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Definition of nanomaterials: analysis, challenges and controversies

Anses opinion
Collective expert appraisal report

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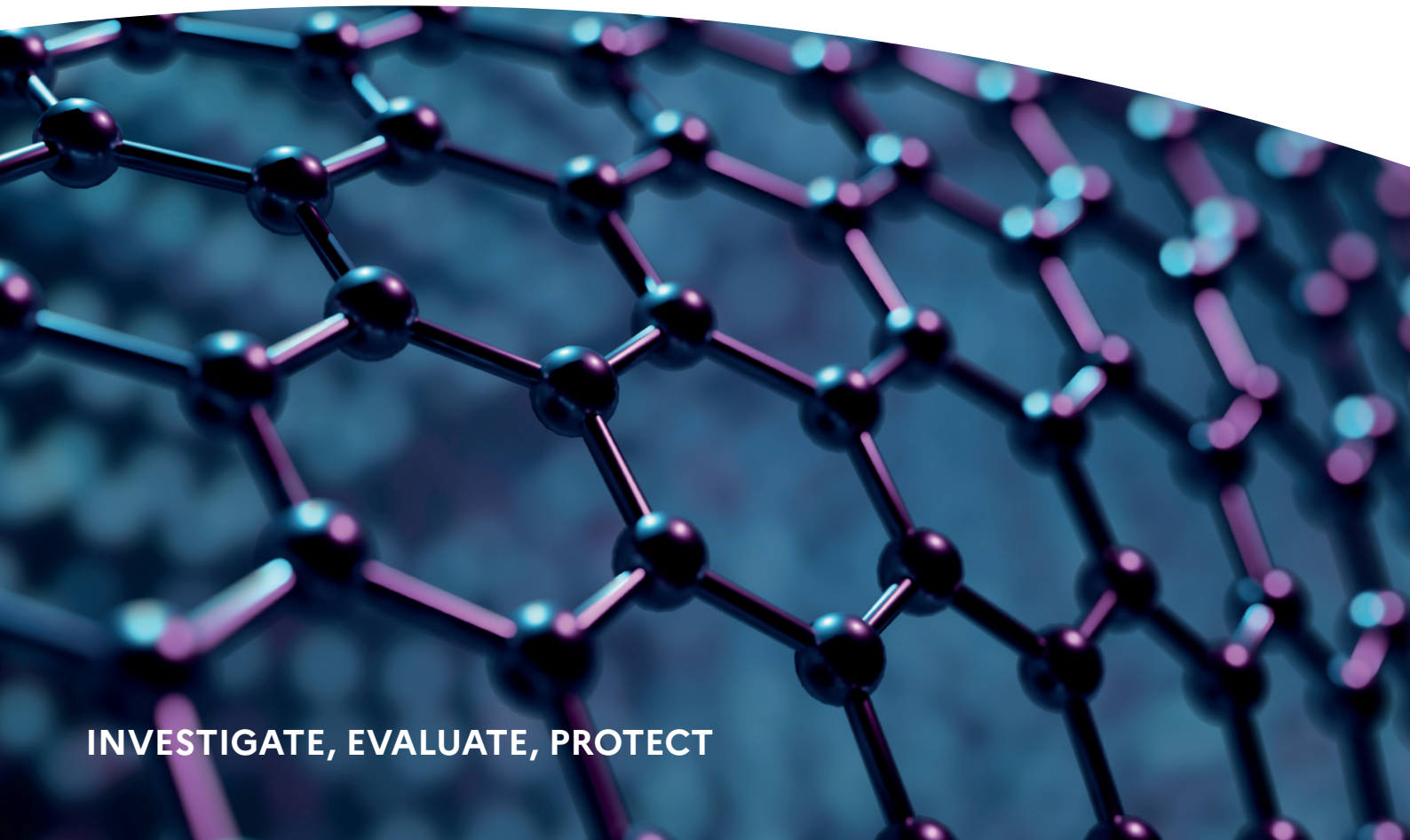

INVESTIGATE, EVALUATE, PROTECT

ANSES Opinion
Request No 2018-SA-0168

The Director General

Maisons-Alfort, 17 April 2023

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

relating to the formal request on "Definition of nanomaterials: analysis, challenges and controversies"

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.
It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 17 April 2023 shall prevail.

On 10 July 2018, ANSES received a formal request from the Directorate General for Health (DGS), Directorate General for Risk Prevention (DGPR), Directorate General for Food (DGAL), Directorate General for Labour (DGT) and Directorate General for Consumer Affairs, Competition and Fraud Control (DGCCRF) for scientific and technical support in drafting a proposal for an updated definition of the term "nanomaterial" based on European Commission Recommendation 2011/696/EU on the definition of nanomaterial.

1. BACKGROUND AND PURPOSE OF THE REQUEST

The growing use of nanoparticle substances in a wide variety of sectors has led the public authorities to adapt national and European regulations in different industry sectors to take account of the specific features of nanomaterials.

The dimensional characteristics of these substances, which may give the materials particular properties or behaviours, also impose specificities in how the associated risks are assessed (toxicity – ecotoxicity and environmental fate). However, while these substances are developed for their specific properties and often regarded as vectors of innovation, the state of knowledge

on their potential effects on health and the environment is generally inadequate to assess the risks (ANSES 2014).

The initial difficulty facing risk assessments of nanomaterials has been the lack of a fully agreed definition of the objects concerned. Consequently, the first step towards a better understanding consisted in harmonising the vocabulary used (nano-objects, aggregates, agglomerates, engineered nanomaterials, etc.), via standardisation work, and then establishing a definition and physico-chemical criteria enabling these substances to be characterised, with regard to their size, distribution, specific surface area, etc.

Commission Recommendation 2011/696/EU of 18 October 2011[1] on the definition of nanomaterial has subsequently served as a reference for various legislative texts. It was drawn up based on work by the Scientific Committee on Emerging and Newly Identified Health Risks (Scenihr), published in 2010 (Scenihr 2010). It is based on two fundamental criteria:

- a first dimensional criterion: the objects considered must have at least one dimension at the nanoscale (defined by this Recommendation as being from 1 to 100 nm);
- a second size distribution criterion (also called "number size distribution"): as the particles of a material are generally polydisperse (meaning that the material comprises particles of different sizes), the Recommendation classifies a material as a "nanomaterial" if 50% or more of its constituent particles meet the first dimensional criterion (i.e. if the majority of its constituent particles are between 1 and 100 nm in size).

This Recommendation on the definition has been used as a reference in various legislative texts, with several European regulations based on it:

- Regulation (EC) No 1907/2006 (REACH), revised in 2018 (Commission Regulation (EU) 2018/1881) in order to adapt it to the specificity of nanoparticle substances, refers to this European Recommendation on the definition. The text and its annexes were voted by the European Commission on 26 April 2018 and came into force on 1 January 2020;
- similarly, Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products includes specific provisions for nanomaterials. These provisions apply to products and substances that meet criteria based on the European Commission's Recommendation on the definition of nanomaterial.

In contrast, other legislation diverges from the content of the European Recommendation:

- in Regulation (EU) 2015/2283 on novel foods, the definition of nanomaterial does not include a number size distribution threshold, unlike the 2011 Recommendation, meaning that an ingredient is declared "nano" as soon as the presence of nanoparticles is confirmed. This same definition is used in Regulation (EU) No 1169/2011 on the provision of food information to consumers (known as "Inco");
- lastly, in Regulation (EC) No 1223/2009 on cosmetic products, a nanomaterial is defined as an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.

At present, therefore, the definition of a "nanomaterial" can differ from one European regulation to another, as the same material can be classified as a nanomaterial in one industry sector but not in another.

[1] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF.

This illogical situation, in addition to the imprecision due to the various criteria considered, is regularly highlighted by various stakeholders (Member States, health agencies, non-governmental associations, industry), who call for a clearer and more harmonised definition.

On several occasions, the EC had announced its intention to revise its Recommendation on the definition, in order to take better account of the specificities of these substances and advances in knowledge, and clarify certain points of the definition. In addition, the Joint Research Centre (JRC), a research service of the European Commission, has published several studies that could provide input for the Commission's debates:

- in 2014, a first report with proposals for criteria that could be considered for defining nanomaterials (Rauscher *et al.* 2015);
- more recently, in 2019, a supporting document defining useful terms and concepts related to the definition (Rauscher, Roebben, *et al*. 2019);
- and then another report, this time on analytical techniques for identifying nanomaterials (Rauscher, Mech, *et al.* 2019).

After several rounds of discussion and preparatory work undertaken since 2013, the Commission finally opened a public consultation, from 6 May to 30 June 2021, in order to gather opinions on the proposed changes to the 2011 European definition. This consultation was followed by the publication of a new Recommendation on the definition on 10 June 2022.

With a view to the European Commission's public consultation on its proposal to change the definition, the DGS, DGPR, DGAL, DGT and DGCCRF made a formal request to ANSES on 10 July 2018, in order to draft a contribution to this public consultation without waiting for its opening date to be announced. ANSES was also asked to determine whether there were any measurement methods compatible with the European Commission's proposed definition and presenting any adaptations it considered necessary, particularly with regard to the health aspects.

To this end, a first report on the characterisation methods for nanomaterials was published by ANSES in 2020[2].

The revised Recommendation on the definition was published by the European Commission[3] on 10 June 2022, while the expert appraisal was being carried out. ANSES had responded to the public consultation that preceded it from 6 May to 30 June 2021, and published this information in the form of a scientific and technical support note[4] in January 2022. This current expert appraisal incorporates the revision of the definition.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

In order to be able to contribute to the French response to the public consultation[5] launched by the European Commission, ANSES entrusted examination of this request to the "Definition of nanomaterials" Working Group (WG) reporting to the Expert Committee on "Physical agents

[2] https://www.anses.fr/fr/system/files/AP2018SA0168Ra.pdf
[3] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32022H0614(01)
[4] https://www.anses.fr/fr/system/files/AP2018SA0168EN.pdf
[5] Open from 6 May 2021 to 30 June 2021.

and new technologies" (CES AP), as soon as the opening date of the public consultation was known. Because this opening date came without any prior indications that would enable this work to be effectively prepared, the WG was convened on 27 May 2021 without a call for applications.

This WG met four times to prepare ANSES's contribution to the public consultation[6]. Its work was presented to the CES on "Physical agents and new technologies" on 17 May 2021, then transmitted to the authorities requesting the expert appraisal on 22 June 2021. ANSES also contributed to the public consultation in its own name on 25 June 2021. Lastly, it drafted a scientific and technical support note bringing together the main points of the analysis and sent it to the authorities requesting the expert appraisal, in order to support them in their response to the European Commission[7]. The French authorities prepared a note to the European Commission based on the information provided.

After the public consultation ended, the WG continued its work to provide in-depth insights into the definition of nanomaterial and European regulations on these objects. This information was intended to provide input for the discussions between Member States as part of the European process to establish this definition. The WG was therefore tasked with conducting an expert appraisal aimed at:

- identifying and then analysing key criteria for the establishment of such a definition;
- inventorying the main coexisting definitions of nanomaterials and analysing their technical differences;
- identifying and documenting the various questions raised and the surrounding controversies.

For this phase of the expert appraisal, the Working Group met 13 times (between 6 September 2021 and 19 October 2022) and its work was regularly presented to the CES on "Physical agents and new technologies".

The European Commission's new Recommendation on the definition of nanomaterial was published on 10 June 2022, while the expert appraisal was still under way. However, as it incorporates almost all of the proposed changes presented during the public consultation, the arguments developed at that time remain fully valid.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public via the website: https://dpi.sante.gouv.fr/.

[6] 27 May 2021, 31 May 2021, 16 June 2021 and 18 June 2021 by videoconference.
[7] https://www.anses.fr/fr/system/files/AP2018SA0168EN.pdf.

3. ANALYSIS AND CONCLUSIONS OF THE CES

3.1. Analysis of the process to revise the Recommendation on the definition by the European Commission

Announced in 2011 when the first Recommendation on the definition of nanomaterial was published, the revision of this definition was supposed to be concluded in 2014. In the end, the process of revising this definition took 10 years. The proposed amendments submitted for public consultation from 6 May 2021 to 30 June 2021 were based on a rationale from the European Commission's Joint Research Centre (JRC), which itself was derived from three reports published between 2014 and 2019[8].

The WG and the CES underline the singular nature of the process of updating the definition. The public consultation was open for a limited period of time (seven weeks) without any timetable being announced to the stakeholders prior to its opening. Furthermore, the proposed format proved to be particularly constrained (questions asked only concerning a few specific points selected by the European Commission[9], answers to be selected from a predefined list, and free text with a limited number of characters) and some passages were confusing. The low participation of European public bodies in this consultation (only 13) reflects the degree to which these conditions made it difficult to contribute. The European Commission did not respond to the comments made during the public consultation, nor did it communicate with respondents. This process also ended just as abruptly with the publication of the new Recommendation on the definition in June 2022, and the responses to the consultation barely being taken into account. In practice, all of the initial suggestions made by the Commission were adopted, except for an adjustment to the threshold value of the volume-specific surface area (VSSA).

The CES notes that this process did not allow for any consultation between Member States on the revision of the Recommendation on the definition.

3.2. New Recommendation on the definition: content, analysis and outlook

As a preamble, the CES reiterates that:

- the definition of nanomaterial drawn up by the European Commission has a regulatory focus and cannot therefore be understood as a purely scientific definition;
- there is no scientific consensus either on the criteria to be taken into account to define nanomaterials, or on the values of the physico-chemical parameters adopted in the definition (e.g. the dimensional range to be considered for the nanoscale, currently from 1 to 100 nm, is arbitrary).

The Recommendation on the definition, at the interface of science and law, is indeed based on scientific knowledge but also on technical and regulatory choices. In this sense, the definition criteria adopted by the European Commission depend not only on scientific evidence, but also on technical aspects, and on the socio-economic conditions for implementing the definition (cost of physico-chemical analyses, availability of equipment, etc.).

[8] (Rauscher *et al.* 2015; Rauscher, Mech*, et al.* 2019; Rauscher, Roebben*, et al.* 2019)

[9] Some discussions, for example on the determination of the nanoscale, were not among the points raised.

Content

The criteria amended in the new version of the Recommendation on the definition are as follows:

- the very terms of the definition indicate that the nanomaterial is no longer considered to be a material (natural, incidental or manufactured) that contains "particles, in an unbound state or as an aggregate or as an agglomerate" (2011 Recommendation) but as a material "consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates" (2022 Recommendation). This new wording introduces several changes:
  - nanomaterials are now described as materials *consisting* of particles instead of materials *containing* particles, in order to avoid possible confusion between a "nanomaterial" and a "product containing nanomaterials";
  - the notion of bonding between particles disappears and is replaced with the notion of "particles that are present on their own";
  - the notion of "identifiable constituent particles" is introduced;
  - lastly, the notion of "particles" is now restricted to "solid" particles;
- the notion of "single molecules" is also introduced to exclude these single molecules from the notion of particle;
- aggregates and agglomerates are partially redefined ("aggregate": a particle consisting of strongly bound or fused particles; "agglomerate": a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components);
- the list of derogations for particles smaller than 1 nm is replaced with a generic rule;
- the flexibility of the number size distribution threshold is abandoned. While this threshold remains at 50%, it can no longer be lowered to 1% as was previously possible for "reasons of environmental protection, public health, safety or competitiveness";
- a criterion for counting number size distributions (particle size analysis) is added: large particles (with at least two dimensions larger than 100 micrometres) are now excluded from the counting of size distributions;
- the volume-specific surface area (VSSA) inclusion criterion of 60 m^2/cm^3 disappears. However, an exclusion criterion based on the same measurand is included with a threshold of 6 m^2/cm^3.

Analysis

Taken together, these amendments result in a more restrictive definition of nanomaterials. The flexibility that was previously possible enabled objects to be included, mainly for public health reasons (see above). This has now been abandoned.

The Recommendation on the definition of nanomaterial and its update by the European Commission, planned since 2011, aimed to achieve two objectives[10]:

- take account of advances in scientific knowledge and regulatory feedback in order to address scientific uncertainties and resolve difficulties relating to the implementation of the current definitions;

[10] Commission Staff Working Document: Review of the Commission Recommendation 2011/696/EU on the definition of nanomaterial, Accompanying the document, Commission Recommendation on the definition of nanomaterial (2022):
https://ec.europa.eu/environment/chemicals/nanotech/pdf/SWD_2022_150_2_EN_part1_v4.pdf

- harmonise the definitions at European level.

The CES regrets that these objectives have not been achieved.

In practice, there is still some confusion over vocabulary and, due to the introduction of new concepts or key terms requiring clarification and technical details (guide being prepared by the JRC), the new 2022 Recommendation on the definition is therefore not operational as it stands.

The European Commission refers to the second objective to justify, for example, removing the flexibility of the number size distribution threshold. However, this definition, which has been kept in the form of a Recommendation that is not legally binding, will in practical terms only supplement the other sectoral definitions and not replace them. This choice will not enable the regulatory texts to be harmonised as desired.

- **Consequences and outlook in Europe and for the French regulations**

The WG identified the main possible regulatory changes at European and French level and performed an initial analysis on them.

For example, in France, the definition on which the mandatory declaration of nanoparticle substances is based is very directly inspired by the 2011 Recommendation. Any amendment to it would then naturally raise questions about the change in the definition to be used at national level.

3.3. CES recommendations for the drafting of a definition of nanomaterial

As it stands, the change in the European Commission's Recommendation on the definition of nanomaterial is unsatisfactory, for the reasons given above. The WG and the CES have identified the points requiring attention in any process designed to produce a definition of nanomaterial, in an approach that supports the assessment of potential risks to human health.

3.3.1. An inclusive and binding definition

The CES reiterates that public health issues related to nanomaterials have historically been linked firstly to the advent of nanotechnologies and secondly to acquired knowledge on the health effects of ultrafine particles (UFPs). The debates focused initially on the consequences of nanotechnology applications and then on the objects themselves (nanoparticles and then nanomaterials). This terminology has been further diversified with the notions of nanoforms (REACH), nanoparticle substances (French mandatory declaration of nanomaterials), nano-objects and their aggregates and agglomerates (ISO), and small particles (EFSA). More recently, the attention of legislators has focused on micro- and nanoplastics.

Considering that the intelligibility of the subject matter is hindered by the increase in and accumulation of terms referring to notions that are sometimes very similar, the CES recommends:

- incorporating in the definition of nanomaterial all objects in this size range, including those already covered by specific provisions in the European regulations (nanoplastics, ultrafine particles, etc.);
- accompanying any new definition of nanomaterial with explanations aimed at positioning it in relation to the other terms used.

The CES believes that the definition of nanomaterial should contribute to the following objectives:

- circumscribe a set of substances whose dimensions warrant them undergoing a dedicated health risk assessment (i.e. a nanospecific assessment);
- give additional texts the possibility of defining potential regulatory constraints and specific management measures based on the results of these assessments;
- give additional texts the possibility of defining sub-sets (of objects or uses) requiring specific provisions.

Thus, in contrast to the choice made by the European Commission, the CES recommends giving a definition that is as inclusive as possible. Its status should be legally binding with regard to sectoral European regulations.

This approach would:

- ensure consistency in terms of the definition across all the industry sectors concerned: the same object should be considered a nanomaterial regardless of its sector of use or application;
- ensure the production of knowledge and an adequate assessment for as many nanomaterials as possible, with regard to a potential health risk;
- avoid including notions related to risk assessment in the definition of nanomaterial, enabling the definition of "nanomaterial" objects to be separated from the potential consequences of their use, whether in terms of the associated risks to health or the environment or even the benefits;
- avoid including considerations related to metrological feasibility (measurement methods and instruments) in the definition of nanomaterial.

3.3.2. Discussion on the main technical criteria for a definition of nanomaterial

- **Dimensional criteria**

The CES and the WG stress the inconsistencies of several directions taken by the European Commission in the changes to the Recommendation on the definition. The experts stress that the definition of nanomaterial should be based essentially on dimensional criteria, despite their limitations. Indeed:

- changes aiming to exclude objects that meet these dimensional criteria (non-solid objects, single molecules, etc.) do not seem appropriate since:
    - such exclusions are not justified in health terms, especially as some of the target applications are growing rapidly (liposomes and nanovectors);
    - they are based on the use of terms for which there is no consensus, or undefined notions (solid or non-solid state at the nanoscale, "identifiable" nature of a nano-object, notion of "single molecule"), thus creating considerable uncertainties;
- the change aiming to consider the measurement of the VSSA as an inclusion or exclusion criterion should not be included in such a definition because the assessment of whether or not a material is nanoscale may differ when using VSSA or particle size analysis. This is because measuring the VSSA does not provide a precise measurement of the size of nanomaterials, only an estimate of their dimensional characteristics. However, such a metrological approach could be included as a screening method in the technical guidance documents and guidelines accompanying the definition.

A number of specific issues, detailed below, have been identified as requiring clarification or choices to be made.

■ Key concepts that still need be validated or defined

The CES points out that various key concepts on which a definition of nanomaterial should be based remain unclear:

- the first of these complex concepts is that of "constituent" particle, to which dimensional criteria apply. Clarification of the notion of "constituent" particle is essential, in particular to avoid any confusion with the notion of primary particle[11];
- in connection with the previous point, objective information (nature, reversibility and strengths of the bonds involved) is also needed to clarify the distinction between aggregates and agglomerates;
- lastly, all the above notions refer, for the most part, to single-component materials (simple cases). In practice, a definition of nanomaterial should also apply to more complex cases (hybrid and/or composite materials).

■ Inclusion or exclusion of nanostructured objects in the scope of the definition of nanomaterial

Although the European Commission's Recommendation on the definition now explicitly excludes objects with surface or volume nanostructure from the scope of nanomaterials, it should be noted that this choice creates a discrepancy with the definition of the International Organization for Standardization (ISO). The CES points out that, in practice, it is very difficult to distinguish nanostructured objects from aggregates and agglomerates of nano-objects. This would require the nature of the interactions of the bonds between particles to be described (complex analyses).

It is generally accepted that these larger objects pose very different hazards to nano-objects. In the current state of knowledge, it cannot therefore be excluded that these nanostructured objects may be associated with specific health or environmental risks due to their nanostructures (compared with objects of the same chemical nature that are not nanostructured).

■ Dimensional limits and number size distribution threshold

The new Recommendation on the definition endorses the previously adopted values for the dimensional limits and the number size distribution threshold. In the public consultation, the European Commission only reopened the debate on the size distribution threshold.

For the reasons mentioned above, the choice of dimensional limits and number size distribution threshold cannot be based on sound scientific arguments. A certain degree of arbitrariness will be needed to establish these parameters.

In order to have the most inclusive definition possible, the CES recommends extending the dimensional limits and advocates a lower value for the size distribution threshold than the one currently used. The CES notes that this may lead to a significant increase in the number of materials considered as nanomaterials. However, this approach is more protective and also

[11] Primary particles constitute the initial (single) forms from which a material is assembled. They may differ from constituent particles, which are morphologically identifiable within a material as aggregates or agglomerates.

less complex than one that automatically excludes too many substances from the scope of the definition.

- **Derogations**

The consideration of a dimensional lower limit to define the nanoscale (currently set at 1 nm) reflects a desire to exclude, for practical and theoretical reasons, objects such as atoms, molecules, etc. Nevertheless, the existence of derogations shows that this dimensional criterion alone is not sufficiently inclusive for objects that are however widely recognised as nanomaterials (single-wall carbon nanotubes, C_{60} fullerenes, etc.). Nor is this criterion sufficiently exclusive to avoid taking into account molecules such as proteins, which can reach dimensions greater than 1 nm. The CES stresses that, up to now, a list of derogations in the 2011 Recommendation on the definition has only been used to correct aberrations linked to this low threshold.

The CES recommends considering derogations in order to correct possible shortcomings linked to the consideration of either dimensional limits (high and low thresholds) or a number size distribution threshold.

- **The challenging case of "biomolecules"**

Certain biological objects and molecules, such as proteins and other macromolecules naturally occurring in living organisms, meet the dimensional criterion of the nanoscale. These seem to be of little relevance to the health issues associated with nanomaterials and are particularly widespread in the environment. However, certain manufactured or intentionally transformed molecules may present health issues (e.g. transformation of lactates into tubular forms and synthesis of cyclodextrins added to foodstuffs to deliver substances).

A choice needs to be made about whether or not to include biological objects in the scope of nanomaterials. The possible options identified by the WG and the CES, and their consequences, are as follows:

- either these objects should all be included in the definition of nanomaterial, regardless of their origin, in which case the number of nanomaterials would increase considerably;
- or, among these objects, biomolecules[12] should be excluded because of their nature. This would introduce criteria specific to these biological objects in the definition of nanomaterial, to the detriment of its universal nature.

3.4. CES recommendations on the implementation of the new Recommendation on the definition

The CES recommends carrying out further work to measure the practical and regulatory consequences, on the one hand, and the health and social impacts, on the other, that could result from the implementation of this new Recommendation on the definition in general and sectoral European and national regulations (in particular the R-Nano mandatory declaration scheme).

[12] Natural molecules that are synthesised by living organisms, are not used for industrial production purposes, and are not transformed.

Furthermore, the CES recommends taking advantage of the revision of the REACH Regulation to incorporate the findings of this expert appraisal and change the definition of nanomaterial in this Regulation.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety notes that following a revision process that was postponed several times and included a short consultation period in June 2021, a new "Recommendation on the definition of nanomaterial" was published by the European Commission in June 2022. ANSES points out that it contributed to this consultation, and published a scientific and technical support note in January 2022 that explained both the content and the reasons for its contribution. Along with the groups involved in this expert appraisal, it concludes that its recommendations have not been taken into account in the establishment of this new recommendation, which it considers detrimental to the health issues. ANSES notes, however, that the status of "Recommendation on the definition" is retained, which does not give it any regulatory value.

ANSES endorses the conclusions and recommendations of its Expert Committee on "Physical agents and new technologies".

ANSES finds that the new recommendation is more restrictive and less flexible than the previous one, thus paving the way for a potential regression in the protection of public health and the prevention of health and environmental risks associated with nanomaterials. It also notes that this approach fits within a situation characterised by the use of nanoparticle substances in numerous sectors and a state of knowledge regarding their potential effects on the environment and health that has made little progress in helping to better determine the scope of such a definition.

The Agency notes that over the past decade, attention has mainly focused on the issue of a regulatory definition of nanomaterials, seeking a scientific consensus, which is inherently difficult to achieve, and thus hindering work on risk management and prevention.

It stresses that a European definition of nanomaterials should first and foremost consist in defining the substances for which the specificities of the nanoscale of the material need to be considered in the assessment (nanospecific risk assessment). The Agency also indicates that such assessment methods are beginning to emerge, particularly for the ingestion route[13]. Based on the findings of these assessments, sectoral European regulations should therefore state which nanomaterials require specific management measures.

ANSES recommends henceforth considering a broader definition of nanomaterials, one that is more inclusive than the current European recommendation, so that nanospecific hazard characterisations concern as many nanomaterials as possible. To achieve this, the expert appraisal report supporting this opinion provides detailed proposals for the different

[13] ANSES opinion on the assessment of the risk of the nanoscale fraction of the food additive E171 (2021), and EFSA guidance (EFSA guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health. EFSA Journal, 2018, 16(7): 5327)

parameters of such a definition, pointing out those requiring choices to be made. With the knowledge gained, this definition could subsequently be adjusted.

At the European level, the Agency recommends that the public authorities:

- take advantage of the revision of the regulations on chemicals (REACH) and cosmetics to propose, stabilise and integrate such a broadened definition, and proceed with the corresponding changes to the technical annexes;
- mobilise their efforts, as soon as the revision of other sectoral regulations begins, in order to promote the introduction of such a definition.

At the national level, the regulatory texts governing the mandatory declaration scheme, which aims to ensure the traceability of nanomaterials in France, should incorporate this broader definition.

Pr Benoit Vallet

KEY WORDS

Nanomatériaux, nano-objets, nanoparticule, particules ultrafines, définition

Nanomaterials, nano-object, nanoparticle, ultrafine particle, definition

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Definition of nanomaterials: analysis, challenges and controversies

Request "No 2018-SA-0168 – Scientific and technical support to update the proposed definition of the word 'nanomaterials' based on Recommendation 2011/696/EU on the definition of nanomaterials"

Collective expert appraisal REPORT

Expert Committee on "Physical agents and new technologies"

"Definition of nanomaterials" Working Group

November 2022

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Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

"DEFINITION OF NANOMATERIALS" WORKING GROUP

Chair

Mr Emmanuel FLAHAUT – Research Director at the National Centre for Scientific Research (CNRS) – materials science, synthesis and functionalisation of carbon nanomaterials, health and environmental impacts of nanomaterials

Members

Ms Armelle BAEZA – University Professor (Paris Cité University) – toxicology of ultrafine particles

Mr Laurent DEVOILLE – Research Engineer at the National Metrology Laboratory – physico-chemical characterisation, food matrices, metrology

Mr Thierry DOUKI – Researcher/Doctor Engineer in Chemistry, French Alternative Energies and Atomic Energy Commission (CEA) – chemistry, toxicology/genotoxicity, *in vitro* models

Ms Valérie FESSARD – Head of the Toxicology of Contaminants Unit at ANSES – *in vivo/in vitro* toxicology

Mr Eric HOUDEAU – Research Director at the French National Research Institute for Agriculture, Food and the Environment (INRAE) – physiology, food toxicology

Ms Stéphanie LACOUR – Research Director at CNRS – law, regulations and control of new technologies

Mr Brice LAURENT – Engineer, Sociologist and Research Manager at MINES ParisTech – sociology of technological innovation (connections between innovation and democracy) (resigned on 1 June 2022[1])

Mr Armand MASION – CNRS Research Director at the European Centre for Research and Teaching in Environmental Geoscience (CEREGE) – environmental bio-geo-nanosciences, environmental dispersion

Mr Stéphane PEYRON – Lecturer at the University of Montpellier – physical chemistry, food contact materials

EXPERT COMMITTEE

The work covered in this report was monitored and adopted by the following Expert Committee (CES):

- CES on "Assessment of the risks related to physical agents and new technologies" – Meetings of 17 June 2021, 16 March 2022, 23 June 2022, 21 September 2022, 19 October 2022 and 17 November 2022.

Chair

Ms Anne PEREIRA DE VASCONCELOS – Research Manager, French National Institute for Health and Medical Research (INSERM), Laboratory of Cognitive and Adaptive Neurosciences – UMR 7364, French National Centre for Scientific Research (CNRS) – University of Strasbourg

[1] Brice Laurent resigned from the Working Group after being appointed Director of ANSES's Social Sciences, Economics & Society Department on 1 June 2022.

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Glossary

Agglomerate: a collection of weakly bound particles, aggregates or a mixture of the two whose resulting outer surface area is similar to the sum of the surface areas of each of the components (ISO/TS 80004-2:2015)

Aggregate: a set of particles comprising strongly bound or fused particles whose resulting external surface area may be significantly smaller than the sum of the calculated surface areas of each of the components (ISO/TS 80004-2:2015)

Dispersion: a multiphase system in which discontinuities of any state (solid, liquid or gas: discontinuous phase) are dispersed in a continuous phase of a different composition or state (note: if solid particles are dispersed in a liquid, the dispersion is referred to as a suspension) (ISO/TR 13097:2013)

Hybrid: a material composed of an intimate mixture of inorganic components, organic components, or both types of components. Note: the components usually interpenetrate on scales of less than 1 µm (IUPAC Recommendations 2007)

Manufactured nanomaterial: a nanomaterial intentionally produced to have selected properties or composition for commercial purposes (ISO/TS 80004-1:2015)

Measurand: a quantity intended to be measured (International vocabulary of metrology – Basic and general concepts and associated terms, JCGM 200:2012, International Bureau of Weights and Measures)

Nanofibre: a nano-object with two external dimensions in the nanoscale and the third dimension significantly larger (ISO/TS 80004-2:2015) (Figure 1, D= 2)

Nanoform: a form of a natural or manufactured substance 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 nanoforms in this document adhere to the concepts and terms used in the European Commission's Recommendation on the definition of nanomaterials (ECHA 2022)

Nanomaterial: a material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale (ISO/TS 80004-1:2015)

Nano-object: a material with one, two or three external dimensions in the nanoscale (ISO/TS 80004-1:2015)

Nanoparticle: a nano-object with all three external dimensions in the nanoscale (ISO/TS 80004-2:2015) (Figure 1, D = 3)

Nanoplate: a nano-object with one external dimension in the nanoscale and the other two external dimensions significantly larger (ISO/TS 80004-2:2015) (Figure 1, D= 1)

Nanoproduct: a finished product containing manufactured nanomaterials.

Nanoscale: the length range approximately from 1 nm to 100 nm (ISO/TS 80004-1:2015)

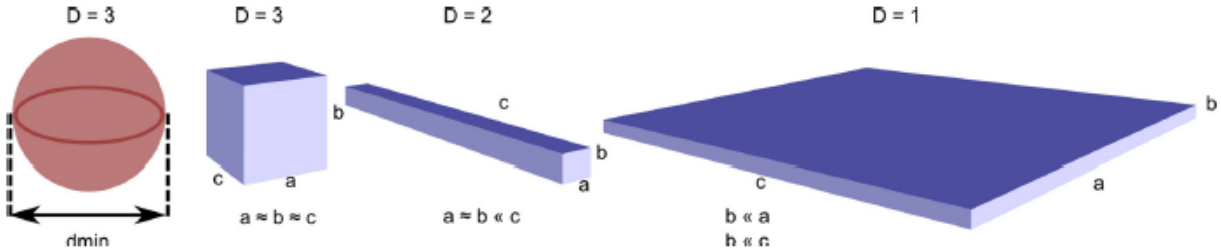

Figure 1: Typical shapes of nanomaterials: nanoparticles (D=3), nanofibres (D=2), nanoplates (D=1) (extracted from the reference (Wohlleben *et al.* 2017))

Solution: a liquid or solid phase containing more than one substance, when for convenience one (or more) substance, which is called the solvent, is treated differently from the other substances, which are called solutes. When, as is often but not necessarily the case, the sum of the mole fractions of solutes is small compared with unity, the solution is called a dilute solution (IUPAC Recommendations 1994).

Acronyms and abbreviations

A4F: Asymmetrical flow-field flow fractionation

AFM: Atomic force microscopy

AICIS: Australian Industrial Chemicals Introduction Scheme

BET: Brunauer-Emmett-Teller method

CES: ANSES Expert Committee

CES AP: Expert Committee on “Physical agents and new technologies”

CLS: Centrifugal liquid sedimentation

CNRS: French National Centre for Scientific Research

DGAL: French Directorate General for Food

DGCCRF: French Directorate General for Consumer Affairs, Competition and Fraud Control

DGPR: French Directorate General for Risk Prevention

DGS: French Directorate General for Health

DGT: French Directorate General for Labour

DLS: Dynamic light scattering

DMA: Differential mobility analysis

EC: European Commission

ECHA: European Chemicals Agency

EFSA: European Food Safety Authority

ELSI: Ethical, legal and social implications

EPA: US Environmental Protection Agency

EU: European Union

FDA: US Food and Drug Administration

ICP-MS: Inductively coupled plasma mass spectrometry

INCO: Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, OJEU 22 November, L 304

ISO: International Organization for Standardization

JRC: Joint Research Centre (European Commission)

MALS: Multi-angle light scattering

NEP: Nano-enabled product

NIOSH: National Institute for Occupational Safety & Health (United States)

NLC: Nanostructured lipid carrier

NOAA: Nano-objects and their aggregates and agglomerates

OECD: Organisation for Economic Co-operation and Development

PTA: Particle tracking analysis

REACH: Registration, Evaluation and Authorisation of CHemicals

SAS: Synthetic amorphous silica

SAXS: Small-angle X-ray scattering

SCENIHR: Scientific Committee on Emerging and Newly Identified Health Risks (European Commission)

SEM: Scanning electron microscopy

SLN: Solid lipid nanoparticle

SOP: Standard operating procedure

SPF: *Santé publique France*

sP-ICP-MS: Single particle inductively coupled plasma mass spectrometry

Spray-DEMA: Differential electrical mobility analysis on sprayed suspensions

SSA: Specific surface area

TEM: Transmission electron microscopy

TRPS: Tunable resistive pulse sensing

UFP: Ultrafine particle

VSSA: Volume-specific surface area

WG: Working Group

WHO: World Health Organization

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1 Background, purpose and procedure for carrying out the expert appraisal

1.1 Background

The growing use of nanoparticle substances in a wide variety of sectors has led the public authorities to adapt national and European regulations to take account of their specific features.

The dimensional characteristics of these substances, which may give the materials particular properties or behaviours, also suggest probable differences in how the associated risks are assessed (toxicity – ecotoxicity and environmental fate). Whereas these substances are often developed for their specific properties and regarded as vectors of innovation, the state of knowledge on their potential effects on the environment and health is generally inadequate to assess the risks (Anses 2014).

In the absence of a fully agreed definition that would enable the scope of the objects concerned to be identified, the first step towards a better understanding consisted in harmonising the vocabulary used (nano-objects, aggregates, agglomerates, manufactured/engineered nanomaterials, etc.), initially via standardisation, and then establishing a definition and criteria enabling these substances to be characterised, with regard to their size, distribution, specific surface area, etc.

At European level, Commission Recommendation of 18 October 2011 on the definition of nanomaterial (2011/696/EU) has several times served as a reference for various legislative texts. It was based on work on this topic conducted by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) that was published in 2010 (Scenihr 2010).

The European Commission had proposed using this definition as a basis for adapting the one in Regulation (EU) No 1169/2011 on the provision of food information to consumers, mainly by introducing a 50% number threshold for particles. This proposal was rejected by the European Parliament on the grounds that there was no justification for introducing such a threshold, which was inappropriate here for responding to consumer demand for information. As a result, only the definition in the Novel Foods Regulation, referred to in Regulation (EU) No 1169/2011, applies as part of the inspections undertaken by the French Directorate General for Consumer Affairs, Competition and Fraud Control (DGCCRF) to ensure that consumers are properly informed of the nanoscale nature of the ingredients used. This definition does not include any threshold, so that an ingredient is declared to be “nano” whenever the presence of nanoparticles is confirmed. In practice, according to the inspection methodology developed by the Joint Laboratory Service, an ingredient is considered to be a nanomaterial when at least 10% of the particles it contains are nanometric in size.

At present, the various European regulations use different definitions of “nanomaterial” (regulations on biocidal products, cosmetic products, novel foods, food information to consumers, medical devices). Work to revise the annexes of Regulation (EC) No 1907/2006 (“REACH”) in order to adapt it to substances in nanoparticle form was published in 2018 (Regulation (EU) 2018/1881). The draft text of these annexes was voted by the EC in committee on 26 April 2018 and came into force on 1 January 2020. The text refers to the European Recommendation on the definition.

The current definitions proposed in the EC's 2011 Recommendation and in the different regulations contain differences and imprecisions (50% number threshold, size, notions of insolubility or biopersistence in the Cosmetics Regulation, etc.). These are regularly highlighted by stakeholders, who would like a clearer and harmonised definition. In several communications relating to this Recommendation, the EC had announced its intention to revise it before December 2014, in order to better take into account the specificities of these substances and advances in knowledge, and to clarify certain points of the definition.

The Joint Research Centre (JRC), a research service of the European Commission, published a first report in 2015 with proposals for criteria that could be considered to define nanomaterials (Rauscher *et al.* 2015). More recently, in preparation for the EC's proposal for a definition, the JRC published

in early 2019 a supporting document defining useful terms and concepts related to the definition (Rauscher, Roebben*, et al.* 2019), followed by another report, this time on analytical techniques for identifying nanomaterials (Rauscher, Mech*, et al.* 2019).

After several rounds of discussion since 2012, the Commission opened a short phase of public consultation (from 6 May 2021 to 30 June 2021) in order to gather opinions on the proposed changes to the 2011 European definition. This consultation phase ended with the publication of a new Recommendation for a definition on 10 June 2022.

1.2 Purpose of the request

With a view to a public consultation on the definition proposed by the European Commission, the Directorate General for Health (DGS), Directorate General for Risk Prevention (DGPR), Directorate General for Food (DGAL), Directorate General for Labour (DGT) and DGCCRF made a formal request to ANSES on 10 July 2018 in order to draft a contribution to this public consultation before the deadline set by the Commission.

ANSES was asked to conduct this work in several phases that involved:

1) initially (before the public consultation) conducting a review of knowledge on existing analytical methods, in order to determine the main parameters for characterising nanomaterials (general principles, advantages and limitations, particularly from a metrological perspective);
2) without waiting for the final wording, examining the consequences of the parameters and thresholds in the definition (e.g. size, particle number proportion, etc.) for the assessment and management of the health risks associated with nanomaterials;
3) in a second step (during the public consultation), determining whether there were any measurement methods compatible with the European Commission's proposed definition and presenting the adaptations it considered necessary, particularly with regard to the health aspects. These insights were detailed in the response to the public consultation.

As the work from the first phase was described in a report published in February 2020[2], the work presented in this document refers to the next two work phases.

Moreover, the Working Group in charge of responding to the formal request sought to incorporate comments on the revision of the Recommendation for a definition published by the Commission on 10 June 2022, i.e. in the course of its work.

1.3 Procedure: means implemented and organisation

In order to make a timely contribution to the French response to the European Commission's public consultation[3] without any prior indication of the time it would have to prepare this work, ANSES urgently entrusted the examination of this formal request to the "Definition of nanomaterials" Working Group (WG), convened without a call for applications, reporting to the Expert Committee on "Assessment of the risks related to physical agents and new technologies" (CES AP).

For this phase related directly to the public consultation, this WG created on 27 May 2021 met four times[4] with a view to producing a document to support the response to this consultation. This work was presented to the CES AP on 17 May 2021, then transmitted to the ministries behind the formal request on 22 June 2021. ANSES also contributed to the public consultation on 25 June 2021 in its own name, based on this work[5].

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[2] "Review of analytical methods available for characterising nano-objects and their aggregates and agglomerates, in order to meet regulatory requirements", ANSES, 2020 https://www.anses.fr/fr/system/files/AP2018SA0168Ra.pdf

[3] Open from 6 May 2021 to 30 June 2021.

[4] 27 May 2021, 31 May 2021, 16 June 2021 and 18 June 2021 by videoconference.

[5] https://www.anses.fr/fr/system/files/AP2018SA0168EN.pdf.

In order to present these reflections more broadly in a more flexible format and provide in-depth insights that could be useful for the Member States’ upcoming discussions in the ongoing European process to establish this definition, this Working Group was tasked with conducting an expert appraisal aimed at:

- identifying and then analysing key criteria for the establishment of such a definition;
- inventorying the main coexisting definitions of nanomaterials and analysing their technical differences;
- identifying and documenting the various questions raised and the surrounding controversies.

For this final work phase, the Working Group met 13 times (between 6 September 2021 and 19 October 2022) and its work was presented to the CES on “Physical agents and new technologies” on the following dates: 17 June 2021, 16 March 2022, 23 June 2022, 21 September 2022, 19 October 2022 and 17 November 2022.

The European Commission's new Recommendation on the definition of nanomaterials was published towards the end of the Working Group's work, on 10 June 2022. However, as it incorporates almost all of the proposed changes presented during the public consultation, the arguments developed at that time remain fully valid.

All of these dates are shown in the timetable of work given in Figure 2.

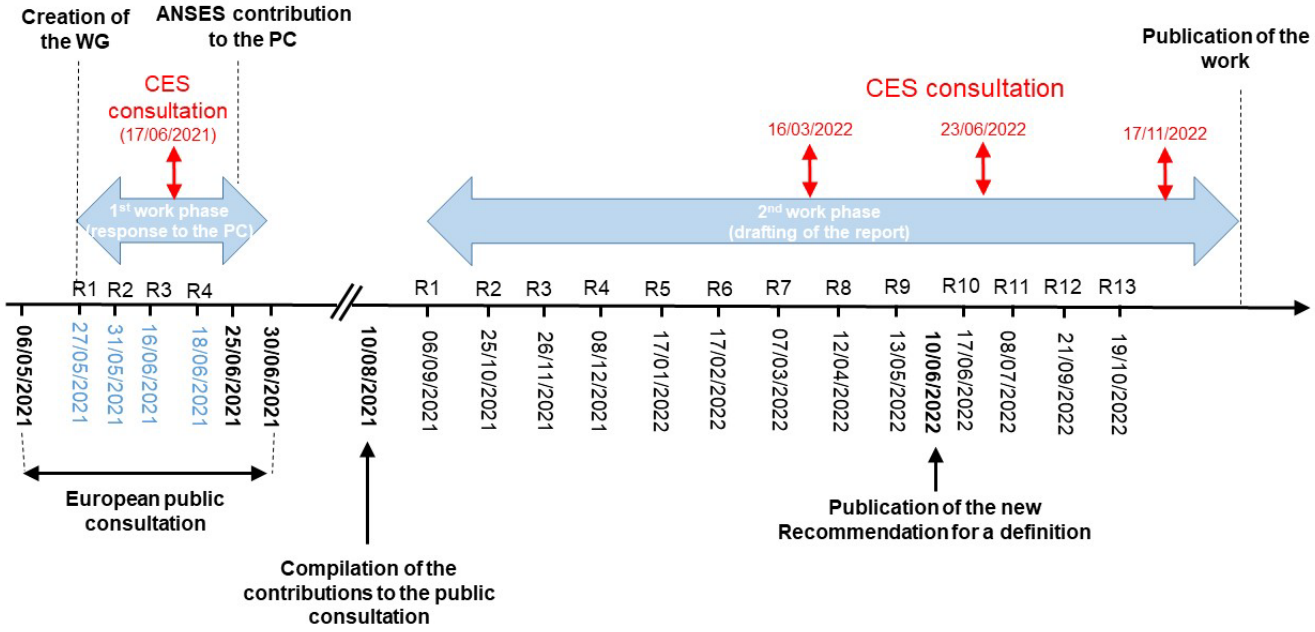

Figure 2: Timetable of the expert appraisal work

The expert appraisal was carried out in accordance with French Standard NF X 50-110 “Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)”.

1.4 Prevention of risks of conflicts of interest

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

Because he was appointed Director of ANSES's Social Sciences Unit on 1 June 2022, Brice Laurent had to resign from the Working Group on that same date.

The experts’ declarations of interests are made public via the ANSES website (www.anses.fr).

2 Introduction to the challenges and difficulties involved in defining nanomaterials

2.1 History of nanomaterials and the use of nanosized particles

The late 20th century was marked by the advent of nanoscience and nanotechnology. The manipulation of matter at the nanoscale led to the design of materials with remarkable properties that had applications in many different fields. As a result, a wide range of nanomaterials were produced, to which humans and the environment could be exposed during their life cycle.

In the early 2000s, voices began to be raised asking that the risks associated with exposure to these nanomaterials be taken into account. Warnings were sounded by occupational physicians and toxicologists specialising in inhaled particulate matter. Indeed, the inhalation of particles, which is common in many work contexts, can cause respiratory diseases. Moreover, epidemiological and toxicological studies have demonstrated the role of ambient air particulate matter in morbidity and mortality related to cardiovascular and respiratory diseases and cancer. For example, the World Health Organization (WHO) has estimated that exposure to fine particulate matter in cities and rural areas is responsible for 4.2 million premature deaths per year worldwide. In France, *Santé publique France* (SPF) considers that 48,000 deaths per year are associated with this class of particulate matter. The finest fraction of aerosols, comprising ultrafine particles, is particularly involved in cardiovascular and also probably extra-pulmonary effects. The small size of these particles gives them the ability to deeply penetrate the respiratory tract, cross the blood-air barrier and promote systemic distribution and action.

Both ultrafine particles and manufactured nanoparticles are in the nanometric size range. The term “ultrafine particles” is specific to the field of air pollution and these particles are different from manufactured nanoparticles in terms of their origin and composition. Manufactured nanoparticles are the result of industrial processes used to produce nanosized materials that have different properties from the same material at the micrometre scale and which are used in specific applications. Ultrafine particles in the air result from natural processes or are by-products of human activities. They are classified into primary particles, i.e. those emitted by natural or anthropogenic sources (combustion processes, volcanic ash, industrial dust, desert dust), and secondary particles, i.e. those resulting from (photo)chemical processes from precursor gases allowing gas-particle conversion. These aerosols undergo several physico-chemical modifications during their ageing in the atmosphere, in connection with heterogeneous chemical reactions on the surface of the particles, gas condensation and oxidation phenomena, etc.

Ultrafine particles are therefore characterised by polydispersity, a very complex composition and morphology, and great spatio-temporal variability. The respiratory system is primarily exposed to these particles because of their occurrence in the air compartment. The compounds put forward to explain their potential toxicity include organic compounds such as polycyclic aromatic hydrocarbons, quinones and metallic compounds. Whether intrinsically or following cellular metabolism, these compounds generate reactive oxygen species that induce oxidative stress, which is why cell damage is observed with these particles. While there are no specific regulations on ultrafine particles, these are considered as fine particles ($PM_{2.5}$), with an aerodynamic diameter of 2.5 µm or less, for which an annual limit value of 25 µg/m^3 has been set, with a quality target of 10 µg/m^3 according to the WHO's recommendation. These regulations are therefore based on mass, although the number of particles increases considerably in the ultrafine class and the composition of the particles is a critical factor in their toxic effects.

Manufactured nanoparticles are different in that they are intentionally produced, generally causing them to be less heterogeneous (in terms of their composition, shape, particle size, etc.). They are used for a wide variety of purposes, which can lead to exposure through multiple routes. The potential toxicity of these nanoparticles can result from many different factors such as their ability to generate reactive oxygen species, their surface properties including the formation of a crown of biomolecules as soon as they enter the body, their form factor, their solubilisation, their crystallinity

and their chemical composition. A number of toxicological studies have characterised the hazards associated with certain manufactured nanoparticles. Even so, the effects on human health remain poorly documented to date, in particular because the epidemiological data are still inadequate.

Within the category of nanosized particles, interest has recently focused on nanoplastics, which are found ubiquitously in the various compartments of the environment. They can result from the fragmentation/degradation of large plastics; in this case, they are known as secondary nanoplastics that are characterised by a wide variety of compositions, morphologies and sizes. They can also be derived from intentionally produced microplastics (primary nanoplastics) for use in cosmetics, paints, personal hygiene products or even fabrics, leading to multi-route exposure. Their toxicity can differ depending on the nature of the polymer, their shape and size, and the additives used to produce them which can migrate from the polymer. They can also act as carriers for other compounds through a Trojan horse mechanism, where they adsorb these compounds and then release them into cells that internalise them (Stone *et al.* 2017).

2.2 Regulatory challenges involved in defining nanomaterials

Nanotechnologies attracted the attention of the public authorities and companies starting in the early 2000s, which led to an increase in the number of programmes combining the awarding of research funds with future development prospects that in some cases were extremely ambitious. American and then European programmes rapidly included notions of health risk (and ethical issues) under the banner of “ethical, legal and social implications” (ELSI), setting an objective of “public engagement”[6]. Debates and controversies relating to biotechnologies were then often cited as examples, to highlight the need to anticipate the risks associated with nanomaterials.

In this context, the regulatory nature of objects whose expected properties are related to their nanometric size became a pressing issue for various national, European and international institutions.

2.2.1 Attempts at standardisation and difficulties encountered

The absence of standards on nanotechnologies was rapidly identified as a problem, both by market stakeholders and by public authorities concerned about possible risks. In 2005, the International Organization for Standardization (ISO) created Technical Committee (TC) 229: Nanotechnologies, which was responsible for producing standardised definitions in this area. Within TC 229, the definition of terms (“Terminology and Nomenclature”) was distinguished from three other tasks: “Measurement and Characterization”, “Health, Safety, and Environmental Aspects”, and “Material Specifications”. This distinction looked at definitions independently of regulatory considerations.

TC 229 thus defined the nanoscale as the “length range approximately from 1 nm to 100 nm” and nanomaterial as “material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale”. By doing so, TC 229 explicitly set an objective of establishing a scientific definition, independently of any regulatory choices.

This approach, in keeping with ISO's role, led the organisation to establish definitions that could not be directly used by the national and European public authorities, in particular because they encompassed a large number of substances without providing a way to identify those that might pose toxicological problems.

Nevertheless, the introduction of the lower limit of the nanoscale and the adverb “approximately” was based on a set of nuances described as follows:

> *“The lower limit (approximately 1 nm) in the definition of nanoscale is introduced to avoid single and small groups of atoms, as well as individual molecules, from being designated as nano-objects or elements of nanostructures, which might be implied by the absence of a lower limit. It should also be recognized that fullerene molecules and single layer planar*

[6] For Europe, refer to: “Towards a European Strategy for Nanotechnology”, COM(2004) 338, 5 December 2004; “Nanosciences and Nanotechnologies: An action plan for Europe 2005-2009”, COM(2005) 243, 7 July 2005.

> *structures (e.g. graphene) that have dimensions below 1 nm are, in practice, considered to be nanomaterials because they are important building blocks for nanotechnology.*
>
> *Further, size-dependent biological effects, specifically particle-cell interactions, and environmental interactions related to nanotechnology, involve structures below 1 nm and above 100 nm. In addition to size, the complex interplay of parameters such as aspect ratio, core chemistry, agglomeration state, physical state, surface properties and others will influence biological and environmental interactions associated with nanostructured materials"*[7]*.*

Therefore, even though the ISO definition of nanomaterials was intended to be technical (in the sense of being independent of regulatory considerations), international standardisation professionals introduced considerations relating to biological effects and the history of scientific research in the new field of nanotechnology ("*they are important building blocks for nanotechnology*"). The characterisation of these considerations is left to the discretion of the potential user of the definitions. Thus, the ISO standardised definition of nanomaterials faces two difficulties:

> (1) through its intention to be independent of regulatory considerations, it condemns itself to be of little use to public authorities,
>
> (2) by introducing nuances that take into account a variety of imprecisely characterised considerations, it fails to secure consensus as to its implications.

2.2.2 European attempts to do without a definition and difficulties encountered

In the 2000s, the anticipation of risks related to novel size-related properties led European stakeholders to consider what regulatory actions should be taken. In a Communication from 2008 entitled "Regulatory Aspects of Nanomaterials"[8], the European Commission concluded that "current legislation covers to a large extent risks in relation to nanomaterials and that risks can be dealt with under the current legislative framework" even though its application to nanomaterials would have to be reviewed, according to the Commission. The Commission acknowledged that there was no widely accepted definition of nanomaterials. It therefore used the term as follows:

> "*In the absence of generally accepted definitions, the term nanomaterials is used in this Communication to cover commonly used terminology such as manufactured (or engineered) nano-sized and nanostructured nanomaterials*".

Here, the term "nanomaterials" therefore does not refer to a precise definition (in the quote above, the term nanomaterials is explained using the term... nanomaterials). This is not problematic because the Commission proposes applying current legislation according to the situations encountered. For example, the Communication explains that the European REACH Regulation on the marketing of chemicals does not explicitly refer to nanomaterials, but that these are "covered by the 'substance' definition in REACH". REACH defines a substance as a "chemical element and its compounds in the natural state or obtained by any manufacturing process". This definition gives rise to a review on a case-by-case basis that distinguishes between substances according to various parameters and that can therefore lead to carbon nanotubes being considered different from other compounds of carbon atoms.

In a 2009 resolution[9], the European Parliament disagreed with the Commission's position[10] and addressed several requests to the Commission, including:

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[7] ISO/TS 80004-1:2015 Nanotechnologies – Vocabulary – Part 1: Core terms

[8] "Regulatory Aspects of Nanomaterials", COM(2008) 366

[9] European Parliament resolution of 24 April 2009 on regulatory aspects of nanomaterials.

[10] The European Parliament: *"Does not agree (…) with the Commission's conclusions that a) current legislation covers in principle the relevant risks relating to nanomaterials, and b) that the protection of health, safety and the environment needs mostly be enhanced by improving implementation of current legislation, when due to the lack of appropriate data and methods to assess the risks relating to nanomaterials it is effectively unable to address their risks".*

- to introduce a comprehensive science-based definition of nanomaterials in Community legislation as part of nano-specific amendments to relevant horizontal and sectoral legislation;
- to promote the adoption of a harmonised definition of nanomaterials at the international level and to adapt the relevant European legislative framework accordingly.

This disagreement between the Commission and Parliament highlighted the difficulty of applying current legislation to nanomaterials based on a case-by-case approach in the absence of a definition:

- it met with opposition from the Parliament, concerned about properly taking into account the specific risks associated with nanomaterials;
- it risked increasing the number of "cases" to be reviewed without managing to define the scope of substances that might be problematic due to size-related properties;
- as a result, it ran the risk of failing to properly regulate these substances.

2.2.3 Attempts at European definitions and difficulties encountered

In line with its 2009 Resolution, the European Parliament added specific provisions on nanomaterials to several European texts, in particular in the regulations on cosmetics, biocides and novel foods[11]. In doing so, the Parliament had to define nanomaterials as part of sectoral regulations, which led, as we will see later on in this report, to the coexistence of specific and sometimes competing definitions of nanomaterials.

This tension was again visible in 2011 when the Commission responded to one of the Parliament's requests by introducing a definition of nanomaterials through a Recommendation[12]. The criteria included in this Recommendation were more detailed than in the previous definitions, and nanomaterials were defined as follows:

> *"'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm".*

The Recommendation therefore included:

- a size criterion ("in the size range 1 nm-100 nm"), justified by Recital 4:
  "The definition of the term 'nanomaterial' in Union legislation should be based solely on the size of the constituent particles of a material, without regard to hazard or risk";
- a size distribution criterion ("50 % or more of the particles in the number size distribution"), justified by Recital 10 ("The number size distribution should cover for the fact that nanomaterials most typically consist of many particles present in different sizes in a particular distribution") and commented on in these terms in Recital 11:
  "There is no unequivocal scientific basis to suggest a specific value for the size distribution below which materials containing particles in the size range 1 nm-100 nm are not expected to exhibit properties specific to nanomaterials. The scientific advice was to use a statistical approach based on standard deviation with a threshold value of 0,15 %. Given the widespread occurrence of materials that would be covered by such a threshold and the need to tailor the scope of the definition for use in a regulatory context, the threshold should be higher".

The size distribution threshold was therefore, by the Commission's own admission, the result of a compromise between "scientific advice"[13] and the anticipated consequences of extending the definition based on the "widespread occurrence of materials", which would be problematic if the

11 See above.

12 Commission Recommendation of 18 October 2011 on the definition of nanomaterial (2011/696/EU).

13 Here, the Opinion issued by the SCENIHR, "Scientific Basis for the Definition of the Term 'nanomaterial' " on 8 December 2010 (Scenihr 2010).

definition targeted risks and hazards (which it was not supposed to do). Although the Recommendation affirmed that the definition "should be based solely on the size (…) without regard to hazard or risk", the criteria chosen consequently combined various considerations (scientific advice, technical feasibility, economic and regulatory consequences, etc.), as seen in the many possibilities for adaptation provided in the Recommendation:

> "*In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %*".
>
> "*By derogation from point 2, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials*".

The Recommendation also affirmed that the boundaries set by the definition were subject to change (as made possible by the chosen normative document, which was relatively non-binding in nature):

> *"It may in some cases be necessary to exclude certain materials from the scope of application of specific legislation or legislative provisions even if they fall within the definition. It may likewise be necessary to include additional materials, such as some materials with a size smaller than 1 nm or greater than 100 nm in the scope of application of specific legislation or legislative provisions suited for a nanomaterial"* (Recital 16).

In this Recommendation and in the accompanying comments[14], the definition was therefore ambiguously positioned:

- On the one hand, it was supposed to be based entirely on size and not prejudge the hazards and risks associated with the substances in question;
- On the other hand, it introduced compromises, derogations and possibilities for adaptation, which were based on considerations related to the risks or benefits of the substances in question.

2.2.4 Practical use of the European definitions following the 2011 Recommendation

In practice, the Recommendation introducing a definition of nanomaterials did not give rise to major changes in the European regulations on nanomaterials:

- The European Parliament continued to intervene by inserting specific provisions into European texts based on the model of the Cosmetics Regulation;
- The case-by-case approach continued to be favoured in REACH, still giving rise to discussions on the distinction between various nanosized substances;
- The ambiguous position of the definition prevented it from being used in practice.

2.2.5 Lessons learned from attempts to establish a definition

The attempts described above highlight the need to position the definition of nanomaterials as being science-based, considering the following:

(1) the definition should be based on the best scientific knowledge but should take account of a set of uncertainties, which extend to measuring methods and instruments and which surround most of the criteria used. The criteria chosen therefore require the broadest possible consensus among specialists in the field;

(2) producing a "scientific" definition as opposed to one based on other "regulatory" considerations has been an objective (ISO definition, affirmation of the size criterion in the European definition of 2011). This objective has given rise to definitions (ISO) that are of little use to regulators, or else it has not been achieved;

(3) successive attempts to define nanomaterials have led to the conclusion that any definition must necessarily be associated with regulatory objectives. It seems desirable to make these regulatory objectives as clear as possible.

[14] Questions and answers on the Commission Recommendation on the definition of nanomaterials, MEMO/11/704.

Based on these considerations, this report considers that a suitable definition of nanomaterials as part of the European regulations should contribute to the following objectives:

- identify a set of substances that have some specific size-related properties;
- define a set of substances whose size-related properties need to undergo a specific review;
- give additional texts the possibility of defining potential regulatory constraints based on the results of this specific review;
- give additional texts the possibility of defining sub-sets subject to specific provisions.

2.3 Current definitions: description and differences

2.3.1 Definitions coexisting in the European regulations

Several definitions of nanomaterials coexist in European Union (EU) law independently of the core definition, proposed by the European Commission in its 2011 Recommendation, which was reviewed during the public consultation and recently redefined in 2022. In addition to making the law difficult to access from a theoretical point of view, this plurality of definitions entails complex forms of legal acrobatics for stakeholders in industrial supply chains ranging from the production of nanomaterials to the finished products incorporating them who, depending on where and when they are positioned in the chain, will have to comply with one or the other of the current definitions; this also has implications for the persons that these different regulations aim to protect (consumers of food products, users of biocides, users of cosmetics, etc.).

▶ Regulation on cosmetic products

The first regulatory text that explicitly adopted a definition of nanomaterials at European level was Regulation (EC) No 1223/2009 on cosmetic products, which included a specific labelling requirement on the presence of nanomaterials and introduced the following definition: a nanomaterial is an "*insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm*"[15].

By introducing the qualifiers "insoluble" and "biopersistent", this definition sought to target the most stable substances that might be problematic for human health.

By using the size criteria inspired by the ISO nanoscale (but without the "approximately"), this definition also made possible a situation where a substance of a size just above 100 nm is used for its novel size-related properties but is not considered a nanomaterial.

This definition illustrates tension between the need to specify thresholds for reasons of legal clarity and technical feasibility and the inability to set such thresholds in a way that unambiguously captures the full range of potentially problematic substances.

▶ INCO (food labelling) and Novel Foods regulations

The constraints related to these issues could also be seen in the definitions that were adopted following the 2011 Recommendation as part of sectoral regulations.

This was the case for the INCO Regulation on the provision of food information to consumers[16], which was adopted just a few days after the publication of this EC Recommendation and which stipulated that an "*'engineered nanomaterial' means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of*

15 Article 2 of Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products, OJEU L. 342/59 of 9 December 2009.

16 Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, OJEU 22 November, L 304.

100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale".

The rest of this definition specified that *"Properties that are characteristic of the nanoscale include:*

(1) those related to the large specific surface area of the materials considered; and/or

(2) *specific physico-chemical properties that are different from those of the non-nanoform of the same material*"

While the form of this definition of engineered nanomaterials clearly reflected the influence of the debates and decisions surrounding the adoption of the core definition, major differences were immediately noted that were repeatedly exploited by stakeholders in the field of nanomaterials to maintain the uncertainties surrounding the definition of their products. It should be noted that these uncertainties worked in both directions, with comparisons with this definition sometimes being used to justify a broader or narrower understanding of the objects considered.

The specific features of this definition in the INCO Regulation that extended the scope of nanomaterials included the absence of a lower limit and a vaguer upper limit for the size range ("of the order of 100 nm or less"). Similarly, the reference to a threshold associated with the word "many" (for nanosized functional parts) was much vaguer and potentially broader than the one finally adopted by the Commission based, as we have seen, on extra-scientific considerations. This was also the case for the inclusion of nanostructured materials (materials with one or more internal nanometric dimensions) in this definition of nanomaterials, even though they were excluded from the scope of the 2011 Recommendation. Similarly, the reference to properties characteristic of the nanoscale had the effect of extending the definition to objects that were not considered as nanomaterials in the Commission's Recommendation.

Conversely, the reference to the notion of intentional production reduced the scope of the definition twofold as compared to the Recommendation, since not only did natural nanomaterials disappear, but above all the notion of intentionality introduced, as far as the materials referred to here were concerned, a subjective dimension that could be interpreted as excluding nanomaterials produced incidentally as part of a manufacturing process.

Either way, whether they restricted or increased the scope of the objects covered, it can be noted that the specificities of this definition were not justified by reasons of legal clarity and technical feasibility. On the contrary, both legally and technically, the notions of "many", characteristic properties and intentionality created even more uncertainty than the provisions of the 2011 Recommendation. It should nevertheless be stressed that this INCO definition of engineered nanomaterials was extended to the field of novel foods in 2015 under the Novel Foods Regulation[17], even though the Commission had hoped, in the meantime, to reintegrate the main parts of the sectoral definition into a narrower scope, similar to the one adopted in the 2011 Recommendation[18].

- **Regulation on biocidal products**

A final regulatory text also gave a specific definition of nanomaterials. It was the Regulation concerning the making available on the market and use of biocidal products[19], which stated that a nanomaterial is a "*natural or manufactured active substance or non-active substance 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 1-100 nm*". Here again, the following paragraph specified that "*fullerenes, graphene flakes and*

17 Regulation (EU) 2015/2283 of 25 November 2015 on novel foods, OJEU, 11 December 2015, L 327/1.

18 See, to that effect, Commission Delegated Regulation (EU) No 1363/2013 of 12 December 2013 amending the INCO Regulation as regards the definition of 'engineered nanomaterials' whose publication ended up being considered as null and void by the European Parliament, dramatically sanctioning the Commission's work, and European Parliament resolution of 12 March 2014 on the Commission delegated regulation of 12 December 2013 amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council on the provision of food information to consumers as regards the definition of 'engineered nanomaterials' (C(2013)08887 – 2013/2997(DEA)).

19 Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products, OJEU, 27.6.2012, L 167.

single-wall carbon nanotubes with one or more external dimensions below 1 nm shall be considered as nanomaterials". In this last case, apart from the notions of substance – undoubtedly adopted in reference to the REACH Regulation – and activity, the model chosen was indeed that of the 2011 Recommendation.

- **REACH Regulation on chemicals**

Lastly, even though it did not refer to nanomaterials as such, one final regulatory text should be mentioned in relation to the potentially problematic coexistence of competing definitions of these objects. It is the REACH Regulation as amended in 2018[20].

The purpose of this text was to adapt the 2006 Regulation on the declaration, registration and authorisation of chemicals; it followed on from a great deal of work noting this Regulation's ineffectiveness with regard to the specific issues associated with nanomaterials, which it attempted to remedy. It stated that "*On the basis of the Commission Recommendation of 18 October 2011 on the definition of nanomaterial, a nanoform is a form of a natural or manufactured substance 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. For this purpose, 'particle' means a minute piece of matter with defined physical boundaries; 'agglomerate' means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components and 'aggregate' means a particle comprising of strongly bound or fused particles. A nanoform shall be characterised in accordance with section 2.4 below*". The Regulation then specified that "*A substance may have one or more different nanoforms, based on differences in the parameters in points 2.4.2 to 2.4.5*" and that "*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. The term 'nanoform', when it is referred to in the other Annexes, shall refer to a nanoform or a set of similar nanoforms, when one has been defined, as defined in this Annex*".

The French Economic, Social and Environmental Council underlined that this adaptation provided "*clarifications and new provisions concerning the characterisation of nanoforms and sets of nanoforms covered by registration (Annex VI), the assessment of chemical safety (Annex I), the information required for registration (Annexes II and VII to XI), and downstream user obligations (Annex VII)*". It mainly consisted of a transposition of the text of the 2011 Recommendation in the body of the annexes of the REACH Regulation, illustrating in passing the difficulties to which the coexistence in the European regulatory environment of multiple sectoral definitions of the same objects gave rise between 2011 and 2018 with the implementation of much more horizontal regulations covering all of the chemicals placed on the market.

2.3.2 The other main definitions provided at international level

This short section does not claim to be exhaustive as it only reflects the situation in a few non-EU countries spread out over other continents (North America, Asia, Africa and Oceania). This brief overview shows that, in general, the definition of nanomaterials can be quite different from the one in the EU in terms of the scope and content.

[20] Commission Regulation (EU) 2018/1881 of 3 December 2018 amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annexes I, III, VI, VII, VIII, IX, X, XI, and XII to address nanoforms of substances, OJEU L 308, 4 Dec. 2018, p. 1.

A common feature for non-EU countries seems to be that the notion of nanomaterial is based on the ISO definition. Therefore, the size range of 1 to 100 nm remains the general framework for defining a nanomaterial. However, it can be noted that, in some cases, there can be significant flexibility with regard to the size range, which is the case for example in Thailand (even though its definition is similar to the EU texts), where encapsulated objects up to 500 nm are still considered as nanomaterials provided they have low polydispersity. Also worth noting is that the US Food and Drug Administration (FDA) considers that a material or end product engineered to exhibit properties or effects (physicochemical properties or biological effects) that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to 1,000 nm, should be considered a nanomaterial (FDA 2014). Health Canada does not apply this dimensional criterion for objects with properties deemed nanospecific[21].

At the other end of the size range considered, flexibility raises questions concerning the appropriateness and/or “common sense” of classifying or re-classifying an object as a nanomaterial. For example, for Health Canada, the fact that certain natural substances/molecules (proteins, DNA, etc.) and cellular structures (ribosomes, flagella, etc.) meet the nanoscale criterion is not sufficient for automatically (re)classifying them as nanomaterials.

This last point highlights a major difference between the European definition and the one of the ISO, which other countries follow: nanostructuring, which is absent from the European texts, is eligible in the ISO standard. It follows that countries using this latter definition implicitly recognise nanostructure as a qualifying criterion. Sometimes this is explicitly reiterated (in Canada, for example).

Another major difference is the notion of number size distribution threshold (currently at 50%), which is an essential and highly controversial criterion in the EU text but is effectively non-existent outside the EU.

An equally sensitive criterion is intentionality. This is not mentioned in the ISO standard, which seems to prevail in English-speaking countries and countries in their sphere of influence. However, in what can be interpreted as a concern for effectiveness, some definitions (e.g. those of the USA, Canada, Australia, and Thailand) explicitly restrict the scope to manufactured compounds. This concept of intentionality is commonly applied to the dimensions of objects and also the desired properties of materials, as proposed by the Australian Department of Health through its Australian Industrial Chemicals Introduction Scheme (AICIS)[22].

These reflections on the definition of nanomaterials are part of the work under way in Europe and at the Organisation for Economic Co-operation and Development (OECD) on the notion of “advanced materials”.

A final point concerns the scope of the definition. In the EU context, the definition of nanomaterials, although only set out in a Recommendation, is presented as being ideally intended to provide general guidance for the resulting sectoral regulations (emphasis on “ideally”). This is apparently unprecedented; indeed, the general trend outside the EU is to refer to sectoral regulations and their respective definitions to get a (not necessarily formalised) idea of what a nanomaterial is. For example, in the United States, the main organisations concerned with nanomaterials are three government agencies, i.e. the US Environmental Protection Agency (US EPA), the National Institute for Occupational Safety and Health (NIOSH), and the FDA. Their non-regulatory definitions of nanomaterials[23] are very similar (sometimes explicitly disclaiming any regulatory status for liability

[21] Health Canada's Policy Statement on the working definition of nanomaterial considers any manufactured substance or product and any component material, ingredient, device, or structure to be nanomaterial if a) it is at or within the nanoscale in at least one external dimension, or has internal or surface structure at the nanoscale, or b) it is smaller or larger than the nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena (Health Canada 2011).

[22] “Industrial materials intentionally produced, manufactured or engineered to have unique properties or specific composition at the nanoscale, that is a size range typically between 1 nm and 100 nm, and is either a nano-object or is nanostructured” (NICNAS 2013)

[23] Like the FDA, the US EPA does not have a formal regulatory definition but offers guidelines for distinguishing between nanomaterials and chemicals. According to “Working Guidance on EPA’s Section 8(a) Information Gathering Rule on Nanomaterials in Commerce”: a material is defined as a solid at 25°C and standard atmospheric pressure, that is manufactured or processed in a form where any particles, including aggregates and agglomerates, are in the size range of 1–100 nm in at least one dimension, and that is intentionally manufactured

reasons), resulting in an overall conceptualisation of nanomaterials that erases inter-agency boundaries without there being any overriding written reference. The American situation is not an exception; other countries follow a similar regulatory logic (Australia, Thailand, Canada, etc.). This shows that the need for a framework definition is not felt as strongly outside the EU. It should be noted that this in itself is nothing new. Prior to the adoption of the 2011 Recommendation, the columns of the journal *Nature* saw an exchange on this topic between those in favour of a definition and those claiming it would have more disadvantages than advantages. Of the latter opinion, Maynard (Maynard 2011) expressed a "refusal to define" that was a call for the status quo. According to this author, since legislating would mean entering a vicious circle of poorly calibrated definitions calling for constant changes, the only solution was to refrain from both defining and legislating. The virtuous circle presented by Stamm (Stamm 2011), on the other hand, was based on the opposite view, according to which a definition would serve the useful purpose of identifying nanomaterials as a specific class of materials that need attention, even if they are not systematically toxic.

These two approaches to the issue of definitions were undoubtedly influenced by the fact that the authors were respectively from the United States and Germany, which have different legal cultures. This controversy is, in reality, symptomatic of the difficulty that emerging objects with properties that are as exciting as they are uncertain create for the law. The positions expressed in this respect by the public authorities and industrial stakeholders illustrate the same ambivalence as to whether it is necessary to regulate the development of these new objects and especially as to the exact terms of this regulation. The issue of producing a definition, which may potentially impact the criteria for implementing the regulations, is logically at the heart of the dilemma today as much as it was in the past[24].

Table 1: Comparison of characteristics in different definitions of nanomaterials (adapted from the work carried out as part of the European RiskGONE project)[25]

	Organisation	Size range considered	Inclusion of agglomerates and aggregates	Size distribution threshold	Criterion related to novel properties
European regulations	**EC Recommendation for a definition**	1-100 nm	Yes	50% based on the number concentration	No
	Biocides Regulation	1-100 nm	Yes	50% based on the number concentration	No
	Medical Device Regulation	1-100 nm	Included	50% based on the number concentration	No
	REACH Regulation (chemicals)	1-100 nm	Yes	50% based on the number concentration	No
	Cosmetics Regulation	1-100 nm	Not specified	Not specified	No
	INCO and Novel Foods Regulations	Of the order of 100 nm or less	Yes	Not specified	Yes
Europe	**Belgium**	1-100 nm	Yes	50% based on the number concentration	No

or processed to exhibit unique and novel properties because of its size. In addition, the rule excludes substances where less than 1% of any particles, including aggregates, and agglomerates, measured by weight are in the size range of 1–100 nm (EPA 2017).

24 S. Lacour, "Définir les nanomatériaux : une controverse scientifique ou normative ?", ANSES *Bulletin de Veille scientifique* No 16, December 2011, p. 38 et seq.

25 https://riskgone.wp.nilu.no/.

	France	1-100 nm	Yes	50% based on the number concentration	No
	Switzerland	1-100 nm and above*	Yes	50% based on the number concentration	No
United States	**FDA**	1-100 nm and above**	Not specified	Not specified	Yes**
	US EPA	1-100 nm	Yes	Not specified	No
Canada	**Health Canada**	1-100 nm and above***	Not specified	Not specified	Yes***
Australia	**AICS**	1-100 nm	Not specified	Not specified	Yes

* manufactured materials are considered nano-relevant if they contain particles in an unbound state as an aggregate or agglomerate where one or more external dimensions are in the size range 1-500 nm.

** up to 1,000 nm if the material or product has been engineered to exhibit properties or effects attributable to its dimension(s).

*** derogation if the material exhibits one or more properties/phenomena at the nanoscale.

2.3.3 The particularities of French law with regard to the definition of nanomaterials

It would not be possible to end this second section dedicated to the challenges and difficulties involved in defining nanomaterials without devoting a few lines to the particularities of French law in this area. The applicable law in France obviously largely incorporates the EU texts, whether directly (for Regulations) or through transpositions (for Directives). Moreover, the French public authorities also closely cooperate with their European counterparts to implement EU-wide policies on chemicals and nanomaterials, applying principles such as the precautionary principle that are common to both legal systems.

However, based on the description we have given thus far of the European situation regarding the definition of nanomaterials, it is not possible to infer exact knowledge of French law on the subject. Indeed, with the adoption of the Grenelle acts[26] in 2009 and 2010, French law reflected a clear desire to better understand and regulate nanomaterials than was possible at the time based on the European texts. This led to the adoption of an obligation to declare nanoparticle substances produced, imported or distributed in France; such an obligation was unique in Europe at the time and was widely commented on (Lacour 2012), although its practical implementation took a long time.

The texts implementing this programme, whether legal or regulatory[27], entrusted ANSES with the management of these declarations and the data they contain, specifying that this system was aimed at the "*prevention of health and environmental risks resulting from exposure to nanoparticle substances*" and that the objectives of the declaration obligation were to "*ensure traceability and*

[26] French Planning Act No 2009-967 of 3 August 2009 on the implementation of the Grenelle environmental round table (French Official Journal No 0179 of 5 August 2009, page 13031) and French Act No 2010-788 of 12 July 2010 on national commitment to the environment (French Official Journal No 0160 of 13 July 2010, page 12905), together known as the "Grenelle acts".

[27] Decree No 2012-232 of 17 February 2012 on the annual declaration of nanoparticle substances pursuant to Article L. 523-4 of the French Environmental Code (French Official Journal No 0043 of 19 February 2012, page 2863) and Ministerial Order of 6 August 2012 on the content and submission conditions of annual declarations of nanoparticle substances (French Official Journal No 0185 of 10 August 2012, page 13166, text no 18)

provide information to the public"[28]. The definition adopted on this occasion was codified in Article R.523-12 of the French Environmental Code. It is as follows:

"*'Nanoparticle substance': a substance as defined in Article 3 of Regulation (EC) No 1907/2006, produced intentionally at the nanoscale, containing particles in an unbound state or as an aggregate or as an agglomerate, of which a minimum proportion of the particles, in the number size distribution, have one or more external dimensions between 1 nm and 100 nm.*

This minimum proportion may be reduced in specific cases where justified for reasons of environmental protection, public health, safety or competitiveness. It shall be specified by a joint order of the Ministers of the Environment, Agriculture, Health, Labour and Industry.

By way of derogation from this definition, fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanoparticle substances.

For the purposes of this definition, the terms 'particle', 'agglomerate' and 'aggregate' are defined as follows:

a) 'Particle' means a piece of matter with defined physical boundaries;

b) 'Aggregate' means a particle comprising strongly bound or fused particles;

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

The influence of the European Recommendation on the French public authorities is immediately apparent from this text. Apart from the change of subject matter, since it is not a question here of nanomaterials but of nanoparticle substances, the two definitions are almost identical. However, this point should be particularly emphasised. Indeed, as we have seen, the 2011 European Recommendation for a definition was intended (and still is, with the Recommendation published in 2022) to serve as a core definition that is not meant to apply directly as part of the European regulations unless it is explicitly included in sectoral regulations. The French definition, on the other hand, plays a completely different regulatory role, since it is intended to apply to all nanoparticle substances circulating in France, regardless of the industrial sectors in which they are or will be used during their life cycle. This point is all the more remarkable considering that, as stipulated in Article R.523-13 of the French Environmental Code, "*every manufacturer, importer and distributor of a nanoparticle substance, whether on its own or contained in a mixture without being bound to it, or of materials intended to release this substance under normal or reasonably foreseeable conditions of use, shall submit the declaration required under Article L. 523-1 whenever it produces, imports or distributes at least 100 grams of that substance per year".* In other words, even though the European and French regulations have undeniably moved closer together since the REACH Regulation was amended to include an explicit reference to the 2011 definition in its annexes, the French regulations on the declaration of nanomaterials still apply much more broadly than the European texts, giving French law a particularly pioneering role in this area that the European Union has not managed to extend to the entire EU, despite its intention to do so.

The amendment of the text of the core definition laid down by the Commission in 2011 will therefore have a major impact on the French regulations, requiring that the national public authorities make a decision that can be summarised as follows:

- Either maintain the definition as set out in the 2012 decree, creating potentially problematic distortions between EU and French law,
- Or change its definition, in which case it would be necessary to evaluate all the consequences that the changes made at European level may have for ANSES's practical implementation of all the mechanisms intended to implement the obligation to declare nanoparticle substances.

[28] Article 185 of the aforementioned Grenelle II Act.

3 Challenges involved in defining nanomaterials

3.1 Possible regulatory structures (and those in progress/conceivable/desired by certain stakeholders)

3.1.1 Reaffirmation of the need for an overall regulatory approach

The first practical difficulty faced by the European authorities when they put the issue of the definition of nanomaterials back on their agenda – running seven years behind the provisional timetable they themselves had set out in the 2011 Recommendation – was the role that this definition should play in the regulatory arsenal dedicated to these objects. As already pointed out above, the choice of the "object" that should be regulated – nanotechnology, nanoparticle, nano-object, manufactured nanomaterial, etc. – is, in reality, far from obvious from a political and regulatory point of view. However, it should be emphasised that, even within the limited scope of nanomaterials, the task of defining these nanomaterials can only be considered in relation to the role the definition is supposed to play in a framework that incorporates social, economic, political and technical dimensions. It is therefore logical that the European Commission chose to raise, before anything else, the issue of the regulatory approach to nanomaterials in the stakeholder consultation it organised in 2021. In Question 1, it thus affirmed that the "general format and fitness for purpose of the Recommendation on the definition of nanomaterial under review is associated with the general regulatory approach to nanomaterials taken in the EU" and then, for all useful purposes, stated that to help interpret responses further in the survey, the respondents were invited to indicate which of the answers corresponded best with their general position regarding the approach to nanomaterials in the EU.

3.1.2 The biases inherent in the suggested approach

Despite the variety of options it offered to stakeholders in response to this first question[29], the Commission had, as we will see, already made choices upstream that ruled out any possibility of making in-depth changes to the general regulatory framework on nanomaterials in Europe. Thus, by subjecting this consultation to the constraints specified in its preamble (revising the 2011 Recommendation, not opening up the discussion to include the definitions of nanomaterials that had been adopted as part of sectoral regulations such as the Cosmetics Regulation and the Novel Foods Regulation) and by directing the questions asked to the stakeholders so that they took a primarily technical view of the nature of nanomaterials as illustrated by all the questions in the second part of the consultation, the Commission was, in our opinion, clearly signalling that the idea of making the regulation of nanomaterials into a coherent whole was not on the agenda.

3.1.3 "Path dependency" as an explanatory factor

This positioning is not in itself particularly surprising. The regulation of nanomaterials is limited by a phenomenon of "path dependency"[30] where any deviation from the path could only be forced by a major crisis.

29

1): Nanomaterials are materials/chemicals like any other and do not require special legislation or special provisions.

2): Nanomaterials do not require legislation as a separate category of materials/chemicals, but specific nanomaterial provisions within legislation may be required in some sectors to ensure efficiency and effectiveness. A definition, triggering such provisions, is thus required.

3): Special, stand alone legislation for nanomaterials may be a more effective way to address at least some EU objectives, like for example high protection of human health and the environment. A definition, determining the scope of this legislation, is thus required.

4): Triggering specific provisions does not require a common definition for this subgroup of materials between sectors; triggers should be tailored to each individual situation.

5): A common definition of nanomaterial used across legislation and sectors increases efficiency and consistency of implementation.

30 Theorised by the economist Paul David in the 1980s, path dependency refers to the act of persisting in the choices one initially made, even if better solutions are available. This theory is derived from the sunk cost fallacy in behavioural economics, which refers to the tendency of individuals to be irrationally influenced by previous decisions (financial investments made, time spent, efforts put in, etc.) (Kirk, Reeves et Blackstock 2007).

The issue of nanotechnology regulation has in fact inspired very clear and repeated policy positions for the past 15 years or so. These have taken the form, for example, of technical drafting instruments, such as the two European Commission Communications on the regulatory aspects of nanomaterials[31], which are formally presented as simple reviews of the legislation but which nevertheless contribute to heavily implementing strong ideas such as the exceptionality of nanomaterials in the broader field of nanotechnologies and the need to approach their regulation without changing the law, i.e. without disrupting the structure of the normative system devoted to the protection of health, safety and the environment in the European Union, which is already implemented in the regulatory texts governing chemicals, the protection of workers, products, and the protection of the environment. Some of the consequences of these policy positions have been recorded in regulatory texts that now include provisions relating to nanomaterials that, in reality, cannot be amended within the framework of the current European institutions given the state of the public debate on these objects.

3.1.4 Limitations on possible regulatory developments

As previously demonstrated, the European Commission's public consultation suggested that it was highly likely that the regulatory approach adopted would continue to combine a more or less harmonised definition with sectoral definitions that would remain – when these existed – different. The very format of this definition published in 2022 as a Recommendation confirmed this analysis. Whatever criticisms one may have of the method used here by the European Commission – it should be recalled that among the stakeholders that responded to the above-mentioned consultation, the vast majority (12 out of 14) of public authorities (EU or Member State Authority) agreed that a harmonised definition across sectors would be more effective than the pre-existing situation – it seems essential to seriously consider this approach.

In this context, it seems necessary to clarify the scope of the definition on which the Working Group is ruling in relation to the provisions of sectoral legislation. This clarification was in fact called for in the next question of the European consultation (Question 2), when it separated the scope of the recommended harmonisation from the issue of the favoured normative document.

3.1.5 The extent of the proposed harmonisation

Regarding the extent of the harmonisation proposed during the revision of the 2011 Recommendation, several options were available as partly indicated in the responses suggested by the consultation[32]. These options included:

- the complete absence of a harmonised definition (Option 4) which would, as had been the case until 2011, refer the issue of the definition of the regulated object to each sectoral regulation concerned;
- a directly applicable harmonised definition (Option 1);
- maintenance of the approach chosen in 2011 (Option 3).

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31 Commission Communication of 17 June 2008 on "Regulatory aspects of nanomaterials" (COM(2008)0366) and Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee on the "Second Regulatory Review on Nanomaterials" (COM(2012) 572 final).

32 *Question 2 (CONSISTENCY OF NANOMATERIAL DEFINITION IN REGULATORY CONTEXT - A)*
Which of the answers below corresponds best with your position regarding the (harmonized) approach to nanomaterials in EU regulation? at least 1 choice(s):

1): A directly applicable and legally binding EU definition in place of the Recommendation would increase efficiency and consistency of implementation across sectors.

2): The present approach (definition from the Recommendation is made legally binding as it is taken up in sectoral legislation) is adequate, but direct reference to the Recommendation rather than copying of the text of the definition, should be made possible.

3): The present approach is adequate.

4): There is no inherent need for harmonisation – any definition needed for triggering specific provisions should be determined within the individual sector.

This last option could potentially be reinforced by a legislative drafting device consisting in not reproducing the definition in sectoral regulations that choose to follow it but rather referring directly to the text of the Recommendation (Option 2).

Two points, which in reality are intertwined, should nevertheless be made with regard to these options. Firstly, it should be stressed that an additional option could have been considered: the total harmonisation of the definitions applicable to nanomaterials. Just like Option 1 suggested by the European Commission, this would formally imply the adoption of a legally binding normative document but in this case, it would be different from a simple Recommendation. Secondly, as the consultation text stood, this option as presented in no way implied that different definitions would necessarily have to be changed, but only that past or future sectoral regulations not expressly defining nanomaterials would refer by their silence to the common definition as far as necessary.

As described above concerning the approach to regulatory developments underpinned by the European Commission's procedure, the issue of the extent of harmonisation achieved through the definition of nanomaterials currently under revision was therefore in reality constrained. No complete harmonisation could emerge from this revision.

3.1.6 The normative document for the proposed harmonisation

Similarly, as regards the choice of the appropriate normative document for revising the definition, two options were in fact suggested by the European Commission under Option 1:

- either a non-binding text (a solution towards which the term “revision” in the Recommendation strongly pointed);
- or a legally binding text.

As part of the consultation, no attention was paid to the choices that could nevertheless be offered under this second alternative. Indeed, if the option of a harmonised definition in a legally binding text were to be favoured, the choice of instrument would still need to be refined. Even if, given the objective, the use of a Directive – which would require transposition into the legislation of the EU Member States and would thus lose a significant share of its potential for harmonisation – was ruled out as being highly illogical, there were still many options. Firstly, it would have been necessary to determine whether a specific Regulation should be adopted as a normative document or whether the terms of a pre-existing, broader Regulation should be amended.

Next, with this second option, the choice of the text in which the harmonised definition should be implemented was not yet settled. In this respect, it seems possible to affirm that the most appropriate and most logical document from a substantive standpoint, given the functions conferred on this definitional undertaking, would undoubtedly have been the REACH Regulation, which governs the placing on the market of all chemicals and organises their evaluation and registration. However, the scale of the mobilisation required for its adoption, as well as the fact that, on this occasion in particular but also during subsequent revisions, the addition of specific provisions on nanomaterials was the subject of even more tense debates, made such a choice rather unlikely. Everything conspired, therefore, to maintain the situation as it was, with a harmonised definition exceptionally set out in a legally non-binding text.

3.1.7 The exact scope of the recommended harmonisation

Even in such a narrow framework, it was still possible to reflect on the form that the revision of the definition should take, going beyond the technical considerations to which the Commission referred in the second part of its consultation. To understand the terms of this reflection, it is important to place the issue under debate in the context of the necessary links between the common definition and sectoral definitions. Put simply, there were two possible options, which would approach the notion of nanomaterials in a way that would either give precedence to the objective of industrial development or would be more inspired by the precautionary principle.

With the first approach, the narrowest possible definition would need be adopted, leaving it to sectoral regulations to cover more objects if necessary in view of the intended applications of

nanomaterials (cosmetic, food, biocidal, medical applications, etc.) and the subsequent risks against which the legislation in question is meant to provide protection.

In the second case, on the contrary, it would be preferable to adopt the broadest possible scope for the core definition in order to ensure the specific assessment of as many nanomaterials as possible and establish the principle that sectoral definitions could only be less inclusive. With this approach, the issue of the assessment of nanomaterials would need to encompass as many substances as possible to determine the actual risks associated with them. The management of these risks, on the other hand, would respond to a logic potentially depending more on questions of expediency, justifying that in some sectors, fewer nanomaterials would be regulated than in the context of the assessment.

The choice of either of these regulatory approaches would clearly have a significant impact on the exact terms that would need be adopted to define nanomaterials. The WG's preference is for the latter approach, and it is therefore in view of such a broad core definition associated with potentially more restrictive sectoral definitions that the rest of this report should be read. This was not, however, the option favoured by the European Commission in its Recommendation of 10 June 2022, which states that[33]:

> *"1. 'Nanomaterial' means a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50 % or more of these particles in the number-based size distribution fulfil at least one of the following conditions:*
>
> *(a) one or more external dimensions of the particle are in the size range 1 nm to 100 nm;*
>
> *(b) the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm and the other dimension is larger than 100 nm;*
>
> *(c) the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm.*
>
> *In the determination of the particle number-based size distribution, particles with at least two orthogonal external dimensions larger than 100 µm need not be considered.*
>
> *However, a material with a specific surface area by volume of < 6 m^2/cm^3 shall not be considered a nanomaterial.*
>
> *2. For the purposes of point 1, the following definitions apply:*
>
> *(a) 'particle' means a minute piece of matter with defined physical boundaries; single molecules are not considered 'particles';*
>
> *(b) 'aggregate' means a particle comprising of strongly bound or fused particles;*
>
> *(c) 'agglomerate' means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components".*

3.2 Physico-chemical characterisation of nanomaterials and metrology

The implementation of regulations on nanomaterials requires the ability to accurately determine whether or not a substance should be considered a nanomaterial. And yet not all of the analytical techniques available are equivalent and not all are necessarily suitable for all situations. The choice of the technique(s) that should be used requires knowledge of the areas of application, and of the advantages and limitations of the various techniques available. Because of these limitations, related to the thresholds proposed in the definition of a nanomaterial (100 nm for the upper limit in the European Recommendation for a definition), it is often necessary to combine several techniques to answer the question of whether or not to classify a substance as a nanomaterial.

[33] Commission Recommendation of 10 June 2022 on the definition of nanomaterial (2022/C 229/01)

Two reports that address the metrological aspects of the characterisation of nanomaterials were published in 2019 and 2020 by the JRC and ANSES respectively. The one by ANSES[34] (Anses 2020) addresses the various physico-chemical parameters listed by ISO (ISO/TR 13014) for the identification and characterisation of nanomaterials and establishes recommendations for determining the nanometric nature of a sample. The JRC report[35] (Rauscher, Mech*, et al.* 2019) takes a very clear position in relation to the 2011 Recommendation for a definition by only addressing dimensional parameters. It sets out recommendations for characterising a material for classification in relation to the 2011 Recommendation for a definition. The conclusions and recommendations of these two reports are similar.

- **ANSES report (2020)**

The 2020 ANSES report recommends the use of several complementary techniques to determine the nanometric nature of a sample. For the measurement of sizes and the establishment of size distributions, the use of at least two techniques is recommended, one of which should be electron microscopy (scanning electron microscopy (SEM) or transmission electron microscopy (TEM)).

To determine the nanometric nature of a substance in relation to the 2011 European Recommendation for a definition, a simplified approach can be implemented and a decision tree from the European NanoDefine project is proposed:

- for powders: the Brunauer-Emmett-Teller (BET) method of measuring specific surface area can be used as a first approach, if the sample is pure and monomodal[36];
- for liquid media: as a first step, a first-level technique (dynamic light scattering (DLS), single particle inductively coupled plasma mass spectrometry (sP-ICP-MS), centrifugal liquid sedimentation (CLS), differential mobility analysis (DMA), etc.) can be used:
  - if the median diameter D50 measured with a first-level technique is below 100 nm, the substance is a nanomaterial;
  - if not, electron microscopy is necessary to determine whether the substance is a nanomaterial.

Lastly, the report mentions specific cases in which certain techniques cannot be used due to the chemical composition and/or the agglomeration and/or aggregation state of the materials: carbon nanotubes, synthetic amorphous silica (SAS)/carbon black, and organic substances.

- **JRC report (2019)**

The 2019 JRC report divides characterisation techniques into two categories: "screening techniques" and "confirmatory techniques".

- *Screening techniques* (DLS, CLS, tunable resistive pulse sensing (TRPS), particle tracking analysis (PTA), sp-ICP-MS, small-angle x-ray scattering (SAXS), asymmetrical-flow field-flow fractionation coupled with multi-angle light scattering (A4F-MALS), differential electrical mobility analysis on sprayed suspensions (spray-DEMA): these are indirect measurement methods used to calculate an equivalent diameter (diameter of a sphere that would give the same result if analysed under the same conditions as the particle being analysed, which may be of a complex shape). They cannot directly measure the number size distribution. They are rapid and inexpensive methods that potentially enable a material to be classified as a nanomaterial if the median diameter D50 measured is below 100 nm[37].

[34] https://www.anses.fr/fr/system/files/AP2018SA0168EN.pdf.

[35] https://publications.jrc.ec.europa.eu/repository/handle/JRC118158.

[36] The monomodal nature of a sample cannot be known a priori. Electronic microscopy images need to be taken to determine it.

[37] The Working Group does not consider SAXS to be a screening method, due to the expertise required to process the data (for example, strong morphology assumptions must be made for the data analysis).

- *Confirmatory techniques* (SEM and TEM, atomic force microscopy (AFM)): these direct measurement techniques can determine the number size distribution. They are more expensive and take longer to implement than screening techniques. They produce more reliable results, allowing doubts or disagreements to be resolved. They are also used when screening methods cannot decide whether a material should be classified as a nanomaterial or not. Lastly, they are able to identify and measure constituent particles in agglomerates/aggregates and deal with cases of non-spherical particles and polydisperse samples.

In the specific case of pure and monomodal powders, the volume-specific surface area (VSSA) can give a first indication of whether a material may be a nanomaterial with respect to the 2011 Recommendation for a definition. Nevertheless, the Working Group stresses the limitations associated with measuring the VSSA, which will be detailed later in this report.

The JRC report emphasises a number of important points for the characterisation and identification of nanomaterials:

- the need for reference methods such as ISO standards and guidelines (e.g. OECD guidelines);
- the importance of using best practices when reference methods are not available. These best practices must be validated, for example through inter-laboratory comparisons;
- the need to clearly define the chosen measurand;
- the importance of sample preparation, which must not change the size distribution of the original material. It is also important to ensure that the prepared sample is stable (points to watch out for: agglomeration/deagglomeration, homogeneity, sedimentation).

The report provides decision trees for the identification of a nanomaterial with a first step consisting of a screening technique distinguishing between liquid dispersions and powders. If this first step is inconclusive (i.e. if the median diameter D50 measured with a screening technique is above 100 nm), a confirmatory technique will need to be used.

Lastly, the report sets out a list of considerations to be taken into account when choosing the technique that will be used to characterise a material so it may be classified as nano or non-nano in relation to the European Recommendation for a definition: is the available physico-chemical information sufficient to guide the choice of technique? Is the chosen technique compatible with the material? What is the purpose of the analysis (screening or confirmation)? Has the method been validated? What type of raw data is produced? Is the sample analysed representative of the original material? Is sample preparation appropriate? How reliable are the results? Etc.

The diagram below summarises the two-step approach presented in the two reports for determining the nanometric nature of a material:

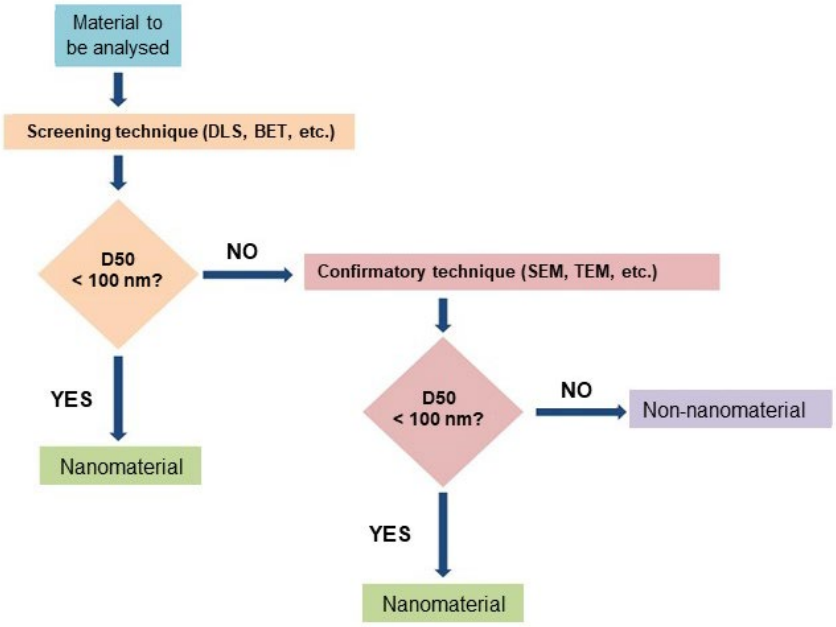


Figure 3: Description of the characterisation steps considered to determine the nanometric status of a sample

3.3 Specific criteria for the identification of nanomaterials

3.3.1 (Objects) or materials to be considered

It is essential to first agree on a conceptual definition before attempting to establish technical criteria that will enable the scope of nanomaterials to be defined more precisely in practice.

The history and the technical and regulatory context of this nanomaterials issue, described in the previous chapter, highlight the various underlying reasons why there has been a proposal to define a group of objects under the term “nanomaterials”. It can also be noted that the vocabulary on this topic has grown more varied over time (nanotechnology, nanoparticles, nano-objects, nanomaterials, nanoforms, nanoparticle substances, etc.). It therefore appears that it is widely agreed that the issue in question involves objects with dimensions at the nanoscale, which can give the material specific properties and/or behaviours (that are new or different compared with objects of the same chemical nature with larger dimensions).

These particularities are exploited and showcased for a wide variety of more or less innovative applications. In terms of health and safety, these possible effects of scale also suggest major differences in terms of risk assessment (toxicity – ecotoxicity and fate in the environment): these data relating to health and ecotoxicological risks, conventionally listed by chemical form, are therefore not directly transposable to nanomaterials of the same chemical form. These uncertainties justify the particular attention paid to nanomaterials in terms of health, and show why it is advisable to at least question or even verify the state of available knowledge on these objects.

3.3.1.1 Dimensions involved and consideration of nanostructured materials

This conceptual definition, which is very evasive, raises questions about the nature of the dimension(s) specifically being considered. That is why technical definitions commonly refer to notions of internal and external dimensions of objects.

As shown in Figure 4, ISO distinguishes between nano-objects, which have one, two or three external dimensions in the nanoscale, and nanostructured materials, which have internal or surface nanostructures (see examples in Figure 5).

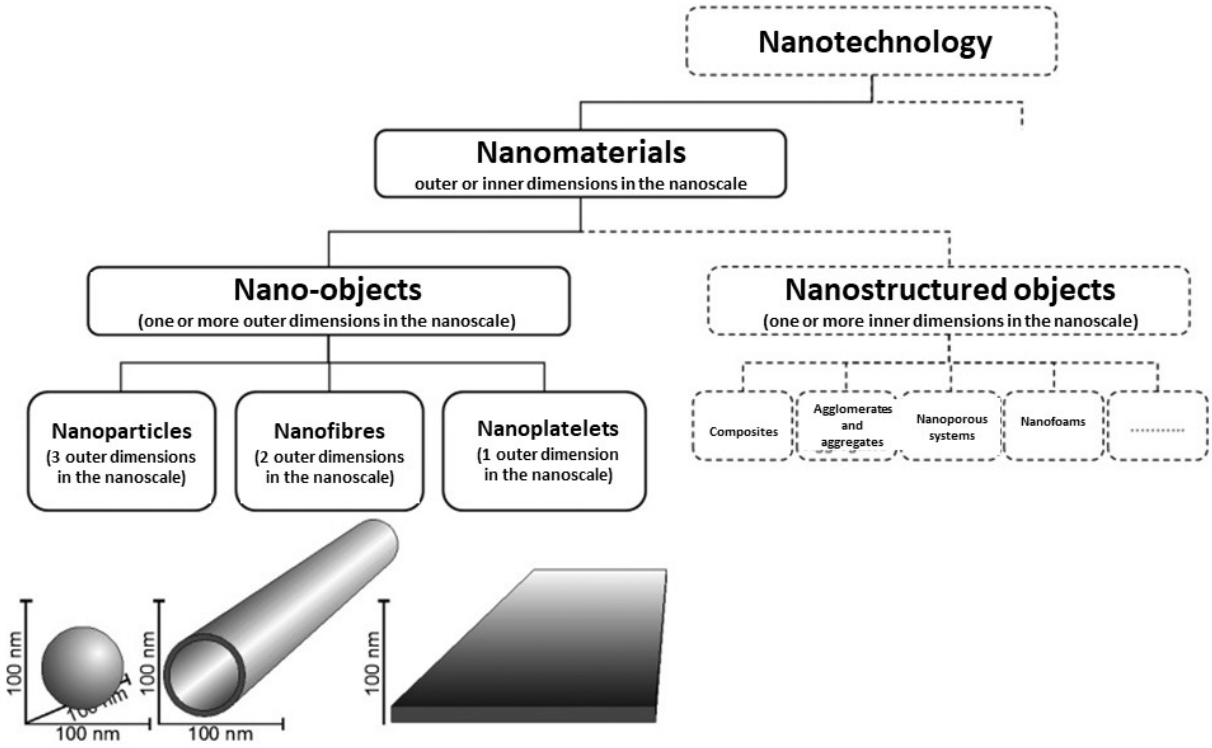


Figure 4: Classification of nanomaterials according to ISO (adapted from (Krug et Wick 2011))

In addition to the one proposed by ISO, there is another classification of nano-objects, commonly used for carbon nanostructures, for which the number D of dimensions (from 0 to 3D) refers, unlike the ISO classification, to dimensions above the nanoscale. For example, in this classification, a fullerene is a 0D nanomaterial, a carbon nanotube a 1D nanomaterial, and a graphene sheet a 2D nanomaterial.

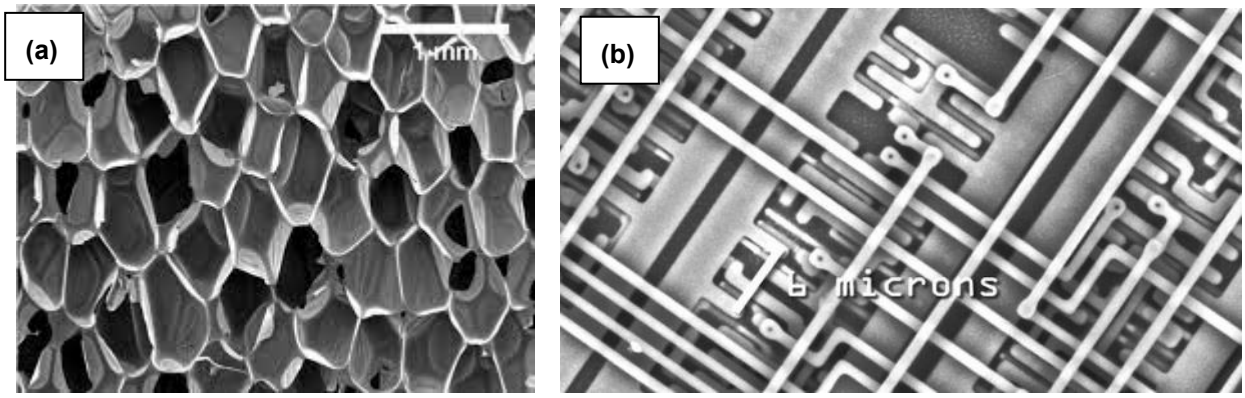


Figure 5: Examples of nanostructured objects:

a) internal structure of polyurethane foam (Kairytė *et al.* 2020)

b) view of a microprocessor surface

The consideration of nanostructured materials with regard to the scope of the definition of nanomaterials shows a significant discrepancy between the definitions produced through standardisation and those proposed by the European Commission. While ISO considers these more massive objects to be included in the definition of nanomaterials, the European Commission thus far only considers nano-objects and their aggregates and agglomerates (NOAAs).

The issue of extending the European definition to all such nanostructured objects, raised in 2011 (see (Linsinger *et al.* 2012)) was not, however, addressed during the public consultation on its revision in 2021, implicitly excluding the consideration of nanostructured objects. The more recent Recommendation published in 2022 then made this exclusion explicit in its Recital 11[38].

The consideration of nanostructured materials raises somewhat different issues from those of nano-objects (characterisation techniques, differentiation between surface nanostructure and surface defects, etc.). In the current state of knowledge, it is possible that these more massive materials may pose specific risks associated with the presence of nanostructures (compared with objects of the same chemical nature that are not nanostructured). However, the related health issues prove very different from those considered for nano-objects (in terms of exposure and spread in the body or in environmental compartments, for example) and are generally considered to be of lower priority.

Therefore, if nanostructured materials were to be included in the scope of the European Commission's definition of nanomaterials, they should nevertheless be distinguished from nano-objects.

3.3.1.2 Constituent particles and hybrid and composite materials

The notion of constituent particles appears essential to the definition of nanomaterials. This term is found in the large majority of current definitions: the dimensions of these constituent particles are examined in relation to the dimensional thresholds, whether they are on their own or aggregated/agglomerated together. Therefore, the aggregates and agglomerates of such objects with nanometric dimensions are unanimously considered as nanomaterials, although the sizes of these assemblies can reach much larger dimensions (of the order of hundreds of microns).

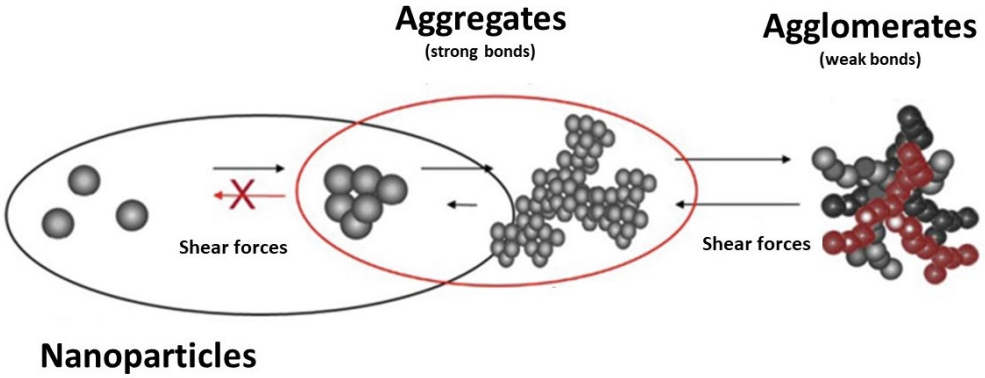


Figure 6: Formation of reversible or non-reversible aggregates and agglomerates from nanoparticles (diagram adapted from (Nasrollahzadeh, Sajadi et Iqbal 2019)).

This consideration is regularly supported through two arguments accepted by the scientific community (Rauscher, Roebben*, et al.* 2019):

- the properties (chemical reactivity in particular) observed for these assemblies differ very little from those observed for the single particles composing such assemblies;
- depending on the bonding strengths involved, the constituent particles may be released more or less readily (see Figure 6).

Complex issues relating to the nature of the material's bonds therefore come into play in this notion of constituent particles in order to be able to distinguish between "classic" materials (composed of atoms that could be considered as the only "building blocks" of the material, strongly bound to one another) and assemblies of these nanometric constituent particles (see § 3.3.3.4).

[38] 11) The definition should not cover large solid products or components, even when they have an internal structure or a surface structure at the nanoscale, such as coatings, certain ceramic materials and complex nanocomponents, including nanoporous and nanocomposite materials. Some of these products or components may have been manufactured by using nanomaterials and may even still contain them.

In the case of nanomaterials, these concepts of aggregates and agglomerates usually refer to objects of the same chemical nature. However, there are also heterogeneous mixtures, known as hybrid and/or nano-composite materials (see § 3.3.3.3). Depending on the dimensions of the various objects associated with each other and the bonds involved, these assemblies can possibly be considered as nanomaterials or objects with surface or volume nanostructure. The dispersion of nanometric elements within a dispersing phase or medium results in a nano-composite. A massive nano-composite object, and more generally a product whose ingredients include nanomaterials, cannot itself be considered a nanomaterial. The term “nano-enabled products” (NEPs) has recently emerged in the scientific community to refer to these massive objects containing nanomaterials and distinguish them from nanomaterials. As such, the diagram of Hansen *et al*., regularly used to categorise the different types of nanomaterials, is obsolete in the context of the EU definition but nonetheless remains useful to illustrate and understand these NEPs (Hansen *et al.* 2007).

The example of the trademarked material “Candurin®” perfectly illustrates this challenge of determining what should be considered as the constituent particle(s): this food colouring compound with a pearl effect is composed of micrometric platelets of mica (E555) on which nanoparticles of titanium dioxide (E171) or iron oxide (E172) are deposited. This object can be considered at least as having a nanostructured surface.

It can also be considered as a hybrid material composed of distinct parts bound together. In the simple case where the bonds are weak (Figure 7-a), two populations of constituent particles are then considered: on the one hand, the bare mica platelets and on the other, the nanoparticles deposited on their surface. In the opposite case, where these bonds between nanoparticles and the surface are very strong (fusion, for example, requiring high energy to dissociate them, or even rupture of the structure, as in Figure 7-b), the whole assembly, i.e. the platelet with the particles deposited on its surface, could then be considered as the constituent particle.

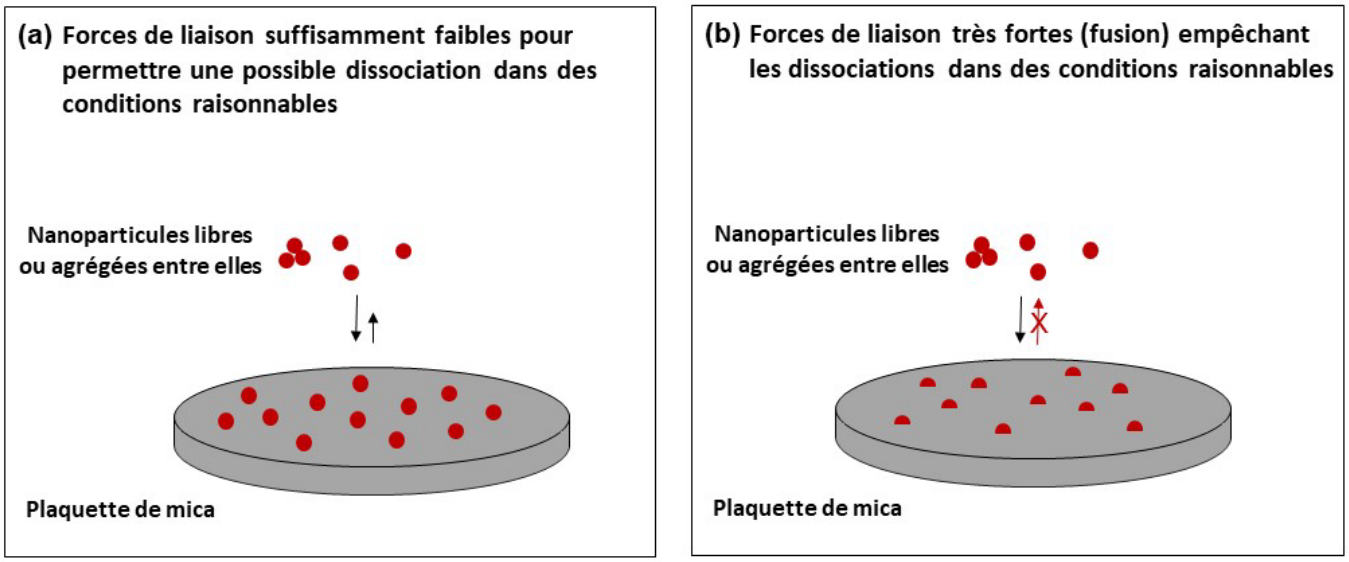


Figure 7: Example of a Candurin® hybrid object (pearlescent pigment) composed of a micrometric platelet of mica on which nanoparticles of metal oxides (TiO_2, FeO) are bound, and consideration of the potential to release constituent particles as a function of the bond, whether (a) weak or (b) strong.

The bound state is therefore critical for the determination of constituent particles, although there is no precise criterion (type of bond or level of bond energy) applicable to all possible cases that would enable bonds between constituent particles to be distinguished from bonds within a constituent particle.

3.3.1.3 Notions of nanoscale and nanospecific properties

The dimensional range defining nanomaterials refers to the notion of nanoscale for which a material exhibits specific properties. It should be stressed at this point that the properties of the material depend on many physico-chemical parameters, including the dimensional aspect. For example, ISO (ISO/TR 13014:2012) considers a limited number (eight) of parameters deemed essential for assessing the health and environmental impact of nanomaterials[39]. Quite logically, the dimensional limits therefore differ at least according to the chemical nature of the material, which means that there can be no universal dimensional thresholds.

More fundamentally, the grouping of objects under the term “nanomaterials” raises questions about the exact nature of the desired properties enabling this nanoscale to be defined. These properties, which are also selection criteria, can be of two types:

- “quantum” or nanospecific properties of the material. In this case, nanomaterials refer to objects acquiring physico-chemical properties at the nanoscale that are different from those known at higher dimensional scales (bulk materials). Such properties can differ widely (increased physico-chemical reactivity, new electrical or optical properties, etc.). According to Auffan *et al*., such changes in the material would only occur below 30 nm and would depend singularly on the proportion of atoms present on the surface (Mélanie Auffan *et al.* 2009) (see Figure 8);
- properties relating to effects on living organisms. In this other case, nanomaterials are objects whose effects on living organisms would be different from those known at higher dimensional scales (bulk materials). The underlying logic associated with this type of criterion is to identify new consequences for living organisms that have not been considered for the materials.

It is important to underline that these comparisons between nanomaterials and their equivalents at the conventional dimensional scale can only be made when this bulk equivalent exists. This logic is, for example, inoperative in the case of carbon nanotubes (there is no equivalent material at the macroscopic scale).

[39] **Appearance:**

1/ Particle size/size distribution
2/ Shape
3/ Specific surface area

Composition:

4/ Chemical composition, crystalline structure and purity
5/ Surface chemistry

Interactions:

6/ Surface charge
7/ Agglomeration/aggregation state in relevant media
8/ Solubility/dispersibility

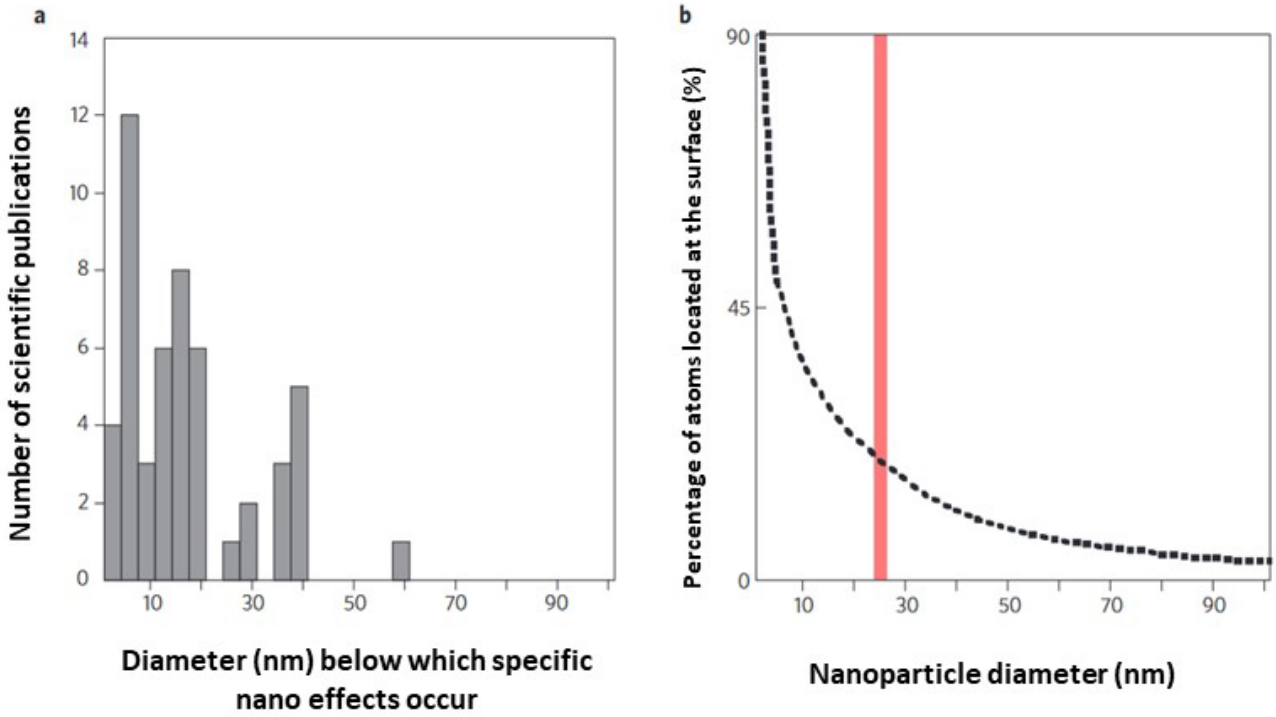


Figure 8: a) Number of scientific articles identified by Auffan *et al.* reporting effects related to the nanoscale as a function of the particle sizes considered (x-axis); b) Estimated percentage of atoms located on the surface of a particle as a function of its diameter (Mélanie Auffan *et al.* 2009)

These two types of criteria do not necessarily overlap: the reduction in particle size may have biological consequences (crossing of biological barriers, for example) without the material acquiring any new physico-chemical properties. Conversely, the material may acquire new physico-chemical properties without having any major consequences for living organisms.

The first type of criterion therefore relates to physico-chemical properties, which are generally intrinsic and therefore simpler to determine than their consequences for living organisms. However, for the reasons mentioned above, it is not completely satisfactory with regard to health issues. The second option aims to respond more broadly to public health and environmental objectives (identification of differences in effects on living organisms due to dimensional aspects); however, the criteria involved are more complicated to define, as the effects on living organisms result from the physico-chemical characteristics specific to the object in question but also from extrinsic parameters (i.e. depending on environmental factors such as exposure conditions, the type of biological target considered, etc.).

This questioning of the line between the material's properties and its effects may seem anecdotal, but in reality, it is fundamental to reach a clear understanding of the logical basis on which “nanomaterials” as a whole are viewed: through the dimensional screen of the nanoscale (intrinsic characteristic), what properties or effects are being sought? Should the physico-chemical properties of the material or rather the effects on living organisms be considered to delimit this nanoscale? These uncertainties, which are too seldom questioned or clarified, still largely add to the confusion surrounding the definition of nanomaterials.

In the absence of any decision on this point, the dimensional aspect is regularly used as a “simple” proxy for identifying objects whose effects on living organisms deserve special attention because they are potentially different from those known at larger conventional dimensions, without, however, there being any clearly established and justified thresholds.

3.3.2 Dimensional criteria

3.3.2.1 Distribution threshold and size distribution threshold

- **Consideration in the 2011 Recommendation for a definition: criteria to be taken into account**

As underlined in the 2019 JRC report, the 2011 EC Recommendation on the definition of nanomaterials only applied to materials consisting of particles. This was made explicit in 2022 when this Recommendation was updated. As there are no generic relationships between particle size and the physico-chemical properties of the end material, the only feature that is common to all nanomaterials is their nanoscale physical dimensions. Therefore, the EC definition is essentially technical and methodological and based on the notion of size, and it categorises a material as "nanomaterial" if 50% or more of its constituent particles fall in the size range from 1 nm to 100 nm, according to the particle number-based particle size distribution. This precise criterion enables its regulatory implementation.

In comparison, the FDA has not established any definitions of nanotechnology/nanomaterials or other related terms, but it considers any regulated product (with or without nanotechnology) based solely on its safety and efficacy characteristics. These terms are, however, commonly used in relation to the engineering (i.e. deliberate handling, manufacture or selection) of materials that have at least one dimension in the size range of 1 to 100 nm. Therefore, to determine whether an FDA-regulated product involves nanotechnology, the FDA[40] asks whether the end material or product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 to 100 nm), without any notion of a size distribution threshold. In addition, because end materials or products can also exhibit specific properties or phenomena attributable to one or more dimensions outside the nanoscale range that are relevant to health risk assessments, the FDA also asks whether the end product is engineered to exhibit properties or phenomena (including physical or chemical properties or biological effects) attributable to its dimension(s), even if those dimensions fall outside the nanoscale range, up to one micrometre (1,000 nm).

The lower limit (1 nm) specified in the EC Recommendation for a definition raises other issues related to this external dimension. Indeed, although this low threshold was established to exclude small molecules from this definition, it excludes certain nano-objects such as fullerenes and graphenes while including, for example, proteins larger than 1 nm that should not be included in the definition of nanomaterials for the obvious reason that they are purely biological. Nanotubes and nanofibres can also have a diameter of less than 1 nm and a length of more than 100 nm and yet will be excluded from the definition based on these thresholds alone. And yet these particular (nano)materials (which are outside the thresholds) can pose specific health risks related to their extremely small size, if not similar to the effects already listed for forms between 1 and 100 nm (Chetyrkina, Fedorov et Nasibulin 2022; Svadlakova *et al.* 2022).

- **Arguments on primary particle size (dimensional threshold)**

Regarding the upper and lower limits, the size of the primary particles (in the sense of individual particles) is the universal criterion in any definition of nanomaterials. As highlighted by the SCENIHR (Scenihr 2010) and reiterated by the JRC (Mech *et al.* 2020), external size is based on the external dimension of the core particle and not the final functionalised form (e.g. after adding organic chains or a coating, corona, etc.). This is a "key" step in establishing the (number-based) size distribution of a given material and a prerequisite for the notion of a "size distribution threshold" enabling a material to be defined as "nano" or not according to the EC Recommendation for a definition.

However, the notion of "particle size" is not clearly defined in the EC Recommendation for the definition of nanomaterials. As underlined in the JRC report (Rauscher, Roebben, *et al.* 2019), the shape of the particles constituting or contained in a material is usually not a simple "sphere" (which

[40] https://www.fda.gov/media/109910/download.

would be easy to measure on account of its actual, geometric diameter); rather, it is much more complex as it has several characteristic external dimensions; in fact, different measurement methods are likely to generate different diameters when applied to the same particle. Except with direct measurements by AFM, SEM or TEM (capable of measuring the geometric diameter), when the external dimension is expressed as an “equivalent sphere” diameter (minimum Feret diameter), it seems clear that any particle with an irregular or non-spherical shape will have multiple external dimensions depending on its orientation. Furthermore, the fact that the term “external dimension” replaces “particle size” in the EC Recommendation for the “nano” definition shows that the particle is considered as a solid object without taking into account possible complex internal structures.

In Canada[41], the Canadian Standards Association defines a nanomaterial as a “material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale”. According to Health Canada, a nanomaterial is “any manufactured substance or product and any component material, ingredient, device, or structure if:

- it is at or within the nanoscale in at least one external dimension, or has internal or surface structure at the nanoscale;
- it is smaller or larger than the nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena”.

For the JRC, the notion of “internal structure” is relevant for complex nanomaterials such as liposomes that can be loaded with active or other substances that vary in nature (including metals) for applications in medicine or plant protection products or for use as food additives or in the cosmetics sector. Many of these liposomes have external dimensions above 100 nm and the inclusion of a notion of “internal structure” with the same upper limit as a dimensional threshold would enable liposomes to be defined as nanomaterials.

The JRC also reiterates that particles of which one of the three orthogonal external dimensions is much smaller than the other two are often called plate-like particles (or “platelet-like”, when small), while particles of which two external dimensions are much smaller than the third are called fibres or elongated particles (this is the case, for example, of multi-wall carbon nanotubes). For the latter, the length and shape of these tubes/fibres can be ignored when determining the size distribution, and the appropriate dimension to be taken into account for a correct assessment against the EC definition is the diameter. For plate-like (such as montmorillonite clay) or flake-like (such as graphene flakes) particles, the appropriate “external dimension” for the application of the EC definition is the average thickness of the platelets/flakes.

■ Aggregates and agglomerates: impacts on the application of the EC definition

The formation of aggregates and agglomerates combining several particles and particle sizes generally complicates the application of the EC Recommendation for a definition. In an agglomerate, the constituent particles are weakly bound to one another, whereas in an aggregate, they are strongly bound. Such assemblies generally result in a shift in the external dimensions to sizes much larger than those of the constituent particles, which may bias the particle measurement methods required for “nano” classification. In aggregates, it should also be noted that strong fusion bonding of the primary particles is also accompanied by deformations (see Figure 12), implying that measurement methods should not proceed by simple addition of the original individual particle sizes prior to their fusion assembly. Therefore, in this context, the JRC notes that the term “primary particle”, which is not mentioned in the Recommendation, is nevertheless often used incorrectly in the case of aggregates and agglomerates. As primary particles are the initial (single) forms from which a material is assembled, they may therefore differ from constituent particles, which are morphologically identifiable within a material as aggregates or agglomerates (see Figure 6) and may potentially be different from the original particles.

[41] https://www.canada.ca/en/employment-social-development/services/health-safety/reports/engineered-nanoparticles.html#h2.2

Furthermore, the JRC insists on the fact that aggregates and/or agglomerates can themselves interact with one another and form even larger agglomerates of aggregates. These secondary structures can be complex and highly dynamic, as they vary depending on the medium in which they form. Therefore, the number of constituent particles in a larger unit can change rapidly, particularly in the case of agglomerates, modifying the particle size distribution of samples. This is the main reason why the EC Recommendation for a definition is based on the size of the constituent particles, which is a "stable" measure and therefore a "reliable" characteristic for defining a nanomaterial (even though the size of the constituent particles can sometimes be difficult to measure, as highlighted above). Therefore, whereas the implementation of the EC definition does not require a distinction between aggregates and agglomerates, these two particular forms and their dynamics in different media have a strong impact on the choice of the appropriate measurement methods.

Lastly, it should be noted that the EC Recommendation for a definition does not mention that aggregates and agglomerates can result from the bonding (whether strong or not) of particles of different crystalline forms and/or chemical natures, or even of particles with different shapes (e.g. spheres, tubes, flakes). Such an association has consequences with regard to the choice of measurement methods, for example for the hybrid material with the brand name "Candurin®", which combines different basic structures (mica microplatelets on which spherical TiO_2 nanoparticles are bound) (see Figure 7) and when nanometric structures within the aggregate/agglomerate are hidden because they are embedded (see § 3.3.3.3).

On these complex morphological grounds, the JRC (Rauscher, Mech*, et al.* 2019) mentions that only electron microscopy (TEM or SEM) can distinguish constituent particles from an aggregate or agglomerate and that this is the only recommended technique for measuring their size (see § 3.2).

- **Arguments on particle size distribution (size distribution threshold)**

In the EC Recommendation for a definition, the classification of a material as a nanomaterial requires that 50% or more of the constituent particles have one or more external dimensions in the size range 1-100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness, the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%.

As discussed above, the choice of the descriptor (or measurand) for measuring the size (median diameter, thickness) depends on the type of particle (sphere, flake, platelet, tube, etc.) and is closely related to applicability and feasibility depending on the type of material (in particular if aggregates and agglomerates are present) and the types of measurements to be taken (minimum and maximum Feret diameters, equivalent sphere diameter). The choice of the dispersion medium for sample preparation is also an essential criterion for determining the particle size distribution, with the reports (SCENIHR, JRC) further stressing that there is no generic preparation method applicable to all materials. Lastly, in practice, the JRC report (Rauscher, Mech*, et al.* 2019) reiterates that the size distribution of a material is often determined based on mass or volume, which can hardly be converted into a number size distribution even if the shapes of the particles are known. Therefore, most volume- or mass-weighted average particle diameters are equivalent diameters based on the assumed particle shape, as they generally do not refer to individual particles but more often to aggregated or agglomerated particles.

The JRC underlines the fact that advocating the number size distribution as the sole distinguishing criterion is another aspect that may have major consequences. This is particularly the case when materials with a very low mass fraction of nanoparticles may escape the EC definition due to measurement uncertainties that may lead to different classifications in different laboratories (a low mass concentration of nanoparticles in a product may still represent a high number of constituent particles).

In this context, the European Food Safety Authority (EFSA) was mandated by the EC in 2021 to develop guidance on technical requirements for food applications to establish the presence of small particles including nanoparticles (More *et al.* 2021). To ensure a high level of protection of human health and consumer interests, this guidance was prepared to meet the requirements of the Novel

Foods Regulation, which does not consider a size distribution threshold value (set at 50% for the EC Recommendation for a definition). In particular, this document outlines appraisal criteria for deciding whether or not to conduct a nanospecific assessment for substances that initially do not meet the definition of “engineered nanomaterials” as mentioned in the Novel Foods Regulation but may nevertheless have nanoparticles formed naturally or during the food process that will need to be assessed. Pragmatically, this guidance should be applied when the large majority of the material is not at the nanoscale, but a tiny tail within the particle size distribution at the nanoscale may be present due to the manufacturing process. It includes a quantitative approach to determine the number-based proportion of particles smaller than 500 nm and then, ultimately, the percentage of possible nanoparticles in the distribution tail. The rationale behind this appraisal route is that particle uptake from the gastrointestinal tract has been generally found to be possible for sizes up to 250 nm. Materials that only contain a negligible fraction of particles smaller than 250 nm would not have to undergo a nanospecific assessment. An uncertainty factor of 2 is applied to account for the limitations of available screening techniques for size measurements, resulting in a limit of 500 nm.

- **Size/size distribution threshold and toxicological concerns**

The upper dimensional limit (100 nm) is thus the first criterion for “nano” classification in the EC Recommendation for a definition. It is a criterion that, in addition to the issue of the material's properties below and above it (it does indeed seem that “nanospecific” properties, in terms of specific physico-chemical reactivity at the nanoscale, disappear for larger materials), also raises the question of its possible significance in the biological sense. Even so, this upper size limit is not a threshold relating to limits of absorption (e.g. through biological barriers such as the lungs, intestines, placenta, etc.) or toxicity for an organism. Dimensions greater than 100 nm (e.g. between 100 and 1,000 nm) can potentially cause materials to have toxic effects similar to those of nanoscale forms and make it easier for them to cross biological barriers compared with dimensions well above one micron.

The dimensional threshold for defining the size of nanomaterials is the subject of considerable debate worldwide as to whether to include particles and materials up to 1,000 nm. For example, in the UK, with regard to nanotechnologies and food, the House of Lords noted in 2009[42] that although nanoscale properties (and as a consequence novel functionality) typically emerge at sizes below 100 nm, a threshold of 100 nm as such has no toxicological significance; larger particles may also exhibit novel properties and should therefore be considered nanomaterials for risk assessment purposes. Therefore, including phrases such as “of the order of 100 nm” in a definition does not appear to assist in the assessment of health risks; on the contrary, using an approximate value of 100 nm creates “blurring” for regulators and industry. Thus, the UK Parliament recommended that the Government should work towards ensuring that any regulatory definition of nanomaterials proposed at European level, in particular in the Novel Foods Regulation, should not include a size limit of 100 nm but instead should refer to the nanoscale (or sub-micrometre scale) to ensure that all materials with a dimension under 1,000 nm are considered. It underlined that any definition of “nanomaterial” should not be limited to an arbitrary dimension of 100 nm but instead should focus on any changes in properties (involving a change in functionality, i.e. in the way a substance interacts with the body) that emerge as a result of a material being at the nanoscale (smaller than 1,000 nm).

While the UK Parliament (2009) also noted that the definition used in the INCO and Novel Foods Regulations also includes materials over 100 nm if they “retain properties characteristic of the nanoscale”, the House of Lords recommended that Government should work within the European Union to clarify the phrase “properties that are characteristic to the nanoscale” by including a more detailed list of what these properties might comprise. It indicated that this list should be regularly reviewed as the understanding of nanomaterials develops, to ensure that it provides comprehensive and up-to-date coverage of relevant properties.

- **Review of the European Commission's proposed changes**

42 https://publications.parliament.uk/pa/ld200910/ldselect/ldsctech/22/2202.htm.

As highlighted by ANSES in its response to the public consultation to revise the EC definition of "nanomaterials", the issue of upper and lower dimensional thresholds (1-100 nm) was not addressed in this consultation. Only the flexibility of the size distribution threshold was the subject of a proposed change, possibly to remove this safety criterion altogether. As for the default threshold of 50%, the EC suggested maintaining this value.

As a reminder, in Recommendation 2011/696/EU, the notion of flexibility had been introduced as a safeguard due to the lack of knowledge and the uncertainties surrounding nanomaterials at this time. However, the EC considered that such a criterion could also create confusion among economic operators, consumers and regulators. Depending on the thresholds used in sector-specific legislation, the same material could be considered a "nanomaterial" under one regulatory framework but not another. This was also the main reason why direct reference to the definition of nanomaterials in Recommendation 2011/696/EU could not be made in some cases.

According to the EC, the review of the definition did not identify any evidence that the default threshold of 50% (meaning that over half of all the particles in the material must be nanosized) should be increased or decreased to address particular concerns or cover or exclude certain materials. Moreover, if the threshold were reduced from 50% to a lower value, the challenges associated with measuring particle size distribution would also be further increased.

For all these reasons, in its 2021 public consultation, the EC suggested removing this flexibility criterion from the definition, leaving only the default size distribution threshold of 50%.

- **The JRC's arguments supporting the European Commission's proposals**

Maintaining the flexibility of the threshold

Flexibility allows regulators to address particular concerns for the environment, health, safety or competitiveness in specific regulatory areas by regarding a material as a nanomaterial even if it contains less than 50% nano-objects; this would open up the possibility of requiring nanospecific assessments for such "non-nano" materials (according to the EC definitions, 2011 and 2022) nevertheless exhibiting nanospecific characteristics or properties because they contain a non-negligible fraction of nano-objects. Conversely, a higher threshold could be considered for substances that do not pose any risks to health with a view to industrial competitiveness.

Lowering the threshold for specific sectors, applications or materials could, on the other hand, create confusion among consumers and economic operators. Application of a lower threshold by EU Member States could lead to the use of different values in individual Member States.

According to the JRC, one should also bear in mind that the definition of nanomaterial is intended to be without regard to hazard or risk, as specified in Article 4 of the EC definition[43]. Still according to the JRC, such concerns could nonetheless be addressed by restricting the use of the materials in question in certain sectors, applications or products, rather than lowering the threshold in the definition, e.g. by limiting the content of certain substances at the product level.

Removing the flexibility of the threshold from the definition

On the one hand, with a fixed threshold, possible concerns regarding the safety of certain materials or uses cannot be addressed by lowering this threshold on a case-by-case basis as provided for in the 2011 version of the Recommendation for a definition. It would then become impossible to trigger additional corrective actions, as discussed in the previous option.

On the other hand, in an in-depth analysis of various aspects of the flexible threshold value, the JRC concluded that "*the flexible approach impacts negatively on the transparency of the legislation addressing nanomaterials due to the fact that materials may be regarded as nanomaterials or not, depending on the legislation. It counteracts the intention that the EC definition should guarantee that a material which would be regarded as nanomaterial in one sector will be given the same*

[43] "*should be based solely on the size of the constituent particles of a material, without regard to hazard or risk*".

classification if used in another one”. Furthermore, the JRC report noted that “*current methods would not allow reproducible and valid measurements at the lower end of the flexible threshold range*”.

- **Consequences of these proposed changes**

A large number of substances composed of nano-objects but with a number fraction below the 50% threshold would not be included in this definition and would risk being assessed by default under a conventional chemicals process if specific sectoral risk management measures were not taken.

- **Debates and arguments from the public consultation**

The Member States other than Belgium and France that responded to the public consultation (Germany, Ireland and Norway) were in favour of the proposal to remove the flexibility criterion and maintain the minimum size distribution threshold at 50%. However, as underlined by Norway and Belgium, given the deadline of 1 January 2020 for providing new information on nanomaterials and their classification, it was considered impossible in this context to decide whether or not to validate the EC's proposed changes to the definition.

Like France, Belgium considered there was no basis to the European Commission's argument that the lack of or limited use of this flexibility option justified removing it from the definition. Similarly, there was no scientific justification for a single threshold of 50%, which was deemed purely arbitrary, and lowering this threshold would therefore not cause any future difficulty in the classification of substances, given improvements in size measurement methods.

EFSA, for its part, stressed the lack of explanations provided by the EC justifying the change in threshold, which was deemed purely technical and not based on any biological considerations in terms of health risk assessment needs. The European agency insisted on the need to take into account substances with a nanometric fraction below this 50% threshold as well as those consisting of “small particles” (with dimensions smaller than 500 nm), which should be included in the new definition.

- **Reasoned opinion of the Working Group**

The issue of flexibility is closely linked to that of the threshold value itself, which means that the answers given cannot be dissociated. The various options were to keep the threshold at 50%, provided that it could be lowered as appropriate, set the threshold at a very low fixed value, or not set a threshold. It should be noted that determining the methods for characterising particle size distribution used to verify this inclusion/exclusion criterion for a material is particularly crucial.

Concerning the flexibility of the threshold, this option has seldom been used in practice and has often been viewed as an obstacle to the harmonisation of the definition. However, it avoids arbitrarily setting a threshold value intended to be applicable to any chemical substance and covers differences between different application sectors (no size distribution threshold for the Novel Foods Regulation, for example).

Specifically regarding the threshold value considered (at least 50%), it has no justification or absolute scientific validity. Indeed, several studies show that this threshold is too high for health criteria, which is why the SCENIHR (also cited by the JRC (Rauscher, Roebben*, et al.* 2019)) proposes much lower thresholds. On these bases, it appears necessary to lower its value.

This particularly complex issue raises the more general question of the precise utility of the definition and calls for a clear explanation of the idea of harmonisation being discussed. To this end, the WG believes it necessary to have a basic definition serving as a common core for all the regulations concerned; it should enable a broad assessment of the risks associated with nanomaterials but should also allow for differentiated management by sector in light of their respective specificities (see §3.1.7). This definition should be understood as a means of identifying materials that warrant special attention on the basis of a dimensional criterion alone. It would then be up to the sector-specific

regulations to stipulate the nanomaterials of interest among these materials and determine the necessary risk management actions.

In a highly sectorised regulatory environment, each sector-specific regulation could then build on this definition and adapt the criteria for identification (determining which nanomaterials warrant special attention in that sector) and management (declaration, additional data required for authorisation, etc.) to the specificities of the sector.

With this in mind, the WG favoured the following position:

- Setting a "low" threshold, establishing a common scope for all regulations, which would encompass all the materials requiring particular attention (with regard to the "nano" problem) by the legislature when drafting the regulatory texts relating to management;
- The issue of flexibility should then come into play in determining how to target nanomaterials that will be subject to sector-specific regulatory constraints. It would therefore be up to the legislature to stipulate for each sector which nanomaterials, among those falling within the scope of the definition, should be subject to management measures, taking the particularities of each sector into account (possibility of considering higher threshold values if it can be demonstrated that there is no risk below the chosen threshold, reversal of the burden of proof).

The Working Group is aware that a low threshold may lead to a significant increase in the number of materials considered as nanomaterials for which specific attention would therefore be required. Questions on the unintentional generation of nanomaterials through wear/friction between non-nano particles have not been ignored. Similarly, the technical difficulties (impossibility) of demonstrating the complete absence of a nanomaterial in a material are well known. However, these disadvantages seem very minor compared to the disadvantages of in principle excluding too many substances from the scope of the definition.

The issue of the lower and upper dimensional criteria in the definition, although much anticipated, was not addressed in the public consultation. The upper threshold of 100 nm has no biological basis, as underlined by EFSA which considers, for example, that objects up to 250 nm in size can be absorbed by the gastrointestinal tract.

As for the low threshold of 1 nm, although it gives rise to measurement difficulties, it seems necessary to retain it so as not to include too many substances in the definition.

The 50% size distribution threshold and its flexibility remain the most sensitive points. The Working Group considers that the fixed value of 50% should be lowered considerably in order to generate a core definition for the legislature encompassing all materials of interest. Other thresholds could be adopted on a sectoral basis if justified by health or environmental considerations.

3.3.2.2 List of derogations (related to the low dimensional threshold)

By nature, a system of derogations is designed to correct aberrations or errors induced by general rules that cannot be properly applied to these exceptions. In the context of a definition, the consideration of such corrections means that the general criteria established to delimit its scope are imprecise, or are not universal, since they require the inclusion or exclusion of specific cases, going against the general rules.

The derogations inserted in the EC Recommendations on the definition of nanomaterials are directly linked to the consideration of a low dimensional threshold (1 nm). The objective of this criterion is to exclude from the scope of the definition a number of objects with dimensions below one nanometre that are not considered relevant to the issues of nanomaterials (e.g. certain biomolecules). In practice, this threshold criterion excludes other objects that are particularly relevant in terms of health (single-wall carbon nanotubes with a thickness of less than one nanometre, for example). This perfectly illustrates the difficulty of selecting values for dimensional criteria common to all chemical

forms, i.e. universal values, on which the definition of nanomaterials should be based (see previous chapter).

▶ Consideration in the 2011 Recommendation for a definition

The EC chose to establish a definition whose scope is restricted by a range of dimensions with imperfect thresholds, and to correct aberrations by including certain substances and objects.

In its Recommendation for a definition published in 2011, a list of the families of substances with a derogation was already provided. For example, "*fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials*".

▶ Review of the European Commission's proposed changes

The EC suggested replacing this finite list, essentially focused on carbon objects, with a more general rule including elongated shapes (i.e. platelets, sheets, tubes and rods) with thicknesses below the low threshold of 1 nm currently considered.

During the public consultation, the Commission proposed several possible answers:

- no need for any additional inclusion of materials through criteria or specific derogation (Option 1);
- maintain the current list of derogations (Option 2);
- update the derogation list (Option 3);
- agree with the replacement of derogations with the inclusion of specific materials as proposed (Option 4);
- agree with the proposal as described (Option 5).

▶ The JRC's arguments supporting these proposals

The JRC points out that the current list of derogations was established based on the knowledge available in 2011 and that it should be updated since it has been agreed that carbon is not the only chemical nature from which such particles can be produced.

However, this list-based approach requires that the definition be periodically reviewed to keep it up to date, probably leading to a continuous mismatch between the list and the materials developed.

A more generic approach to cases with a general rule as proposed would resolve these shortcomings and extend the scope of the definition to certain substances (e.g. certain specifically adapted forms of silicate minerals, oxides, nitrides and halides) while excluding fullerenes.

▶ Consequences of these proposed changes

The consideration of a low threshold for the dimensional criteria of nanomaterials, despite the absence of such a universal threshold (suitable for all chemical forms), leads to the use of derogations in order to correct aberrations (retaining objects that are considered nanomaterials but were excluded from the scope of the definition because of their small size).

The main consequences of the suggested approaches have been widely described by the JRC (see previous section).

▶ Debates and arguments from the public consultation

While the vast majority of respondents (92%) did not favour the first three options (no derogation, maintained or updated derogation list), the proposal as put forward by the EC also did not gain clear support (Option 5: 34%), since more than half of the respondents considered either that none of the proposals were satisfactory (43%) or that the generic rule needed to be adjusted (Option 4: 14%).

Unfortunately, the format of the public consultation did not allow the respondents to provide detailed arguments.

- **Reasoned opinion of the Working Group**

The solution proposed by the EC extends the scope of the definition to similar current or future materials but excludes the iconic fullerene C_{60}. From C_{70} onwards, fullerenes no longer necessarily have a completely spherical shape and may have a form factor (length/diameter) above 1, but it would then be necessary to precisely determine from what form factor a nanomaterial is considered to be "elongated". Even if these objects are encountered fairly rarely, some applications do already exist and it is quite possible that they could be developed in the near or distant future. From a health perspective, there is no justification for their exclusion.

The Working Group stresses that not a lot is missing from this proposal for it to be satisfactory. However, the change should not exclude fullerenes. In this sense, the WG proposed retaining this proposal to apply a generic rule (Option 5) but also supplementing it a with a non-restrictive list (modified Option 3), which would ensure and reinforce the consideration of notable exceptions (fullerenes in particular).

The need for derogations to replace a general rule in this definition demonstrates that the consideration of universal dimensional thresholds (1-100 nm) as defining criteria does not succeed in satisfactorily delimiting the scope of nanomaterials.

In its successive Recommendations for a definition, the EC chose to consider a low dimensional threshold (1 nm) in order to have a restrictive definition corrected by inclusive derogations, enabling objects below this low threshold to be retained.

It should be noted that no derogation has been used so far to correct possible shortcomings linked either to the consideration of a high threshold (100 nm) or to the consideration of a size distribution threshold.

3.3.2.3 Size distribution counting (relating to the size distribution threshold)

- **Review of the European Commission's proposed changes**

The proposed change on this topic involved the exclusion of particles with at least two external dimensions above 100 micrometres for the purpose of the number size distribution[44].

- **The JRC's arguments supporting these proposals**

According to the JRC, this exclusion allows for "increased clarity and ease of implementation. Excluding from counting the particles with at least two orthogonal external dimensions above 100 micrometre that are themselves not aggregates or agglomerates of smaller constituent particles can address some of the practical measurement issues. It can also help to avoid in practice any potential ambiguity in differentiating between a particle and a larger solid product such as a large material sheet that should not be covered by the definition. The limit of 100 micrometres is based on the total suspended particle size as the largest particle size explicitly set by any regulation in the EU, i.e. air emission regulation. In reasonably foreseeable practical cases, the relative contribution of particles in the size range 1 nm to 100 nm to the total number of particles would not be significantly influenced by either counting or excluding these large particles. Such upper limit means that a material with a majority of such particles, even if the third dimension of these particles is within 1-100 nm, is not considered a nanomaterial".

- **Consequences of these proposed changes**

44 *"Restriction of the particles to be considered in point 2): Particles with at least two orthogonal external dimensions larger than 100 micrometre shall not be counted for the purpose of the number size distribution".*

This exclusion may lead to a bias in the number size distribution and therefore to an erroneous conclusion as to the classification of the material under consideration with respect to the definition of a nanomaterial.

- **Debates and arguments from the public consultation**

The majority of the respondents to the public consultation were in favour of this proposed change (55% “mostly agree” + “fully agree”).

The main argument put forward to support this change was simplification, as the presence of these large particles can pose technical problems during characterisation. Some respondents recommended going further and excluding particles with a single dimension above 100 µm. Another argument was toxicological: the inclusion of these large particles is inappropriate in view of their toxicology and the possible exposure routes. However, some respondents, although in favour of this change, warned against the risk of ending up with an erroneous number size distribution by excluding these large particles. In addition, some respondents in favour of this change questioned the relevance of the 100 µm limit.

The main argument put forward by the respondents against this proposed change was that the definition should take into account the entire number size distribution and not be limited to a pre-filtered fraction of the sample analysed, in order to avoid unacceptable biases. A second argument against this proposed change was that if particles are excluded from the analysis by pre-treatment, the sample no longer represents the whole of the actual product placed on the market. In addition, the pre-treatment required for this exclusion is non-standardised: this would create even more confusion and make the measurement process more difficult, therefore running counter to the clarification intention of this proposed change. Lastly, if large particles are excluded from the size distribution, then there will be a bias towards smaller sizes in this distribution. For example, for a material with a bimodal distribution with a majority share above 100 µm and smaller particles with at least one dimension below 100 nm (e.g. debris from the manufacturing process), the material could be classified as a nanomaterial when it is not one.

- **Reasoned opinion of the Working Group**

For the Working Group, this proposal corresponds to the search for a technical simplification that should not appear in a definition.

This change would result in certain objects being excluded and this exclusion is not justified: sheet-like objects are indeed nanomaterials as long as their thickness falls within the range considered. Many 2D nanomaterials are beginning to find new applications (MoS_2, h-BN, graphene derivatives, etc.). The Working Group questions the logic behind distinguishing a part of a material rather than considering it as a whole. From a health perspective, incidentally, there is no reason to exclude them (in ecotoxicology, such objects can be considered as vectors).

There is also no scientific basis for the proposed threshold of 100 microns.

If this change were to be maintained, the question of the feasibility of excluding the target particles arises: how can this be achieved in practice? The distinction can be made with some tools but not with others. Or else it would be necessary to filter the measurements beforehand, but with results that are not guaranteed. This metrological topic should be clarified in an *ad hoc* technical guideline.

Depending on how the particle size distribution is determined, this change will have the effect of increasing the percentage of objects regarded as nano-objects (by eliminating the largest particles) or conversely decreasing it (if these objects are indeed considered to be nano-objects due to their thickness being between 1 and 100 nm, as determined by electron microscopy).

As this is a metrological practice, the exclusion of the largest particles for establishing a size distribution for a sample should not be included in a definition of nanomaterials but could possibly appear in the accompanying technical documentation.

3.3.3 Notions of particles considered

3.3.3.1 Solid/non-solid particles

- **Consideration in the 2011 Recommendation for a definition**

The concept of solid particles is not at all emphasised in the 2011 Recommendation for a definition. It is only mentioned in the introductory remark concerning the BET method for measuring specific surface areas.

- **Review of the European Commission's proposed changes on this topic**

The proposed change was to add the word *solid* before *particles* (“*material consisting of **solid** particles...*”).

- **The JRC's arguments supporting these proposals**

The word “solid” can be defined in several ways. It can be seen as one of the four fundamental states of matter, characterised by structural rigidity and resistance to changes in shape or volume. In the rheological sense, a solid undergoes finite deformations, which distinguishes it from a fluid which has ductile behaviour. According to the Commission, the definition should be limited to solid particles to ensure that the highly dynamic nature of the dimensions of non-solid objects, which could also be considered as particles, does not prevent external size from being used as a defining property. Nanosized micelles and droplets in emulsions are explicitly mentioned as examples.

- **Consequences of these proposed changes**

Introducing the word “solid” in the definition would have the effect of excluding certain manufactured objects, such as nanomicelles and liposomes, which are increasingly being used in many sectors of activity for the *in vivo* delivery of various compounds, for example in food, cosmetics and medicine.

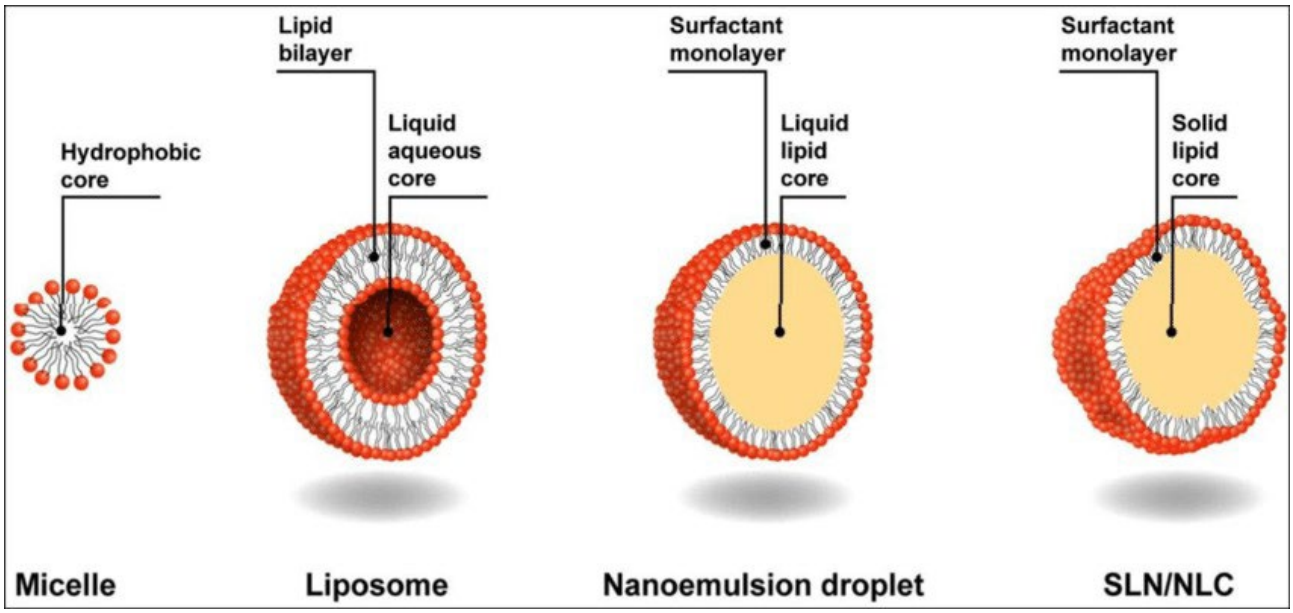
- **Debates and arguments from the public consultation**

No comments were made on this point during the public consultation.

- **Reasoned opinion of the Working Group**

If the definition of solid state is the presence of strong bonds between molecules, ions or atoms of a substance that prevent any movement and stiffen the structure, manufactured nanomaterials such as liposomes and other complex lipid architectures do not fall in this category. The same comment applies to hybrid nanoparticles containing polymers (Soares *et al.* 2020). These are composed, for example, of a metal oxide or silica fraction on which a polymer is grafted. However, these non-solid objects are indeed nanoparticles in the sense of the 2011 Recommendation for a definition where “particle” means a “*minute piece of matter with defined physical boundaries*”. It should also be noted that the notion of solid should be clarified in the EC Recommendation. The concept is sometimes questioned at the nanoscale.

Applications of non-solid nano-objects in health, food or agriculture require the crossing of biological barriers. Hydrophobicity is a key parameter, which is why lipid structures are often used (Gordillo-Galeano et Mora-Huertas 2018). In particular, early developments used micelles and especially liposomes, which are particles that have an outer lipid bilayer and an aqueous core. More recently, more complex objects comprising solid lipids at room or body temperature (solid lipid nanoparticles (SLNs)) have been developed. A recent trend has also been to include liquid lipids (nanostructured lipid carriers (NLCs)) to generate complex objects.



Micelles with a hydrophobic core formed by the tails of the surfactant molecules. Liposomes with an aqueous core surrounded by a double phospholipid layer. Nanoemulsion droplets with a hydrophobic liquid core composed of the oil that is dispersed in the water and stabilised by a surfactant monolayer. SLNs and NLCs with a hydrophobic core of solidified lipid; often, the solidification/crystallisation of the lipid results in a non-spherical shape of the particles.

Figure 9: "*Comparison between micelles, liposomes, nanoemulsions and solid lipid nanoparticles*" (Balamurugan et Chintamani 2018)

Size is also a key criterion for the crossing of barriers (Danaei *et al.* 2018). While small objects can get stuck in particular anatomical structures, they generally penetrate physiological barriers most efficiently and also redistribute most readily. It is considered that objects in the size range 20 to 100 nm can pass through the walls of capillaries and blood vessels. In the lungs, particles smaller than 150 nm are more persistent and penetrate deeper into the bronchi than microparticles. Tumours are another category of targets studied. An optimum size of 50 to 100 nm has been determined for the passage of liposomes into tumours. Another well-studied barrier is the blood-brain barrier, which is partially permeable to some particles smaller than 100 nm. Lastly, in the skin, sizes below 70 nm enable absorption through the epidermis via pores or follicular structures (Bahari et Hamishehkar 2016; Bertrand et Leroux 2012; Blasi *et al.* 2007; Danaei *et al.* 2018).

Therefore, the number of nano-objects on the market that are made with lipids is increasing. They have a dynamic structure due to molecular movements in the lipid layers and lipid/water interfaces, the presence of liquid parts, or changes in the structure of the solid portions as a function of temperature (Khosa, Reddi et Saha 2018). They therefore clearly do not fit in the category of solids. Even so, they share many properties with other nanoparticles. Their dynamic structure in no way prevents them from being stable, and lipid nano-objects can retain their size for months when suspended or dry. This is due, for example, to their often high (in absolute value) *zeta* potentials that limit interactions between particles. In addition, lipid nano-objects can be arranged in agglomerates. Similarly, "non-solid" nanoparticles are able to resist mechanical effects just like "solids". In their interactions with cells, they follow the same internalisation pathways by endocytosis as solid nanoparticles.

Nevertheless, one specific feature of non-solid nano-objects should be underlined. Unlike with nanoparticles, such as mineral oxides, the stability of these objects strongly depends on the surrounding medium. For example, lipid nanovectors are stable in aqueous media but not in organic solvents, which cause the outer layers to break up and the object to become completely disorganised. In this sense, the phenomenon is different from the solubilisation known for certain compounds. However, these considerations do not prevent non-solid particles from being considered in the definition for media in which they are stable.

An important point for the implementation of regulations or the application of the definition is access to metrological methods. These are available for non-solid particles (Gordillo-Galeano et Mora-Huertas 2018). Benchmark electron microscopy techniques can be used, although they require prior labelling with heavy elements to compensate for the fact that lipid nano-objects mainly contain low-atomic-number atoms. Other approaches such as DLS and AFM are also techniques of choice in this field.

From a health perspective, most of these objects are used as nanovectors for various applications. While the transported compounds are often included from the synthesis step, the hydrophobic outer layers of lipid nano-objects are preferred surfaces for the adsorption of various molecules. As these nanovectors are designed to spread through the body, efficiently cross physiological barriers and pass through cell membranes, they are therefore responsible for the spread of toxic potentials.

In conclusion, it appears that non-solid nano-objects cannot be excluded from the definition either because of their physico-chemical properties or because of their potential health impacts. Moreover, they are already widely used. From a more general point of view, the objective of this change in the definition, which was explicitly to exclude non-solid nanoparticles, is not supported by arguments. Lastly, from a semantic perspective, introducing the adjective “solid” does not provide any clarification because its meaning at the nanoscale is a matter of debate depending on the disciplinary field. More consensual criteria should be provided (at the very least, refer to technical guides in the definition). Consequently, in practice, as it stands, this change would not enable the objects concerned (mainly lipid nano-objects) to be excluded, if that were desirable.

The Working Group considers that it appears difficult to make a fundamental distinction between solid and non-solid nanoparticles. A first argument is that the notion of solid, which is easily understood at the macroscale, becomes more complex at the nanoscale.

The second reason is that there are many more or less complex non-solid nano-objects, such as lipid nanovectors and polymer-based hybrid nanoparticles, that are within the dimensional thresholds considered in the definition, stable over time, and do not exhibit more agglomeration properties than solid nanoparticles. It can be added that these objects are used in many different fields (medicine, nutrition, agriculture) and cannot be overlooked.

Therefore, it does not seem justified to exclude non-solid particles from the definition. An important point for discussion, however, is that these non-solid nano-objects are often building blocks for small molecules and are only stable in specific media.

3.3.3.2 Single molecules

- **Consideration in the 2011 Recommendation for a definition**

The European Commission's Recommendation for a definition of 18 October 2011 did not mention the notion of “single molecule”, which would appear in the update of this Recommendation in 2022. It should be noted that, by derogation, some objects that could be considered as single molecules, e.g. fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm, are considered as nanomaterials.

- **Review of the European Commission's proposed changes**

For clarification purposes, the EC proposed that single molecules should not be considered as particles and that these objects should therefore be excluded from the scope of the definition of nanomaterials.

- **The JRC's arguments supporting these proposals**

Single molecules, including macromolecules such as proteins and polymers that may be larger than 1 nm, should not be considered particles within the definition. Given that the word “molecule” can be interpreted in various ways, the JRC states that these very specific situations may need to be

considered on a case-by-case basis. This aspect should be included in the guidance document and in a discussion on real-life cases (e.g. fullerenes, proteins, polymers).

In the 2019 JRC report, it was reported that single molecules are not considered as particles under the EC definition with the exception of fullerenes, graphene and single-wall carbon nanotubes, which are explicitly included by derogation. It was stated that single molecules are building blocks of many chemical substances and are addressed in the regulations independently of their size. But this document also underlined that there is potential ambiguity for a number of specific cases:

- fullerenes, which are well-defined molecules and were explicitly included in the 2011 Recommendation by derogation, together with graphene flakes and single-wall carbon nanotubes;
- proteins, which are organic compounds whose shape and conformation can vary largely and which very often have sizes above 1 nm;
- macromolecules, which are very large molecules (organic or inorganic) and include polymers. As with proteins, individual macromolecules often have sizes above 1 nm.

Individual proteins, polymers and macromolecules are also excluded from the scope of the definition as they are considered single molecules. However, if these molecules are assembled into solid objects with clearly defined and stable external boundaries, and if they are stable enough to retain their shape over a long period and allow their external dimensions to be measured, these objects should be considered as particles. Liquid or gaseous objects are not included because the definition is intended to cover only entities with a defined rigid shape. Furthermore, single molecules cannot be solid (nor liquid), because the classification can only be applied to ensembles big enough to form a phase for which the state can be assessed. This is one reason why single molecules, aside from the exemptions listed, do not fall under the definition.

▶ Consequences of these proposed changes

The fact that the definition does not consider particles as single molecules risks excluding certain nanomaterials that may only be considered via a derogation. Such derogation is based on a list that may change over time, which requires regular updating and is therefore not very responsive in a highly innovative context.

▶ Debates and arguments from the public consultation

Few responses were given during the public consultation with regard to the notion of single molecule. This notion was in fact associated with the proposed revision of the derogation listing certain molecules (fullerenes, single-wall carbon nanotubes, graphene flakes) as nanomaterials. However, the explanatory responses pointed out that with the changes to the definition on these points, it was not clear whether these elements considered as nanomaterials should be kept in the scope of the definition.

▶ Reasoned opinion of the Working Group

According to the definition in the Larousse French dictionary, a molecule is a particle made up of atoms that represents the smallest amount of matter that can exist in a free state in a pure substance. According to the website https://www.cnrtl.fr/definition/molécule affiliated with the French National Centre for Scientific Research (CNRS), it is the smallest unit of a pure substance (element or compound) that is capable of existing in a free state and in which the composition and characteristic chemical properties of the substance are preserved. For its part, the IUPAC gives a definition that is not very accessible to non-specialists and that illustrates the complexity of the subject matter[45]. A single molecule can be defined as the smallest unit of a substance that is composed of one or more atoms and that retains the properties of the substance. The atoms are linked by covalent bonds, which means that it takes a lot of energy to break a molecule.

[45] https://goldbook.iupac.org/terms/view/M04002

Concerning oligomers and polymers, under the REACH Regulation (ECHA 2012), only the terms "monomer" and "polymer" are defined. A monomer is a "*substance which is capable of forming covalent bonds with a sequence of additional like or unlike molecules under the conditions of the relevant polymer-forming reaction used for the particular process*" (Article 3(6)). And a polymer is defined as a substance "*containing at least three monomer units which are covalently bound to at least one other monomer unit or other reactant*". As the properties of monomers and polymers are not equivalent, it is considered that the assembly of monomers (the polymer itself) corresponds to a single molecule. In this sense, oligomers or polymers meeting the size thresholds in the definition should be considered as nanomaterials.

However, while some nanomaterials may well take the form of single molecules, it seems appropriate to exclude from the nanomaterial category natural molecules such as proteins that are synthesised by living organisms, are not used for industrial production purposes, and are not transformed (biomolecules). Indeed, while some macromolecules are smaller than 1 nm and therefore do not fall under the definition of a nanomaterial, other larger molecules such as certain proteins reach or exceed this limit (by a few nanometres) (le Maire *et al.* 1986). For example, a protein of about 5 kDa has a minimum radius of around 1.1 nm (Erickson 2009). And yet these objects are particularly ubiquitous and are naturally present in the living environment without being relevant to the health issues associated with nanomaterials.

The Working Group recommends distinguishing between unintentional, naturally occurring single molecules and those that are generated or transformed via any intentional production process.

Therefore, regarding the term "single molecule":

- either all single molecules should be included in the scope of the definition of nanomaterials, opening the door to (too) many objects;
- or their consideration should involve a notion of intentionality for this type of object but not for others, which would lead to a discrepancy in the definition.

This binary choice complicates the issue at hand and thus goes against the objective of clarification stated by the EC when revising the Recommendation for a definition.

Some single molecules meet the dimensional criteria for nanomaterials and should be included in the scope of this definition. However, the notion of single molecule is not easy to define. As a result, the inclusion of this notion in the definition would create difficulties. This is because:

- either all single molecules should be included in the scope of the definition of nanomaterials, causing all molecules to be inappropriately included regardless of their origin;
- or their consideration should involve a notion of intentionality for this type of object but not for others, which would lead to a discrepancy in the definition.

Therefore, it does not seem appropriate to consider this aspect in the definition.

3.3.3.3 Hybrid and composite materials

The words "hybrid" and "composite" both refer to materials made up of several components of different natures.

While the definitions of these two terms may seem to converge, it is important to note that composite materials are generally considered to be heterophase systems composed of a dispersed phase within a dispersing (or continuous) medium. The word "nanocomposite" is used specifically when the dispersed elements have at least one dimension that is nanometric. On this basis, (nano)composite materials can be considered condensed solid materials with dimensions beyond the nanoscale range. They therefore fit in with the definition of "hybrid" systems without overlapping it. Conversely,

hybrid materials are commonly considered to include different materials than "composite" materials, in particular granular (or particulate) media.

The EC Recommendations for a definition of nanomaterials are explicitly limited to particulate materials and, as stated in the JRC report on "*Concepts and terms used in the European Commission's definition of nanomaterials*" (Rauscher, Roebben*, et al.* 2019), their provisions specifically apply to this type of material. This approach was inspired by earlier reports from the SCENIHR (Scenihr 2010) and the JRC (Linsinger *et al.* 2012) which stated that "*human and environmental exposure to particulate materials with a nano-specific character is more likely than exposure to materials with 'embedded' nanostructural features, or particles embedded in a solid matrix*". Therefore, for a definition that denotes a class of materials that may require specific regulatory attention in legislation, particulate materials are considered most relevant and nanocomposite materials (or NEPs) are *a priori* excluded.

Recommendation 2011/696/EU nonetheless stated that this definition may, in light of scientific and technological developments, need to be reviewed (by 2014) to include materials with internal or surface structure in the nanoscale, such as complex nanocomponent nanomaterials (including nanoporous and nanocomposite materials) that are used in some sectors. This topic was not addressed in the recent public consultation; however, the revised definition published in 2022 now explicitly excludes large nanostructured objects[46].

The definitions provided by other organisations and standardisation bodies already cover such materials. For example, ISO's definition includes materials with larger external dimensions (i.e. above 100 nm) as long as they have internal structures or surface structures in the nanoscale. On the other hand, certain types of nanostructured materials (as defined by ISO) may meet the EC definition. Such materials are:

(i) nanostructured materials consisting of aggregates and/or agglomerates of particles, where at least half of those constituent particles have an external dimension between 1 nm and 100 nm;

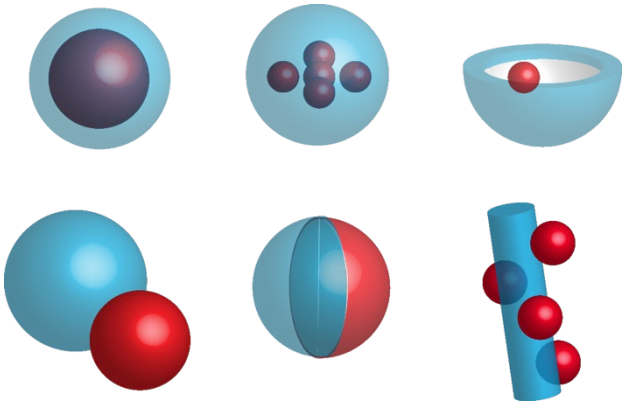
(ii) particles with an internal or surface structure in the nanoscale but also with at least one external dimension between 1 nm and 100 nm.

It should also be noted that if one or more external dimensions of a particle are in the nanoscale, ISO recommends using the term "nano-object".

The JRC report (Rauscher, Roebben*, et al.* 2019) concluded that including other types of nanostructured materials not covered by the EC definition (e.g. materials consisting of particles with all external dimensions larger than 100 nm but with nanoscale surface structures, nanocomposite materials, nanoporous materials) would significantly change the scope of the definition, as the broad scope of the term "nanostructured" would cover a large number of traditional materials.

The issue of whether particulate hybrid materials should be included in the EC definition is based on very different considerations as it is related to the size of the constituent elements and the strength of the bonds (or interactions) that hold the structure together. Particulate hybrid materials can be assembled in a wide variety of ways, resulting in highly polymorphic structures (Figure 10):

[46] (11) "The definition should not cover large solid products or components, even when they have an internal structure or a surface structure at the nanoscale, such as coatings, certain ceramic materials and complex nanocomponents, including nanoporous and nanocomposite materials. Some of these products or components may have been manufactured by using nanomaterials and may even still contain them".



(1) Single-core/single-shell nanoparticle
(2) Multi-core/single-shell nanoparticle
(3) Yolk-shell nanoparticle
(4) Heterodimer nanoparticle
(5) Janus nanoparticle
(6) "Decorated" nanoparticle

Figure 10: The various structures of particulate hybrid materials (limited to two components here)

In the strict sense of the current EC definition, which specifies that a nanomaterial must contain at least 50% particles in the size range 1 nm to 100 nm, nanohybrid structures meet this definition under the following two separate conditions:

- Both components are nanometric;
- Only one component is nanometric and is present in a free form (dissociated particle) in such a proportion that it represents more than 50% of the total number of particles in the mixture.

These arguments can be used to support the implementation of a process to validate/monitor whether commercial products or fractions comply with this definition. In this respect, the approach that can be suggested is to prioritise these criteria as shown in the flowchart in Figure 11.

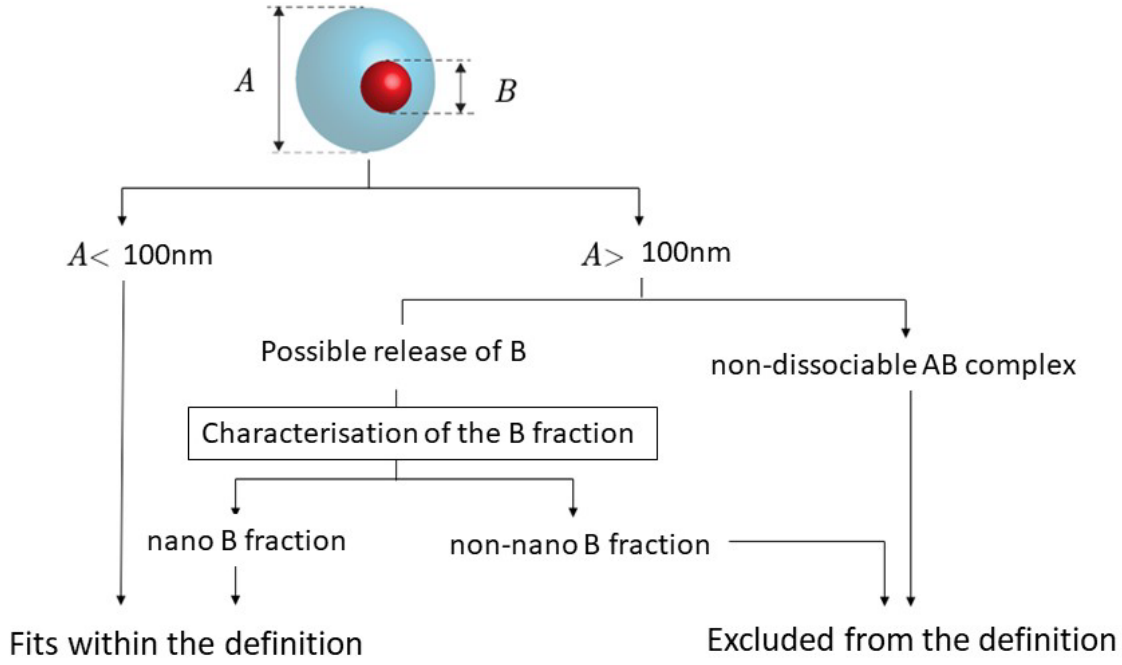


Figure 11: Flowchart showing the process of inclusion in the "nanomaterial" definition applied to hybrid particles

From a practical point of view, it is understood that the qualitative analysis of hybrid materials does not impose any specific prerogatives and can, as with any other fraction or sample, follow the process described in "The NanoDefine Methods Manual" (Mech *et al.* 2020), which sets out recommendations related to the process and methods of characterising nanomaterials according to the EC definition.

It is important to recall that the restriction of the current EC definition of nanomaterials to granular (or particulate) media is based on human and environmental exposure considerations. However, in this respect, multi-component nanomaterials, whether hybrid (in the broad sense) or nanocomposite, are associated with some "nanospecific" concerns, depending on the environmental conditions and/or at certain stages of their life cycles. Some nanocomposite systems are developed with the aim of enabling the controlled release of "active" nanomaterials. These include, for example, packaging and coating materials that contain silver, iron or titanium nanoparticles intended to be released over time with the goal of producing distinctly antioxidant, antimicrobial or surface decontaminant effects. These nanocomposite materials therefore do not meet the current definition but provide a platform for the "programmed" release of nanomaterials. In the longer term, these concerns may relate to the degradation rates and toxicity of the separate interacting components, as well as to their various interactions with biological and environmental systems. It is recognised, for example, that nanocomposite materials consisting of a biodegradable polymer matrix end up releasing the nanomaterials they contain at the end of their lifetime. As mentioned in 2008 in a circular drawn up by the Directorate General for Labour (DGT Note of 18 February 2008[47]), other composites can, through mechanisms of physical fatigue, ageing, abrasion or corrosion or simply through exposure to high temperatures, produce fragments or particles belonging to the nano domain. Beyond issues of definition, these materials or objects, which in their initial form are not classified as nanomaterials, are nevertheless sources of exposure to nanomaterials. As such, they could, if necessary, give rise to specific recommendations on the adaptation and improvement of the guidelines on the exposure and hazard assessment of multi-component nanomaterials. Such an approach could be based on a categorisation principle that would allow sector-specific multi-component nanomaterials to be grouped together by assessing their nanospecific properties in real environments.

Despite the relevance of clarifying the definition of nanomaterials in this respect, issues relating to the consideration of hybrid and composite materials were not addressed in the public consultation and are not clarified in the new Recommendation for a definition.

Of the hybrid materials resulting from the combination of two or more materials of different natures, only materials in the particulate state meet the recommended definition of nanomaterials. Their inclusion in the definition is, in the same way as for single compounds (or "mono-substances"), subject to the same size distribution criteria within a population of particles (see general flowchart in Figure 13).

(Nano)composite materials consisting of a solid matrix in which nano-objects are dispersed are excluded from the definition, even though it has been established that they should be given special attention in the event of a risk assessment, in particular because of their ability to release nanoparticles at different stages of their life cycle.

3.3.3.4 Bound/unbound states

- **Consideration in the 2011 Recommendation for a definition**

The notion of bound or unbound state appears in the Recitals of the 2011 Recommendation for a definition, before the definition itself. It is mentioned that "*Agglomerated or aggregated particles may exhibit the same properties as the unbound particles. Moreover, there can be cases during the life-cycle of a nanomaterial where the particles are released from the agglomerates or aggregates. The definition in this Recommendation should therefore also include particles in agglomerates or aggregates whenever the constituent particles are in the size range 1 nm-100 nm*".

[47] DGT Note of February 2008: "Workplace health protection against risks associated with exposure to chemicals in the form of nanoparticles".

The definition itself reiterates this as follows: *"'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm".*

It is therefore relatively clear that the notion of bonding concerns interactions between the nanoparticles themselves (to form agglomerates or aggregates), and not interactions between these same nanoparticles and the rest of their environment (for example, interactions between nanoparticles and a matrix for a massive nanocomposite, or a dispersion in a non-solid phase such as a sunscreen). On closer inspection, there are different views of what constitutes an aggregate, which for some authors can even be confused with a molecule. According to ISO, an aggregate is a collection of "strongly bonded" or fused primary particles where the resulting external surface area can be significantly smaller than the sum of the calculated surface areas of the individual components. On the other hand, an agglomerate (also termed a secondary particle according to ISO) is a collection of "weakly" bound particles where the resulting external surface area is similar to the sum of the calculated surface areas of the individual components. While it is stated that the forces holding an aggregate together may be covalent bonds or those resulting from sintering or physical entanglement, the notions of "strong" or "weak" bonding forces are not actually quantified by ISO and it is difficult to find a consensus in the literature. However, it is generally accepted that bonding forces are stronger in the case of an aggregate. The result is that an agglomerate can more readily dissociate to release the nanoparticles that constitute it than an aggregate (considered to be much more stable).

▶ Review of the European Commission's proposed changes

The proposed rewording on this point[48] was the subject of three separate questions submitted for public consultation:

- the first was the replacement of "containing particles" with "consisting of particles";
- the second was to remove the reference to the "unbound state" of particles to refer to particles:
  - "on their own",
  - or "as identifiable constituent particles".

The introduction of the notion of "solid particles" is discussed in § 3.3.3.1.

▶ The JRC's arguments supporting these proposals

■ On the replacement of "*containing*" with "*consisting of*"

The JRC argued that the term "containing" might suggest that a nanomaterial could contain a (possibly large) fraction of matter present in non-particulate form, such as a matrix (whether solid or not). In that case, it would be useful to discuss what fraction of nanoparticles should be considered in order to describe the mixture as a "nanomaterial". The example given is that of a milk to which a vitamin is added: should the milk be considered a vitamin simply because a certain amount of vitamin is added? Or from what amount of vitamin should it be considered that it is no longer a milk but a vitamin? This issue goes back to the notions of thresholds and the JRC considered that it was confusing.

It is again interesting to note that in the preliminary review described in the 3rd JRC report published in 2015 (Rauscher *et al.* 2015), the expression "*mainly* consisting of" had been proposed.

■ On the replacement of "*unbound state*" with "*present on their own*"

48 *"'Nanomaterial' means a (…) material **containing** particles, **in an unbound state** or as an aggregate or as an agglomerate (…)*" replaced with: "*'Nanomaterial' means a (…) material **consisting of** solid particles **that are present, either on their own** or **as identifiable constituent particles** in aggregates or agglomerates* (…)".

The JRC considered the term “unbound” to be potentially ambiguous as it could relate to interactions between constituent particles of an aggregate/agglomerate or to interactions between particles and their environment. The proposal was therefore to remove the word “unbound” and add “identifiable constituent particles” which may be present in isolation or grouped together in aggregates or agglomerates. The JRC also argued that the term “constituent” should remove ambiguity as to what the definition refers to in terms of size and number issues. The addition of the word “identifiable” was intended to reiterate that the notion of constituent particles is linked to the ability to observe/describe them as such, but the JRC emphasised the difficulties that may arise in the case of aggregates of very strongly bound particles, for example. On this topic, the JRC indicated that technical guides should be proposed to clarify these notions.

It is interesting to note that in its preliminary analysis (Rauscher *et al.* 2015), the JRC had used the term “individual entity” rather than “constituent particle”.

▶ Consequences of these proposed changes

These changes to the text were essentially intended to make it more intelligible and easier to understand. However, these proposals could have consequences for the scope of the definition, depending on how they are interpreted (see below).

▶ Debates and arguments from the public consultation

- **Replacement of “*containing*” with “*consisting of*”**

Some Member States pointed out that replacing “containing” with “consisting of” did not meet the expected need for clarification and in particular, still would not make it clear whether the objective was to exclude the consideration of other components with nanoscale dimensions such as impurities, stabilisers and additives. Some suggested combining the two descriptions instead of replacing one with the other (“containing *or* consisting of”), while others were still concerned that the term “containing” could lead, as mentioned above, to any product containing nanomaterials being considered a nanomaterial itself. One suggestion was to mention the identification of phase boundaries within aggregates/agglomerates. The need for clear and accepted terms (for example, as defined by ISO) was mentioned, as was the need to clarify the notion of “primary particle” or “primary structure”. Some indicated that the word “identifiable” should refer to the smallest indivisible object (which could be the aggregate).

These considerations show that most of the terms discussed here (“consisting of”, “containing”, “identifiable”, “bound/unbound”) can hardly be discussed independently, and most of the arguments laid down by the stakeholders combine them. Not only does this make it impossible to analyse them “criterion by criterion”, but it also leads stakeholders to make the same text say everything and its opposite. The need to use terms whose definitions are clearly established and accepted (ISO) is obvious, even if it means clarifying them further when ambiguities persist.

- **Replacement of “*unbound state*” with “*present on their own*”**

Several Member States pointed out that the phrase “present on their own” (as used in REACH) did not necessarily clarify the definition.

Most stakeholders agreed with the replacement of the term “unbound”, which was unclear. Comments mainly concerned the definition of an aggregate and an agglomerate (discussing the strength of the bond between particles). Some went so far as to ask for a clear definition of most of the terms used in the definition (“particle”, “unbound”, “aggregate”, “agglomerate”, “nanostructured”, “primary particle”, etc.). To illustrate this need, it can be noted that there were some requests for clarification concerning whether an aggregate (or even an agglomerate) should be considered a particle. The notion of bond energy between particles (strong or weak) would need to be clarified.

- **Introduction of the word “*identifiable*”**

The stakeholders agreed that the word “identifiable” was subjective. They also raised the issue of the intention to provide means of characterisation (time, energy, cost) and agreed that this metrological aspect would heavily depend on the analytical method implemented. If methods such

as the use of a synchrotron for example were necessary, it would not be realistic to require them. The notion of constituent particle was vague (ISO considers both primary particles and aggregates as "constituent"). There was general agreement on the need for technical guidance detailing the analytical methods to be used and the conditions under which they should be applied. The possibility of aggregates/agglomerates present in the initial product releasing primary particles during the preparation of a sample was mentioned, as it would lead to a potential bias in identification. Frequent reference was made to current definitions (e.g. those of ISO) and the need to validate terms between all stakeholders was often highlighted.

▶ Reasoned opinion of the Working Group

■ Replacement of "*containing*" with "*consisting of*" and introduction of "*identifiable*"

The Working Group was quite opposed to this proposed change for the following reasons.

One of the main points highlighted by the Working Group is that introducing the term "*consisting of*" could clarify that we are talking about the substance at the nanoscale and not a product containing it as an ingredient (i.e. differentiating a nanoscale ingredient from a whole "sunscreen" product containing it). In general, the target object should be the ingredient and not what it is incorporated into (in the example given, a finished product or a mixture such as a sunscreen is not a nanomaterial).

However, the WG noted several points that warrant attention:

- this change seems to result in a more restrictive definition and could therefore exclude certain objects such as nano-objects grafted onto larger objects. If it excludes hybrid materials (e.g. core-shell or other assemblies such as Candurin® for which the nano aspect of TiO_2 could be ignored) in practice, then it is not desirable;
- the very word "*consisting*" could be interpreted as including a notion of intentionality. This notion is open to multiple interpretations because it depends on an assessment by stakeholders, whoever they may be. Certainty is one of the qualities expected from the drafting of a legal text, in the sense that it must produce effects that everyone can foresee in advance so that they can refer to it appropriately;
- the Working Group stresses that this change should in no way exclude unintentionally created materials; intentionally and unintentionally created materials are still present in the introduction of the definition.

■ Replacement of "*unbound state*" with "*present on their own*"

The entire Working Group agreed that removing the mention of "*unbound state*" clarifies matters and avoids discussions on bound and unbound states, which are very difficult to objectively determine. It notes that while replacing the notion of "bound particle" with "particle present either on its own or as a constituent particle" is acceptable, the use of the term "identifiable" is more problematic. This is ultimately a metrological exclusion criterion and the WG points out that metrological criteria should not be used at this stage in a definition but should be set out in a technical guide, as it should not be difficulty in characterisation that guides a definition. Legally, this change would clearly open up the possibility of excluding "what cannot be identified".

Moreover, the term "identifiable" is vague and raises several questions:

- is it only a matter of identifying particles as constituent particles by being able to distinguish between them in an aggregate/agglomerate?
- are the particles present within an aggregate/agglomerate (and therefore not directly observable) non-identifiable?
- if an object is not identified, will it therefore be considered as non-identifiable by default? A technical guide should indicate the means to be used for identification in order to clarify this point;
- core-shell micelles are difficult to characterise, not to mention nano-objects vectorised in micelles, which are certainly even more difficult to "identify".

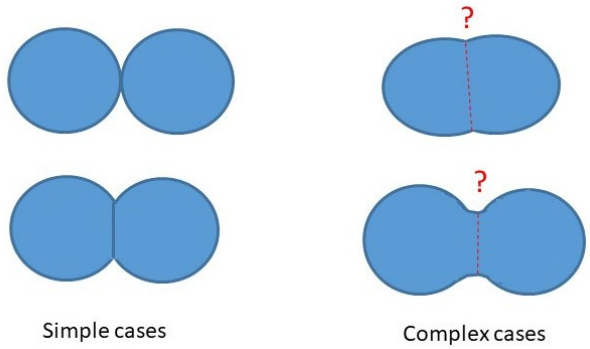


Figure 12: Examples of cases of particles in an aggregate

In what cases can constituent particles easily be “identified”? The use of high-resolution electron microscopy techniques can answer this question, even though their implementation is not a routine exercise.

Determination of this criterion is highly dependent on the analytical techniques used to identify the objects (depending on the analytical techniques and methods, it may or may not be possible to distinguish between them). This raises the underlying question of the metrological method implemented. Therefore, if this term were to be retained, it seems necessary to accompany it with details on the analytical methods used to identify these objects (technical guidelines clearly referred to in the definition), as already underlined by the JRC.

In the 2011 version of the Recommendation for a definition, the notion of bonding referred to interactions between the (constituent/primary) nanoparticles themselves, not to possible bonds with a matrix (composite, mixture).

The question of bonding is inseparable from the notions of aggregate (in particular) and primary/constituent particles. Because there are several possible definitions (or even ambiguities in the same definition [ISO]) – and due to the vagueness surrounding the “bonding strength” between particles in an aggregate/agglomerate – it is necessary to clarify these terms.

The new version of the Recommendation for a definition clarifies the issue of the nature of the bonds by stating that they are those between the particles themselves. However, it relies on the possibility of identifying “constituent particles”, which raises further doubts about:

1) the exact nature of the “constituent particles”;

2) the ability to identify these “constituent particles” (need to recommend an experimental protocol as well as one or more observation techniques: in this regard, the Working Group recommends electron microscopy, in line with previous reports).

The Working Group reiterates that distinguishing between an aggregate and an agglomerate remains difficult using electron microscopy alone, since the conditions under which the sample is prepared for observation are likely to alter the nature of the assemblies observed.

Most of the terms discussed here (“consisting of”, “containing”, “identifiable”, “bound/unbound”) can hardly be discussed independently, and most of the arguments laid down by the stakeholders combine them. Not only does this make it impossible to analyse them “criterion by criterion”, but it also leads stakeholders to make the same text say everything and its opposite.

The Working Group considers it essential to only refer to clearly defined terms. Definitions of these terms may exist elsewhere, for example in an ISO standard, or in the text of the Recommendation itself where appropriate.

3.3.3.5 Consideration of particle origin

The Recommendation on the definition of nanomaterials published in 2011 specified that they are particles of natural, incidental or manufactured origin. This comprehensiveness was due to the fact that the occurrence of nanosized particles in the environment did not emerge with the advent of nanotechnology. For example, ultrafine particles (UFPs) resulting from combustion and atmospheric chemistry processes that may involve anthropogenic precursors are well known to have cardiovascular effects. This very broad definition thus allowed for the inclusion of a very large number of particles regardless of whether they were novel and man-made for specific applications or already present in the environment naturally or as by-products of human activities.

The new definition has not changed this part of the original Recommendation. The purpose of this comprehensiveness in terms of particle origin is to allow for broad application in European legislation. In specific legislation, restrictions are introduced; for example, the Cosmetics Directive limits the definition to "*intentionally manufactured nanomaterials*", the Biocides Directive to "*natural and manufactured substances*", and the Novel Foods Directive to "*engineered/intentionally produced nanomaterials*".

One limitation lies in the interpretation of what natural, incidental and manufactured particles are, as they are not defined.

Natural particles are considered to be those that can be found in nature in connection with:

i) natural events such as volcanic eruptions, sea spray, forest fires, etc.;

ii) geological structures (nanominerals such as nanoclays);

iii) or biological processes (nanobiomineralisation).

Incidental particles are by-products of anthropogenic activities such as:

i) combustion or industrial processes (grinding, welding, sanding, abrasion, etc.) leading to the emission of "primary" particles;

ii) or chemical reactions in the environment with precursor compounds related to human activities that produce "secondary" particles.

These natural and incidental particles are ubiquitous and can take on a wide variety of shapes and compositions.

Manufactured particles are engineered and produced for a specific application, although they themselves may be identical in composition/structure to natural particles.

In addition to defining of the origin of nanoparticles, there is the issue of the feasibility of determining whether manufactured nanoparticles are intentional or else natural/incidental. A distinction is required in sectoral legislation limiting its scope to certain categories of nanoparticles. There are currently no standardised methods for quantifying them and distinguishing them from background particulate matter related to natural/incidental particles. In some situations, for a nanoparticle that may have a natural/incidental origin but also be the result of synthetic processes, it may be difficult to make a distinction.

The proposed definition submitted for public consultation included a wide range of nanomaterial origins (natural/incidental/manufactured), with the origin not prejudging possible health risks.

Moreover, it can be difficult to determine the origin of nanoparticles based on their physico-chemical characterisation alone.

3.3.4 Specific surface area criteria (VSSA)

- **Consideration in the current definition**

Point 5 of the 2011 Recommendation for a definition referred to an inclusion criterion based on measuring the volume-specific surface area (VSSA) as an alternative to the basic definition based

on particle size measurements. It indicated that if the VSSA of a material was greater than 60 m^2/cm^3, then the material should be considered a nanomaterial. But the opposite was not true[49].

▶ Review of the European Commission's proposed changes

The European Commission made two proposals to change this criterion:

- the first proposed change was to remove the existing reference to the VSSA in Point 5 of the current definition[50];
- the second was to add a new reference to the VSSA, with a low threshold of 5 m^2/cm^3. This low threshold was an exclusion threshold. Any material with a lower VSSA should not be considered a nanomaterial[51].

▶ The JRC's arguments supporting these proposals

■ Removal of the existing reference to the VSSA (inclusion criterion)

"In the Recommendation 2011/696/EU, the identification of a nanomaterial through its VSSA value is possible but the number size distribution would prevail in case of conflicting results. The VSSA value may be subject to interpretation, as high surface area may be due to the internal nanostructure, not attributable to aggregates or agglomerates of constituent particles. Moreover, particle shape and size polydispersity can strongly influence the relation between thresholds in number-based size distribution (50%) and in VSSA (60 m^2/cm^3) (Wohlleben *et al.* 2017). The NanoDefine project concluded that such an identification was not appropriate.

This is without prejudice to the continued use of VSSA as a screening method for selection/identification of materials that might fulfil the definition as outlined also in the JRC Report (Rauscher, Mech*, et al.* 2019). Relevant support in the Guidance is being planned".

■ Addition of a new reference to the VSSA (exclusion criterion)

"VSSA measurements can be considered as a tool for the exclusion of a material as a nanomaterial and thus to avoid additional costly measurements. The NanoDefine project demonstrated with a large set of different materials that the materials with a volume specific surface area of 5 m^2/cm^3 or less with great certainty do not have the number-based particle size distribution of a nanomaterial. Therefore, those materials should not be considered as a nanomaterial".

▶ Consequences of these proposed changes

The proposed changes were to remove an inclusion criterion and add an exclusion criterion. However, as affirmed by the JRC, there may be conflicting results between the VSSA measurement and the size distribution. While removing the current inclusion criterion would eliminate the risk of "false positives" (materials considered as nanomaterials because they have a VSSA above 60 m^2/cm^3 but whose number size distribution shows a relative contribution of particles in the size range 1-100 nm below 50%), adding an exclusion criterion could generate cases of "false negatives". More

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49 "Where technically feasible and requested in specific legislation, compliance with the definition in point 2 may be determined on the basis of the specific surface area by volume. A material should be considered as falling under the definition in point 2 where the specific surface area by volume of the material is greater than 60 m^2/cm^3. However, a material which, based on its number size distribution, is a nanomaterial should be considered as complying with the definition in point 2 even if the material has a specific surface area lower than 60 m^2/cm^3" (Point 5 of Recommendation 2011/696/EU).

50 *"Change 1: Remove existing reference to VSSA '5. Where technically feasible and requested in specific legislation, compliance with the definition in point 2 may be determined on the basis of the specific surface area by volume. A material should be considered as falling under the definition in point 2 where the specific surface area by volume of the material is greater than 60 m^2/cm^3. However, a material which, based on its number size distribution, is a nanomaterial should be considered as complying with the definition in point 2 even if the material has a specific surface area lower than 60 m^2/cm^3".*

51 *"Change 2: Insert the following VSSA reference: a material with a specific surface area by volume of 5 m^2 /cm^3 or less shall not be considered a nanomaterial".*

generally, any criterion based on the VSSA could pose a risk of conflicting results between the VSSA and electron microscopy size measurements.

▶ Debates and arguments from the public consultation

The majority of the respondents to the public consultation were in favour of the two changes concerning the VSSA (70% “*Mostly agree*” + “*Fully agree*” for the first change and 77% for the second).

The respondents in favour of the proposed changes concerning the VSSA mostly put forward arguments based on the relevance of measuring it to determine the nano nature of a material with regard to the Recommendation for a definition, as the VSSA method is easier to implement than size measurement and can be used for screening. Some argued that it would be useful to include an alternative method for identifying a nanomaterial in the definition, in cases where it is not feasible or is too costly to measure the external dimensions. Some respondents also argued that in some cases, the VSSA when used with appropriately chosen thresholds can be as reliable (or possibly even more so) than size distribution methods for positively or negatively classifying a material with regard to the definition. Therefore, they considered that the VSSA should be taken into account, for example in a guidance document. Lastly, for EFSA, the empirical values indicated in the proposed changes were in line with the results of research into products on the market. Nevertheless, many respondents affirmed that the low threshold for exclusion should be 6 m^2/cm^3 and not 5 m^2/cm^3 (the Working Group had interpreted the choice of 5 m^2/cm^3 as adding a “safety margin” compared with the threshold of 6 m^2/cm^3; however, the EC revisited this particular point when updating the Recommendation in 2022). In addition, some respondents in favour of one (or both) of these changes asked for clarification concerning which density value should be used to move from the specific surface area (SSA) to the VSSA.

Among the respondents not in favour of the proposed changes concerning the VSSA, the arguments supporting their position could be divided into two categories: the first involved whether the VSSA has a place in the definition itself and the second the limitations of the measurement technique. For example, it was considered that the VSSA should be included not in the definition but in a guidance document. Some added that the VSSA criterion should be eliminated altogether, whether with a high or a low threshold, as the addition of this criterion resembles a second definition that complicates the simple definition based on size, especially for particles of various shapes. Moreover, measuring the VSSA precisely at the nanoscale is unreliable and difficult: the techniques used have limitations (existence of false positives and false negatives, influence of porosity and particle shape, method not suitable in the event of polydispersity). And since there is no available uncontroversial conversion table between particle size and VSSA, the definition of a nanomaterial would need to be based solely on the external dimensions of the particles. Similarly, the relevance of specific thresholds based on a problematic metric appeared questionable (there are known exceptions). Therefore, as the VSSA is not appropriate for identifying nanomaterials, it should be removed as an alternative method. However, it was considered that the method could be used as a screening tool for pure materials but should not be used to exclude materials from the scope of the definition. Lastly, some respondents asked why the recommendations of the NanoDefine project (with VSSA criteria taking into account particle shape and applicable thresholds) were not considered a valid alternative.

▶ Reasoned opinion of the Working Group

The volume-specific surface area (VSSA) criterion is combined with the dimensional criterion. In practice, this can lead to contradictory results (if the results differ according to these two criteria), and therefore potentially to confusion.

The inclusion of a VSSA criterion in a definition can be interpreted in two ways:

- as a simple proxy for the dimensional criteria discussed above (i.e. a practical indirect approach enabling the dimensional criterion to be verified);

- as a way to include nanostructured objects (objects that do not correspond to NOAA but have a surface or internal nanostructure) in the scope of the definition of nanomaterials. It should be stressed that the question of whether or not these nanostructured objects should be included in the nanomaterials category is not clarified (see § 3.3.1.1).

Whatever meaning is assigned to this type of criterion, it seems inappropriate to include it in a definition of nanomaterials for two separate reasons. Firstly, it is fundamentally undesirable to include a measurand, which requires the use specific techniques, in a definition. Next, the reliability of the VSSA, when used to include or exclude objects in/from the scope of nanomaterials, is widely questioned. The VSSA threshold values currently used were calculated based on dimensional (high nanoscale threshold of 100 nm for the inclusion criterion and low threshold of 1 nm for the exclusion criterion) and size distribution (50%) thresholds for non-porous spherical objects. These VSSA threshold values should therefore not only be recalculated if these key values were to be modified, but they should also in any event be adjusted based on the morphology of the objects studied (NanoDefine results).

Various sources (including the European NanoDefine project and very recently, Claire Dazon's thesis (Dazon 2019)) indicate that although the VSSA can be useful for screening purposes, there are several problems associated with its implementation and the methods used to characterise it:

- difficulties in implementation: the density of materials (especially porous ones), which is a key factor in this type of measurement (see review of methods), is not easy to obtain or determine. These measurements are therefore not feasible for all materials;
- the existence of false positives and false negatives, even when the measurement is carried out correctly, especially in the case of powders with high polydispersity or strong particle aggregation (Wohlleben *et al.* 2017).

Nevertheless, considering on the one hand the usefulness of the specific surface area measurement as a screening tool, and on the other that in general, the nanoscale status of a material should be determined by comparing different analytical methods[52] (see ANSES 2021), the Working Group considers that this measurand, together with the techniques and analytical methods used to measure it, should necessarily be included in the JRC’s technical guidelines accompanying the definition.

There is consensus on using VSSA measurement as a screening method. However, it cannot replace the determination of the number size distribution (false positives and false negatives are known to exist) and its inclusion in the definition itself may lead to confusion.

3.3.5 Criteria associated with properties: the example of solubility

The common definition of “solubility” according to the Larousse French dictionary is the “ability of a substance to dissolve in another one”. It is an important property of a material in general. In the case of nanomaterials, also referred to as nanoforms of substances by the European Chemicals Agency (ECHA), this property may change significantly compared with macroscopic equivalents due to the very structure of these materials, resulting in an increase in surface tension that accelerates for sizes below around 30 nm. In a health context, solubility is a factor that can modify the degree of oxidation and/or speciation and therefore the toxic effects of a substance. Therefore, dissolution can modulate toxicity; this is the very principle of metallic silver (Ag^0) biocides whose nanoforms will dissolve as more toxic Ag^+ ions. The opposite phenomenon is also observed for iron and aluminium, where toxicity is reduced or even eliminated through simple dissolution of the initial nanoforms (Melanie Auffan *et al.* 2008; Shann et Bertsch 1993).

Knowledge of a compound's solubility is therefore an integral part of its risk assessment, particularly from a life cycle perspective. This solubility criterion is considered in some decision flowcharts to

[52] And therefore that the VSSA cannot be regarded as a sufficient criterion, i.e. that materials that do not fulfil this single criterion cannot be excluded from the scope of nanomaterials based solely on this result

determine whether or not a nanospecific risk assessment is necessary. For the WG, it does not seem reasonable to exclude in principle any nanospecific assessment based on this criterion alone. The importance of this aspect is reflected in the large number of articles devoted to it (more than 25,000 results in Web of Science when searching for “*nanopart** or *nanomat**” in combination with “*solubility or dissolution*”).

The enthusiasm that this topic generates in the scientific community contrasts with a lack of interest in the regulatory context. Indeed, this property does not appear in the initial text of the Recommendation for a definition of nanomaterials, nor in the proposed revision. Only Regulation (EC) No 1223/2009 on cosmetic products mentions this factor. Although solubility is indeed a criterion in this Regulation, the document does not mention or refer to any technical specifications regulating this factor in a practical manner.

The main reason why solubility is virtually absent from European (pre-) regulatory texts is most likely that behind this seemingly trivial notion, complex phenomena are hidden. Indeed, several challenges are combined:

- the absence of a single definition of this term;
- the extrinsic nature of this property and its variability during the life cycle;
- and lastly, the technical difficulties associated with its measurement, particularly in view of the kinetics of these changes.

There is no single definition of solubility; a quick search produces a variety of definitions of this term that differ essentially in terms of the restrictions they impose (e.g. definition focused solely on the aqueous medium) and are therefore not sufficiently generic. It therefore seems reasonable to rely on an “open” definition produced by a body or authority that has the support of the international scientific community. As a result, the following discussion considers the IUPAC definition according to which dissolution is the “*mixing of two phases with the formation of one new homogeneous phase (i.e. the solution)*”. This definition does not prejudge the physical phases (solid, liquid, gas) or the mechanisms governing this phenomenon (IUPAC 2019).

In this context, it is clear that solubility is not an intrinsic property of a material but depends on the environmental conditions in which it is determined. Moreover, solubilisation does not occur by a single mechanism; it can be the result of solvation, ionisation, redox phenomena, etc. In more operational terms, the solubility of a material depends on how it is used. It follows that this value varies, as is briefly discussed below.

It is of course tempting to define a “standard” and “neutral” medium, such as pure H_2O, pH 7, 25°C, in order to establish a reference point. This is immediately countered by the fact that such a medium would not correspond to any real situation (not to mention difficulties such as routinely measuring a pH in a medium with no ionic strength, and what is meant by “pure water” often cited as a reference medium?).

The variability of solubility is a known phenomenon. This is well illustrated by the solubility curves of metal hydroxides, Pourbaix diagrams, etc. These two examples alone illustrate how complicated it can be to determine solubility and it seems obvious that any increase in the complexity of a medium is accompanied by an increase in variability.

Other difficulties, sometimes of a more practical nature, are added to this variability. Solubilisation can be accompanied by new precipitation of the dissolved form (e.g. Ag^0 in an NaCl medium), making it difficult or even impossible to measure. Therefore, determining solubility can involve more complicated analyses than simply measuring the dissolved species. Another very important factor is solubilisation kinetics. Indeed, solubility is usually determined for systems in equilibrium or pseudo-equilibrium. Therefore, there can be cases of objects that are highly soluble in terms of their (thermodynamic) dissolution constant but whose solubilisation is (very) slow. This kinetic control becomes important if it delays solubilisation beyond the material's lifetime in its end use.

It is therefore evident that a solubility value cannot be dissociated from the medium in which it is measured.

Several technical procedures for determining solubility are currently available (OECD, Malta Initiative[53], standard operating procedures (SOPs) from European programmes such as NANoREG via Deliverable 2.9). They are most often intended to measure (or help measure) exposure to a material and its toxicity rather than defining the material as such. Solubility can be broken down by category of medium, but efforts at categorisation are ineffective at this level. A recent study showed that measuring the effects of nanomaterials on the same biological target requires several protocols causing variations in solubility that can exceed several orders of magnitude (Keller *et al.* 2021).

There is one additional difficulty related to the context of this document. The definition of nanomaterial applies to any compound that meets the criteria, regardless of the origin and duration of the compound's nanomaterial form. Therefore, the dissolution of a macroscopic material leads to the emergence of nanomaterials whose lifetime, in the absence of saturation, is under the control of kinetics. It should be noted in passing that the same issue arises during the synthesis of materials (e.g. nucleation and growth phenomena) likely to temporarily generate nanometric phases.

To summarise, solubility is an essential factor in the risk assessment of a nanomaterial, especially as a predictive tool. However, its strong dependence on environmental conditions should prevent it from being considered as a criterion for a definition that should remain independent of the intended use of the material studied. However, the Working Group stresses that the issue of solubility deserves to be reviewed again in the context of sectoral Directives.

Solubility is a property that depends on the nature of a material but also on the conditions of the medium in which it is found. This strongly extrinsic nature should therefore exclude solubility from the criteria to be considered in the definition.

3.3.6 Summary

All of the Working Group's reflections on the determination criteria have been summarised in the form of a flowchart (see Figure 13) showing the key stages in the construction of a definition that remain uncertain due to unstable parameters (whether scientific or extra-scientific) (red boxes); it also indicates the process for determining the values of the thresholds to be set (also in red).

[53] https://www.nanosafetycluster.eu/international-cooperation/the-malta-initiative/

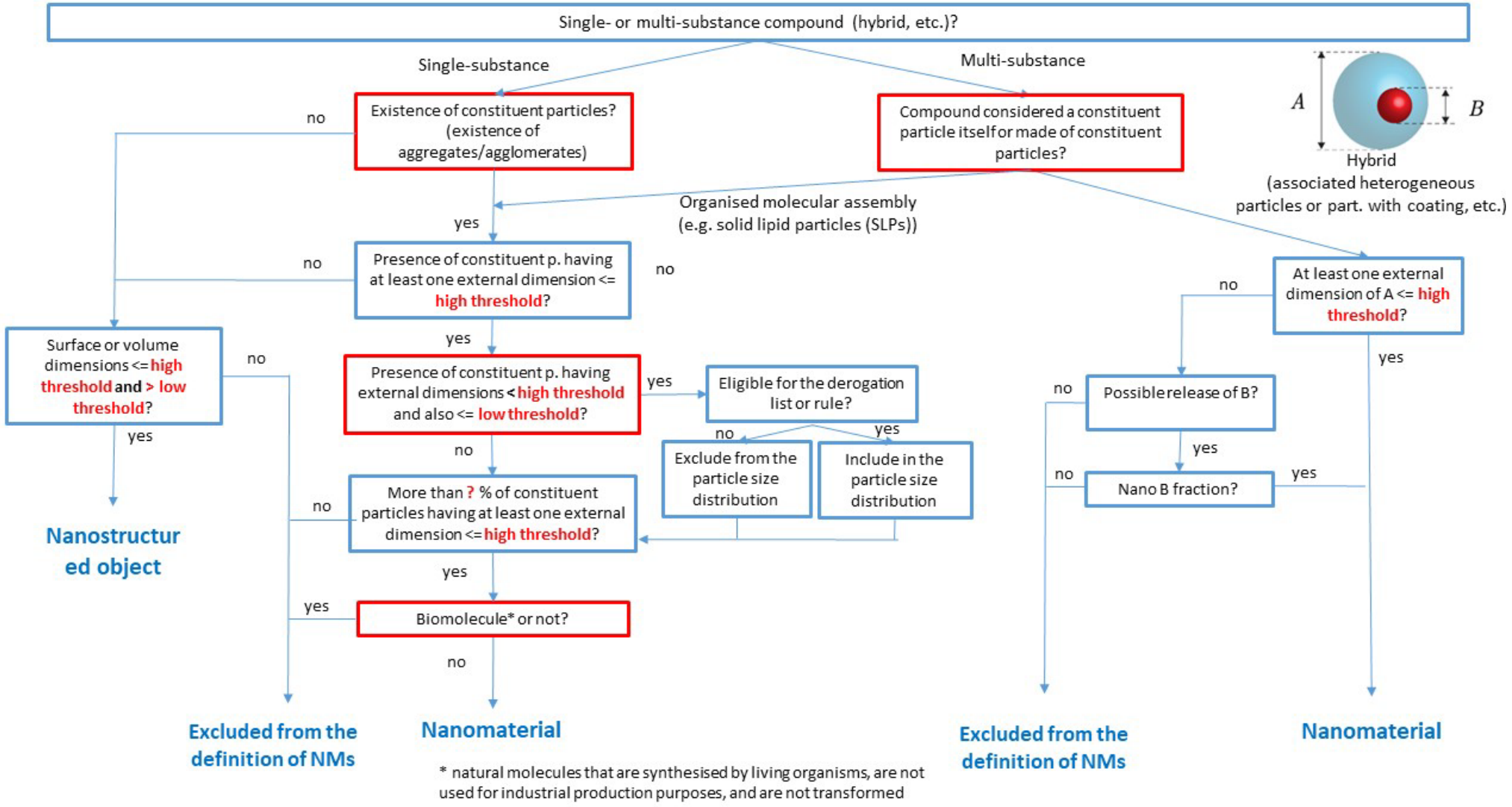

Figure 13: Decision flowchart based on the Working Group's reflections

4 Conclusion and recommendations of the Working Group

Announced since 2011 when the first Recommendation on a definition of nanomaterials was published, the 2021 revision took 10 years to be submitted for consultation. It is based on the JRC's arguments, which themselves are derived from three reports published between 2014 and 2015, from which the main points of discussion have been extracted. The main changes are described as aiming to clarify the terms used and simplify certain characterisation challenges in order to make the definition “easier to apply”. In reality, some vocabulary issues are still confusing. Overall, these changes seem to make the definition even more restrictive by excluding a number of nanomaterials from its scope and ruling out any possible flexibility, in particular for public health reasons (see below).

In keeping with the EC's initial proposal, the criteria that have been modified in the new version of the Recommendation for a definition are as follows:

- syntactically, a nanomaterial is considered to be a material (natural, incidental or manufactured) that no longer contains “particles, in an **unbound state** or as an aggregate or as an agglomerate” (2011 Recommendation) but is one “**consisting** of **solid particles** that are present, **either on their own or as identifiable constituent particles** in aggregates or agglomerates” (2022 Recommendation). This wording introduces several changes:
    - nanomaterials are now described as materials consisting of instead of containing particles, in order to avoid possible confusion between a nanomaterial and a product containing nanomaterials;
    - the notion of bonding between particles (“unbound particles”) disappears and is replaced with the notion of particles that are present on their own;
    - the notion of “identifiable constituent particles” is introduced;
    - lastly, the notion of particle is now restricted to “solid” particles
- the notion of “single molecules” is also introduced to exclude these objects from the notion of particle;
- aggregates and agglomerates are partially redefined (“aggregate”: a particle comprising of strongly bound or fused particles; “agglomerate”: a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components);
- the list of derogations for particles smaller than 1 nm is replaced with a generic rule;
- the flexibility of the size distribution threshold, which was 50% but could be reduced to 1% “where warranted by concerns for the environment, health, safety or competitiveness”, is abandoned and the threshold is set at 50%;
- in the practice of counting size distributions, particles larger than 100 micrometres are excluded;
- the volume-specific surface area (VSSA) inclusion criterion of 60 m^2/cm^3 disappears. However, an exclusion criterion based on the same measurand is included with a threshold of 6 m^2/cm^3.

The public consultation, organised within a very short time frame and with an extremely restricted response format, did not allow for effective feedback to be provided to the EC. The EC also largely ignored the content of the contributions to this consultation, except with regard to the increase in the exclusion threshold initially proposed for the VSSA. This had the effect of making the definition even more restrictive.

The new 2022 Recommendation for a definition will need to be accompanied by multiple technical guides that can provide support for its implementation.

In the end, the Working Group considers that this regulatory update's objective of harmonisation has not been achieved and that the opportunity to make it a core regulatory text has been missed.

4.1 Socio-political context of the regulatory update

4.1.1 A definition at the interface of science and law

Following its work, the Working Group reiterates that:

- the European Commission's Recommendation on the definition of nanomaterials applies in essence to a regulatory definition and therefore cannot be understood as a purely scientific definition;
- there is no consensus on the scientific criteria for defining nanomaterials (e.g. on the dimensional range to be considered for the nanoscale, currently restricted to 1 to 100 nm).

The Recommendation for a definition is indeed based on scientific knowledge but also on technical and regulatory choices that can be better understood by setting out the various possible alternatives. In that sense, the definition criteria depend on scientific and technical considerations and also on considerations relating to the socio-economic conditions for implementing the definition (behaviour of stakeholders; cost of operations; availability of equipment, etc.).

4.1.2 The importance of the regulatory environment in which the definition applies

The establishment of a definition of nanomaterials involves legal technical constraints that are linked to the choice of the types of texts that will essentially determine its legal scope. Therefore, the fact that the European Commission updated the definition in the form of a Recommendation (i.e. a definition that is not legally binding) in 2022 means that this definition will probably only have a very limited impact on sectoral regulations, unless they are revised to potentially incorporate it.

Following the entire process dedicated to the European revision of the definition of nanomaterials, the Working Group considers that a suitable European definition of nanomaterials still needs to be constructed. This definition should, according to the WG, contribute to the following objectives:

- circumscribe a set of substances whose dimensions warrant them undergoing a dedicated (nanospecific) assessment;
- give additional texts the possibility of defining potential regulatory constraints and specific management measures based on the results of this dedicated assessment;
- give additional texts the possibility of defining sub-sets (of objects or applications) requiring specific provisions.

Thus, in contrast to the choice made by the European Commission, the Working Group recommends considering a core definition that is as inclusive as possible. Its status should be legally binding with regard to sectoral European regulations, which could only be less inclusive in principle. A fundamental distinction would thus be made between:

- definition criteria, which help determine whether or not objects belong to the category of nanomaterials;
- and sectoral management rules (restrictions on use, bans, labelling rules, etc.).

This distinction would:

- ensure consistency in terms of the definition across all the industry sectors concerned: the same object should be considered a nanomaterial regardless of its sector of use or application;

- ensure the production of knowledge and an adequate assessment for as many nanomaterials as possible;
- maintain the sectoral specificity of management measures;
- avoid including notions related to risk assessment in the definition of nanomaterials, enabling the definition of “nanomaterial” objects to be separated from the potential consequences of their use, whether in terms of the associated risks to health or the environment or even the benefits;
- avoid including instrumental or technological considerations (e.g. metrology) in the definition of nanomaterials.

4.1.3 Competing or parallel notions and definitions

The Working Group reiterates that public health issues related to nanomaterials have historically been linked to the advent of nanotechnologies and accumulated knowledge on the health effects of UFPs. The debates focused initially on the consequences of nanotechnology applications and then on the objects themselves (nanoparticles and then nanomaterials). This terminology has been further diversified with the notions of nanoforms (REACH), nanoparticle substances (French R-Nano declaration registry), NOAA (nano-objects and their aggregates and agglomerates), and small particles (EFSA). More recently, the attention of legislators has focused on micro- and nanoplastics.

Considering that the increase in and accumulation of terms referring to notions that are sometimes very similar and partially overlap but sometimes are very subtly different is detrimental to the intelligibility of the subject matter, the WG recommends:

- including in the definition of nanomaterials all objects in this size range, including those already covered by specific provisions in the European regulations (nanoplastics, UFPs, etc.);
- accompanying any definition work with explanations aimed at positioning the definition in relation to what already exists.

4.2 Technical definition criteria

Beyond the legal particularities of the definition and its regulatory environment discussed above, the WG points out the inconsistencies of several EC policies set through the changes in the Recommendation for a definition.

The entire group of experts stresses that, despite the associated limitations, the definition of nanomaterials should be based essentially on dimensional criteria. Indeed:

- changes aiming to exclude objects that meet these dimensional criteria (non-solid objects, single molecules, etc.) do not seem appropriate since:
  - these exclusions are not justified for health impact assessment purposes, especially as some applications are growing rapidly (liposomes and nanovectors);
  - they are based on the use of sometimes very confusing terms for which there is no consensus, thus creating considerable uncertainties that are incompatible with the objective of clarification.
- the change to consider the measurement of the volume-specific surface area (VSSA) as an inclusion or exclusion criterion should not be included in such a definition because:
  - it is an approach to estimating the dimensional characteristics of the material, not a criterion in itself;
  - to a lesser extent, it may cause confusion when VSSA results differ from those of particle size analyses.

However, this metrological approach could be included as a screening method in the technical guidance documents and guidelines accompanying the definition.

The Working Group has identified several specific obstacles that will need to be clarified or require that choices be made.

4.2.1 Key concepts that still need be validated or defined

Various key concepts on which the definition is based remain unclear. An interpretation of these concepts, and even of the technical documents that characterise them, would greatly clarify the definition:

- the first of these complex concepts is that of “constituent” particle, because it is difficult to determine whether this refers to the smallest “identifiable” particle in a nanomaterial or the smallest indivisible element. Clarification is needed to avoid confusion with the notion of primary particle in particular;
- in connection with the previous point and the notion of bound or unbound state, technical considerations that would enable a distinction to be made between aggregates and agglomerates (nature, reversibility and strength of the bonds involved) should help clarify these notions;
- lastly, most of the above notions of bonding refer to single-component materials (simple cases). In practice, a definition of nanomaterials should also apply to more complex cases (hybrid and/or composite materials).

It should be noted that some physico-chemical concepts are introduced in the new Recommendation for a definition as exclusion criteria. Once again, these are unfortunately not well defined:

- determination of the solid or non-solid state at the nanoscale – a criterion now described in the proposed amendment to the REACH Regulation;
- “identifiable” nature of a nano-object;
- notion of single molecule.

4.2.2 Inclusion or exclusion of nanostructured objects in the scope of nanomaterials

Although the European Commission's Recommendation for a definition now explicitly excludes from the scope of nanomaterials objects with surface or volume nanostructure that do not correspond to nano-objects (aggregated or agglomerated), it must be noted that this choice creates a discrepancy with the ISO definition.

In the current state of knowledge, it is possible that these more massive materials may pose specific health/environmental risks related to the presence of nanostructures (compared with objects of the same chemical nature that are not nanostructured). However, it is generally accepted that these objects involve very different hazards and exposure levels than nano-objects.

4.2.3 Dimensional and size distribution thresholds and derogation list

The notions of dimensional and mixture thresholds remain difficult to address. The new Recommendation for a definition endorses the previous values (1 to 100 nm and 50%), as the European Commission only reopened this debate during the public consultation and only focused it on the size distribution threshold.

Many stakeholders agree that the current thresholds are not based on sound science. However, no alternative values seem to have a stronger scientific basis. This state of affairs is due to two fundamental issues, which make the establishment of these dimensional thresholds intractable:

- on the one hand, the properties for which objects should be grouped under the term “nanomaterial” (“quantum” properties of the material or its effects on living organisms) have not been clearly defined (see § 3.3.1.3.). They are largely dependent on the reason why these

nanomaterials are being studied. This uncertainty still largely adds to the confusion surrounding the definition of nanomaterials;

- on the other hand, whatever the criterion considered to justify these threshold values, it seems unrealistic that they should be the same for all possible nanomaterials, as the properties and effects of these objects are highly specific to their nature (chemical composition, surface coating, etc.). These thresholds will necessarily be arbitrary but should encompass as many nanomaterials as possible.

The inclusion of a dimensional lower limit to define the nanoscale (currently set at 1 nm) reflects a desire to exclude, for practical and theoretical reasons, objects such as atoms, molecules, etc. Nevertheless, the existence of derogations shows that this dimensional criterion alone is not sufficiently inclusive for objects widely recognised as nanomaterials (single-wall carbon nanotubes, C_{60} fullerenes, etc.) and is not sufficiently exclusive to not consider molecules such as proteins, which can reach dimensions larger than 1 nm.

Concerning the latter, the Working Group stresses that, up to now, the use of a list of derogations has only been intended to correct aberrations linked to this low threshold, not to correct possible shortcomings linked to the consideration of either a high threshold (100 nm) or a size distribution threshold.

The Working Group therefore recommends using a generic rule, as proposed by the EC in its public consultation and included in the new Recommendation for a definition, while:

- also supplementing it with a non-restrictive list that would ensure and reinforce the consideration of notable exceptions (e.g. fullerenes);
- and not restricting this list to the sole consideration of the low threshold, i.e. including objects with dimensions above 100 nm as well as materials whose nanometric share in the number size distribution is below 50%.

Beyond this low limit set at one nanometre, it appears that certain biological objects and molecules, such as proteins and other macromolecules naturally occurring in living organisms, meet the dimensional criteria of the nanoscale. These seem to be of little relevance to the health issues associated with nanomaterials and are particularly widespread in the environment. Nevertheless, it would be unfortunate to exclude all proteins and macromolecules from the definition, since certain manufactured or intentionally transformed molecules are, on the contrary, entirely relevant to these same health issues (e.g. transformation of lactates into tubular forms and synthesis of cyclodextrins added to foodstuffs to deliver substances). And yet there is no way to easily distinguish (based on objective criteria) between a naturally occurring biomolecule and one that has been intentionally manufactured.

In this respect, a choice needs to be made about whether or not to include biological objects in the scope of nanomaterials. The possible options identified by the Working Group, and their consequences, are as follows:

- either all of these objects should be included in the definition of nanomaterials, regardless of their origin, in which case the number of nanomaterials would increase drastically but the definition would remain consistent (only the dimensional criterion would come into play);
- or among these objects, biomolecules[54] should be excluded due to considerations (intentionality, naturalness) that are conceptually easy to understand but are complicated to express in the form of objective criteria. Such considerations focusing exclusively on these biological objects would induce an inconsistency in the definition (since this criterion of intentionality or naturalness would only come into play for this type of object).

[54] Natural molecules that are synthesised by living organisms, are not used for industrial production purposes, and are not transformed.

As with the dimensional limits, the size distribution threshold is not based on sound scientific arguments. The issue of its flexibility, as allowed by the 2011 Recommendation for a definition, is closely linked to that of the threshold value itself. These issues therefore cannot be separated.

On this topic, the Working Group recommends setting a lower value for this threshold than the one currently considered. The Working Group is aware that lowering this threshold value may lead to a significant increase in the number of materials considered as nanomaterials for which specific attention would therefore be required.

Questions on the unintentional generation of nanomaterials through wear/friction between non-nano particles have not been ignored. Similarly, the technical impossibility of demonstrating the complete absence of nanomaterials in a material is well known. Nevertheless, for the WG, these disadvantages are very minor compared to the disadvantages of in principle excluding too many substances from the scope of the definition (precautionary principle).

4.3 Opinion of the Working Group on the process of revising the European Commission's definition

The work to revise the 2011 Recommendation for a definition gave rise to the publication of several reports (2014 and 2015) by the JRC describing the various possible practical arrangements for this update prior to the public consultation; this was followed by the publication of the new Recommendation on the definition of nanomaterials in June 2022.

The European Commission's long-planned update of the Recommendation on the definition of nanomaterials was intended to meet two objectives:

- take account of advances in scientific knowledge and regulatory feedback in order to address scientific uncertainties and those relating to the implementation of the current definitions;
- harmonise the definitions at European level.

Unfortunately, the first of these objectives could not be achieved. Indeed, as presented in this report, most of the key issues associated with this definition do not stem from a lack of scientific knowledge but are more structural. For example, the establishment of dimensional limits to define the nanoscale (currently 1 – 100 nm) is confronted with the fact that the criteria for determining them are not clearly defined (see § 3.3.1.3).

The EC refers to the second objective to justify, for example, the disappearance of the flexibility of the size distribution threshold. However, this definition, which has been kept in the form of a Recommendation that is not legally binding, will only supplement the other sectoral definitions and will not replace them. It should therefore be noted that this form will not, as it stands, enable the regulatory texts to be harmonised.

Moreover, one of the underlying aims of this work was to clarify the terms used as much as possible in order to have the clearest and most objective definition possible. And yet the recently published Recommendation for a definition is more difficult to apply because it includes new notions and key terms requiring technical clarification and further details (guide being prepared by the JRC).

Lastly, the Working Group underlines the singular nature of the process of updating this definition. The public consultation was open for a limited period of time (seven weeks) without any timetable being announced to the stakeholders prior to its opening. Furthermore, the proposed format proved to be particularly simplistic (questions asked only concerning a few specific points selected by the EC[55], answers to be selected from a predefined list, and free text with a limited number of characters) and some passages were confusing. The low participation of public bodies in this consultation (only

[55] Some long-awaited discussions, for example on the determination of the nanoscale, were not among the points discussed.

13) certainly illustrates the difficulty generated by these conditions. This process ended just as abruptly with the publication of the new Recommendation for a definition in June 2022, with minimal consideration of the responses to the consultation; all of the suggestions made by the EC were adopted, except for the VSSA threshold value.

This process, with regard to both its form and its lack of transparency, raises serious questions about the European Commission's stated intention to consult.

4.4 Consequences and outlook in Europe and for the French regulations

The WG recommends carrying out further work to fully measure the health, scientific, social, etc. impact that the implementation of this new Recommendation for a definition could have in general and sectoral European and national regulations.

To the WG's knowledge, the R-Nano registry is the most comprehensive inventory of uses of nanomaterials in a national context. And yet the definition on which the declaration of nanoparticle substances is based in France is very directly inspired by the 2011 Recommendation, which means that any change in the latter raises questions about the French definition.

Following the revision of the European Commission’s Recommendation on the definition of nanomaterials, the French public authorities will need to choose from several options. The most unfortunate choice would be to align French law with the European system by simply abolishing the R-Nano registry. We are not considering this hypothesis, which would be absurd and counter-productive. On the other hand, extending such a mandatory declaration registry to the European level would favour a form of harmonisation more respectful of the precautionary principle, on which the European Green Deal is based.

Pending this further work, several options and lines of thinking are explored below:

■ In Europe

The new Recommendation for a definition is not more binding than the previous one. It does not lead to any change in the current definitions in sectoral legislation. Similarly, it will only be taken into account in the context of the REACH Regulation if a revision amends the text of this Regulation's annexes. The situation therefore remains similar to that which has existed since 2011, with many different definitions applying depending on the industrial sector and/or the marketing stage of products and materials containing nanomaterials, which is unsatisfactory.

The European Commission seems to be aware of this situation, as it itself has opened up the possibility of adopting this new definition in a more binding normative document. It is currently difficult to predict how the European Parliament will respond to this change in the definition.

■ In France

As for the object to be declared, for each of the options considered below, we will quickly outline the advantages and disadvantages that we can already anticipate, pending further work.

- Option 1: Leave the provisions of the French Environmental Code unchanged and maintain the definition adopted in 2012, which was largely inspired by the content of the 2011 Recommendation, as regards the application of national law and the obligation to declare nanoparticle substances. This is a real possibility, as the French text was adopted independently and does not relate to exactly the same subject matter.
    - Advantages: stability of the law for national stakeholders; stability over time of the data submitted as part of annual declarations on the R-Nano online declaration site, enabling more detailed comparisons and market analyses to be performed;
    - Disadvantages: the definition is not really technically appropriate and has attracted valid criticism from the JRC in particular. At European level, maintaining our definition

will add an additional element of complexity that French market stakeholders will need to consider for their nanomaterials.

- Option 2: Amend the Environmental Code to replace the current definition for nanoparticle substances with the new one (2022 Recommendation), but limit it to manufactured nanomaterials.
    - Advantages: alignment of the French definition with the default European definition;
    - Disadvantages: as we have shown through this expert appraisal, the new definition is highly unconvincing from a scientific and technical point of view. Amending French law in this way would require revising all the regulatory and administrative instruments for its implementation (R-Nano), leading to considerable legal instability in a complex field where stakeholders have already had and are still having difficulty in bringing themselves up to speed. The advantages of this choice are not immediately perceptible in terms of health and environmental protection.
- Option 3: Amend the Environmental Code to extend the core definition as recommended by our Working Group.
    - Advantages: a better, more inclusive definition, enabling better use to be made of the declarations submitted in R-Nano to target the nanomaterials to be assessed without restricting the freedom of the public authorities in terms of subsequent management;
    - Disadvantages: an additional definition to be considered for European market stakeholders; need to revise the French regulatory and administrative framework related to the definition; legal instability.

None of these options are ideal. Nevertheless, the Working Group considers that the third option would be the most appropriate in the short term in France.

With a view to harmonising all the relevant regulations at European level, the best solution would undoubtedly be for the European Union to adopt a binding core definition that meets the objectives described in this report.

If this is not achieved quickly, it seems that the REACH Regulation may be revised in the medium term to include a definition of nanomaterials. The investment of the French authorities in this revision work, based on this expert appraisal in favour of a core definition, should influence the subsequent harmonisation of sectoral definitions.

Date of validation of the collective expert appraisal report by the “Definition of nanomaterials” Working Group and the Expert Committee on “Assessment of the risks related to physical agents and new technologies”: 17 November 2022.

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ANNEXES

Annex 1: Formal request letter

2018 -SA- 0 168

COURRIER ARRIVE
10 JUIL. 2018
DIRECTION GENERALE

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RÉPUBLIQUE FRANÇAISE

Ministère de la Transition écologique et solidaire

Direction générale
de la prévention des risques

Ministère des Solidarité et de la Santé

Direction générale de la santé

Ministère de l'Economie et des Finances

Direction générale de la concurrence, de la consommation et de la répression des fraudes

Ministère de l'Agriculture

Direction générale de l'alimentation

Ministère du Travail

Direction générale
du travail

Les Directeurs généraux

à

Monsieur le Directeur général

de l'Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail

14 rue Pierre et Marie Curie

94701 MAISONS ALFORT CEDEX

Paris, le 10 juillet 2018

Objet : Demande d'appui scientifique et technique relative à l'élaboration d'une proposition de définition actualisée du terme « nanomatériaux » à partir de la Recommandation 2011/696/UE relative à la définition des nanomatériaux.

L'utilisation croissante des substances à l'état nanoparticulaire dans des secteurs d'activité très variés a conduit les pouvoirs publics à faire évoluer la réglementation nationale et européenne pour prendre en compte les spécificités de ces substances. La France s'est d'ailleurs dotée dès 2013 d'un outil dédié : le registre « r-Nano ».

Les substances à l'état nanoparticulaire ont été développées pour leurs propriétés spécifiques, comme vecteurs d'innovation. Cependant les connaissances de leurs effets potentiels sur l'environnement et la santé restent très limitées, souvent insuffisantes pour en évaluer les risques.

Une première étape vers une meilleure connaissance a été d'élaborer une définition et des critères communs pour caractériser ces substances tels que leur taille, leur distribution, leur surface spécifique etc. Au niveau européen, la recommandation 2011/696/UE de la Commission a servi de référence à plusieurs reprises dans les travaux législatifs d'adaptation des textes. La Commission européenne avait proposé de s'appuyer sur cette définition pour adapter celle figurant dans le règlement n°1169/2011 relatif à l'information du consommateur sur les denrées alimentaires, notamment en y introduisant le

seuil de 50 % de particules en nombre. Cette proposition a été rejetée par le Parlement européen au motif que rien ne justifiait l'introduction d'un tel seuil, inadapté en l'occurrence pour répondre à la demande d'information du consommateur. A ce stade, dans ses contrôles destinés à s'assurer de la bonne information du consommateur sur le caractère nano des ingrédients mis en œuvre, la DGCCRF applique la définition figurant dans le règlement relatif aux nouveaux aliments, à laquelle renvoie le règlement n°1169/2011. Cette définition ne comporte pas de seuil, de sorte qu'un ingrédient est déclaré nano dès lors que la présence de particules nano est avérée. En pratique, selon la méthodologie de contrôle développée par le Service commun des laboratoires, l'étiquetage est exigé lorsque 10 % au moins des particules en présence sont de taille nano.

Actuellement, plusieurs règlements européens (règlements sur les produits biocides, sur les produits cosmétiques, sur les nouveaux aliments, sur l'information des consommateurs sur les denrées alimentaires) comportent leur propre définition des nanomatériaux sans pour autant être identiques. Les travaux portant sur la révision des annexes du règlement 1907/2006 « Reach » pour l'adapter aux substances à l'état nanoparticulaire devraient également bientôt se conclure. Le projet de la Commission a été voté en comité le 26 avril dernier et devrait entrer en application le 01 janvier 2020. Le texte se réfère à la définition de la recommandation européenne.

Les définitions actuelles proposées dans la recommandation de la Commission de 2011 et dans les différents règlements comportent des différences et des imprécisions (seuil de 50 % en nombre, taille, insolubilité ou bio-persistance dans le règlement cosmétique…), qui sont régulièrement mises en avant par les parties prenantes qui souhaitent obtenir une définition plus claire et harmonisée. La Commission européenne avait annoncé dans plusieurs communications[1] relatives à cette recommandation son intention d'en réviser la définition avant décembre 2014 pour mieux prendre en compte les spécificités de ces substances et préciser certains points de la définition.

Le Joint Research Center (JRC), service de recherche de la Commission a publié un rapport en 2014[2] comportant des propositions relatives aux critères pouvant être considérés pour définir les nanomatériaux.

Après plusieurs phases de discussion engagées dès 2012, la Commission a soumis en septembre 2017 le projet de feuille de route relative à la révision de la définition des nanomatériaux dans le cadre d'une procédure de consultation publique : la Commission envisage une mise à consultation du public de son projet à l'été 2018 pour une durée de 14 semaines. Cette révision doit permettre d'obtenir une définition harmonisée qui serait déclinable aux différents secteurs d'activité.

En perspective de ces travaux, l'expertise de l'ANSES est demandée pour l'élaboration d'une contribution à cette consultation du public pour l'échéance qui sera fixée par la Commission. L'ANSES évaluera l'existence de méthodes de mesure compatibles avec la proposition de définition, et présentera dans son avis les adaptations qui lui paraissent nécessaires à la définition actuelle proposée dans la recommandation 2011/696/UE.

[1] Notamment http://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:52012DC0572&from=fr

[2] https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/towards-review-ec-recommendation-definition-term-nanomaterial-part-2-assessment-collected

Vous voudrez bien produire les résultats de l'expertise à l'échéance de la consultation publique mentionnée plus haut.

Nous vous remercions de bien vouloir accuser réception de la présente demande.

Le Directeur général
de la prévention des risques

Cédric BOURILLET

Le Directeur général
de la santé

Jérôme SALOMON

La Directrice générale
de la concurrence,
de la consommation
et de la répression des fraudes

Virginie BEAUMEUNIER

Le Directeur général
de l'alimentation

Patrick DEHAUMONT

Le Directeur général
du travail

Yves STRILLOU

Annex 2: Summary of the contributions to the public consultation

Public consultation

Summary of the Member States' positions

Table of contents

INTRODUCTION

This brief summary of the European Commission's public consultation on the definition of nanomaterials is based on data published in August 2021 at the end of the fiscal year.

The contributions are separated according to the status of the respondents: Member States or representatives (14), associations (66), companies (38) and European citizens (21). This summary focuses on the contributions of the 14 public bodies, while the responses of the other contributors are not detailed.

The contributing public bodies are as follows:

- Germany:

  - *Bundesinstitut für Risikobewertung* (BfR – German Federal Institute for Risk Assessment)
  - *Bundesanstalt für Arbeitsschutz und Arbeitsmedizin* (BAuA – German Federal Institute for Occupational Safety and Health)
  - Federal Institute for Occupational Safety and Health – Federal Office for Chemicals (FIOSH – FOC)
- Belgium:
  - Federal Public Service Health, Food Chain Safety and Environment – DG Environment, Department of Risk Management of Chemicals
  - Federal Public Service Economy, SMEs, Self-employed and Energy – DG Quality and Security Metrology Division
- France
  - ANSES
  - French government
- Ireland: Food Safety Authority of Ireland (FSAI)
- Norway
- Sweden: *Kemikalieinspektionen* (KEMI – Swedish Chemicals Agency)
- European Food Safety Authority (EFSA)
- Lastly, of these respondents, three bodies responded anonymously.

PART 1. GENERAL OBSERVATIONS

QUESTION 1 (REGULATORY APPROACH TO NANOMATERIALS)

The general format and fitness for purpose of the Recommendation on the definition of nanomaterial under review is associated with the general regulatory approach to nanomaterials taken in the EU. To help interpret responses further in the survey, please indicate which of the answers below correspond best with your general position regarding the approach to nanomaterials in the EU. Choose maximum three.

Possible answers:

- **OPTION 1:** Nanomaterials are materials/chemicals like any other and do not require special legislation or special provisions.
- **OPTION 2:** Nanomaterials do not require legislation as a separate category of materials/chemicals, but specific nanomaterial provisions within legislation may be required in some sectors to ensure efficiency and effectiveness. A definition, triggering such provisions, is thus required.
- **OPTION 3:** Special, standalone legislation for nanomaterials may be a more effective way to address at least some EU objectives, like for example high protection of human health and the environment. A definition, determining the scope of this legislation, is thus required.
- **OPTION 4:** Triggering specific provisions does not require a common definition for this subgroup of materials between sectors; triggers should be tailored to each individual situation.
- **OPTION 5:** A common definition of nanomaterial used across legislation and sectors increases efficiency and consistency of implementation.
- **None of the above.**
- **I have no view.**

Summary of the answers

Member States		Option 1	Option 2	Option 3	Option 4	Option 5	NOTA	IHNW	
DE	BfR			X		X			
	BAuA				X				
	FIOSH		X			X			
BE	FPS Health			X		X			
	FPS Eco			X		X			
IR	FSA					X			
S	KEMI			X		X			
NO			X			X			
FR	ANSES			X		X			
FR	Ministries		X	X		X			
EFSA			X	X		X			
Anonymous MS 1			X			X			
Anonymous MS 2			X		X				
Anonymous MS 3			X						
Sum of the MSs			7 (50%)	7 (50%)	2 (14%)	11 (79%)	-	-	/14
NGOs		22 (33%)	51 (77%)	12 (18%)	4 (6%)	55 (83%)	2 (3%)	-	/66
Companies		12 (32%)	27 (71%)	5 (13%)	6 (16%)	26 (68%)	-	-	/38
Citizens		2 (10%)	9 (43%)	7 (33%)	3 (14%)	15 (71%)	-	-	/21
Total sum		**36 (25%)**	**94 (66%)**	**55 (40%)**	**21 (15%)**	**107 (77%)**	**2 (1%)**		**/139**

QUESTION 2 (CONSISTENCY OF NANOMATERIAL DEFINITION IN REGULATORY CONTEXT - A)

Which of the answers below corresponds best with your position regarding the (harmonized) approach to nanomaterials in EU regulation? At least 1 choice(s)

Possible answers:

- **OPTION 1:** A directly applicable and legally binding EU definition in place of the Recommendation would increase efficiency and consistency of implementation across sectors.
- **OPTION 2:** The present approach (definition from the Recommendation is made legally binding as it is taken up in sectoral legislation) is adequate, but direct reference to the Recommendation rather than copying of the text of the definition, should be made possible.
- **OPTION 3:** The present approach is adequate.
- **OPTION 4:** There is no inherent need for harmonization – any definition needed for triggering specific provisions should be determined within the individual sector.
- **None of the above.**
- **I have no view.**

Summary of the answers

Member States		Option 1	Option 2	Option 3	Option 4	NOTA	IHNW	
DE	BfR	X	X					
	BAuA				X			
	FIOSH	X		X				
BE	FPS Health	X						
	FPS Eco	X						
IR	FSA	X						
S	KEMI	X	X					
NO		X	X					
FR	ANSES	X						
FR	Ministries	X						
EFSA		X						
Anonymous MS 1			X					
Anonymous MS 2				X	X			
Anonymous MS 3		X	X					
Sum of the MSs		11 (79%)	5 (36%)	2 (14%)	2 (14%)	-	-	/14
NGOs		30 (45%)	37 (56%)	5 (8%)	2 (3%)	2 (3%)	1 (2%)	/66
Companies		13 (34%)	16 (42%)	2 (5%)	4 (11%)	4 (11%)	1 (3%)	/38
Citizens		12 (57%)	5 (24%)	0	4 (19%)	-	1 (5%)	/21
Total sum		**66 (47%)**	**63 (45%)**	**9 (6%)**	**12 (9%)**	**6 (4%)**	**3 (2%)**	

QUESTION 3 (CONSISTENCY OF NANOMATERIAL DEFINITION IN REGULATORY CONTEXT – B)

Do you agree with the interim review findings regarding the present Recommendation 2011/696 /EU, as presented in the bullets a) to d) in the introduction?

Reminder of points (a) to (d):

a) The definition is fit for purpose, its main elements are generally accepted;
b) Uptake of the definition in EU regulation to date has not been as comprehensive as anticipated. While some delay in the uptake can be attributed to the anticipation of the results of the review of the definition, direct uptake has been hindered by the lack of clarity of some of the definition's elements in particular in relation to the term particle and to particle properties
c) Limiting the default inclusion of a number of materials to only carbon-based materials (fullerenes, graphene flakes and single wall carbon nanotubes) may be outdated;
d) Implementation of the definition remains challenging. Because of the high diversity among nanomaterials, a single universally applicable and affordable particle size measurement method is unlikely to become available.

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don't know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR			X			
	BAuA			X			
	FIOSH			X			
BE	FPS Health			X			
	FPS Eco			X			
IR	FSA				X		
S	KEMI				X		
NO				X			
FR	ANSES			X			
FR	Ministries			X			
EFSA			X				
Anonymous MS 1				X			
Anonymous MS 2			X				
Anonymous MS 3				X			
Sum of the MSs		-	2 (14%)	10 (71%)	2 (14%)	-	/14
NGOs		-	12 (18%)	40 (61%)	10 (15%)	4 (6%)	/66
Companies		1 (3%)	8 (21%)	21 (55%)	7 (18%)	1 (3%)	/38
Citizens		-	2 (10%)	12 (57%)	5 (24%)	2 (10%)	/21
Total sum		1 (1%)	24 (17%)	83 (60%)	12 (9%)	7 (5%)	/139

QUESTION 4 (CONSISTENCY OF NANOMATERIAL DEFINITION IN REGULATORY CONTEXT – C)

Overall, as compiled in the attached document, are the considered modifications of the Recommendation sufficiently comprehensive and clear?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don't know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR			X			
	BAuA			X			
	FIOSH				X		
BE	FPS Health		X				
	FPS Eco			X			
IR	FSA				X		
S	KEMI		X				
NO				X			
FR	ANSES		X				
FR	Ministries		X				
EFSA				X			
Anonymous MS 1				X			
Anonymous MS 2				X			
Anonymous MS 3			X				
Sum of the MSs		-	5 (36%)	7 (50%)	2 (14%)	-	/14
NGOs		1 (2%)	22 (33%)	39 (59%)	1 (2%)	3 (5%)	/66
Companies		-	15 (39%)	18 (47%)	2 (5%)	3 (8%)	/38
Citizens			2 (10%)	17 (81%)	1 (5%)	1 (5%)	/21
Total sum		1 (1%)	44 (32%)	81 (58%)	6 (4%)	7 (5%)	/139

PART 2. REVISION CONSIDERATIONS (INDIVIDUAL TECHNICAL ELEMENTS)

QUESTION 5 (E1 WORDING: CONTAINING / CONSISTING OF)

Change: 'Nanomaterial' means a … material ~~containing~~ consisting of solid particles…'

Rationale in the attached motivation: Paragraph 5.

Main rationale:

Increased clarity. “Material” is a generic term for what is evaluated in specific legislation: chemical substance, cosmetic ingredient etc. The material should be evaluated based on what it mainly “consists of”, or in other words on what it is made of and without taking into account other components that may be present such as impurities, additives or stabilizers. Application of the definition still allows for the existence of another fraction or phase beside the particles in the material under assessment.

Does the change from 'containing' to 'consisting of' clarify the scope of the definition?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don’t know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR			X			
	BAuA				X		
	FIOSH				X		
BE	FPS Health				X		
	FPS Eco				X		
IR	FSA				X		
S	KEMI						
NO						X	
FR	ANSES		X				
FR	Ministries	X					
EFSA					X		
Anonymous MS 1				X			
Anonymous MS 2			X				
Anonymous MS 3					X		
Sum of the MSs		1 (8%)	2 (15%)	2 (15%)	7 (54%)	1 (8%)	/13
NGOs		1 (15%)	7 (11%)	23 (35%)	26 (39%)	4 (6%)	/66
Companies		1 (3%)	2 (5%)	6 (16%)	21 (55%)	4 (11%)	/38
Citizens		1 (5%)	1 (5%)	7 (33%)	9 (43%)	1 (5%)	/21
Total sum		4 (3%)	12 (9%)	27 (20%)	45 (33%)	7 (5%)	/138

QUESTION 6 (E2 PARTICLE - CHANGE 1: SOLID)

Change 1. '…material consisting of solid particles…'

Rationale in the attached motivation: Paragraph 8.

Main rationale:

Increased clarity. The definition in the current Recommendation 2011/696/EU is interpreted in the existing Questions&Answers prepared by the European Commission and the JRC Report EUR 29647 EN “An overview of concepts and terms used in the European Commission’s definition of nanomaterial” to cover only solid particles. The term “Solid” is here used in its meaning as one of the four fundamental states of matter, characterized by structural rigidity and resistance to changes of shape or volume, considered in this context under normal conditions. This excludes emulsions (liquid particles dispersed in liquid media) and micelles (agglomerates of dispersed surfactant molecules in a liquid). Restriction to solid particles is considered to ensure that the highly dynamic nature of the external dimensions of such nonsolid objects does not prevent the use of external size as the defining property.

Do you agree with the restriction to solid particles only?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don’t know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR		X				
	BAuA				X		
	FIOSH				X		
BE	FPS Health		X				
	FPS Eco		X				
IR	FSA				X		
S	KEMI						
NO					X		
FR	ANSES	X					
FR	Ministries	X					
EFSA			X				
Anonymous MS 1				X			
Anonymous MS 2						X	
Anonymous MS 3				X			
Sum of the MSs		2 (15%)	4 (31%)	2 (15%)	4 (31%)	1 (8%)	/13
NGOs		7 (11%)	3 (5%)	9 (15%)	40 (66%)	2 (3%)	/61
Companies		2 (6%)	2 (6%)	6 (18%)	23 (66%)	1 (3%)	/34
Citizens		-	1 (5%)	6 (32%)	12 (63%)	-	/19
Total sum		11 (9%)	10 (8%)	23 (18%)	79 (62%)	4 (3%)	/127

QUESTION 7 (E2 PARTICLE - CHANGE 2: UNBOUND)

Change 2. particles~~, in an unbound state or as an~~ that are either present on their own or as identifiable constituent particles in aggregates…'

Rationale in the attached motivation: Paragraphs 7 and 9.

Main rationale:

Increased clarity and ease of implementation. The term 'unbound' has been identified in the JRC survey as potentially ambiguous. Understanding that the definition applies to the material itself and not to its interaction with the environment (which might as well literally 'bind' the particle), the reference to 'unbound' is not strictly necessary and is replaced by 'present on their own', as identifying a particle itself is sufficient to implement the definition.

The qualifying term 'constituent' for particles in aggregates and agglomerates should eliminate doubts to which particles the definition refers (i.e. regarding sizing, counting).

The additional qualifier 'identifiable' in the definition proper makes it explicit that the application of the concept of constituent particle is bound by the practical consideration of properly identifying and measuring the constituent particles. Guidance on the implementation of the definition will include the specific situations where the identification of constituent particles as part of larger structures, in particular in strongly bound aggregates, is challenging.

Do you agree with the replacement of the reference to the 'unbound state'?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don’t know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR				X		
	BAuA			X			
	FIOSH				X		
BE	FPS Health				X		
	FPS Eco				X		
IR	FSA				X		
S							
NO					X		
FR	ANSES				X		
FR	Ministries					X	
EFSA					X		
Anonymous MS 1					X		
Anonymous MS 2				X			
Anonymous MS 3				X			
Sum of the MSs		-	-	3 (23%)	9 (69%)	1 (8%)	/13
NGOs		-	3 (5%)	31 (51%)	23 (38%)	4 (7%)	/61
Companies		3 (9%)	3 (9%)	11 (32%)	16 (47%)	1 (3%)	/34
Citizens		-	-	8 (42%)	10 (52%)	1 (5%)	/19
Total sum		3 (2%)	6 (5%)	53 (42%)	58 (46%)	7 (6%)	/127

QUESTION 8 (E2 PARTICLE - CHANGE 2: IDENTIFIABLE CONSTITUENT PARTICLES)

Do you agree with the reference to the 'identifiable constituent' particles?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don’t know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR			X			
	BAuA				X		
	FIOSH				X		
BE	FPS Health				X		
	FPS Eco				X		
IR	FSA				X		
S	KEMI						
NO						X	
FR	ANSES	X					
FR	Ministries		X				
EFSA					X		
Anonymous MS 1					X		
Anonymous MS 2				X			
Anonymous MS 3				X			
Sum of the MSs		1 (8%)	1 (8%)	3 (23%)	7 (54%)	1 (8%)	/13
NGOs		2 (3%)	24 (39%)	18 (30%)	12 (20%)	5 (8%)	/61
Companies		4 (12%)	11 (32%)	11 (32%)	6 (18%)	2 (6%)	/34
Citizens		4 (21%)	2 (11%)	5 (26%)	7 (37%)	1 (5%)	/19
Total sum		11 (9%)	38 (30%)	37 (29%)	32 (25%)	9 (7%)	/127

QUESTION 9 (E2 PARTICLE - CHANGE 3: 100 MICRON PLATELETS)

Change 3. Restriction of the particles to be considered in point 2): Particles with at least two orthogonal external dimensions larger than 100 micrometre shall not be counted for the purpose of the number size distribution.

Rationale in the attached motivation: Paragraph 14.

Main rationale:

Increased clarity and ease of implementation. Excluding from counting the particles with at least two orthogonal external dimensions above 100 micrometre that are themselves not aggregates or agglomerates of smaller constituent particles can address some of the practical measurement issues. It can also help to avoid in practice any potential ambiguity in differentiating between a particle and a larger solid product such as a large material sheet that should not be covered by the definition. The limit of 100 micrometres is based on the total suspended particle size as the largest particle size explicitly set by any regulation in the EU, i.e. air emission regulation [1]. In reasonably foreseeable practical cases, the relative contribution of particles in the size range 1 nm to 100 nm to the total number of particles would not be significantly influenced by either counting or excluding these large particles. Such upper limit means that a material with a majority of such particles, even if the third dimension of these particles is within 1-100 nm, is not considered a nanomaterial.

[1] For example, Directive (EU) 2016/2284 of the European Parliament and of the Council of 14 December 2016 on the reduction of national emissions of certain atmospheric pollutants, amending Directive 2003/35 /EC and repealing Directive 2001/81/EC (Text with EEA relevance), OJ L 344, 17.12.2016, p. 1

Do you agree that particles with at least two orthogonal external dimensions larger than 100 micrometres should not be counted for the number based size distribution?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don't know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR		X				
	BAuA				X		
	FIOSH				X		
BE	FPS Health			X			
	FPS Eco			X			
IR	FSA				X		
S	KEMI						
NO					X		
FR	ANSES	X					
FR	Ministries			X			
EFSA					X		
Anonymous MS 1					X		
Anonymous MS 2						X	
Anonymous MS 3			X				
Sum of the MSs		1 (8%)	2 (15%)	3 (23%)	6 (46%)	1 (8%)	/13
NGOs		7 (11%)	11 (18%)	15 (25%)	13 (21%)	15 (25%)	/61
Companies		5 (15%)	4 (12%)	5 (15%)	10 (29%)	10 (29%)	/34
Citizens		4 (21%)	1 (5%)	7 (37%)	6 (32%)	1 (5%)	/19
Total sum		17 (13%)	18 (14%)	30 (24%)	39 (31%)	27 (21%)	/127

QUESTION 10 (E2 PARTICLE - CHANGE 3: PLATELETS CLASSIFICATION)

As you do not fully agree please provide further clarification below. Choose one or more answers. (Between 1 and 5 choices)

Possible answers:

- **Option 1:** The implicit exclusion of very large but thin (1-100 nm) platelets is not appropriate
- **Option 2:** An upper limit is useful but the proposed value or constraint regarding at least two orthogonal dimensions is not appropriate.
- **Option 3:** The upper limit should apply only to specific types of particles.
- **Option 4:** The definition should explicitly allow flexibility in whether particles larger than the upper limit are included or excluded in the tally.
- **Other**

Summary of the answers

Member States		Option 1	Option 2	Option 3	Option 4	Other	
DE	BfR	X	X		X	X	
	BAuA						
	FIOSH						
BE	FPS Health					X	
	FPS Eco					X	
IR	FSA						
S	KEMI						
NO						X	
FR	ANSES	X					
FR	Ministries					X	
EFSA							
Anonymous MS 1						X	
Anonymous MS 2						X	
Anonymous MS 3						X	
Sum of the MSs		2 (22%)	1 (11%)	-	1 (11%)	8 (89%)	/9
NGOs		15 (38%)	2 (5%)	-	13 (33%)	23 (58%)	/40
Companies		7 (26%)	1 (4%)	2 (8%)	3 (13%)	15 (63%)	/24
Citizens		1 (8%)	5 (42%)	2 (17%)	5 (42%)	-	/12
Total sum		**25 (29%)**	**9 (11%)**	**9 (11%)**	**22 (26%)**	**46 (54%)**	/85

QUESTION 11 (E2 PARTICLE - CHANGE 4: SINGLE MOLECULES)

Change 4. Subdefinition of a particle in point 2a): 'Single molecules are not considered particles.'

Rationale in the attached motivation: Paragraph 12.

Main rationale:

Increased clarity. The explicit exclusion of single molecules is in line with the current interpretation of the Recommendation 2011/696/EU as laid down in the European Commission's Questions&Answers and the JRC Report EUR 29647 EN “An overview of concepts and terms used in the European Commission’s definition of nanomaterial”. A single molecule, including macromolecules such as proteins or polymers that may be larger than 1 nm, should not be considered a particle for the purpose of the definition. As there are different interpretations of the term ‘molecule’, a case-by-case consideration may be required in such very specific situations. This aspect will therefore be picked up in the Guidance and would include discussion of concrete cases (e.g. fullerenes, proteins, polymers).

Do you agree not to consider single molecules as “particles” in the definition?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don’t know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR		X				
	BAuA				X		
	FIOSH				X		
BE	FPS Health	X					
	FPS Eco	X					
IR	FSA				X		
S	KEMI						
NO		X					
FR	ANSES		X				
FR	Ministries			X			
EFSA					X		
Anonymous MS 1					X		
Anonymous MS 2					X		
Anonymous MS 3			X				
Sum of the MSs		3 (23%)	3 (23%)	1 (8%)	6 (46%)	-	/13
NGOs		1 (2%)	8 (13%)	9 (15%)	40 (66%)	3 (5%)	/61
Companies		-	5 (15%)	2 (6%)	27 (79%)	-	/34
Citizens		2 (11%)	-	4 (21%)	13 (68%)	1 (5%)	/19
Total sum		6 (5%)	16 (13%)	16 (13%)	86 (68%)	4 (3%)	/127

QUESTION 12 (E2 PARTICLE - CHANGE 5: CARBON BASED NM EXCEPTION)

Change 5: Delete derogation for specific carbon-based materials '3. By derogation from point 2, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.' , and include additional conditions b) and c) in the definition under point 2:

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

a) one or more external dimensions of the particle are in the size range 1 nm to 100 nm; or

b) the particle has an elongated shape, such as a rod, fibre or tube, the external dimensions of which do not satisfy point a), but where at least one external dimension is smaller than 1 nm;; or

c) the particle is in a plate-like shape, the external dimensions of which do not satisfy point a), but where one external dimension is smaller than 1 nm.

Main rationale:

Generalization of an existing derogation. Ideally, a definition would cover all materials using one straightforward rule, without the need for derogations. However, avoiding exceptions by extending or narrowing the basic criteria may result in unwanted inclusion or exclusion of other materials. Complementing the core definition with lists of explicitly included or excluded materials can be a pragmatic way to tackle the problem; the existing derogation was based on the knowledge of materials at the time (in 2011), making sure that some flagship nanomaterials (e.g. carbon nanotubes, graphene) with particles which may be thinner or smaller than 1 nm, are included.

This approach could be maintained. The review has however identified that it is not only carbon from which such particles can be manufactured and the list should be updated. The weakness of a list is a need for periodic update of the definition and the probable constant gap in the list compared to materials development.

Removing the list altogether would revise the present scope and leave some flagship materials out of the definition.

A more generic treatment of cases as presented above should potentially resolve this issue, increasing at the same time also the internal consistency of the definition by relying solely on counting the particles. But such replacement would identify as nanomaterials beside the single wall carbon nanotubes and single layer graphene flakes also certain other forms of substances or ingredients placed on the market (e.g. some specifically tailored forms of silicate minerals, oxides, nitrides or halides) that will extend the present scope of the definition, while excluding the presently included single-molecule fullerenes.

The questions below address the appropriateness of the technical solution considered. The questions in Part 3 explore the potential consequences of applying this change.

Indicate your preferred solution in relation to the potential revision of existing derogation that specifically includes fullerenes, single wall carbon nanotube and graphene flakes as nanomaterials:

Possible answers:

- **Option 1:** No need for any additional inclusion of materials through criteria or specific derogation
- **Option 2:** Maintain current derogation
- **Option 3:** Update the derogation list
- **Option 4:** Partially agree with the replacement of derogation but conditions need to be modified
- **Option 5:** Agree with the replacement of derogation with the inclusion of fibre- and plate-like materials as proposed
- **None of the proposed or no opinion**

Summary of the answers

Member States		Option 1	Option 2	Option 3	Option 4	Option 5	NOTP	
DE	BfR				X			
	BAuA					X		
	FIOSH					X		
BE	FPS Health				X			
	FPS Eco				X			
IR	FSA		X					
S	KEMI							
NO						X		
FR	ANSES						X	
FR	Ministries				X			
EFSA						X		
Anonymous MS 1						X		
Anonymous MS 2							X	
Anonymous MS 3						X		
Sum of the MSs		-	1 (8%)	-	4 (30%)	6 (43%)	2 (15%)	/13
NGOs		2 (3%)	2 (3%)	-	10 (16%)	18 (30%)	29 (48%)	/61
Companies		1 (3%)	2 (6%)	1 (3%)	3 (9%)	8 (24%)	19 (56%)	/34
Citizens		-	3 (16%)	-	1 (5%)	11 (58%)	4 (21%)	/19
Total sum		**3 (2%)**	**8 (6%)**	**1 (1%)**	**18 (14%)**	**43 (34%)**	**54 (43%)**	**/127**

QUESTION 13 (E2 PARTICLE - CHANGE 5: CARBON BASED NM EXCEPTION)

Do you agree that with these five changes particles are clearly and adequately defined for the purpose of the definition?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don’t know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR		X				
	BAuA			X			
	FIOSH				X		
BE	FPS Health		X				
	FPS Eco		X				
IR	FSA				X		
S	KEMI						
NO				X			
FR	ANSES		X				
FR	Ministries			X			
EFSA				X			
Anonymous MS 1				X			
Anonymous MS 2						X	
Anonymous MS 3			X				
Sum of the MSs		-	5 (38%)	5 (38%)	2 (15%)	1 (8%)	/13
NGOs		5 (8%)	24 (39%)	22 (36%)	5 (8%)	5 (8%)	/61
Companies		3 (9%)	10 (29%)	14 (41%)	4 (12%)	3 (9%)	/34
Citizens		-	1 (5%)	14 (74%)	2 (11%)	2 (11%)	/19
Total sum		8 (6%)	40 (31%)	55 (43%)	13 (10%)	11 (9%)	/127

QUESTION 14 (E3: SIZE DISTRIBUTION THRESHOLD FLEXIBILITY)

Change: Removal of flexibility clause 'In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %.', leaving only default threshold of 50%.

Rationale in the attached motivation: Paragraph 7.

Main rationale:

In Recommendation 2011/696/EU, a certain flexibility was introduced as a safeguard in the light of the uncertainties and lack of knowledge on nanomaterials at the time. However, it may create confusion among business operators, consumers and regulators. Depending on the thresholds used in specific legislation, the same specific material could be considered as a nanomaterial under one regulatory framework but not under another. It has also been the main reason why direct reference to the nanomaterial definition in Recommendation 2011/696/EU was not possible in some instances.

The current review has not found evidence that the existing default threshold of 50% (i.e. more than half of all particles in the material are in the nanosize range) should be increased or decreased to address a particular concern or to cover or exclude specific materials. With a reduction of the threshold, from 50% to a lower value, the challenges associated with the measurement of particle size distribution would also be further increased (point elaborated in the JRC report EUR 26744 EN).

Do you agree with removing the flexibility of the threshold?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don’t know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR			X			
	BAuA				X		
	FIOSH				X		
BE	FPS Health		X				
	FPS Eco		X				
IR	FSA				X		
S	KEMI						
NO						X	
FR	ANSES		X				
FR	Ministries					X	
EFSA		X					
Anonymous MS 1				X			
Anonymous MS 2		X					
Anonymous MS 3					X		
Sum of the MSs		2 (15%)	3 (23%)	2 (15%)	4 (31%)	2 (15%)	/13
NGOs		7 (12%)	-	11 (18%)	37 (61%)	6 (10%)	/61
Companies		1 (3%)	1 (3%)	2 (6%)	29 (85%)	1 (3%)	/34
Citizens		3 (16%)	-	5 (26%)	9 (47%)	2 (11%)	/19
Total sum		13 (10%)	4 (3%)	20 (16%)	79 (62%)	11 (9%)	/127

QUESTION 15 (E3: SIZE DISTRIBUTION THRESHOLD)

Do you agree with maintaining the default threshold value of 50%?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don’t know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR			X			
	BAuA			X			
	FIOSH				X		
BE	FPS Health	X					
	FPS Eco		X				
IR	FSA				X		
S	KEMI						
NO				X			
FR	ANSES	X					
FR	Ministries					X	
EFSA			X				
Anonymous MS 1				X			
Anonymous MS 2						X	
Anonymous MS 3					X		
Sum of the MSs		2 (15%)	2 (15%)	4 (31%)	3 (23%)	2 (15%)	/13
NGOs		6 (10%)	5 (8%)	24 (39%)	20 (33%)	6 (10%)	/61
Companies		3 (9%)	2 (6%)	15 (44%)	14 (41%)	-	/34
Citizens		4 (21%)	3 (16%)	4 (21%)	6 (32%)	2 (11%)	/19
Total sum		15 (12%)	12 (9%)	47 (26%)	43 (34%)	10 (8%)	/127

QUESTION 16 (E4 VSSA – CHANGE 1: INCLUSION CRITERION)

Change 1: Remove existing reference to VSSA '5. Where technically feasible and requested in specific legislation, compliance with the definition in point 2 may be determined on the basis of the specific surface area by volume. A material should be considered as falling under the definition in point 2 where the specific surface area by volume of the material is greater than 60 m^2/cm^3. However, a material which, based on its number size distribution, is a nanomaterial should be considered as complying with the definition in point 2 even if the material has a specific surface area lower than 60 m^2/cm^3.'

Rationale in the attached motivation: Paragraph 15.

In the Recommendation 2011/696/EU, the identification of a nanomaterial through its VSSA value is possible but the number size distribution would prevail in case of conflicting results. The VSSA value may be subject to interpretation, as high surface area may be due to the internal nanostructure, not attributable to aggregates or agglomerates of constituent particles. Moreover, particle shape and size polydispersity can strongly influence the relation between thresholds in number-based size distribution and in VSSA.

The NanoDefine project concluded that such an identification was not appropriate.

This is without prejudice to the continued use of VSSA as a screening method for selection/identification of materials that might fulfil the definition as outlined also in the JRC Report EUR 29942 EN “Identification of nanomaterials through measurements”. Relevant support in the Guidance is being planned.

Do you agree with deleting the use of VSSA as a surrogate for particle size distribution measurement for classifying materials as nanomaterials?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don’t know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR		X				
	BAuA					X	
	FIOSH				X		
BE	FPS Health				X		
	FPS Eco		X				
IR	FSA				X		
S	KEMI						
NO					X		
FR	ANSES				X		
FR	Ministries					X	
EFSA					X		
Anonymous MS 1					X		
Anonymous MS 2						X	
Anonymous MS 3					X		
Sum of the MSs		-	2 (15%)	-	8 (62%)	3 (23%)	/13
NGOs		10 (16%)	9 (15%)	11 (18%)	22 (36%)	9 (15%)	/61
Companies		7 (21%)	4 (19%)	4 (12%)	15 (44%)	4 (12%)	/34
Citizens		4 (21%)	1 (5%)	5 (26%)	5 (26%)	4 (21%)	/19
Total sum		21 (17%)	16 (13%)	20 (16%)	50 (39%)	20 (16%)	/127

QUESTION 17 (E4 VSSA – CHANGE 1: EXCLUSION CRITERION)

Change 2: Insert the following VSSA reference: a material with a specific surface area by volume of 5 m^2 /cm^3 or less shall not be considered a nanomaterial.

Rationale in the attached motivation: Paragraph 16.

Main rationale:

VSSA measurements can be considered as a tool for the exclusion of a material as a nanomaterial and thus to avoid additional costly measurements. The NanoDefine project demonstrated with a large set of different materials that the materials with a volume specific surface area of 5 m^2/cm^3 or less with great certainty do not have the number- based particle size distribution of a nanomaterial. Therefore, those materials should not be considered as a nanomaterial.

Do you agree with adding a possibility to use a VSSA threshold value of 5 m^2/cm^3 as a threshold value to exclude materials from the definition of a nanomaterial?

Possible answers:

- Fully disagree
- Mostly disagree
- Mostly agree
- Fully agree
- Don't know

Summary of the answers

Member States		Fully disagree	Mostly disagree	Mostly agree	Fully agree	Don't know	
DE	BfR			X			
	BAuA					X	
	FIOSH				X		
BE	FPS Health	X					
	FPS Eco			X			
IR	FSA				X		
S	KEMI						
NO					X		
FR	ANSES	X					
FR	Ministries					X	
EFSA					X		
Anonymous MS 1					X		
Anonymous MS 2						X	
Anonymous MS 3			X				
Sum of the MSs		2 (15%)	1 (8%)	2 (15%)	5 (38%)	3 (15%)	/13
NGOs		3 (5%)	13 (21%)	25 (41%)	8 (13%)	12 (20%)	/61
Companies		2 (6%)	5 (15%)	15 (44%)	8 (24%)	4 (12%)	/34
Citizens		1 (5%)	-	8 (42%)	6 (32%)	4 (21%)	/19
Total sum		8 (6%)	19 (15%)	50 (39%)	27 (21%)	23 (18%)	/127

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