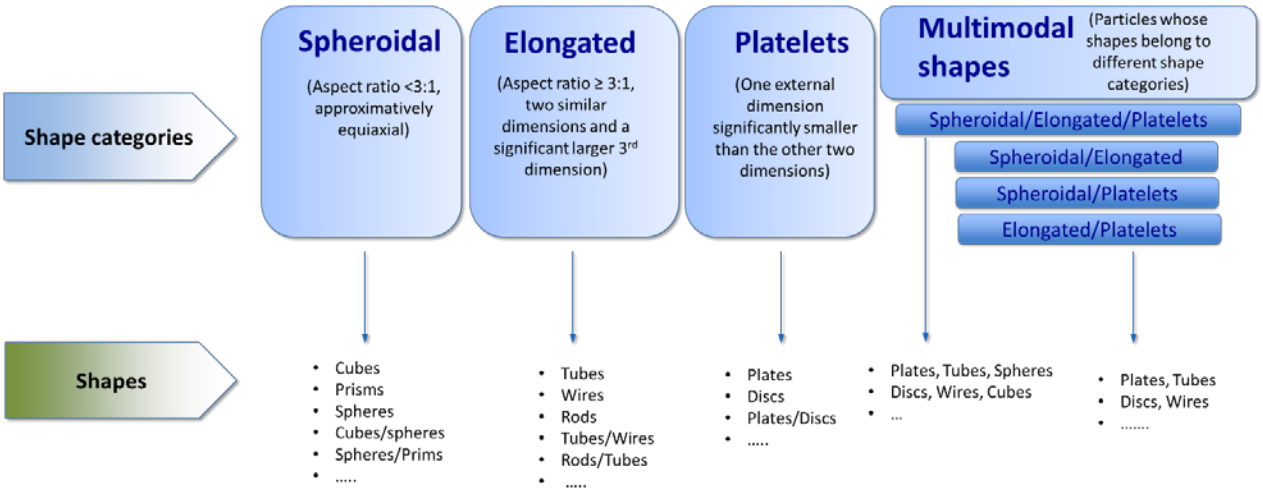

Figure 1: Schematic representation of shape categories and examples of some shapes for the categories a) spheroidal, b) elongated, c) platelets and d) multimodal shapes.

i. In order to qualitatively describe the shape of particles constituting a certain nanoform, at first instance the registrant must identify under which of the four shape categories (spheroidal, elongated, platelets, multimodal shapes) the specific nanoform would fall. The shape of the particles that constitute a nanoform will be allocated to one of the shape categories for reporting purposes. However, it should be noted that particles originating from distinct manufacturing processes resulting in different shapes falling within a same category (e.g. spherical and cubical) are to be considered as different nanoforms.

ii. Within such generic categories of shape, a more precise description of the shape of the particles must also be provided by registrants (e.g. spherical particles with regular shape, for nanoforms that fall within the category spheroidal).

iii. Further specific information must be reported in the situations explained below:

i. For nanoforms made of particles falling under the elongated shape category (i.e. aspect ratio ≥ 3:1) and for platelets the aspect ratio must be provided. The **aspect ratio** is a geometrical shape descriptor defined as the length (or longest dimension) to width ratio of a particle. It is obtained from particle size measurements performed on the nanoform: by measuring the length/ lateral dimension (or longest dimension) and the width (or the smallest dimension perpendicular to the length dimension) of individual particles in the nanoform [18]. Where the nanoform in question contains elongated particles or platelets, the registrant should report the average aspect ratio with an indication of the variation (as a range), as well as the length/ lateral dimension (longest dimension of the particle), in addition to the width/ thickness of the particle (as also specified in 3.1.1.2). This information concerns specifically nanoforms consisting of elongated particles or platelets.

ii. For nanoforms made of particles with an **assembly structure**, specific information on the assembly structure must also be provided. Examples of assembly structures are those found in high aspect ratio nanoparticles with hollow structures such as nanotubes, or nano-onion spherical nanoparticles with concentric multiple shell structure, as described in ISO/TS 80004-2 [19, 20]. Another example is the one of the multi-layers formed in platelets, for example in graphene-based materials that consist of multi-layers rather than mono-layers. For these materials, information on the number of multiple walls/shells/layers formed will must be provided.

iii. For elongated particles and for platelets, registrants are recommended to provide information on (flexural) **rigidity**. Rigidity, in the context of this Guidance, is the ability of an elongated particle or platelet to retain its shape, without damage, when subject to mechanical (bending) forces. The rigidity, together with aspect ratio, is known to influence the toxicity of all high aspect ratio nanoparticles (HARN) [21]. While there is currently no agreed measurement method for a parameter "rigidity", an indication of the rigidity of particles can be provided for example based on electron microscopy images (e.g. coiled/tangled versus straight particles), based on the particle width (covered by the requirement under section 2.4.2 of Annex VI of REACH) and length, number of walls (for particles with an assembly structure), etc.

iv. For nanoforms with multimodal shapes, details on the reporting are provided in the summary below.

Summary of reporting for shape:

To summarize, when reporting information on shape for a single nanoform, the registrant must provide:

- the shape category under which the nanoform falls (e.g. spheroidal);
- the specific shape of the nanoform (e.g. cubic);
- an indication of the (average) number of walls or layers for particles with an assembly structure (e.g. nanotubes, nano-onions) with an indication of the variation (as a range);
- electron microscopy image(s).

In addition to the above:

For a **nanoform** made of **elongated particles** the registrant:

- must provide the average length (longest dimension) of the particles, the range reflecting the batch-to-batch variability and the supporting analytical data;
- must provide the value of the average aspect ratio with an indication of the variation (as a range);
- is recommended to provide an indication of the rigidity: the registrant is recommended to indicate in the dossier if the particles that constitute the nanoform are rigid or not.

For **platelets,** the registrant**:**

- must provide the average value of the lateral dimensions (two orthogonal external dimensions other than thickness, which is already covered under the requirement under REACH Annex VI section 2.4.2) of the platelets, the range reflecting the batch-to-batch variability and the supporting analytical data;
- must provide the value of the average aspect ratio with an indication of the variation (as a range);
- is recommended to provide an indication of the rigidity: the registrant is recommended to indicate in the dossier if the platelets are rigid or not.

For a **nanoform containing particles with different shapes falling under a same category,** the registrant must provide:

- the shape category (e.g. spheroidal);
- an indicative composition in terms of specific shapes of the individual nanoform (e.g. 30% spherical and 70% cubic particles or 90% spherical and 10% cubic particles) and the range reflecting the batch-to-batch variability;
- reporting of particle size according to the selected shape category: for spheroidal

particles reporting of size distribution as described under 3.1.1, for elongated additional reporting of length and aspect ratio and for platelets reporting of thickness, lateral dimensions and aspect ratio, as described above.

For a **nanoform containing particles with multimodal shapes (the shapes fall under different shape categories),** the registrant must provide:

- the shape categories and the specific shapes of the particles;
- an indicative composition in terms of specific shapes of the individual nanoform e.g. 30% spherical particles and 70% nanotubes or 90% spherical particles and 10% nanotubes) and the range reflecting the batch-to-batch variability;
- reporting of particle size according to the shape categories. This means that if a nanoform is made of 70% cubic particles and 30% nanotubes, the dimensions related to the two different shapes (following the rules described above), should be reported separately.

3.1.2.2. Crystallinity

According to section, 2.4.4 of Annex VI of the REACH Regulation information on crystallinity must be assigned to each nanoform. Nanoforms can consist of atoms organized in periodic arrays (crystalline nanoform) or of atoms arranged in random assemblies without long-range atomic/molecular periodicity (amorphous nanoform). Moreover, in case of crystalline nanoforms of a substance, different crystal structures may (co-)exist.

3.1.2.2.1. Distinguishing one nanoform from another

Each nanoform of a substance has a specific amorphous or crystalline structure or a mix of the two. Any change in the structure beyond batch-to-batch variability creates another nanoform.

It must be noted that certain nanoforms may consist of particles with different crystal structures present simultaneously. This kind of nanoforms are not obtained by physically mixing particles of two different crystal structures, but are rather manufactured by specific processes that result in powders containing particles with different crystal structures. An example is that of a titanium dioxide powder, where anatase and rutile particles are present in the powder [22]. When a variation on the proportion of the different crystal structures occurs that goes beyond the batch-to-batch variability, a different nanoform is defined.

3.1.2.2.2. Requirements for measurements or calculation method

Information on crystallinity can be obtained through electron diffraction or (more often) through X-ray diffraction (XRD) analysis of the material. XRD can provide information on crystal structure (e.g. symmetry of the atoms in the unit cell and unit cell size); it can allow identification and indicative quantification of the crystal structures contained in a mixture. Different experiments or diffracting/scattering techniques may be used (e.g. small or wide-angle diffraction/scattering) depending on the type of structural information that one wants to gain [23].

For the characterisation of amorphous or partially amorphous nanoforms, the interplay of more than one technique (e.g. XRD and X-ray absorption spectroscopy (XAS)) may be needed to obtain a complete picture of amorphous and crystalline fractions of nanoforms) [24]. A quantitative analysis using the Rietveld method can be performed on an X-ray diffraction pattern. The method involves fitting the diffraction pattern with calculated profiles and backgrounds to obtain precise quantitative analysis of a form containing particles with different crystalline and/or amorphous structures [25]. High-resolution TEM images may also be needed to demonstrate the amorphous nature of nanoforms.

3.1.2.2.3. Reporting in the dossier

When reporting in the dossier information on crystallinity of an individual nanoform, the registrant must specifically provide:

- analytical data proving the amorphous/crystalline nature of the nanoform;
- a description of the analytical method(s) used (including information on reference material), the functions and calculation method(s) used, as well as a description of the method uncertainties. The description should be given in such detail that the method can be reproduced;
- for crystalline nanoforms the registrant must report the name of the crystal structure (e.g. rutile) or the related crystallographic parameters (crystal system, Bravais lattice parameters).

In addition to the above, the registrant must clearly report in the dossier:

For **crystalline nanoforms** consisting of particles with more than **one crystal structure**:

- the percentage and type of each different crystalline structure present (e.g. 20% (w/w) rutile, 80% (w/w) anatase) and the range reflecting the batch-to-batch variability.

For **partially crystalline nanoforms**:

- the percentage and type of crystalline structure(s), the percentage of amorphous fraction (e.g. 20% (w/w) rutile, 70% (w/w) anatase, 10% (w/w) amorphous) and the ranges reflecting the batch-to-batch variability.

3.1.3. Surface functionalisation or treatment and identification of each agent including IUPAC name and CAS or EC number

According to section 2.4.3. of Annex VI of the REACH Regulation, characterisation of a nanoform of a substance must include a "*Description of surface functionalisation or treatment and identification of each agent including IUPAC name and CAS or EC number*".

3.1.3.1. Distinguishing one nanoform from another

Surface functionalisation or treatment can be defined as a reaction between the functional groups on the surface of a particle and a substance called surface treating substance. The surface of particles can be modified by single or multiple surface treatments and the treatment(s) can fully or only partially cover the surface of the particles.

Particles can be extensively modified with the addition of various agents to their surfaces (e.g. inorganic treatment, organic treatment) or modification of their surface functionalities (e.g. oxidative treatment, reductive treatment). For example, particles of synthetic amorphous silica can be functionalised with very different surface treating agents (e.g. alumina, trichloromethylsilane, low silanol group density, high silanol group density, etc.).

Surface functionalisation/treatment can be applied to control particle properties like dispersibility in specific solvents (water, organic, polymers, etc.), reactivity (e.g. enhance catalytic activity or switch it off completely), solubility/dissolution rate (e.g. treatment of calcium carbonate, silver, ZnO, etc.), etc.

Surface treatment can refer to organic surface treatment (e.g. silica particle surfaces modified with alkylsilane), inorganic surface treatment (e.g. TiO_2 particle surfaces modified with alumina, zirconia, silica, etc.) or sequential inorganic and organic treatments to a given particle core (e.g. TiO_2 particle surfaces modified sequentially with zirconia, alumina, silica and

alkylsilane giving layers of different chemistries with the alkylsilane as the last/outer layer).

A good schematic of possible types of surface treatments/functionalisations is provided in the DaNA website at the following link: https://nanopartikel.info/en/nanoinfo/cross-cutting/993-coatings-cross-cutting-section [26].

Any variation beyond the batch-to-batch variability on the surface treating agent applied, of the reaction conditions, of the molar ratio of surface treating agent applied generates a different nanoform.

3.1.3.2. Requirements for measurement or calculation method

The registrant must select the most appropriate analytical method(s) that allow obtaining a full picture on the overall composition of the nanoform (the composition of the particle as a whole, including its surface treatment). The registrant is also recommended to provide, when feasible, analytical data that would support specifically the identification of the functionalities/treatment layer(s) formed on the particle's surface. Based on the nature of the treating agent (e.g. inorganic or organic), different types of analytical techniques (e.g. IR, NMR, TGA, ICP-MS, XRF, XPS, EDX, GC-MS, MALDI-TOF, etc.) may be used for both the identification and the quantification of the surface treatment. Specific protocols have been developed for quantitative analysis of both inorganic and organic surface coatings within the context of NANOREG [27] and by ISO [28].

3.1.3.3. Reporting in the dossier

When reporting information on surface treatment/functionalisation of a nanoform, the registrant must report the following:

- IUPAC name and CAS or EC number of each agent used for surface functionalisation/treatment;
- description of the main features of the process: a description of the type of process/reaction (hydrolysis, oxygen treatment, acid washing, etc.), together with relevant ranges of process parameters such as reaction conditions (pH, temperature) and any purification step applied;
- molar ratio of each surface treating agent used;
- a description of the functionalities introduced by the treatment (e.g. carboxyl, amino, hydroxyl groups);
- information on the indicative weight-by-weight contribution of the surface treating agent(s) over the total weight of the particle;
- when possible, an indication of the percentage of coverage of the particle's surface. Weight-by-weight contribution and indicative percentage of coverage of the particle's surface can be provided based on knowledge of the type of reaction occurring, amount of starting materials used, purification steps, combined with information achieved by using standard analytical techniques, such as ICP, XRF, IR, elemental analysis of C, H, N, O and S (as part of the determination of the overall composition of the nanoform);
- a description of the analytical method(s) used for determining the overall composition of the nanoform, including its surface treatment. The description of the methods must be given at a level of detail that would allow the methods to be reproduced.

Schematics of the functionalisation/treatment can also be provided to visually describe the treatment, including the functionalities formed on the surface of the particles that constitute (a) certain nanoform(s).

For example, organosilanes are important coupling agents used to modify surface chemistry [29]. An illustrative example of an organosilane coupling chemistry is given in Figure 2.

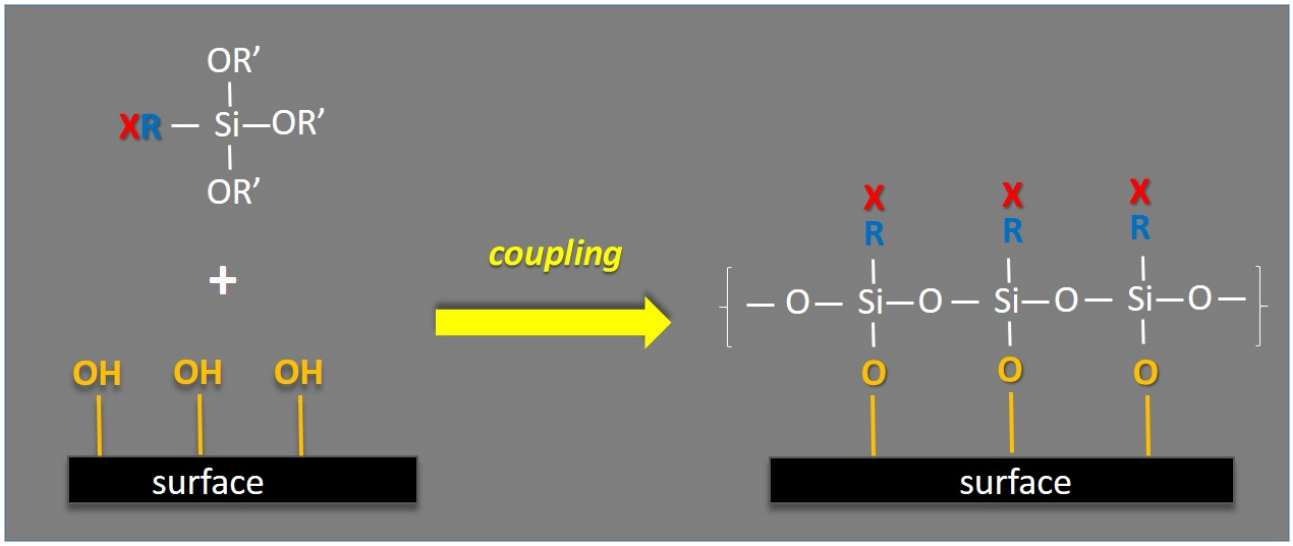

Figure 2: Schematic of an organosilane surface treating agent XR-Si-$(OR')_3$ and the chemistry it imparts to the surface of the particle after surface treatment.

The alkoxysilane groups -Si-$(OR')_3$ react via hydrolysis and condensation reactions with the surface hydroxyl groups to covalently bond functional polysiloxanes to the surface. Note that the chemistries of the agent and the treated surface are different. X-R-Si$(OR')_3$ is an organosilane molecule where X = a non-hydrolyzable organic moiety e.g. vinyl, OR' = a hydrolysable group like e.g. an alkoxy group that can react with various forms of hydroxyl groups. R is a spacer that can be for example a linear alkyl chain.

Multiple / sequential surface treatments

When sequential surface treatments are applied to a nanoform multiple layers can be formed (see Figure 3) that can either fully or partially cover the particle's surface.

When multiple layers are formed, information on surface functionalisation/treatment as described above must be provided for each different surface layer. The registrant must therefore provide identification of each agent used for each sequential surface functionalisation/treatment, including IUPAC name and CAS or EC number.

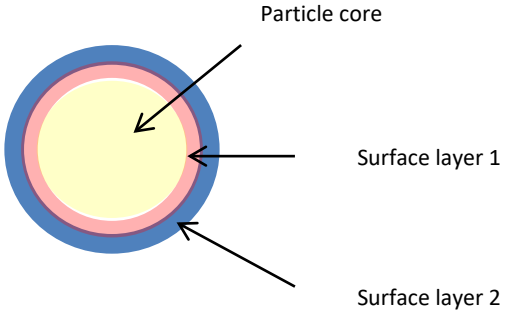

Figure 3: Idealised schematic representation of a nanoform whose surface has been modified by sequential surface treatments.

The registrant must provide the weight-by-weight contribution of each surface treating agent and, when possible, an indication of the percentage of coverage of the particle's surface for each individual layer.

When incomplete/not homogeneous coverage is obtained on the surface of the particles, the registrant is recommended to provide an indication (e.g. as a scheme) of the distribution and amount of the different surface treatment components on the surface of the particles.

3.1.4. Surface area (specific surface area by volume, specific surface area by mass or both)

In accordance with Annex VI, Section 2.4.5 of the REACH regulation, information on surface area (specific surface area by volume, specific surface area by mass or both) is required for nanoforms of a substance.

The surface area of a material may also be a useful metric in deciding whether the particular material meets the definition of a nanomaterial. According to the current EC recommendation for the definition of a nanomaterial, materials with a volume specific surface area > 60 m^2/cm^3 are nanomaterials, though materials with a volume specific surface area < 60 m^2/cm^3 are considered nanomaterials if the number based particle size distribution meets the criteria in the definition. A number of factors, such as particle shape, porosity, and aggregation may impact the application of this VSSA criterion [30]. Further information on role, as well as challenges of using the surface area to determine whether a material is a nanomaterial can be found in the JRC report “An overview of concepts and terms used in the European Commission’s definition of nanomaterial” [8], as well as the NanoDefine methods manual [10].

3.1.4.1. Distinguishing one nanoform from another

For nanoforms, the specific surface area represents one of the characterisation parameters required by the regulation. Each nanoform will have a specific surface area with batch-to-batch variability. Any variability in the specific surface area beyond batch-to-batch variability creates another nanoform. The batch-to-batch variability is reflected by the range of the values to be reported as described in the section 3.1.4.3.

As the specific surface area in principle is related to the size of the particles (with smaller particles in general having relatively larger specific surface areas, and vice versa, all other things including shape and porosity being equal), the particle size and specific surface area of any particular nanoform are linked together. Therefore, because deliberate changes to particle size distribution result in new nanoforms (as described in the section on particle size distribution), this will in most cases be accompanied with changes to the specific surface area of the (new) nanoform.

3.1.4.2. Requirements for measurement or calculation method

The surface area is measured as the total surface of the substance, including both the internal and external surface of the substance. The information can represent the total surface area of the nanoform per unit mass (specific surface area by mass, in units of m^2/g), or alternatively the surface area of the nanoform per unit volume (specific surface area by volume, in units of m^2/cm^3).

The specific surface area of a nanoform is generally measured via gas adsorption using the Brunauer-Emmett-Teller (BET) isotherm. In this technique, an inert gas, typically nitrogen, is used as an adsorbate. It should be noted that the identity of the adsorbate gas used in the measurement can impact the results obtained. The measurement of the specific surface area by volume using BET requires information on the density of the substance in question.

The principle of the method is to measure the adsorbate that is adsorbed to the surface of the material as a monolayer. The technique measures that amount of the adsorbed gas as a function of pressure, while holding the temperature constant, and this adsorbed amount is

plotted against the relative pressure in order to obtain an adsorption isotherm. The adsorption isotherm is used then to calculate the area of the monolayer equivalent with the amount of adsorbed gas by applying the BET equation. The ISO method ISO 9277:2010 [31] provides a standardised method for the determination of the specific surface area of solids by gas adsorption-BET[7]. However, the BET method is not applicable to all materials, and the ISO standard above is only applicable to adsorption isotherms of type II and type IV. Annex C of the ISO standard provides a strategy for the determination of specific surface area of materials with a type I isotherm. Further information regarding the application of gas physisorption to the evaluation of surface area can be found from the IUPAC Technical Report on this subject. [32] The measurement of specific surface area can be performed using methods other than gas adsorption, and may in fact be necessary in some cases (e.g. suspensions).

The calculation of a volume specific surface area via the BET method requires information about the density of the substance in question. Information on **relative** density is an information requirement under the REACH regulation Annex VII, 7.4, and detailed information on how to measure and report relative density can be found under the relevant ECHA guidance [33]. However, some important distinctions must be taken into account in order to derive a correct value for volume specific surface area.

- The term density, as well as relative density can refer to different values/concepts. The relative density represents the density of a substance in relation to the density of water, and this is a dimensionless value (see Chapter R.7a of the Guidance on IR&CSA) [33]. Nevertheless, in order to report relative density, information on true density is needed. Furthermore, density often can refer to different values, including: bulk density, tap density, and skeletal density.

The measurement of these different values is done using different methods. In order to calculate volume specific surface area, information on **skeletal density** is needed, whereas information on bulk or tap density are inappropriate for the purposes of calculating volume specific surface area. Density is the quotient of the mass m and its volume V. The skeletal density is obtained when the volume measurement excludes measurement of void space between particles, and pore space within a particle. Skeletal density is usually measured using gas pycnometry (e.g. using ISO standard ISO 12154:2014). The current draft OECD Test Guideline on the measurement of surface area using the BET method provides further information on the appropriate measurement of density for the purpose of converting mass specific surface area to volume specific surface area.

3.1.4.3. Reporting in the dossier

When reporting information on individual nanoforms, registrants must report the following for each nanoform:

- the specific surface area of the nanoform (either by weight, volume, or both);
- the range of values for a single nanoform, reflecting batch to batch variability;
- a description of the method used to determine the surface area;
- when reporting volume specific surface area derived from BET measurements, the registrant must also submit information on the skeletal density that is necessary for determination of the volume specific surface area.

[7] According to the JRC Report [9] the nanomaterial must be solid material containing (or consisting of) particles.

4. Sets of 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.*

Thus, registrant(s) can identify and characterise nanoforms in the form of *"sets of similar nanoforms"*, subject to explicit conditions:

1) 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, for further information on what situations create different nanoforms).

2) A justification must be provided as to:

- Why the hazard assessment can be performed jointly, i.e. 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.

  It should be noted that this is the case for all the information provided according to Annex VII-X. The submitted information must be representative for each nanoform covered within the set. This includes information according to the new nano-specific endpoints like Annex VII point 7.14 bis Dustiness.

  The development of a set of nanoforms must not replace the development of a read-across approach between nanoforms. If a registrant can demonstrate that the hazard assessment is valid for several nanoforms based on a justification that applies generically to all the endpoints, they can create a set. However, when the registrant needs to rely on specific hypothesis for different endpoints, they have to report the nanoforms separately.

  Nevertheless, this does not necessarily mean that the registrant has to develop different data sets per nanoform. Instead, this can be addressed via read across between those nanoforms in accordance with Section 1.5 of Annex XI of REACH.

  The justification should always be accompanied by the data supporting it, and it may include proposals for the testing to support the hypothesis.

- Why the exposure and risk assessment can also be performed jointly for the set of nanoforms. In practice if the same hazard profile is applicable and a common conclusion on exposure assessment can be reached for the set, the risk assessment should also cover the set.

  The assessment of the hazards of nanoforms and the evaluation of the exposure serve as a basis for the risk assessment. The *developments mentioned below focus on the*

conditions under which the hazard assessment of the nanoforms in a set can be performed jointly.

Regarding the exposure assessment for the nanoforms or the sets of nanoforms: it is not required to create different nanoforms or sets only because the individual nanoforms have different uses. However, the set of nanoforms needs to detail the complete list of uses (and corresponding contributing activities) for all the individual nanoforms. Where relevant, the identified uses must be assessed and demonstrated to be safe. Such assessment must be relevant to all nanoforms, even if in practice a specific nanoform does not have a specific use (yet).

In order to facilitate the building of a set of nanoforms this guidance provides for each parameter principles clarifying the boundaries of a set of nanoforms. These principles explain when differences in the characterisation parameters in 2.4.2 to 2.4.5 in Annex VI may trigger the need to build a different set of nanoforms. The guidance also provides advice on the information to be submitted for justifying each set of nanoforms.

In the same way as for the identification of nanoforms (see section 3), the explanations on how to build a set of nanoforms are given per individual parameter, for clarity. However, when building a set, variability of all the characterisation parameters in 2.4.2 to 2.4.5 in Annex VI needs to be taken into account together with chemical composition.

Where the registrant constructs a set of nanoforms, the information reported must be applicable to the entire set. The principles of reporting defined in section 3 for individual nanoforms should be applied to report the characteristics of the nanoforms defining the boundaries of the set.

A nanoform can only belong to one set of nanoforms.

4.1. Particle size distribution and number fraction of constituent particles

4.1.1. Principles on the boundaries of sets of nanoforms

If existing scientific knowledge shows that for a certain substance there is a threshold particle size within the range 1-100 nm, which induces a specific effect for particles with size below/above that size, the registrant must define two different sets of nanoforms. If a certain nanoform contains particles with size below and above the threshold, the registrant may consider, upon justification, where to allocate the nanoform (e.g. including such a nanoform to a set based on worst-case scenario considerations). The threshold size is substance dependent and the impact on some properties can be more or less significant in each specific case. The particle size dependent threshold effect may be related to quantum confinement or to other properties affecting hazard (e.g. rigidity). The registrant must assess based on available information whether a threshold effect exists for the nanoforms included in the set. The Registrant must include this assessment in the justification.

Given the impact of the particle size on the properties of the substance, including the hazard of the substance, the registrant must take into account the impact of particle size distribution when constructing any sets. The registrant must justify why the particle size distribution of the different nanoforms included within the set does not change the hazard assessment, exposure assessment, and risk assessment of those nanoforms. The registrant's justification must address as a minimum the following:

- How does the particle size of the different nanoforms impact the dissolution rate and solubility of the set members?

- How does the particle size of the different nanoforms within the set impact the toxicokinetic behaviour as well as fate and (bio)availability of the set members?
- How does the particle size of the different nanoforms within the set impact the (eco)toxicity of the set members? Is there a direct relationship between the particle size and the (eco)toxicity?

4.1.2. Reporting in the dossier

As a minimum and in accordance with the requirements under section 3.1.1.2.1 for a single nanoform, a registrant reporting a set of nanoforms must provide the particle size distribution and the number fraction of constituent particles of the nanoforms included in the set with the smallest and largest d_{10}, d_{50}, and d_{90} value. The registrant must also report the boundaries for the set of nanoforms defined by smallest d_{10} and largest d_{90} value.

The registrant must submit a justification demonstrating that the hazards of the nanoforms covered by the set can be assessed jointly. Based on the principles on the boundaries described above, a justification must be submitted to demonstrate that the hazards of the nanoforms covered by the set can be assessed jointly. The registrant must also submit the adequate and reliable scientific evidence on which this justification is based.

4.2. Shape, aspect ratio and other morphological characterisation

4.2.1. Shape, including aspect ratio and information on assembly structure

4.2.1.1. Principles on the boundaries of sets of nanoforms

Particle shape can influence the mechanism of interaction of a nanoform with a cell (e.g. shape is an important factor that determines internalisation of nanoparticles) [34] and may affect the kinetics of deposition and absorption in the body [35]. For example, particle shape can influence the deposition of nanomaterials in the lungs upon inhalation [35].

Given the impact that the shape of the particles can have on the (eco)toxicological properties of nanoforms, differences in the shape of the particles must always be considered when building sets of nanoforms. If nanoforms of the registered substance fall under different shape categories (spheroidal, elongated, platelets or multimodal shapes as defined in section 3.1.2.1.3), those nanoforms must a priori not be part of a same set of nanoforms. The registrant may consider including nanoforms in a same set (e.g. spheroidal and elongated), if no significant differences in aspect ratio exist (e.g. nanoforms with aspect ratio of 3:1 and nanoform with aspect ratio of 4:1), however a justification must be provided.

Spheroidal nanoforms

Nanoforms with particles with different shapes all falling into the category of spheroidal particles (e.g. spherical and pyramidal nanoforms) may or may not have a different hazard profile. Separate reporting in different sets may be necessary if scientific publications / (eco)toxicological tests indicate that the difference in the shape of the particles leads to a difference in the (eco)toxicological profile. Therefore, if the registrant decides to report in a same set nanoforms with particles with different shapes all falling into the category of spheroidal particles, the registrant must justify why the differences in shape do not affect the hazard profile of the different nanoforms. For instance, this can be demonstrated by providing supporting literature demonstrating that the difference in shape of a nanoform does not affect the hazard profile or following criteria from available frameworks on grouping, see for instance the framework developed by ECETOC applicable for inhalation toxicity [36].

Platelets

The specific shape (plates, discs, etc.) and the thickness and lateral dimensions of the platelets can vary. The registrant must justify how these parameters will affect the (eco)toxicological profile of the different nanoforms. When different nanoforms are reported together, the registrant must justify why the variations do not affect the hazard profile.

Elongated nanoforms

Nanoforms with particles with different shapes (e.g. nanotubes, nanowires, nanorods) all falling into the category of elongated particles are likely to have different properties and a different hazard profile. As a principle, they should not be included in the same set.

Moreover, for elongated particles and especially for high aspect ratio particles, different parameters can have an influence on their (eco)toxicity. The registrant must first consider the variation in width (i.e. cross sectional diameter).

The width, together with length, is considered as a critical parameter that can be used as an indication of the rigidity of these nanoforms. Consideration on rigidity is therefore linked to the requirement on particle size distribution in point 2.4.2 of Annex VI of REACH and the registrant must justify how the variation in width of the particles of the different forms will affect the rigidity of the particles and consequently the (eco)toxicological profile of the different nanoforms. When there is a variability in the width of the particles constituting the nanoforms covered by the set, the registrant must provide a justification demonstrating that this variation does not affect the joint hazard assessment of these nanoforms.

The registrant must also take into account variations in the length and aspect ratio of elongated particles when building the set of nanoforms. When there is a variation in length and/or aspect ratio of the particles of the nanoforms covered by the set, the registrant must provide a justification demonstrating that this variation does not affect the joint hazard assessment of these nanoforms.

Therefore, the registrant needs to decide whether to create additional sets based on these additional parameters and justify the choices made in the registration dossier. In cases where threshold values in length are known (e.g. from literature or from tests) to trigger a different behaviour, e.g. are linked to the carcinogenic potential typical of fibre-like materials, the registrant must take these thresholds into account when a set is created. This means that if a different hazard is foreseen when length is higher than e.g. 15 µm, and some nanoforms have length above and others below 15 µm, two different sets must be created. If a certain nanoform contains particles having values of length below and above the threshold, the registrant may consider, upon justification, where to allocate the nanoform (e.g. including such a nanoform to a set based on worst-case scenario considerations).

Multimodal shapes

In the situation that a nanoform consists of particles with shapes that fall into different shape categories (e.g. of spheres and wires), as a principle this nanoform should be reported on its own (i.e. a new set should be defined). The registrant may still consider including such a nanoform in a set where the particles of the other nanoforms fall into one of these shape categories, but this decision must be justified, based on the grounds identified above for the respective shapes.

For instance, it may be known that a form with high aspect ratio particles has a higher (eco)toxicity than the nanoform with particles with other shapes, and therefore the nanoform with particles with other shapes can be included in a set of nanoforms with high aspect ratio particles by justification via worst-case scenario. It must be highlighted that the justification

shall cover all different endpoints, i.e. the registrant shall be able to justify that the specific shape has a lower (eco)toxicity for all endpoints.

4.2.1.2. Reporting in the dossier

When reporting a set of nanoforms, the registrant must always provide:

- the shape category of the set (e.g. spheroidal);
- a list of the specific shapes covered under a certain set (e.g. spherical, cubic, pyramidal);
- the range of number of walls or of layers for particles with an assembly structure (e.g. nanotubes, nano-onions). The range must reflect the variation between the nanoforms that are part of the set;
- an electron microscopy image for each nanoform with a different shape included within the set (i.e. one for the spherical, one for cubic) or for each nanoform with a different combination of different shapes. This practically means that if a set includes two nanoforms consisting of 100% spherical particles, two nanoforms consisting of 100% cubic particles and three nanoforms with different concentrations of both cubic and spherical particles, three electron microscopy images must be provided in total (one for the 100% spherical, one for the 100% cubic and a representative image for the nanoforms with the spherical/cubic combination of shapes).

In addition to the above:

For a set of **elongated nanoforms** the registrant must provide:

- the range of the aspect ratios of the different nanoforms covered under the set;
- the maximum and minimum length of the nanoforms that are part of the set;
- where relevant (e.g. when rigidity is a part of the justification), an indication of the rigidity of the nanoforms that are part of the set (e.g. based on the cross sectional diameters/widths).

For a set of nanoforms consisting of **platelets** the registrant must provide:

- the range of the aspect ratios of the different nanoforms covered under the set;
- the boundaries of the set for what concern the lateral dimensions (i.e. the two orthogonal dimensions, other than thickness): the maximum and minimum value of the lateral dimensions of the nanoforms that are part of the set;
- where relevant (e.g. when rigidity is a part of the justification), an indication of the rigidity of the nanoforms that are part of the set.

For **a set including nanoforms that consist of particles with different shapes that fall under a same shape category** the registrant must provide:

- the shape category of the nanoforms included in the set (e.g. spheroidal);
- the range (as number based %) of the shapes covered under the set (e.g. the set includes nanoforms consisting of 20-40% spherical and 80-60% cubic particles);
- reporting of particle size ranges according to the shape categories.

For **a set including nanoforms that consist of particles with different shapes that fall under different shape categories (multimodal shapes)** the registrant must provide:

- the shape categories of the different nanoforms that are part of the set;
- the range (as number based %) of the shapes covered under the set (e.g. the set includes nanoforms consisting of 20-40% spherical and 80-60% plates);
- reporting of particle size ranges according to the shape categories.

Based on the principles on the boundaries described above, a justification must be submitted to demonstrate that the hazards of the nanoforms covered by the set can be assessed jointly. The registrant must also submit the adequate and reliable scientific evidence on which this justification is based.

4.2.2. Crystallinity

4.2.2.1. Principles on the boundaries of sets of nanoforms

Crystallinity may affect the behaviour and (eco)toxicity of nanoforms. Amorphous and crystalline forms (e.g. amorphous versus crystalline silica) can have a different hazard profile and the same may apply to different crystal structures of the same substance.

Therefore, fully amorphous and fully crystalline nanoforms must a priori not be part of a same set of nanoforms.

In the same way, nanoforms with different crystal structure (e.g. a rutile nanoform and an anatase nanoform) must a priori not be part of a same set of nanoforms.

Upon justification, nanoforms with different crystalline structure could be grouped in the same set. For instance, when there is existing scientific knowledge showing no difference in hazard for two structures or where the nanoforms are readily soluble in relevant biological and environmental media.

In relation to nanoforms of mixed crystallinity, the following situations are possible:

1. Nanoform that consists of amorphous particles and particles with one precise crystal structure (e.g. 30% (w/w) amorphous TiO_2 and 70% (w/w) rutile)

2. Nanoform that consists of amorphous particles and particles with more than one crystal structure (e.g. 20% (w/w) amorphous TiO_2, 30% (w/w) rutile, 50% (w/w) anatase)

3. Nanoform that consists of particles with two or more precise crystal structures (e.g. 70% (w/w) rutile, 30% (w/w) anatase)

The number of combinations increases rapidly when more than two crystalline forms are possible.

All these different nanoforms must be reported separately from nanoforms that are uniquely crystalline or uniquely amorphous, unless one crystal structure is widely known to be more toxic and therefore considerations based on worst-case scenarios may be possible when creating the sets.

It must be highlighted that information on crystallinity obtained by XRD analysis performed on the nanoform(s) will also be used in combination with other techniques (e.g. ICP, TGA, etc.) to derive the complete chemical composition of the nanoform(s) (concentration ranges of the constituents/impurities/additives).

4.2.2.2. Reporting in the dossier

When reporting in the dossier information on the crystallinity of a set of nanoforms, the registrant must specifically provide:

For a **set including amorphous nanoforms**:

- a representative analysis (e.g. XRD) proving the amorphous nature of the nanoform(s)

covered within the set;
- a description of the analytical method(s) used;
- a clear indication that the set includes only amorphous nanoforms.

For a **set including crystalline nanoforms with precise crystal structure**:

- the name of the specific crystal structure covered (e.g. rutile);
- a typical diffraction pattern;
- a description of the analytical method(s) used;
- a clear indication that the set includes nanoforms made of particles with only specific crystal structure (e.g. rutile).

For a **set including crystalline nanoforms where the individual nanoforms** consist of particles **with more than one different crystal structure**:

- the names and the ranges (as w/w percentage) of different crystal structures covered by the set (e.g. 20-40% (w/w) of crystal structure 1, 80-60% (w/w) of crystal structure 2);
- typical diffraction patterns recorded on nanoforms representing the boundaries of the set;
- a description of the analytical method(s) used.

For a set including **partially crystalline nanoforms**:

- the range(s) (as w/w percentage) and the name of different crystal structure(s) and the range of amorphous fraction (e.g. 20-40% (w/w) rutile, 60-10% (w/w) anatase, 20-50% (w/w) amorphous titanium dioxide) covered by the set;
- a typical diffraction pattern recorded on nanoforms representing the boundaries of the set;
- a description of the analytical method(s) used.

Based on the principles on the boundaries described above, a justification must be submitted to demonstrate that the hazards of the nanoforms covered by the set can be assessed jointly. The registrant must also submit the adequate and reliable scientific evidence on which this justification is based.

4.3. Surface functionalisation or treatment

4.3.1. Principles on the boundaries of sets of nanoforms

Due to the high specific surface area of nanomaterials, the surface chemistry of a nanoform can have a profound influence on its properties ([37], [38], [39]).

Where both surface-treated and non-surface-treated nanoforms are covered by a registration, surface treated and non-surface-treated nanoforms must a priori not be included in one unique set of nanoforms. The registrant must rather create, as a minimum, two sets of nanoforms; one for the non-surface-treated nanoforms and one for the surface treated nanoforms (assuming other parameters remain the same).

Any difference in the surface treating agent(s) applied and/or in reaction conditions is likely to result in a different surface chemistry of the resulting nanoform. Consequently, the resulting different surface chemistries can result in a nanoform with a different hazard profile.

Accordingly, in principle, when a nanoform of a substance is subject to different surface treatments, each different surface treatment must result in the reporting of a separate nanoform in section 1.2 of the registration dossier.

Alternatively, the registrant may decide to group different surface treated nanoforms under one set of similar nanoforms, but only if each of the following conditions is met:

1) The surface treating agents used are chemically similar (common functional groups, similar alkyl chains, etc.)

2) The surface chemistry resulting from the treatment is similar in terms of the specific functionalities formed at the surface of the particles and the overall composition of the particle surface.

3) No significant variability is expected in the percentage of coverage of the particle surface.

4) There is no difference in the (eco)toxicity of the surface treating agent used and surface functionalisation/treatment does not alter toxicokinetic behaviour

The registrant must explain and justify in the dossier how all the points mentioned above are met for the nanoforms with different surface treatments that are part of the set.

Where sequential surface treatments are applied and multiple layers are formed, the different order of the layers must be taken into account, and not only the nature/composition of the most external layer, when/if a set of nanoforms is built.

4.3.2. Reporting in the dossier

When reporting information on surface chemistry for a set of nanoforms, a registrant must provide:

- a list of all the agents used for surface treatment of all the nanoforms covered under a set (i.e. list of IUPAC names, CAS and EC numbers);
- a description of the common type of reaction/treatment applied and of the functionalities introduced by the chemical treatment(s). Schematics may be provided to visually describe the functionalisation/treatment of the nanoform(s) included in the set;
- a description of the functionalities introduced by the treatment(s) (e.g. carboxyl, amino, hydroxyl groups);
- an indication of the upper and lower percentage of coverage of the particle's surface for the nanoforms that are part of the set and the relative weight-by-weight contribution and surface treating agent linked to those;
- representative analytical data for determining the overall composition of the nanoform(s) that are part of the set, including their surface treatment and a description of the analytical methods used.

Based on the principles on the boundaries described above, a justification must be submitted to demonstrate that the hazards of the nanoforms covered by the set can be assessed jointly. The registrant must also submit the adequate and reliable scientific evidence on which this justification is based.

4.4. Surface area (specific surface area by volume, specific surface area by mass or both) for sets of nanoforms

4.4.1. Principles on the boundaries of sets of nanoforms

The surface area of nanoforms may have an influence on the hazard assessment of a particular nanoform. Higher surface area materials, all other things being equal, exhibit higher reactivity

on the surface of the nanoform[8]. This in turn may impact properties such as dissolution kinetics, as well as toxicity and ecotoxicity.

Given the impact of the surface area on other properties of the substance, including the hazard of the substance, the registrant must take into account the impact of surface area when constructing any sets. The registrant must justify why the range of specific surface areas of the different nanoforms included within the set does not change the hazard assessment, exposure assessment, and risk assessment of those nanoforms. The registrant's justification must address as a minimum the following:

- How does the surface area of the different nanoforms impact the dissolution rate and solubility of the set members?
- How does the surface area of the different nanoforms within the set impact the toxicokinetic behaviour as well as fate and (bio)availability of the set members?
- How does the surface area of the different nanoforms within the set impact the (eco)toxicity of the set members? Is there a direct relationship between the surface area and the (eco)toxicity?

Where needed for the purposes of the hazard assessment, registrants should build separate sets for high surface area and low surface area nanoforms. This guidance does not provide any specific numerical boundaries for the ranges of surface area within a particular set. This is because the guidance recognises that the boundaries will be dependent on the material in question.

4.4.2. Reporting in the dossier

Given that a set of nanoforms may cover nanoforms with different specific surface areas, and given that the boundaries of a particular set must be clearly specified, registrants who construct a set of nanoforms must report the range of specific surface areas covered by the particular set (**the minimum and maximum** specific surface areas covered). Where the registrant reports the volume specific surface area range of the set, derived from BET measurements, they should also provide information on the skeletal density of the substance under the section 1.2 of IUCLID. Information on the method(s) used to measure the (volume) specific surface area must also be provided.

Based on the principles on the boundaries described above, a justification must be submitted to demonstrate that the hazards of the nanoforms covered by the set can be assessed jointly. The registrant must also submit the adequate and reliable scientific evidence on which this justification is based.

[8] The reactivity can be normalised per unit surface area. The reactivity per unit surface area may remain constant as the surface area is increased, although the total reactivity will increase.

5. The registration process

The registration process for a substance covering nanoforms is to a large extent similar to that of any other forms of a substance and is described in the Guidance on Registration [1]. This section focusses on explaining the main specificities related to the registration of substances when nanoforms are covered. An overview of the nano-specific steps in the registration process are given in section 5.5.

Practical instructions for the preparation of a registration dossier covering nanoforms are available in the manuals *How to prepare registration and PPORD dossiers* and *How to prepare registration dossiers covering nanoforms* accessible at: http://echa.europa.eu/manuals.

5.1. Information requirements

Under REACH, manufacturers and importers have the responsibility to generate data and obtain information on the substances they manufacture or import; to use this information to assess the risks arising from the manufacture and uses of the substances; and to ensure that the risks that the substances may present are controlled. They must then document all of the above information in the registration dossier and submit it to ECHA.

The amendment of the REACH Annexes to address nanoforms of substances establishes that every manufacturer or importer of nanoforms of a substance must report specifically each of their nanoforms in the registration dossier of the corresponding substance.

Therefore, as per REACH Annex VI, 2.4, each registrant has the obligation to characterise each nanoform of the substance they manufacture/import and report this information in their registration dossier.

Furthermore, for each tonnage band, REACH defines the minimum information that the registrant must provide on the intrinsic properties of their substance. These are explained in section 4.1.1 of the Guidance on Registration [1]. The total volume of all forms of the manufactured or imported substance, including all nanoforms and non-nanoforms, determines the applicable information requirements for the registered substance. The amendment of the REACH Annexes introduced certain changes to the information requirements for intrinsic properties when a nanoform of a substance is covered:

- REACH Annexes VII-XI include certain specific information requirements for nanoforms (e.g. dustiness) and modifications to the existing ones in the form of adaptation possibilities.
- the information required by Articles 10 and 12 of REACH (or Articles 17 and 18 for isolated intermediates) and related Annexes must be provided specifically for each of the nanoforms or set of nanoforms. In other words, specific information must be provided for each nanoform or set of nanoforms to fulfil each information requirement at the tonnage band of registration,

- Information on uses: information on the manufacture and uses of each nanoform of the substance is to be provided as part of a registration dossier. The dossier must show clearly which uses correspond to each specific nanoform or set of nanoforms.
  A registration may cover a 'supported downstream use' corresponding to the generation of a nanoform from a non-nanoform of the substance or to the modification of a nanoform into a different nanoform. In this case, the description of the 'supported downstream use' in the registration dossier must include the characterisation information set out in section 2.4 of Annex VI of the nanoform resulting from that use, as well as the (eco)toxicity information required for this nanoform, as indicated above.

For further information about the process for information gathering and data generation for nanomaterials, see the Appendices to the *Guidance on information requirements and chemical safety assessment* available at: https://echa.europa.eu/guidance-documents/guidance-on-reach.

5.1.1. Fulfilling information requirements for single nanoforms

As noted in section 5.1, the information requirements applicable to the substance must be fulfilled separately for each specific nanoform or set of nanoforms. As a consequence, for registrations covering several nanoforms, for every nanoform, and for every information requirement as per Annex VII-X, the registrant must submit either:

(i) a study performed on the nanoforms concerned; or
(ii) a study performed on another form of the substance accompanied by an endpoint-specific justification as to why this information is adequate for assessing the nanoform concerned; or
(iii) a relevant adaptation as foreseen by Annex XI of REACH or Column 2 of the relevant Annex VII-X; or
(iv) a testing proposal for a study performed on the nanoform concerned.

Registrants must provide clear identification and characterisation of the nanoform(s) used in the studies to fulfil the information requirements. When the available information on the identification and characterisation of the nanoform(s) tested is not adequate to demonstrate that the study relates to the nanoform concerned, additional testing of that nanoform must be performed or must be proposed (in case of studies involving vertebrate animals required under Annex IX and X).

When data generated on a non-nanoform of the substance are used to fulfil an information requirement on a nanoform of the substance, a justification for this read-across must always be provided in accordance with section 1.5 of Annex XI. Similarly, the use of data generated on one nanoform of the substance to fulfil an information requirement on another nanoform of the substance, must always be justified in accordance with section 1.5 of Annex XI. If additional testing is needed, non-animal methods (in silico, in chemico, and in vitro) must be considered first to fulfil the requirements. Further information on the use of read-across for nanomaterials can be found under ECHA Guidance Appendix R.6-1: Recommendations for nanomaterials applicable to the Guidance on QSARs and Grouping.

5.1.2. Fulfilling information requirements for sets of nanoforms

As explained in section 4 of this document, by derogation to the obligation to submit characterisation and hazard information as well as information on exposure and risk assessment on each single nanoform, registrants may register individual nanoforms via a set of nanoforms, if two conditions are fulfilled:

(i) the registrant(s) specify/ies clearly defined boundaries for the set of nanoforms in terms of characterisation parameters of the nanoforms, which are part of the set;
(ii) the registrant(s) justify/ies that the hazard, exposure and risk assessment of the nanoforms can be performed jointly.

When individual nanoforms are registered through a set of nanoforms, the requirements of Annex VII-X can be fulfilled by submitting a single hazard dataset covering all the nanoforms covered by the set. Similarly, the requirement to perform a chemical safety assessment for the nanoforms covered by the set can be addressed by a CSA of the set of nanoforms.

5.1.2.1. Clear boundaries of the sets of nanoforms

As a set covers several nanoforms, the characterisation parameters listed in section 2.4 of Annex VI must be described in the form of a range of variation (e.g. range of particle size distribution) or as an information on one or several features (e.g. description of one or several shapes). Information must be reported on all the characterisation parameters listed in section 2.4 of Annex VI for each set of nanoforms. This information must be reported in the registration dossier as a boundary composition.

5.1.2.2. Justification for sets of nanoforms

As noted above, each set of nanoforms must be based on a specific justification demonstrating that the hazard assessment, exposure assessment and risk assessment of the nanoforms in that set can be performed jointly. The justification must apply to all the applicable information requirements and must always be substantiated by supporting data. More specifically, the justification must fulfil the conditions below:

- The justification must address separately all the characterisers listed in section 2.4 of Annex VI.
- The justification must be substantiated by scientific evidence demonstrating that the information requirements of Annexes VII-X (physicochemical, environmental fate, ecotoxicity and toxicity properties) of nanoforms that are within the boundaries of the set of nanoforms can be assessed jointly. For each characteriser, the justification must summarise the supporting data.
- Each scientific evidence relied upon in the justification must be submitted in the form of a (robust) study summary.
- For each characteriser, the justification must explain how the scientific evidence demonstrates that all the nanoforms in the set can be assessed jointly. This explanation must include a demonstration that the nanoforms used to generate the supporting data are representative of all the nanoforms included in the boundaries of the set.

5.1.2.3. Annex VII-X data for sets of nanoforms

Once a set of nanoforms has been established and scientifically justified, the applicable Annex VII-X information must be generated and provided for the set of nanoforms. The information to be submitted for each information requirement for a set of nanoforms is the same as described in section 5.1.1.

The registration of several nanoforms via a set of similar nanoforms allows for the submission of one set of data for fulfilling all the information requirements of Annexes VII-X of all the nanoforms in the set. Therefore, any study submitted must be performed on one of the nanoforms covered by the set of nanoforms. Registrants must provide clear identification and full characterisation of the nanoform(s) used in the study.

When a study performed on a non-nanoform of the substance or on a nanoform not covered by the set are used to fulfil an information requirement applicable to the set of nanoforms, a justification for this read-across must always be provided in accordance with section 1.5 of Annex XI. Further information on the use of read-across for nanomaterials can be found under ECHA Guidance Appendix R.6-1: Recommendations for nanomaterials applicable to the Guidance on QSARs and Grouping.

5.2. Joint submission of data

Regardless of whether registrants choose to submit information for individual nanoforms, sets of nanoforms, or a combination of both, the REACH regulation requires that all registrants of

the same substance submit their registrations within the same joint submission, and co-operate on their registration strategy to avoid unnecessary duplication of testing and to reduce costs.

The information required by Annex VI, including the characterisation of nanoforms, must always be submitted separately by each registrant in their IUCLID dossier. The Annex VII-X information can be submitted jointly in the lead registrant dossier on behalf of the member registrants. Alternatively, this information can be submitted separately by each registrant via the opt-out mechanism (see also section 5.2.3 of this guidance). In any case, it must be clear which information pertains to which nanoform or set of nanoforms.

The next subsections cover the specificities of registration of substances covering nanoforms within a joint submission, when this is done as single nanoforms and via sets of nanoforms.

5.2.1. Registration of single nanoforms within a joint submission

When registering a single nanoform, there must not be any variability of the Annex VI characterisation parameters for this nanoform, except the batch-to-batch variability of the nanoform resulting from a specific manufacturing process, as defined in section 3.1 of this document. This means that for example two nanoforms manufactured by two different manufacturing processes cannot be considered as the same nanoform (see also section 3.1 on the definition of a nanoform).

As described in Section 3, different manufacturing processes may result in almost identical characterisers. These different nanoforms can be registered as part of a set of nanoforms. In such cases, the creation of a set of nanoforms will be simple as the variation of the different characterisers will be small (see section 4). The smaller the variation the easier the justification to cover different nanoforms in the same set.

The registrant(s) can consider covering all these nanoforms under one or several sets of nanoforms, if they fulfil the conditions described in section 5.1.2. above. If not, the information requirements need to be fulfilled separately for each nanoform of the substance.

5.2.2. Registration of sets of nanoforms within a joint submission

This section provides an overview of how to define sets of nanoforms within a joint submission, and what are the reporting obligations of the co-registrants. Detailed information on how to

carry out this reporting in IUCLID is provided in the relevant IUCLID manual. Figure 4 provides an overview of the process to identify nanoforms and define sets of nanoforms.

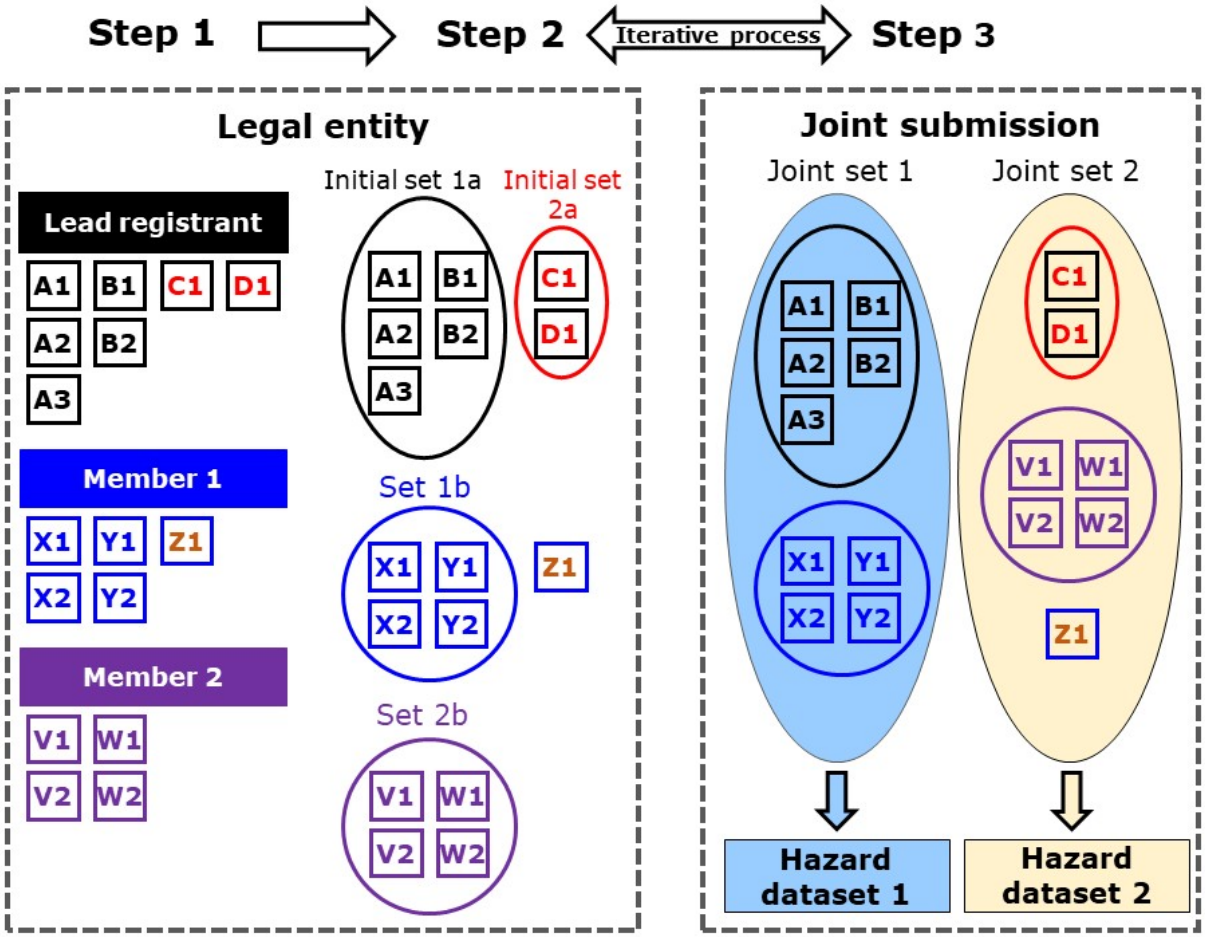

Figure 4: A schematic overview of the steps to identify nanoforms, define the initial sets at the level of each legal entity and at the level of the joint submission (boundary compositions) and ultimately submit the dataset(s) (REACH Annex VII-XI data).
In Figure 4, each box with letter-number combination represents a specific nanoform. The nanoforms with same colour of letter-number combination are nanoforms for which the corresponding registrant considers that a joint hazard, exposure, and risk assessment can be justified. Black, red, blue, and purple ovals/circles represent the set of nanoforms as reported by each registrant in its dossier under Annex VI of REACH. The nanoform Z1 represents a single nanoform for which the corresponding registrant cannot justify a joint hazard, exposure, and risk assessment with the other nanoforms they manufacture or import.

Joint set 1 (oval with light blue background) represents the set of nanoforms agreed by various registrants for which a joint set of hazard information is submitted under Annex VII-X of REACH (the set of nanoforms described in the boundary composition), as well as exposure, and risk assessment. This boundary composition is defined for the purposes of linking full hazard dataset (Hazard dataset 1) to nanoforms A1, A2, A3, B1, B2, X1, X2, Y1 and Y2 (reported as Set 1a and 1b in the dossiers of the lead registrant and Member 1, respectively) and for developing a justification that the hazard assessment, exposure assessment and risk assessment of these nanoforms can be performed jointly. Same applies in analogy to Joint set 2 (oval with yellow background) and the Hazard dataset 2. The Hazard dataset 2 is applicable for nanoforms C1, D1, V1, V2, W1, W2 and Z1.

Step 1: Identification of each nanoform manufactured or imported
Each registrant (Member 1 and 2 and the lead registrant in Figure 4) must identify first the nanoforms (e.g. A1, A2, X1, V2, etc.) that they manufacture/import. The members should also discuss the inclusion of nanoforms generated in downstream uses that are jointly supported. Each box in Figure 4 represents a nanoform (see section 3).

Step 2: Reporting nanoforms under Annex VI of REACH
Each registrant must characterise under Annex VI of REACH the nanoforms they manufacture or imports. A registrant may create a set of nanoforms together when they consider that they can justify that the hazard, exposure, and risk assessment of these nanoforms can be done jointly. For example, in Figure 4, the lead registrant reports two groups of nanoforms for which they consider the hazard, exposure and risk assessment of these nanoforms can be done jointly. Member 1 and Member 2 reported one group of nanoforms for which they consider the hazard, exposure, and risk assessment of these nanoforms can be done jointly. Member 1 also considered that they have a separate nanoform Z1.

Step 3: Joint submission of hazard information under Annex VII-X of REACH
In this specific case, the co-registrants agreed that their individual nanoforms reported under Annex VI can be joined in one or more sets of nanoforms. This means that, for each set of nanoforms within the joint submission, they considered that the hazard, exposure, and risk assessment of the nanoforms covered could be done jointly. The registrants must ensure that each set of nanoforms fulfils the conditions set out in section 5.1.2 above.

In each boundary composition of the respective set of nanoforms, the lead registrant will provide:

- a clear description of the boundary of the set of nanoforms, as described in section 5.1.2.1 above;
- the justification why the hazard assessment, exposure assessment and risk assessment of all the nanoforms in the set can be performed jointly, as described in section 5.1.2.1 above.

Finally, for each set of nanoforms, the corresponding Annex VII-X information as well as exposure, and risk assessment must be provided by the lead registrant (in Figure 4 Hazard dataset 1 for the Joint set 1 and Hazard dataset 2 for the Joint set 2), in such a manner that it is clear which information pertains to which set of nanoforms.

Each co-registrant must report in their registration dossier the set(s) of nanoforms they rely on for fulfilling the hazard information requirements under Annex VII-X of REACH as well as exposure, and risk assessment. Each co-registrant must link their nanoforms reported under Annex VI to the corresponding hazard information submitted for the corresponding set of nanoforms under Annex VII-X. This link must be made by referring to the boundary composition of the corresponding set of nanoforms reported in the lead registrant dossier.

5.2.3. Conditions for opting out from the jointly submitted data

As described in the Guidance on Registration [1], the aim of the one-substance-one-registration principle is the submission of one set of Annex VII-X information per substance. However, a registrant may submit part, or all the data of the registration dossier separately via the opt-out mechanism when at least one of the conditions listed in Article 11(3) of REACH are met. This general principle also applies for the joint submission of data for substances covering nanoforms. However, special considerations apply when using the concept of sets of nanoforms (Section 5.2.3.2)

However, unlike for non-nanoforms of a substance, when nanoforms are covered by the registration, the registration dossier must contain information specific to each nanoform (or set

of nanoforms) for every applicable information requirement. This leads to certain specific scenarios that are explained below.

5.2.3.1. Registration of single nanoforms within a joint submission

When a nanoform is registered as an individual nanoform, it is expected to pertain to the manufacturing/importing activity of a particular registrant, and as such, have its own specific Annex VII-X information (see section 5.2.1). The Annex VII-X information for this nanoform can only be used to cover the information requirements of another nanoform or a set of nanoforms if this is scientifically justified in the dossier.

In this case where a nanoform is registered as a single nanoform, and this information is only relevant to only one of the co-registrants, registrants need to decide how to submit the Annex VII-X information for this particular nanoform. The registrants must be decided whether this particular nanoform will be covered by the jointly submitted information in the lead registrant dossier despite only being relevant for one of the co-registrants; or whether the co-registrant in question will be responsible for submitting all the information for this nanoform separately, via the opt-out mechanism. In case the opt-out mechanism is used, the information to be submitted separately includes all the Annex VII-X information corresponding to the nanoform at the registrant's tonnage band, as well as the resulting classification and labelling, hazard conclusions and safety assessment.

5.2.3.2. Registration of a set of nanoforms within a joint submission

When a nanoform is registered as a set of nanoforms, two possibilities exist: (i) the set of nanoforms is agreed at the level of the joint submission; (ii) the set of nanoforms is defined only by (a) specific co-registrant(s). Advice for these two circumstances is given below:

(i) The fundamental principle for registering a nanoform of a substance by using set of nanoforms is that the hazards, exposure and risk of all the nanoforms included in the set must be assessed jointly. Therefore, if the joint submission uses the approach to build a set of nanoforms, a registrant that relies on this set to register their nanoforms must refer to all the information submitted jointly by the lead registrant for the set of nanoforms in order to comply with the requirements of Annexes VII-X. A registrant relying on a set of nanoforms that is jointly submitted cannot submit separately any information required under Annexes VII-X.

(ii) If a particular registrant or registrants has defined a set of nanoforms on its own, it must be decided whether this particular set of nanoforms is already or will be covered by the jointly submitted information in the lead registrant dossier despite only being relevant for one or some of the co-registrants; or whether the relevant co-registrant(s) will be responsible for submitting all the information for this set of nanoforms separately, via the opt-out mechanism. In case the opt-out mechanism is used, the information to be submitted separately must include all the Annex VII-X information corresponding to the set of nanoforms at the registrant's tonnage band, the justification for building a set, as well as the resulting classification and labelling, hazard, exposure and risk assessment. If the set of nanoforms is relevant for more than one co-registrant and the corresponding information will be separately submitted by the relevant co-registrant(s), it is essential that the information submitted is identical.

Instructions on how to report information in different scenarios can be found in the manual 'How to prepare registration dossiers covering nanoforms' accessible at http://echa.europa.eu/manuals.

5.3. Confidentiality and electronic public access to registration information

ECHA has an obligation to make certain information from registration dossiers publicly available on its website, in accordance with Article 119 of REACH. For parts of this information, specified in Article 119(2), registrants can request confidentiality by submitting a justification as to why such publication is potentially harmful for the commercial interests of the registrant or any other party concerned, and by paying a fee.

Most of the characterisation information on nanoforms required under REACH Annex VI are considered to fall within the information available in safety data sheets. Such information can be requested as confidential according to Article 119(2)(d) of REACH.

A (robust) summary of a study performed on a nanomaterial can be claimed confidential in accordance with Article 119(2)(c) of REACH. Such a confidentiality claim does not cover all of the information provided in the study summary. The results of a study are always published, in accordance with Article 119(1)(d) and 119(1)(e) of REACH, even if the (robust) study summary is claimed confidential.

Further information on confidentiality requests and publication can be found in the manual ‘Dissemination and confidentiality requests under REACH Regulation’ accessible at http://echa.europa.eu/manuals.

5.4. Updating a registration covering nanoforms

In cases where a registration of a substance needs to be updated to cover additional nanoforms, the decision needs to be made whether the additional nanoforms are covered by the current registration dossier or whether (i) they are considered and registered as separate nanoforms; (ii) registered as a new set of nanoforms; or (iii) whether they can be included in an already existing set of nanoforms by modifying the already registered set of nanoforms.

If the nanoforms are added to the joint submission dossier as separate nanoforms or as a new set of nanoforms, they will not impact the already registered set of nanoforms. When reporting new nanoforms or sets of nanoforms, it should be noted that a nanoform can only belong to one set of similar nanoforms. Similarly, as for the existing set, they must be registered by including in the dossier the appropriate characterisation of the set, the set justification and the Annex VII-X information corresponding to the set.

If the nanoforms are added to the registration in an existing set of nanoforms, the registrant needs to ensure that the nanoforms fit within the clearly defined boundaries of characterisers of the existing set. If this is not the case, the registrant needs to analyse whether the boundaries of the set can be expanded without affecting the joint hazard assessment, exposure assessment and risk assessment of all the nanoforms covered by the set. This analysis must be reflected in the provided justification for the set.

If an existing joint set of nanoforms is modified to change the boundaries of the characterisers, the relevant co-registrant dossiers must be updated to reflect this change. Similarly, where information relevant to the set changes (e.g. new information affecting the information requirements of Annexes VII-X, information on uses, exposure, volumes, etc), the dossier must be updated to reflect this change in the relevant dossier.

5.5. Overview of main steps of registering substances covering nanoforms

In the following, the main steps of registering a substance covering nanoforms are

summarised. The process within step 2 is iterative, with the decisions on registering nanoforms as single nanoforms or sets of nanoforms, and the joint provision of Annex VII-X information closely interlinked.

Step 1
Each registrant identifies each specific nanoform they manufacture or import and the available data on the intrinsic properties of these nanoforms.

Step 2
After the identification of the nanoforms by each registrant, all co-registrants must discuss and agree on the registration strategy, and decide on:

(i) The approach to register the nanoforms of the registrants as single nanoforms or via sets of similar nanoforms, or a combination of these two.

(ii) Which nanoform or set of nanoforms will be covered by the joint submission, i.e. by jointly submitted Annexes VII-X data, and which nanoform or set of nanoforms will be submitted separately by the registrant concerned.

Registrants should consider issues related to sharing confidential business information when considering the registration strategy. The formation of sets of nanoforms, and the joint submission of Annex VII-X data will require sharing information on the characterisation of the nanoforms being registered, as well as the test material(s) used to fulfil any information requirements. Registrants should consider appropriate mechanisms (e.g. the use of a trustee) to avoid disclosure of confidential business information.

Step 3
The registrants agree on the data to be jointly submitted and the approach to generate data in the case of data gaps. The jointly submitted data can be representative for concern single nanoform(s) and/or set(s) of nanoforms.

Step 4
The lead registrant submits the joint submission dossier covering the nanoforms or sets of nanoforms agreed to be jointly submitted. For each nanoform or set of nanoforms to be covered by the joint submission, the lead registrant reports a separate boundary composition, which characterises the nanoform or set of nanoforms, as well as the Annex VI information for the lead registrant. For boundary compositions referring to sets of nanoforms, a justification must be included. The boundary composition must be clearly linked to the corresponding Annex VII-X information in the dossier.

Step 5
The co-registrants submit their registration dossiers. If they rely on jointly submitted information for all their nanoforms, they must only include in their registration dossier the characterisation of their nanoforms under Annex VI, as single nanoforms or sets of nanoforms. They must furthermore refer each of their nanoforms or sets of nanoforms to the corresponding boundary composition in the lead registration dossier, to establish the link to the Annex VII-X data, and in the case of a set of nanoforms, to the justification for the joint set of nanoforms.

If a co-registrant decides to submit separately information on any of the nanoforms of their substance, they must report this via the opt-out mechanism, as foreseen in Article 11(3) of REACH. In this case, the co-registrant must report in their dossier the boundary composition(s) characterising the nanoform or set of nanoform for which they submit separate Annex VII-X information.

References

[1] ECHA, “Guidance on registration,” [Online]. Available: http://echa.europa.eu/guidance-documents/guidance-on-reach.

[2] ECHA, “Guidance for identification and naming of substances under REACH and CLP,” [Online]. Available: http://echa.europa.eu/guidance-documents/guidance-on-reach.

[3] ECHA, “Appendix R.6-1: Recommendations for nanomaterials applicable to the Guidance on QSARs and Grouping,” [Online]. Available: https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

[4] ECHA, “Appendix R7-1 Recommendations for nanomaterials applicable to Chapter R7a Endpoint specific guidance,” [Online]. Available: http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

[5] ECHA, “Appendix R7-1 Recommendations for nanomaterials applicable to Chapter R7b Endpoint specific guidance,” [Online]. Available: http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

[6] ECHA, “Appendix R7-2 Recommendations for nanomaterials applicable to Chapter R7c Endpoint specific guidance,” [Online]. Available: http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

[7] ECHA, “ECHA Q&A nanoforms,” [Online]. Available: https://echa.europa.eu/support/qas-support/browse/-/qa/70Qx/view/scope/REACH/Nanoforms+of+substances.

[8] EUROPEAN COMMISSION, “Commission Recommendation of 18 October 2011 on the definition of nanomaterial,” [Online]. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32011H0696.

[9] H. Rauscher, G. Roebben, A. Mech, N. Gibson, V. Kestens, T. P. J. Linsinger and J. R. Sintes, “An overview of concepts and terms used in the European Commission's definition of nanomaterial. Publications Office of the European Union, Luxembourg, EUR 29647 EN, doi: 10.2760/459136, JRC113469,” JRC, 2019.

[10] A. e. a. Mech, “A. Mech et al., The NanoDefine Methods Manual. EUR 29876 EN, Publications Office of the European Union, Luxembourg, ISBN 978-92-76-11950-0, doi: 10.2760/79490, JRC117501,” 2020.

[11] C. Gaillard, A. Mech, W. Wohlleben, F. Babick, V. Hodoroaba, A. Ghanem, S. Weigel and H. Rauscher, “A technique-driven materials categorisation scheme to support regulatory identification of nanomaterials,” *Nanoscale Adv.,* vol. 1, no. 2, pp. 781-791, 2019.

[12] NanoDefine, “NanoDefiner e-tool,” [Online]. Available: http://www.nanodefine.eu/index.php/nanodefiner-e-tool.

[13] Joint Committee for Guides in Metrology, “JCGM 100:2008, GUM 1995 with minor corrections. Evaluation of measurement data — Guide to the expression of uncertainty in measurement,” 2008. [Online]. Available: https://www.bipm.org/utils/common/documents/jcgm/JCGM_100_2008_E.pdf. [Accessed June 2019].

[14] ISO, “ISO/TR 16196:2016: Nanotechnologies – Compilation and description of sample preparation and dosing methods for engineered and manufactured nanomaterials.”.

[15] OECD, “OECD/ENV/JM/MONO(2012)40. Guidance on sample preparation and dosimetry for the safety testing of manufactured nanomaterials.,” 2012.

[16] ISO, “ISO 14488:2007. Particulate materials – sampling and sample splitting for the determination of particulate properties.,” 2007.

[17] T. Uusimäki and P. Hallegot, “Protocols for preparation of products for microscopy methods,” [Online]. Available: http://www.nanodefine.eu/publications/reports/NanoDefine_TechnicalReport_D2.4.pdf.

[18] NIOSH, “NIOSH Manual of Analytical Methods. MEASUREMENT OF FIBERS,” [Online]. Available: https://www.cdc.gov/niosh/docs/2003-154/pdfs/chapter-l.pdf.

[19] ISO, “ISO/TS 80004-2 'Nanotechnologies —Vocabulary — Part 2: Nano-objects: nanoparticle, nanofibre and nanoplate',” [Online].

[20] ISO, “ISO/TS 80004-1: Nanotechnologies -- Vocabulary -- Part 1: Core terms,” [Online].

[21] C. Tran, S. Hankin, B. Ross, R. Aitken and A. Jones, “An outline scoping study to determine whether high aspect ratio nanoparticles (HARN) should raise the same concerns as do asbestos fibres. IOM,” 2008. [Online]. Available: http://nanotech.law.asu.edu/Documents/2009/07/Michael%20Vincent%20IOM%20(2008),%20An%20outline%20scoping%20study_182_2184.pdf.

[22] T. Ohno, K. Sarukawa, K. Tokieda and M. Matsumura, “Morphology of a TiO2 Photocatalyst (Degussa, P-25) Consisting of Anatase and Rutile Crystalline Phases,” *Journal of Catalysis,* vol. 203, no. 1, pp. 82-86, 2001.

[23] C. Giannini, M. Ladisa, D. Altamura, D. Siliqi, T. Sibillano and L. D. Caro, “X-ray Diffraction: A Powerful Technique for the Multiple-Length-Scale Structural Analysis of Nanomaterials,” *Crystals,* vol. 6, no. 8, 2016.

[24] L. M. Moreau, D.-H. Ha, H. Zhang, R. Hovden, D. A. Muller and a. R. D. Robinson, “Defining Crystalline/Amorphous Phases of Nanoparticles through X-ray Absorption Spectroscopy and X-ray Diffraction: The Case of Nickel Phosphide,” *Chemistry of Materials,* vol. 25, no. 12, pp. 2394-2403, 2013.

[25] D. L. Bish and S. Howard, “Quantitative phase analysis using the Rietveld method,” *Journal of Applied Crystallography,* vol. 21, pp. 86-91, 1988.

[26] “DaNa2.0 (Data and knowledge on Nanomaterials) Website.,” [Online]. Available: https://nanopartikel.info/en/nanoinfo/cross-cutting/993-coatings-cross-cutting-section. [Accessed June 2019].

[27] NANOREG Project, [Online]. Available: https://www.rivm.nl/en/about-rivm/mission-and-strategy/international-affairs/international-projects/nanoreg.

[28] ISO, “ISO/TR 14187:2011. Surface chemical analysis -- Characterization of nanostructured materials,” 2011. [Online].

[29] L. Rösch, P. John and R. Reitmeier, Silicon Compounds, Organic. Ullmann's Encyclopedia of Industrial Chemistry., 2000.

[30] W. Wohlleben, J. B. A. Mielke and e. al., “Reliable nanomaterial classification of powders using the volume-specific surface area method,” *J Nanopart Res,* vol. 19, no. 61, 2017.

[31] ISO, “ ISO 9277:2010. Determination of the specific surface area of solids by gas adsorption. BET method.,” [Online].

[32] M. Thommes, K. Kaneko, A. V. Neimark, J. P. Olivier, F. Rodriguez-Reinoso, J. Rouquerol and K. S. Sing, “Physiosorption of gases, with special reference to the evaluation of surface area and pore size distribution (IUPAC Technical Report),” *Pure Appl. Chem.,* vol. 87, no. 9-10, pp. 1051-1069, 2015.

[33] ECHA, “Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance,” [Online]. Available: http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment.

[34] K. Kettler, K. Veltman, D. van de Meent, A. van Wezel and A. Hendriks, “Cellular uptake of nanoparticles as determined by particle properties, experimental conditions, and cell type,” *Environmental Toxicology and Chemistry,* vol. 33, no. 3, pp. 481-492, 2014.

[35] G. Oberdörster, A. Maynard, K. Donaldson, V. Castranova, J. Fitzpatrick, K. Ausman, J. Carter, B. Karn, W. Kreyling, D. Lai, S. Olin, N. Monteiro-Riviere, D. Warheit and H. Yang, “Principles for characterizing the potential human health effects from exposure to nanomaterials: elements of a screening strategy,” *Particle and Fibre Toxicology,* vol. 2, no. 8, 2005.

[36] J. Arts, M. Hadi, M. Irfan, A. Keene, R. Kreiling, D. Lyon, M. Maier, K. Michel, T. Petry, U.

Sauer, D. Warheit, K. Wiench, W. Wohlleben and R. Landsiedel, “A decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping)”, *Regulatory Toxicology and Pharmacology,* vol. 71, no. 2, Supplement, pp. S1-S27, 2015.

[37] ECETOC, “Synthetic Amorphous Silica. ECETOC JACC REPORT No. 51,” [Online]. Available: http://www.ecetoc.org/publication/jacc-report-51-synthetic-amorphous-silica.

[38] US-EPA, “Fact Sheet: Nanoscale Materials,” [Online]. Available: https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca/fact-sheet-nanoscale-materials.

[39] ECHA, “Assessing human health and environmental hazards of nanomaterials-Best practice for REACH Registrants-Second GAARN meeting,” 2013. [Online]. Available: http://echa.europa.eu/documents/10162/5399565/best_practices_human_health_environment_nano_en.pdf.

EUROPEAN CHEMICALS AGENCY
ANNANKATU 18, P.O. BOX 400,
FI-00121 HELSINKI, FINLAND
ECHA.EUROPA.EU