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EXPLANATORY NOTE

HOW THE COMMENTS RECEIVED DURING THE PUBLIC CONSULTATION WERE TAKEN INTO ACCOUNT FOR THE FINAL SCENIHR OPINION ON THE SCIENTIFIC BASIS FOR THE DEFINITION OF THE TERM "NANOMATERIAL"

This note sets out the rationale for the modifications made to the opinion of the European Commission Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on the Scientific Basis for the Definition of the Term "Nanomaterial" following a public consultation.

Introduction

In March 2010, the European Commission requested the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to provide a scientific opinion on the current status of issues on the Scientific Basis for the Definition of the Term "Nanomaterial". This work was needed to help ensure the consistency of forthcoming regulatory developments, to guide, as appropriate, the effective implementation of existing legislation, and to contribute to international work and dialogue on nanotechnology definitions.

It was stressed that establishing a policy for a working definition of "nanomaterials" was required as a matter of urgency. Thus based on current knowledge, the SCENIHR was invited to provide advice on the essential elements of a science-based working definition of "nanomaterials". More specifically they were asked to identify:

• the types of physical and chemical properties particular to nanomaterials;

• the threshold(s) at which nanomaterial-specific properties could be expected to occur; and

• potential methodology for nanomaterial characterisation.

A SCENIHR Working Group was formed, comprising of five members of the SCENIHR, one member of the Scientific Committee on Consumer Safety (SCCS) and five experts from academia with experience on the subject. The WG produced a draft opinion which was discussed and adopted by the SCENIHR plenary on 28 June 2010 as suitable for public consultation (pre-consultation opinion).

In line with its procedures for stakeholder dialogue, implemented in the Rules of Procedures of the new Scientific Committees[1], the European Commission's Directorate General for Health and Consumers (DG SANCO) then conducted a public consultation on this pre-consultation opinion between 12 July and 15 September 2010.

Results/participation

By the deadline, 94 contributions were received of which seven were from public authorities, 39 from businesses, 7 from trade associations, 4 from academia, 8 from individuals, 14 from NGOs and 15 others (e.g. private or international organisations). Several submissions notably those from industry and the NGOs were identical.

During the consultation process, comments were invited to 11 sections 'abstracted' from the pre-consultation opinion (See annex). This approach was undertaken to guide the responders to address key questions, in what is a very complex matter, thus providing more focussed feedback in terms of both general comment (agreement/disagreement) and specific comment regarding the underlying scientific justification for the conclusions drawn in the Draft Opinion. Comments were additionally invited to the pre-consultation opinion document as a whole. A broad sweep analysis of the overall responses (grouping the agree/mostly agree categories and the disagree/disagree categories) showed that:

• There was a consensus of agreement to points 1 (~60%), 2 (~82%), 3 (~72%), 5 (~58%) and 9 (~89%)

• There was a general consensus of disagreement to points 6 (~58%) and 11 (~60%)

• For the other points, the opinion was obviously split between agreement and disagreement i.e. point 4 (agreement ~47 %), 7 (agreement ~ 47%), 8 (agreement ~ 51%) and 10 (agreement ~ 46%).

The specific scientific comments made to the pre-consultation opinion illustrate the difficulty of unifying the terminology and methodology for nanomaterial characterisation such that it could be acceptable for all stakeholders, and across all those European agencies responsible for evaluation of acceptable risk/benefit of nano-sized materials/objects.

Modifications to the opinion

All comments were reviewed by the Working Group during its meetings of 24 September and 18-19 October 2010 and taken into account. The appropriate modifications were subsequently introduced into the opinion which was then discussed and adopted by the SCENIHR by written procedure on December 8th 2010.

The Working Group modified the opinion to reflect all submitted comments which were assessed to be pertinent and relevant for the subject matter and respected the clear separation between risk assessment and risk management that underpins the Scientific Advisory structure of the European Commission. Comments on issues like policy, risk management, legal clarification, ethics, and the precautionary principle, were not considered as, although pertinent to the subject matter, they are outside the competences of the Scientific Committees.

[1] set up by Commission Decision 2008/721/EC of 5 September 2008

Detailed explanations of the way the comments received were treated by the SCENIHR are provided below. They are structured according to the eleven sections used to organize the public consultation (see annex). The numbering of pages and sections correspond to the final opinion adopted by the SCENIHR.

Section 1 – Categorization by size

Comments that led to a modification of the text of the opinion:

A number of comments made reference to applicability of current risk assessment methodology for nanomaterials but this was out of the scope of this opinion. Risk assessment as such is outside of the scope of the opinion and is only mentioned as introduction to the problem. The SCENIHR considers so far that the current risk assessment methodology is generally adequate but that for some types of testing for hazard identification and exposure measurement/estimation, an adaptation of methodology might be necessary. As a result, the SCENIHR adapted the opinion to clarify that it does not intend to suggest that nanomaterials necessarily carry new hazards but that currently, and until more knowledge is obtained, these materials present an uncertainty with regard to potential risk, as does any newly developed and previously unknown chemical.

The SCENIHR is of the opinion that the current risk assessment methodology allows for sufficient flexibility to be used also for nanomaterials. However, in view of the specific particulate nature of nanomaterials not all currently applied methodologies for the evaluation of chemicals may be applicable to nanomaterials. Therefore a careful consideration is indicated in the opinion. With respect to the desire expressed in many comments to focus the definition only on substances of concern, the SCENIHR wishes to state that a definition should not be based on the materials of possible concern as these cannot be identified beforehand. Therefore, the SCENIHR proposes to develop a general definition. The risk assessment of each nanomaterial will have to identify hazardous and non-hazardous materials, in a similar fashion to existing compounds.

As a result, the SCENIHR supports the intention to have a broad definition, and then, just like for other particulate materials, to generate information whether such a material may pose a risk for man and the environment.

Comments that did not lead to a modification of the text of the opinion:

The comments received on this section were broadly in agreement with the SCENIHR opinion and many agreed on the need to develop an overarching definition of nanomaterials. Some proposed an alternative terminology in line with the specific sector of operation of the author or in reference to the REACH regulation and some preferred a definition based on properties.

The SCENIHR acknowledges that specific properties may occur at certain size thresholds. However, there is no scientific evidence that there is a general threshold that can be applied to all nanomaterials, nor is there a general property that changes for all nanomaterials. The precise physico-chemical properties of a nanomaterial largely depend on its precise chemical composition and physical form.

There was general agreement on the SCENIHR statement that nanomaterial is "*a categorisation of a material by the size of its constituent parts*" and "*does not imply a*

specific risk, nor does it necessarily mean that this material actually has new hazardous properties compared to its constituents".

Section 2 – change in properties with size

Comments that led to a modification of the text of the opinion:

A number of comments claim that changes in properties, and especially quantum effects, always occur in the size range of 20-30 nm and that 100 nanometre therefore represents a conservative upper limit with respect to the nano-specific properties.

The SCENIHR wishes to clarify that, for certain materials the size at which physicochemical properties change is above 100 nm. Quantum effects do exist, but in view of the large number of different uses of nanomaterials, all kinds of possible changes in characteristics should be considered and not just quantum effects. The SCENIHR acknowledges the results of Auffan *et al.* but notes that they only describe the size – effect relationship of a very specific subgroup of nanomaterials. Additional literature has been added to the opinion indicating that size specific changes in physicochemical characteristics also can occur above 100 nm. In addition, for certain physico-chemical properties a continuous effect was observed when related to size increase or decrease.

Some comments remark that there is no scientific justification for the upper and lower size limits chosen and that there should be no substantial difference made between a 102 nm particle and a 99 nm one. The SCENIHR agrees. The rationale for the choice of the different levels proposed by the SCENIHR is explained in the opinion. Some adaptation of the text has been done for further clarification, especially with regard to the use of mean and/or median sizes. However, there is a need for a regulatory definition. So, in addition to just mentioning the mean/median size also the size distribution is introduced as additional criterion.

Comments that did not lead to a modification of the text of the opinion:

A number of comments put in doubt the validity of animal tests and propose to replace them by human cell-based assays and other *in vitro* methods, claiming that they are applicable to nanotechnology.

The EU scientific committees are in favour for the use of alternative methods but only when they are validated against current practices used in risk assessment[2]. One major question mark on the use of many *in vitro* alternatives is the lack of a proper validation. In addition, the relationship between dose-response effects in an *in vitro* system and possible harmful effects in humans remains unknown.

One comment asked to clarify the nature of nanomaterials in the food chain by stating more clearly that many natural compounds present in food are nanoscale, and that the human body has evolved mechanisms to digest and gain nutritional benefit from them. The SCENIHR agrees with this comment and has expressed the need to define clearly

[2] Memorandum on the Actual Status of Alternative Methods on the Use of Experimental Animals in the Safety Assessment of Cosmetic Ingredients in the European Union, 19 June 2007 (http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_s_06.pdf)

some exclusions/exceptions when using the proposed definition within a regulatory context.

Other comments refer to the JRC report with respect to the policy implications of any regulatory definition. The SCENIHR agrees with the JRC report but this question is outside of the scope of this opinion.

With respect to the comments on surface reactivity the SCENIHR is of the opinion that it is the interaction of the surface (re)activity and any organism that is the key issue in risk assessment of compounds. So, these surface activities are highly relevant and important for the risk assessment and safety of such materials.

One comment expressed the view that the use of specific size limits and specific surface to volume ratios does not help to conclude on a certain risk or necessary safety studies. However, in the opinion of the SCENIHR, a definition is needed to identify particulate matter that may exert specific interactions or behaves differently from common compounds. Even when a case by case approach is used, some specific kind of adaptation to the testing methodology may be needed in view of the particulate nature of the test compound. If dissolution occurs, the compound can be evaluated in its soluble form. However, until the material is dissolved the particulate nature of the compound should be taken into consideration in its risk assessment.

With respect to the comment on dose metric, and the particulate nature of nanomaterials, one should always recall that if no exposure occurs, there is no risk. Adding the prefix "nano-" to materials/compounds such as using "nano-particulate matter" as descriptive would also require the definition of the "nano" part.

With respect to the distribution of nanomaterials (either in the environment or in the body), uptake and tissue distribution can be dependent on the size of a particulate material, however, it cannot be considered to be part of the intrinsic physicochemical properties of a nanomaterial.

Section 3 – Caveats around the 100 nm limit

Comments that led to a modification of the text of the opinion:

Many comments under this section referred in fact to section 11 (VSSA, 0.15%...). The number size distribution is based on the variation in the production method. Nanomaterials of a given specific size do not consist of particles with all the same unique size. There is a variation in size and this size distribution can be determined and described by the mean/median and/or standard deviation/geometric standard deviation. Based on these data one can calculate if more than 0.15% would fall below the upper limit of 100 nm. Therefore, the 0.15% is a fraction to be derived from the known variation within the final product, and should not be seen as a percentage that has to be measured directly. The text of the Opinion was adapted for clarification.

Some comments confused the concept of size distribution with that of mixture. The opinion was clarified on the issue of size distribution and of nanocomposites. Materials may contain a fraction at the nanoscale.

Several comments argued that the 100 nm limit was sufficiently high to cover the size distributions of nanomaterials. However, changes in physicochemical properties are probably occurring at a gliding scale. For a specific subgroup of nanomaterials, the

threshold was identified to be between 20 and 30 nm (Auffan et al 2009). Additional information was provided in the opinion to indicate that changes in properties are not limited to the 30 nm threshold. Therefore, the upper size of 100 nm, although widely accepted cannot be seen as a conservative threshold and further description of the interpretation of the figure 100 was needed. The SCENIHR has clarified the point that there is no scientific justification for any single threshold and the values proposed in the opinion are used as examples.

Regarding the critiques offered on the proposed measuring methodology, the SCENIHR clearly identified the need for appropriate methodology and the relevant statement was clarified. Yet it may be that there still is a need for further development of the measurement methodology. In terms of cost, semi-automated systems for particle measurement are already available. In addition, a thorough description, including measurement, is needed to identify a product in a risk assessment dossier. While such detailed measurement may be needed for risk assessment and marketing authorisation, simpler measurements may be sufficient for industrial production.

Comments that did not lead to a modification of the text of the opinion:

The VSSA can be easily determined for dry powders and for this group of materials, it can be used as an additional parameter to identify whether the product would comply with the definition of a nanomaterial. Other methods exist that can be used for the analysis of both powders and particles dispersed in liquids but most still remain difficult to use on a routine basis. More developments are needed in this domain.

The term "nanomaterial" is used in the opinion to describe the products that are discussed. It is a generally accepted terminology. The Opinion is intended to advise on a definition for these nanomaterials.

With respect to remarks on the ISO definition of "nanomaterial", with its upper (100 nm) and lower (1 nm) bounds, the opinion follows the general nomenclature of ISO, the exception being that for a regulatory definition the term nano-objects is not followed.

Some comments argued for a use of risk and properties to define nanomaterials. The SCENIHR is of the opinion that in a regulatory definition on which SCENIHR has been asked to comment, risk cannot be used as a determining factor. If risk was considered as a factor, all particulate material would have to be evaluated to identify those that pose a risk and those that don't. The definition for which the SCENIHR was asked to consider the scientific basis is needed to identify the materials for which additional considerations may exist when performing a risk assessment.

With respect to the comments on the use of the word “approximately” in the ISO definition, one should note that, in a regulatory context, the word as used in ISO would introduce uncertainty on its interpretation. Therefore, more restrictive definitive figures are needed. However, in the case of nanomaterials, the size range is important to consider and a regulatory definition needs clear criteria to determine when something is designated a nanomaterial or not. To that end, the SCENIHR has proposed a fraction, either based on the size distribution of the nanomaterial like the 0.15%, or a fixed percentage, that has to be below the upper limit in order to identify a nanomaterial.

Until more knowledge is obtained on nanomaterials in general, the SCENIHR proposes to follow a case by case evaluation.

Section 4 – Size measurement, number based distribution, aggregates and agglomerates

Comments that led to a modification of the text of the opinion:

Regarding the comments on terminology, the SCENIHR used the term nanomaterial in the opinion to describe also nanostructured materials. In addition, the opinion addresses the definition and thus the size of primary particles. The text has been adapted for clarification. The text regarding atoms and molecules has also been clarified.

Some comments focussed on the cost and limitations of the methods to measure the size of nanomaterials. The SCENIHR refers to the response given under Section 3. The need for appropriate methodology was identified. Yet, it may be that there still is a need for further development of the measurement methodology. In terms of cost, nowadays semi-automated systems for particle measurement are available. In addition, a thorough description including measurement is needed to identify a product in a dossier. Such detailed measurement may not be necessary for routine industrial operation. The relevant text was clarified.

Figure 1 was clarified to address the comments received, according to which it was not clar how to handle the different types of nanomaterials.

Numerous comments called for the use of a weight based size distribution. However, the specific concerns raised by nanomaterials in terms of toxicity relate mostly to their small size or large specific surface area. Therefore, looking at size distribution based on weight would tend to minimize the lower part of the distribution curve, which contains the nanoscale particles that need to be considered in view of their specific nanoscale properties. While this fraction would be minor based on weight, it might be the largest fraction when based on number and the one most relevant from a toxicological point of view. Therefore, the number size distribution has to be taken into account to identify a nanomaterial. The terminology "number size distribution" is maintained.

In addition, the text of the opinion has been adapted to clarify that in the case of particulate materials, the primary particle and its size distribution should be considered/measured.

The opinion has also been adapted to clarify the issue of multi-component nanomaterials. The word "widely" has been removed from the sentence referring to medical and cosmetic applications. It should be realised that liposomes is a collective designation for a variety of different liposomes with different compositions. So, a liposome is not one single material

Comments that did not lead to a modification of the text of the opinion:

The SCENIHR agrees that from a scientific and health risk point of view the inclusion of the internal structure is correct but that it may lead to materials being included that should not be, in particular in the food area. Therefore certain “problem” areas like globular proteins in food, and a large material like a car tyre, that includes nano carbon black are given as examples of such potential problems when the proposed definition is used. So, it is clear that a solution should be found for these areas. On the other hand, for large materials like car tyres containing nanomaterials during the production phase and at the end of the life-cycle there may be an exposure to the used nanomaterials that should

be taken into consideration when performing a risk assessment.

With respect to "internal structures", the SCENIHR considers that they need to be considered to be able to address the safety aspects linked to large reactive internal surface areas, or when a nanomaterial is used in the production phase of a product, and for possible harmful environmental and health effects at the end of the life-cycle of a composite product.

With respect to the comment that the nanoscale is generally accepted to range from 1 nm to 100 nm, it should be noted that the SCENIHR statement that "*in the metric system, the "nanoscale" is the range below 1 micrometre (µm) and above 999 picometre (pm)*" is correct and was intended as an explanation of possible measuring problems at the nanoscale. The statement referred to in the comment was not meant to be the definition.

Some comments considered that referring to size as "one or more external dimensions" is not adequate when it comes to labelling of nanomaterials, and that, in terms of labelling, it is important for consumers to be aware that the product they are using is safe. As size is the predominant factor for describing the nanoscale, it is also predominant in a definition of nanomaterials. The issue of safety is unrelated. The safety of products should be ensured, irrespective of whether they use nanomaterials or not.

Concerning the remark that "particles" that are nano (< 100 nm) in just one dimension do not raise concerns, the SCENIHR considers that in the risk assessment it would be obvious from the beginning that, as long as they are fixed on some other material, plates, sheets or (nano)-coatings would not pose a risk in terms of exposure. However, during production, use-wear and at the end of the life-cycle the situation may be different and may need specific attention in the RA process.

Regarding the comments related to the size and nature of molecules, ambiguities around the lower threshold remain to be solved. Also, many biological structures have sizes in the nanoscale and should be addressed by using specific exclusion criteria.

With respect to the term "engineered", the SCENIHR proposed to include manufactured/engineered as part of the definition. In addition, also processing should be included as the final result of such processing may be materials in the nanoscale.

Concerning the comment that the opinion is vague in providing any guidance on the characterization and /or measurement of nanoparticles it should be remembered that the mandate of the SCENIHR was to consider various aspects that might be suitable to include in a definition of a nanomaterial. The mandate did not include the evaluation of various measuring/detection techniques used on nanomaterials

Some comments addressed the issue of certain structures that should or should not be included in the definition. The inclusions or exclusions as indicated by the opinion have been discussed in the context of potential risks due to particulate matter in the nanoscale. However, it is also obvious that certain materials/products that would be included by the currently proposed definition do not pose a risk to human and/or environmental health. Although it is not easy to distinguish such material in a definition, the possible problems associated by using any definition should be considered, and are thus mentioned in the opinion.

Section 5 – Validity of limits, VSSA

Comments that led to a modification of the text of the opinion:

Also agglomerates/aggregates are composed of primary structures in the nanoscale. The opinion has been adapted to clarify more explicitly that size measurements should be performed on the primary particles. Especially for agglomerates with their weak binding forces, the release of individual nanoparticles might be possible.

With respect to comments relating to a fraction of a material having a VSSA higher than the threshold, the text of the opinion has been clarified. It is difficult to determine whether a fraction of a material would have a VSSA larger than the threshold as this would require the physical separation of that fraction.

Comments that did not lead to a modification of the text of the opinion:

A number of comments focussed on the limitation of the VSSA and on the choice of the threshold value to determine a nanomaterial. The limitations of the VSSA to determine if a material can be considered a nanomaterial are known. This value is therefore introduced as an additional parameter that might be helpful to determine when a material should be considered a nanomaterial when it can be measured. The VSSA is in SCENIHR's view independent of the shape of a material. However, although the measurement can be performed on nanowires, nanorods and nanotubes, the resulting data might not be suitable to identify such structures as nanomaterials. As mentioned in Answers to Section 4, there may be an issue with biological structures when a size of 1 nm – 100 nm is used in a definition of a nanomaterial.

In that context, the VSSA is an additional parameter that may be helpful in identifying a nanomaterial. The risk assessment should be performed with the possible presence of nanoscale particles in the product. The current risk assessment methodology is in general applicable, however, in view of the possible uses, the particulate nature, and the size of the particles more dedicated or adapted tests may be needed (e.g. to determine the size distribution, exposure).

Section 6 - Size distribution threshold – 0.15%

Comments that led to a modification of the text of the opinion:

A number of comments indicated that many nanomaterials do not have a normal distribution. The SCENIHR agrees. This issue was considered and the opinion adapted accordingly. Size limits are considered by the tiered approach proposed by the opinion. The SCENIHR also considers that any risk assessment has to be performed on the nanomaterial as a whole. So, if a risk would be present due to a minimal fraction this should be turn up at the safety evaluation of the nanomaterial.

Comments that did not lead to a modification of the text of the opinion:

Regarding the claim that there is no metrological technology for "size" distribution analysis, the SCENIHR reiterates its view that the determination of the size distributions is key to the definition of nanomaterials. Some methods exist but the SCENIHR has identified the need for appropriate methodology. It is quite possible that there still is a need for further development of appropriate and reliable measurement methodology.

A number of comments also questioned the workability of the 0.15% cut-off. However, it

should be realized that the production of nanomaterials will result in a variation in the size of the produced nanomaterial. Theoretically, using a normal distribution as an example, the measured size distribution may be used to derive a standard deviation and thereby estimate the fraction of the preparation below 100 nm. The SCENIHR agrees that its proposal to use 3 SD may be challenging and may not be applicable to all materials. However, it was felt important to give an example of an approach that would allow discrimination of a fraction of particles that would fall beneath the 100 nm threshold. In addition, this cut-off can be determined in many cases by a calculation using the statistical parameters of the size distribution. Therefore, it is not always necessary to actually count and measure the tail of the distribution, which can be a difficult task.

Section 7 - Coatings, stability, solubility and physicochemical parameters

Comments that led to a modification of the text of the opinion:

None

Comments that did not lead to a modification of the text of the opinion:

The SCENIHR is of the opinion that physicochemical properties do not show sufficient discrimination and universality to generally identify the wide variety of nanomaterials. In particular, solubility can be affected by the surface properties that in their turn may be prone to manipulation using coatings. Therefore the SCENIHR does not consider solubility a suitable determinant for identifying nanomaterials. However, the SCENIHR agrees that solubility is a key element in the potential risk for any material. For particulates, the timing of the dissolution determines the possible risk. Until it is dissolved, the fate of particulate matter will be governed by the particulate nature of the material. After dissolution, a classical risk assessment of the chemical components can be performed.

Some contributions disagree that each combination of a nanomaterial with a coating has to be considered as an individual case for safety evaluation. Indeed the number of possible variations between supports and coatings is indefinite. The SCENIHR agrees that not every surface treatment will have an effect on the risk of a material. But, as the effect of the surface treatment can be crucial for the toxicological properties of the nanomaterials and is unknown beforehand such materials should be evaluated on a case-by-case basis.

Some contributors would like to restrict the definition of nanomaterials to those that are insoluble and that degradability/(bio)persistence criteria should be included as elements in regulatory definitions of nanomaterials. The SCENIHR agrees that non–degradability or (bio)persistence does not mean by itself that a material is toxic and these properties are important to consider in a risk assessment. However, as mentioned in the opinion “these features cannot be translated into an element of a definition as they are part of the characterisation of a nanomaterial and can change for each individual nanomaterial”. In addition, degradability/solubility may be dependent on surface characteristics like coatings.

Some contributors consider that "a universal, regulatory (ISO, CEN) definition/convention is not appropriate for regulative purpose because only a specific fraction of nanomaterials has to be addressed". The SCENIHR notes that this position is

not coherent as it confers a universal value to the term "nanomaterial" in the expression "a specific fraction of nanomaterials". The SCENIHR agrees that not all nanomaterials are toxic and that the scope of each piece of legislation can be reduced to fit its specific purpose. However, this does not detract any value from a general definition. The main basis for the definition of a nanomaterial is the size. For regulatory purposes, the size by itself has to be further defined in terms of the occurring size distributions present in nanomaterials. Within each separate regulation additional requirement may be needed for the specific applications of a nanomaterial.

Section 8 – Internal structures – nanocomposites – scope of the definition

Comments that led to a modification of the text of the opinion:

None

Comments that did not lead to a modification of the text of the opinion:

A number of comments delved into the scope that any definition should have. Some expressed a preference for a general description in abstract terms, others for a focus on solid particulate substances, others considering that macroscopic materials containing nano-objects should be excluded. A number of comments also considered the concept of “internal structure” as too broad and voiced concerns about making the regulatory burden too heavy.

The SCENIHR considers that nanostructured materials should fall within the scope of a definition of the term "nanomaterial" but recognizes that by including internal structures in the definition of a nanomaterial, indeed also larger structures would be included that are clearly not “nano”. Car tyres are cited as an example. However, the possible risks associated with nanomaterials may occur either at the production phase (when the nanomaterial is added to the product), during use-wear or at the end of the life-cycle (when nanomaterials might be released form the product).

The SCENIHR agrees with the proposal to include a review clause to any definition to allow for adjustments in view of scientific progress.

Section 9 -Types of nanoscale materials based on their origin

Comments that led to a modification of the text of the opinion:

None

Comments that did not lead to a modification of the text of the opinion:

The comments received under this section mostly stated that there is no link between the origin of a nanomaterial and its toxicity profile and on what regulation should focus. The SCENIHR agrees that there is no link between the origin of a nanomaterial and its toxicity profile. The other comments concerned issues outside of the scope of the SCENIHR mandate.

Section 10 - Conclusion, size, size distribution, lower limit

Comments that led to a modification of the text of the opinion:

The SCENIHR agrees that a 1 nm lower limit does not solve the problem of molecules (e.g. proteins, polymers) that are larger and of materials that are commonly considered as nanomaterials (e.g. fullerenes, carbon nanotubes) that are smaller. As stated in the opinion the lower size limit does create ambiguity and thus uncertainties. The opinion has been adapted to further clarify this issue.

The SCENIHR agrees that the VSSA is a very useful tool for implementing the definition especially as it covers aggregates and agglomerates and that it has to be carefully considered in how to deal with the practical limitations in its applicability. The text of the opinion has been adapted for clarification.

Comments that did not lead to a modification of the text of the opinion:

Regarding the question of "performance" of nanomaterials, as this “performance” might differ for each nanomaterial, it would not be a good determinant for a definition. What type of performance is meant in the definition would be unknown. The argument is similar to that used for the physicochemical properties considered in the opinion.

Many contributions disagree with the use of a number based size distribution and argue for a weight based size distribution. This point was already addressed under Section 4. The SCENIHR wishes to emphasize that the specific concerns raised by nanomaterials in terms of toxicity relate mostly to their small size or large (reactive) surface area. Therefore, looking at size distribution based on weight would tend to minimize the lower part of the distribution curve, which contains the nanoscale particles that need to be considered in view of their specific nanoscale properties. While this fraction would be minor (and possibly neglected) based on weight, it might be the largest fraction when based on a numbers and the one most relevant from a toxicological point of view. Therefore, the number size distribution has to be taken into account to identify a nanomaterial. The terminology "number size distribution" is maintained.

Many contributions also disagree with the inclusion of a reference to “internal structures”, arguing that doing so would lead to a broadening of the definition that would not be manageable or meaningful. The SCENIHR considers that, from a scientific and health risk point of view, internal structures need to be considered in order to be able to address the safety aspects linked to large reactive internal surface areas, linked to the use of a nanomaterial in the production phase of a product and for possible harmful environmental and health effects at the end of the life-cycle of a composite product. Therefore, taking the internal structure into account is correct but may lead to materials being defined as nanomaterials that should not be. Certain materials like globular proteins in food or large objects like car tyres, that includes nano carbon black, are given as example of such potential problems when the proposed definition is used. So, it is clear that a solution has to be found for these specific areas.

On the other hand, for large materials like car tyres containing nanomaterials, during the production phase, use-wear and at the end of the life-cycle there may be an exposure to the used nanomaterials that should be taken into consideration when performing a risk assessment.

In the public consultation, a number of proposals were made for different cut-off limits to

the 0.15% taken as an example in the opinion. This is a question of risk management and therefore outside of the scope of the mandate to the SCENIHR. The 0.15% was provided as an example to illustrate the approach proposed by the SCENIHR on the basis of a widely accepted practice in research. See comments under Section 6.

One comment indicated that size as the universally applicable criterion to all nanomaterials is not justified for food ingredients. The position of the SCENIHR is that "*size is universally applicable to define all nanomaterials and is the most suitable measurand*" and that nanomaterials should not be defined on the basis of properties, origin or type of application.

Section 11 – Tiered approach

The comments given to this section essentially repeat those provided under all the other sections. Some express doubt on the applicability of current risk assessment approaches to nanomaterials.

Comments that led to a modification of the text of the opinion:

The opinion has been adapted to clarify how the SCENIHR envisages using size in a tiered way to identify an approach for the risk assessment of nanomaterials (See Figure 1 in the opinion). The designation “nanomaterial” might not be applicable when information on the product/material can be provided that the size distribution is well above 100 nm.

Also, the exercise of defining a nanomaterial does not make any inference as to whether such a material is hazardous or not. The SCENIHR proposes the VSSA as an additional qualifier to assist in defining whether a material is a nanomaterial or not. The VSSA is independent of the shape and size distribution of a material. The text of the opinion regarding the VSSA and its determination has been clarified.

A number of contributions were of the opinion that the current safety testing procedures for bulk chemical forms are not adequate for nanomaterials. The SCENIHR agrees that scientifically robust safety testing procedures are essential to assess potential risks from nanomaterials. The SCENIHR has produced relevant opinions previously that address these points[3] and proposes a case-by-case approach for the risk assessment of nanomaterials. The text has been adapted for clarity and coherence with the previous relevant SCENIHR opinions.

While some comments put in doubt the choice of the 500 nm limit and of the 0.15 % threshold value, other comments support the use of a tiered approach. The opinion has been adapted to clarify the tiered approach. With respect to the choice of size limits, the position of the SCENIHR is that there is no scientific evidence to justify the choice of a single upper limit. The 500 nm value was chosen as a matter of example to illustrate the proposed tiered approach. Similarly, the value 0.15% was chosen as a matter of example to illustrate an approach for designating a cut-off level for a size fraction. The choice of specific values in a regulatory definition is a question of risk management and outside of the scope of this opinion.

[3] http://ec.europa.eu/health/scientific_committees/emerging/opinions/scenihr_opinions_en.htm#nano

The comments relating to the VSSA, some in support, some against, were addressed under Section 4. Additional clarifications on this issue have been introduced in the opinion.

Additional clarifications have also been introduced in the opinion to address the comments on non-normal size distributions.

The title and flow chart of Figure 1 have also been changed for clarification.

Comments that did not lead to a modification of the text of the opinion:

The comments on the possible metrological challenges that could arise from the implementation of size thresholds fall outside of the scope of this opinion which is meant to identify the scientific elements to be taken into account when drafting a definition of the term "nanomaterial". As such, the opinion does not propose any definition but proposes certain figures as a matter of example of a possible approach.

ADDITIONAL COMMENTS

Comments that led to a modification of the text of the opinion:

Some comments expressed support for a regulatory definition and agreed that defining a material as a nanomaterial on the basis of its small size does not imply a specific risk. The SCENIHR adapted the opinion to clarify that it does not intend to suggest that nanomaterials necessarily carry new hazards but that currently, and until more knowledge is obtained, these materials present an uncertainty with regard to potential risk, as does any newly developed and previously unknown compound.

Some contributors argued for a clarification around the lower threshold to make sure that molecules be explicitly excluded from the chosen definition. The text of the opinion has been adapted to clarify that point.

Comments that did not lead to a modification of the text of the opinion:

Numerous additional comments were provided. Some expressed fear of the metrological challenges that would derive from some of the proposals of the opinion. The SCENIHR is conscious of the metrological issues that may arise from some of its proposals but this does not invalidate the concepts supporting a definition of the term "nanomaterial". Developments in measurement technology may be needed and are likely to be able to address many of the issues raised.

A group of comments insisted on basing the definition of nanomaterials on properties, either physicochemical or hazard based. The opinion explains why properties cannot be used as a basis for a regulatory definition of "nanomaterials". See also comments under Section 3.

Yet other comments supported the development of an internationally agreed definition and remarked that ISO/TC 229 already proposes a nanotechnology terminology with world-wide definitions. While the SCENIHR is in favour of internationally agreed definitions in general, this was outside of the scope of this opinion.

Other comments support a restriction of the definition to engineered or manufactured materials. The SCENIHR notes that the qualifiers "engineered" and "manufactured" can

easily be applied to a generic definition of the term "nanomaterial".

Some contributors supported the use of a broader size range (e.g. 0.3 nm - 300 nm) than 1 nm - 100 nm and argued for flexibility. There were also remarks about the need to include a revision clause in any definition. This is compatible with the approach proposed by the SCENIHR (see in particular comments under section 3).

The SCENIHR also agrees with a comment that a characterization for hazard identification and risk assessment has to be far more detailed than that needed for a regulatory framework.

Another contributor noticed that the definition of "article" in the REACH regulation ("*Article means an object which during production is given a special shape, surface or design which determines its function to a greater degree than its chemical composition.*") would be applicable to nanomaterials in general and that this must be clarified. This is out of the SCOPE of the SCENIHR and is a task for the EU regulators.

A number of comments presented the case of nanocomposites, saying that defining them as nanomaterials could create large practical difficulties. Other comments argued against developing a definition that would "unintentionally and unnecessarily" regulate as nanomaterials an enormous range of substances which are already adequately addressed in existing regulation. Additional contributions also argued that referring to both external size and internal size contributes to confusion. In its opinion, the SCENIHR acknowledges that the question of inclusions and exclusions must be clarified in any regulatory definition both to avoid capturing macroscopic objects such as car tyres, and to capture materials smaller than the lower limit that are commonly considered as nanomaterials (e.g. fullerenes). The SCENIHR supports the intention to have a broad definition to be used as a basis for further regulations in which specific adaptations might be applied in line with the purpose of that regulation. Depending on each regulation information can then be generated indicating whether such a material poses a risk for health and/or environment.

ANNEX

Structure of the Consultation Response Form for the

SCENIHR pre-consultation opinion on the

Scientific Basis for a Definition of the Term "Nanomaterial"

Please find below the question posed by the Commission and the answer given by the Committee. This answer is extracted from the pre-consultation opinion of the SCENIHR (Section 4) and is split into sub-sections.

QUESTION - *Based on current knowledge, the Committee was invited to provide advice on the essential elements of a science-based working definition of "nanomaterials" and, specifically, to identify the most appropriate metrics to define materials at nanoscale, taking into account:*

(i) Reported size ranges and other relevant characteristics and corresponding metrics: The size ranges and other relevant characteristics (e.g., specific surface area, shape, density, spatial arrangements, aggregation, agglomeration, etc.) and corresponding metrics of materials reported as "nanomaterials" in the scientific literature;

(ii) Characteristics: A first indication of possible characteristics and associated mechanisms that alone or in various combinations may lead to different properties;

(iii) Physico-chemical properties: The physical and chemical properties that materials may show as a result of being at nanoscale or having a nanoscale structure;

(iv) Threshold(s): The threshold(s) at which properties identified in (iii) above may be expected to occur (the threshold(s) may be "below" or "above" depending on the relevant characteristic(s) and associated metric(s)).

ANSWER Section 1 - It should be stressed that 'nanomaterial' is a categorization of a material by the size of its constituting parts. It does neither imply a specific risk nor does it necessarily mean that this material actually has new hazard properties compared to its constituents. However, size will influence biodistribution (and distribution kinetics) in an organism or in an ecosystem. One should also consider whether the definition should aim to be over-arching so as to include next-generation nanomaterials and avoid quickly becoming obsolete. Although the toxicological profile of the chemical components of a given nanomaterial may be well known, there may be cases where its specific properties raise concerns on their specific potential for harm to humans and the environment. This raises the question whether the current risk assessment methodology as used for "classic" substances (chemicals) in the EU can be used for nanomaterials or whether there is a need to perform another kind of risk assessment.

ANSWER Section 2 - There is sufficient evidence that with a decrease in size into the nanoscale there is a change in some properties of the material which is for instance due to the increase in surface-to-volume ratio. This results in an increased surface reactivity that may or may not be associated with an increase in biological activity or toxicity. It is

this uncertainty that warrants the careful evaluation of possible risks associated with nanotechnology products. However, although a change in properties may occur at the nanoscale, and indeed many nanomaterials are specifically produced for such properties, it is at the moment not possible to identify a specific size at which a property would change or appear, nor a specific property that is introduced with size.

ANSWER Section 3 - The definition of the nanoscale as having a size between approximately 1 and 100 nanometre is commonly accepted, although (i) there is no scientific evidence in favour of a single upper limit, (ii) there is no scientific evidence to qualify the appropriateness of the 100 nm value, and (iii) the term "approximately" or "of the order of" cannot be used in a regulatory context; (iv) it does not take into account that a nanomaterial will comprise a range of sizes; (v) methodology needs to be adequate to support the applications of the definition.

ANSWER Section 4 - When considering any definition for nanoscale and nanomaterial it is obvious that size is the predominant feature. Size, when used to refer to one or more external dimension, will capture most nano-objects such as plates or sheets, fibres and nanoparticles. However, within a regulatory context, any size mentioned should be controllable and enforceable. This requires that adequate validated methodologies are available. For measuring at the nanoscale (i.e. below 1 µm) several techniques are available, which, however, do not always confirm each other. So, not only is size itself important, but also the method used to measure it. Any nanomaterial should be described by its size and number size distribution including the methodologies used for the measurement.

Solely referring to size as “one or more external dimensions” will NOT capture aggregates and agglomerates of primary particles nor, importantly, more complex multi-component nanomaterials that are widely used in medical and cosmetic applications as their external dimension is likely to be larger than a specified upper size limit. In terms of the size limit, the lower and upper cut-offs of 1 and 100 nm, respectively were considered. However, a lower size limit of 1 nm for one or more external dimensions is complicated by the fact that many molecules would then also be included. The upper size limit for one or more external dimensions of 100 nm is also complicated by the potential exclusion of aggregates, agglomerates and multi-component assemblies that would have external sizes greater than this. The inclusion of a reference to “internal structure” with the same specified range as the external dimensions will include such materials within the scope of definition. This would also include nanoporous and nanocomposite materials.

A definition using the range of approximately 1 nm to 100 nm, even with the addition of “engineered” or “manufactured”, would include biological materials that are commonly used and processed and thus can be considered to be “engineered” in the food industry.

ANSWER Section 5 - The definition of the nanoscale as having a size between approximately 1 and 100 nanometre is commonly accepted, although (i) there is no scientific evidence in favour of a single upper limit, (ii) there is no scientific evidence to qualify the appropriateness of the 100 nm value, and (iii) the term "approximately" or "of the order of" cannot be used in a regulatory context; iv) it does not take into account that a nanomaterial will comprise a range of sizes; v) methodology needs to be adequate to support the applications of the definition.

To distinguish a nanostructured material from a non-nanostructured material, the volume specific surface area (VSSA) can be a complementary criterion, based on its integral material surface area per unit volume. For dry, solid materials, including agglomerates and aggregates, the VSSA can be estimated from the BET specific surface area and the bulk density, a well known parameter. A limitation of the BET method is that it is only applicable to powders and/or dry solid materials and is not directly applicable to suspensions. Expressing the surface area related to the volume instead of mass allows for an additional criterion independent of the density of the nanomaterial. A VSSA above $60 m^2/cm^3$ would indicate a nanomaterial. Similar to size, the VSSA is not an absolute discriminator for the "nano" size of materials as, even with a VSSA below 60 m^2/cm^3, a fraction of the material may have a VSSA above 60 m^2/cm^3 in view of the size distribution within it.

ANSWER Section 6 - Data on the size distribution should be taken into account when describing a nanomaterial. When only a part of the material has a size within the size range of the definition or description it should be clear whether and when such a material will be considered a nanomaterial. This may be by allowing a part (certain %) of the number size distribution to be below a certain threshold or by using the information on the size distribution itself. For example, a material might be considered as a nanomaterial when >0.15% of the material, based on number concentration, has a size below the designated upper size limit. So, materials might be defined as NOT being a nanomaterial when the mean size minus 3 times the Standard Deviation (SD) of the number concentration shows that 99.85% of the sizes are above the designated upper size limit. Different distribution thresholds might be required for specific areas of application.

As size is a key element to a definition, there is a need for the development of validated standardised methods to determine size and its corresponding distribution to ensure comparability in results.

ANSWER Section 7 - There is a multitude of possibilities for the application of coatings and surface modifications to nanomaterials. Purposely applied and environmentally acquired coatings can have a major impact on nanomaterial interaction with biological systems. The coating and core together control the properties of a given nanomaterial and it is not useful to look at either the properties of the core or of the coating in isolation as they may not be representative of how the nanomaterial will behave in a given environment. So, each combination of a nanomaterial with a coating has to be considered as an individual case for safety evaluation. The variability in coatings on nanomaterials prohibits the feasibility of including criteria based on surface properties within a definition as these properties may vary with coatings.

Several properties from the OECD WPMN list of 16 physico-chemical characteristics that are considered to be relevant for the characterisation of nanomaterials for toxicological testing, were evaluated as possible discriminators for the identification of a nanomaterial. These were crystalline phase, photocatalytic activity, zeta potential, redox potential, radical formation potential, water solubility and the octanol-water partition coefficient. It was concluded that while all of these properties are very useful for risk assessment, none appears to meet the universal applicability criterion required for a definition.

Solubility and degradability are highly relevant for the risk assessment of nanomaterials: like any other material, nanomaterials can be degraded either chemically or by

solubilisation; in fluids, they can form agglomerates or stable dispersions depending on their surface coating. As for the other properties listed here, they affect crucially the behaviour of a nanomaterial of concern but they are not sufficiently characteristic to be included in a definition nor to serve as a criterion for the definition of nanomaterial. They may however be valid criteria to assess the lifetime of a certain nanomaterial in one or the other environment and its potential to release free nanoparticles.

Features associated with solubility (and degradability) of nanomaterials are very important for risk assessment in view of the possibility for persistence and accumulation both in man and the environment. These features include size and shape, water solubility, surface charge and surface reactivity. However, these features cannot be translated into a definition as they are part of the characterization of a nanomaterial and can change for each individual nanomaterial depending on chemical composition, surface modification and the immediate environment of the nanomaterial.

Most physico-chemical parameters mentioned may be important to know for risk-assessment purposes. Whether they each individually show sufficient discrimination to generally identify the wide variety of nanomaterials is doubtful.

It was also considered if nanomaterials could be differentiated based on whether they are inorganic or organic. The most common distinction between so called “hard” and “soft” is based on their origin being inorganic or organic compounds, respectively and is used as an indication for potential biopersistence. However, this distinction between "hard" and "soft" nanomaterials is not absolute as certain persistent nanomaterials may be organic and certain oxides may be (bio)degradable. It would also not capture hybrid nanomaterials with inorganic and organic components. Thus, terms like hard nanomaterial as marker for potential biopersistence would not be a useful criterion to include in a definition.

ANSWER Section 8 - Certain nanomaterials and composite materials may have incorporated internal or external structures at the nanoscale to confer nanospecific characteristics to that composite. The internal structure with a size at the nanoscale would be an element to include in a definition, as then nano-composites will be included in the definition of a nanomaterial. As the external dimensions of nanocomposites would be typically larger than 100 nm, most nanocomposites would not be considered to be nanomaterials with a definition based solely on external size.

There are nanocomposites where one phase is a bulk one. It was noted that the inclusion of “internal structure” as an element of the definition would also mean that those nanocomposites would be defined as nanomaterials. Exclusion criteria would have to be developed to avoid considering macroscopic composite objects as nanomaterials.

ANSWER Section 9 - Based on their origin, three types of nanoscale materials (natural, by-products of human activity, engineered) can be distinguished. As a result, a general definition should include all these three types of nanoscale materials, the distinction being provided by the use of the words natural, by-products of human activity or engineered (or manufactured).

In order to designate more specifically purpose made nanomaterials within regulations, the term “engineered" or "manufactured” may be used. When considering the purposely made nanomaterials, the meaning of “engineered" or "manufactured” also needs to

include the processing (e.g. grinding or milling resulting in size reduction, chemical processing) of materials to obtain materials at the nanoscale.

ANSWER Section 10 - In conclusion, size is universally applicable to all nanomaterials and is the most suitable measurand. A defined size range would facilitate a uniform interpretation. For regulatory purposes the number size distribution should also be considered using both the mean size and its standard deviation for further refinement of the definition. Alternatively, a specific fraction of the number size distribution might be allowed to be within the specified size ranges of the definition. For dry powders, the volume specific surface area (VSSA) may be added to the size as a discriminator to identify nanomaterials. In addition, the definition should include both external and internal nanostructures.

For the lower limit of the definition of nanomaterials, the size of 1 nm is proposed. However, around 1 nm, there is an ambivalence between molecules, nanoclusters and nanoparticles.

ANSWER Section 11 - At the moment, no scientific data are available to indicate that a specific size associated with special properties due to the nanoscale can be identified for nanomaterials in general. There is no scientific evidence in favour of a single upper limit. However, there is by convention an upper limit of 100 nm which is commonly used. There is no scientific evidence to qualify the appropriateness of this value.The use of a single upper value might be too limiting for the classification of nanomaterials and a differentiated approach might be more appropriate. This approach could be based on a relative high upper threshold for which it is assumed that the size distribution at the lower end will always be above the lower, more critical threshold. The lower threshold would be the critical threshold for which extensive nano-specific information has to be provided in order to perform case-by-case risk assessment.

An example is presented below using 500 nm as high upper threshold and 100 nm as low upper threshold.

<u>Category 1 median size > 500 nm</u> for materials for which further information is missing

If the median size of the material is above 500 nm it is assumed that the size distribution at the lower end will always be above the designated lower threshold of 100 nm. So, no further information regarding possible nanospecific properties may be needed and classical risk assessment can be performed taking into consideration the particulate nature of the material.

<u>Category 2 median size <500 nm</u>

When the median size is <500 nm a material is considered a nanomaterial and a more detailed nanospecific risk assessment is necessary taking into consideration possible nanospecific characteristics of the material.

When the size is <500 nm but >100 nm the nanospecific risk assessment may be waived when additional information is provided that the number size distribution and volume specific area demonstrate that the material has <0.15% (or any specified percentage) of the number size distribution <100 nm. For dry materials, the VSSA (<60 m^2/cm^3) may be used as an additional qualifier. In these cases a classical risk assessment can be performed taking into consideration the particulate nature of the material.

Category 3 median size <100 nm, and >1 nm

The material is considered a nanomaterial and nanospecific risk assessment has to be performed when >0.15% (or a specified percentage) of the number size distribution is <100 nm. For dry materials, the VSSA (>60 m^2/cm^3) may be used as an additional qualifier.

In addition to size, any regulatory definition should be limited to purposely designed nanomaterials, e.g. engineered or manufactured nanomaterials, including the processing of nanomaterials.

Based on specific requirements regarding risk assessment for regulatory purposes, for specific areas and applications, modifications of any overarching definition may be needed.

ADDITIONAL COMMENTS

If you have additional comments on this pre-consultation opinion, please provide them here