RECOMMENDATIONS

COMMISSION RECOMMENDATION

of 18 October 2011

on the definition of nanomaterial

(Text with EEA relevance)

(2011/696/EU)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 292 thereof,

Whereas:

(1) The Commission Communication of 7 June 2005 'Nanosciences and nanotechnologies: An action plan for Europe 2005-2009' [1] defines a series of articulated and interconnected actions for the immediate implementation of a safe, integrated and responsible approach for nanosciences and nanotechnologies.

(2) The Commission, in line with the commitments made in the Action Plan, carefully reviewed relevant Union legislation with a view to determine the applicability of the existing regulations to the potential risks of nanomaterials. The result of the review was contained in the Commission Communication of 17 June 2008 'Regulatory aspects of nanomaterials' [2]. The Communication concluded that the term 'nanomaterials' is not mentioned specifically in Union legislation but that existing legislation in principle covers the potential health, safety and environmental risks in relation to nanomaterials.

(3) The European Parliament in its resolution of 24 April 2009 on regulatory aspects of nanomaterials [3] called, inter alia, for the introduction of a comprehensive science-based definition of nanomaterials in Union legislation.

(4) The definition in this Recommendation should be used as a reference for determining whether a material should be considered as a 'nanomaterial' for legislative and policy purposes in the Union. 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. This definition, based only on the size of a material, covers natural, incidental or manufactured materials.

(5) The definition of the term 'nanomaterial' should be based on available scientific knowledge.

(6) Measuring size and size distributions in nanomaterials is challenging in many cases and different measurement methods may not provide comparable results. Harmonised measurement methods must be developed with a view to ensuring that the application of the definition leads to consistent results across materials and over time. Until harmonised measurement methods are available, best available alternative methods should be applied.

(7) The European Commission Joint Research Centre Reference Report 'Considerations on a Definition of Nanomaterial for Regulatory purposes' [4] suggests that a definition of nanomaterials should address particulate nanomaterials, be broadly applicable in Union legislation and be in line with other approaches worldwide. Size should be the only defining property which necessitates a clear definition of the nanoscale limits.

(8) The Commission mandated the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) to provide scientific input on elements to consider when developing a definition of the term 'nanomaterial' for regulatory purposes. The opinion 'Scientific basis for the definition of the term "Nanomaterial" ' was subject to a public consultation in 2010. In its opinion of 8 December 2010 [5], SCENIHR concluded that size is universally applicable to nanomaterials and the most suitable measurand. A defined size range would facilitate a uniform interpretation. The lower limit was proposed at 1 nm. An upper limit of 100 nm is commonly used by general consensus, but there is no scientific evidence to support the appropriateness of this value. The use of a

[1] COM(2005) 243 final.
[2] COM(2008) 366 final.
[3] P6_TA(2009) 0328.
[4] EUR 24403 EN, June 2010.
[5] http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_032.pdf

single upper limit value might be too limiting for the classification of nanomaterials and a differentiated approach might be more appropriate. For regulatory purposes, the number size distribution should also be considered using the mean size and the standard deviation of the size to refine the definition. The size distribution of a material should be presented as size distribution based on the number concentration (i.e. the number of objects within a given size range divided by the number of objects in total) and not on the mass fraction of nanoscale particles in the nanomaterial as a small mass fraction may contain the largest number of particles. SCENIHR identified certain specific cases where the application of the definition can be facilitated by using the volume specific surface area as proxy to determine if a material falls within the defined nano size range.

(9) The International Organisation for Standardisation defines the term 'nanomaterial' as 'material with any external dimensions in the nanoscale or having internal structure or surface structure in the nanoscale'. The term 'nanoscale' is defined as size range from approximately 1 nm to 100 nm ([1]).

(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. Without specifying the number size distribution, it would be difficult to determine if a specific material complies with the definition where some particles are below 100 nm while others are not. This approach is in line with the opinion of SCENIHR that the particle distribution of a material should be presented as the distribution based on the number concentration (i.e. the particle number).

(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. A nanomaterial as defined in this recommendation should consist for 50 % or more of particles having a size between 1 nm-100 nm. In accordance with SCENIHR's advice, even a small number of particles in the range between 1 nm-100 nm may in certain cases justify a targeted assessment. However, it would be misleading to categorise such materials as nanomaterials. Nevertheless there may be specific legislative cases where concerns for the environment, health, safety or competitiveness warrant the application of a threshold below 50 %.

([1]) http://cdb.iso.org

(12) 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.

(13) At present it is possible to measure the specific surface area by volume for dry solid materials or powders with the nitrogen adsorption method ('BET-method'). In those cases the specific surface area can be used as a proxy to identify a potential nanomaterial. New scientific knowledge may expand the possibility to use this and other methods to other types of materials in the future. There can be a discrepancy between the measurement of the specific surface area and the number size distribution from one material to another. Therefore it should be specified that results for number size distribution should prevail and it should not be possible to use the specific surface area to demonstrate that a material is not a nanomaterial.

(14) Technological development and scientific progress continue with great speed. The definition including descriptors should therefore be subject to a review by December 2014 to ensure that it corresponds to the needs. In particular, the review should assess whether the number size distribution threshold of 50 % should be increased or decreased and whether to include materials with internal structure or surface structure in the nanoscale such as complex nano-component nanomaterials including nano-porous and nano-composite materials that are used in some sectors.

(15) Guidance and standardised measurement methods as well as knowledge about typical concentrations of nanoparticles in representative sets of materials should be developed where feasible and reliable to facilitate the application of the definition in a specific legislative context.

(16) The definition set out in this Recommendation should not prejudge nor reflect the scope of application of any piece of Union legislation or of any provisions potentially establishing additional requirements for those materials, including those relating to risk management. 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.

(17) Given the special circumstances prevailing in the pharmaceutical sector and the specialised nano-structured systems already in use, the definition in this Recommendation should not prejudice the use of the term 'nano' when defining certain pharmaceuticals and medical devices,

HAS ADOPTED THIS RECOMMENDATION

1. Member States, the Union agencies and economic operators are invited to use the following definition of the term 'nanomaterial' in the adoption and implementation of legislation and policy and research programmes concerning products of nanotechnologies.

2. '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.

   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 %.

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.

4. For the purposes of point 2, 'particle', 'agglomerate' and 'aggregate' are defined as follows:

   (a) 'particle' means a minute piece of matter with defined physical boundaries;

   (b) '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;

   (c) 'aggregate' means a particle comprising of strongly bound or fused particles.

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.

6. By December 2014, the definition set out in points 1 to 5 will be reviewed in the light of experience and of scientific and technological developments. The review should particularly focus on whether the number size distribution threshold of 50 % should be increased or decreased.

7. This Recommendation is addressed to the Member States, Union agencies and economic operators.

Done at Brussels, 18 October 2011.

For the Commission

Janez POTOČNIK

Member of the Commission

EUROPEAN
COMMISSION

Brussels, XXX
[…](2017) XXX draft

COMMISSION REGULATION (EU) …/…

of XXX

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

(Text with EEA relevance)

COMMISSION REGULATION (EU) …/…

of XXX

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(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC[1], and in particular Article 131 thereof,

Whereas:

(1) Regulation (EC) No 1907/2006 lays down specific registration duties and obligations on manufacturers, importers and downstream users to generate data on substances they manufacture, import or use to assess the risks related to these substances and to develop and recommend appropriate risk management measures.

(2) Commission Recommendation 2011/696/EU[2] sets out a definition of the term 'nanomaterial'. A nanomaterial can be a form of a substance or a distinct substance.

(3) The Commission Communication on the Second Regulatory Review on Nanomaterials[3] concluded that Regulation (EC) No 1907/2006 sets the best possible framework for the risk management of nanomaterials when they occur as forms of substances or mixtures but more specific requirements within the framework are necessary.

(4) The Commission performed an impact assessment[4] and further concluded that it is necessary to clarify the registration duties and obligations for nanomaterials. The term 'nanoform' should be used for the purposes of Regulation (EC) No 1907/2006 to identify any form of a substance or a distinct substance that fulfils the definition of nanomaterial.

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1 OJ L 396, 30.12.2006, p. 1.

2 Commission Recommendation of 18 October 2011 on the definition of nanomaterial (OJ L 275, 20.10.2011, p. 38).

3 COM(2012) 572 final.

4 Impact assessment on Possible amendments of Annexes to REACH for registration of nanomaterials [SWD REFERENCE TO BE ADDED LATER]

(5) Nanoforms may have specific toxicological profiles and exposure patterns and may therefore require specific risk assessment and adequate sets of risk management measures.

(6) Without the minimum standard information in the technical dossier and the chemical safety report for substances with nanoforms, it is not possible to ascertain whether the potential risks have been adequately assessed. Clarifications to requirements for the registration of substances with nanoforms and related downstream user obligations should be included in the Annexes I, III and VI to XII to Regulation (EC) No 1907/2006. This should ensure a clear and effective implementation with proportionate costs and avoid adversely affecting innovation and competitiveness. The adopted changes for nanoforms should be without prejudice to the performance and documentation of risk assessment of other forms of the registered substance.

(7) Manufacturers and importers should assess and where relevant, generate the necessary information and document in the chemical safety report that the risks, arising from the identified uses of the substance with nanoforms they manufacture or import, are adequately controlled. To ensure clarity, the chemical safety report should describe whether and which different nanoforms are covered by the assessment and how the information is compiled in the report. A use may modify the nanoforms of the substance, potentially changing one nanoform into another form or generating a new nanoform. Downstream users should provide this information up the supply chain to ensure that the use is adequately covered by the registration dossier of the manufacturer or importer, or alternatively cover the specific use in their own chemical safety report.

(8) As the majority of nanomaterials are expected to be nanoforms of phase-in substances, the conditions for the requirements for generation of new toxicological and ecotoxicological information on phase-in low volume substances should be elaborated to ensure that the assessment criteria are based also on the predicted properties of nanoforms. The existing qualitative or quantitative structure-activity relationship (QSAR) and other tools do not yet enable prioritisation; therefore, the insolubility information should be applied as a surrogate for potential toxicological and ecotoxicological aspects for the nanoforms of a substance.

(9) For nanoforms, specific minimum characterisation information should be provided as part of the composition information under the substance identification. Particle size, shape and surface properties of a nanoform may influence its toxicological or ecotoxicological profile, exposure as well as behaviour in the environment.

(10) For reasons of workability and proportionality, it should be possible to group nanoforms with similar properties in sets and provide the characterisers of the different nanoforms or sets of nanoforms in ranges of values to allow for limited variations in actual materials placed on the market. A justification has to be provided why the sets are appropriate for the hazard assessment, exposure assessment and risk assessment of the individual nanoforms.

(11) All different nanoforms and sets of nanoforms should be considered by the registrant in the demonstration of safety. Similarly, the information on volume, use and exposure of the different nanoforms or sets of nanoforms of the substance should be provided separately to demonstrate their safe use.

(12) Nanoforms or sets of nanoforms should be identified in the joint submission using the same nanoform characterisation principles and should provide the link between the

nanoforms identified in the individual registrations and the relevant information in the joint submission.

(13) To allow for adequate assessment of the relevance of any physicochemical, toxicological and ecotoxicological information for the different nanoforms, the test material should be appropriately characterised. For the same reasons, test conditions documented and a scientific justification for the relevance and adequacy of the utilised test material for the different nanoforms or sets of nanoforms should be provided. The relevance and adequacy of the information obtained from means other than testing should be approached in a similar manner.

(14) Certain physico-chemical properties such as water solubility or partition coefficient in octanol-water serve as input to well established QSARs and other predictive models that can be used for adaptations of some of the information requirements. As the underlying assumptions may not always apply to nanomaterials, such adaptations should be used for nanoforms only with scientific justification.

(15) To allow efficient assessment of the potential exposure for inhalable nanoforms, in particular in workplaces, information on dustiness should be provided for the different nanoforms or sets of nanoforms.

(16) The specific properties of the nanoform may prevent their uptake through the cell wall of bacteria, rendering the **i**n vitro gene mutation study in bacteria (the AMES test B.13-14, OECD TG 471) inappropriate for some nanoforms. To ensure that the tiered strategy for mutagenicity can still be implemented also in such cases, one or more other in vitro mutagenicity study(ies) in mammalian cells or other internationally recognised methods should be provided in such cases also for low-volume substances.

(17) Although acute toxicity testing for the lowest tonnage is required via the oral route, for nanoforms, inhalation or in very specific cases the dermal route may be considered as more appropriate route of exposure.

(18) For the generation of information on short term repeated dose and sub-chronic toxicity via inhalation route, testing of a nanoform should always include histopathological determination of brain, lung tissues as well as examination of bronchoalveolar lavage (BAL) fluid, kinetics and an appropriate recovery period, in line with the OECD technical guidance. In case a nanoform generates persistent inflammation, the potential for adverse outcomes should be assessed as part of short term repeated dose, sub-chronic and chronic toxicity study.

(19) The distribution of a nanoform in the body may affect the toxicological profile when compared to other forms of the same substance. Therefore, a basic assessment of the toxicokinetic behaviour should be available for the chemicals safety assessment of a nanoform, when one is required. This should allow the development of effective testing strategy or its adaptation for the substance with nanoforms with the aim of minimizing animal testing. Where needed, a study complementing the compilation of existing toxicokinetic information should be proposed by the registrant or may be requested by the European Chemicals Agency (the Agency) in accordance with Article 40 or 41 of the Regulation (EC) No 1907/2006.

(20) A number of specific physico-chemical properties in addition to those used to identify the different nanoform or sets of nanoforms may be considered relevant for scientific understanding of properties of a nanomaterial, with the necessary parameters depending on the individual case. For reasons of workability and proportionality, only registrants for higher volume substances than 100 tonnes/year should be required to

explicitly consider such further information in case other particle properties significantly influence hazard or exposure to those nanoforms.

(21) The adaptation of the standard testing requirements in Annexes VII to X to Regulation (EC) No 1907/2006 applying general rules for adaptation under Section 1 of Annex XI should address different nanoforms or sets of nanoforms separately. For grouping of different nanoforms or sets of nanoforms, the molecular structural similarity alone cannot serve as justification for the application of read-across or grouping.

(22) Compliance with the provisions of this Regulation should not be required immediately in order to allow all registrants and downstream users adequate time to adapt to the more specific requirements for substances with nanoforms. However, it should be possible for registrants to apply those provisions already before the deadline for compliance.

(23) The Agency, in cooperation with Member States and stakeholders, should further develop guidance documents for the application of the test methods and waiving possibilities for the standard information requirements provided by this Regulation for the purposes of Regulation (EC) No 1907/2006.

(24) Annexes I, III and VI to XII to Regulation (EC) No 1907/2006 should therefore be amended accordingly.

(25) Compliance with the provisions of this Regulation should not be required immediately in order to allow all registrants and downstream users adequate time to adapt to the more specific requirements for substances with nanoforms. However, it should be possible for registrants to comply with those provisions already before the date of application.

(26) The measures provided for in this Regulation are in accordance with the opinion of the Committee established under Article 133 of Regulation (EC) No 1907/2006,

HAS ADOPTED THIS REGULATION:

Article 1

Annexes I, III and VI to XII to Regulation (EC) No 1907/2006 are amended in accordance with the Annex to this Regulation.

Article 2

By way of derogation from the second paragraph of Article 3, manufacturers and importers registering substances with nanoforms either as non-phase-in or phase-in substances pursuant to Article 5 of Regulation (EC) No 1907/2006 as well as downstream users generating chemical safety reports may comply with this Regulation before 1 January 2020.

Article 3

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from 1 January 2020.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels,

For the Commission
The President
[…]

EN

ANNEX

1. Annex I to Regulation (EC) No 1907/2006 is amended as follows:

(a) Subsection 0.1. is replaced by the following:

"0.1. The purpose of this Annex is to set out how manufacturers and importers are to assess and document that the risks arising from the substance they manufacture or import are adequately controlled during manufacture and their own use(s) and that others further down the supply chain can adequately control the risks. The chemical safety report shall also describe whether and which different nanoforms of substances as characterised in Annex VI are manufactured and imported, including an adequate justification for each information requirement describing when and how information on one form is used to demonstrate safety of other forms. The requirements specific to nanoforms of a substance in this Annex apply without prejudice to requirements applicable to other forms of that substance. This Annex shall also apply adapted as necessary to producers and importers of articles required to make a chemical safety assessment as part of a registration.";

(b) Subsection 0.3. is replaced by the following:

"0.3. The chemical safety assessment of a manufacturer shall address the manufacture of a substance and all the identified uses. The chemical safety assessment of an importer shall address all identified uses. The chemical safety assessment shall consider the use of the substance on its own (including any major impurities and additives), in a mixture and in an article, as defined by the identified uses. The assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses. The assessment shall address nanoforms that are covered by the registration. The justifications and conclusions drawn from the assessment shall be relevant to these nanoforms. The chemical safety assessment shall be based on a comparison of the potential adverse effects of a substance with the known or reasonably foreseeable exposure of man and/or the environment to that substance taking into account implemented and recommended risk management measures and operational conditions.";

(c) Subsection 0.4. is replaced by the following:

"0.4. Substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. If the manufacturer or importer considers that the chemical safety assessment carried out for one substance is sufficient to assess and document that the risks arising from another substance or from a group or 'category' of substances are adequately controlled then he can use that chemical safety assessment for the other substance or group or 'category' of substances. The manufacturer or importer shall provide a justification for this. Where any of the substances exists in one or more nanoforms and data from one form are used in demonstration of the safe use of other forms, in accordance with the general rules set out in Annex XI, a scientific justification shall

be given on how, applying the rules for grouping and read-across, the data from a specific test or other information (e.g. methods, results or conclusions) can be used for the other forms of the substance. Similar considerations apply to exposure scenarios and risk management measures.";

(d) The last paragraph in subsection 0.5. is replaced by the following:

"If the manufacturer or importer considers that further information is necessary for producing his chemical safety report and that this information can only be obtained by performing tests in accordance with Annex IX or X, he shall submit a proposal for a testing strategy, explaining why he considers that additional information is necessary and record this in the chemical safety report under the appropriate heading. Where considered necessary, the proposal for a testing strategy may concern several studies addressing respectively different forms of the same substance for the same information requirement. While waiting for results of further testing, he shall record in his chemical safety report, and include in the exposure scenario developed, the interim risk management measures that he has put in place and those he recommends to downstream users intended to manage the risks being explored. The exposure scenarios and interim risk management measures recommended shall address nanoforms that are covered by the registration.";

(e) Point 0.6.3 is replaced by the following:

"0.6.3. Where as a result of steps 1 to 4 the manufacturer or importer concludes that the substance or, when applicable, nanoforms thereof fulfils the criteria for any of the following hazard classes or categories set out in Annex I to Regulation (EC) No 1272/2008 or is assessed to be a PBT or vPvB, the chemical safety assessment shall also include steps 5 and 6 in accordance with Sections 5 and 6 of this Annex:

(a) hazard classes 2.1 to 2.4, 2.6 and 2.7, 2.8 types A and B, 2.9, 2.10, 2.12, 2.13 categories 1 and 2, 2.14 categories 1 and 2, and 2.15 types A to F;

(b) hazard classes 3.1 to 3.6, 3.7 adverse effects on sexual function and fertility or on development, 3.8 effects other than narcotic effects, 3.9, and 3.10;

(c) hazard class 4.1;

(d) hazard class 5.1.";

(f) After subsection 0.11. the following subsection 0.11.bis is added:

"0.11.bis When nanoforms are covered by the chemical safety assessment, an appropriate metric for the assessment and presentation of the results in steps 1-6 of the chemical safety assessment under 0.6.1 and 0.6.2 shall be considered, with the justification included in the chemical safety report and summarised in the safety data sheet. A multiple metric presentation, including mass metric information, is preferable. When possible, a method for reciprocal conversion shall be indicated.";

(g) The following sentence is added after the first line of section 1.0.3:

"The assessment shall address nanoforms that are covered by the registration.";

(h) The second paragraph of point 1.3.1. is replaced by the following:

"The assessment should always include a statement as to whether the substance or, when applicable, nanoforms thereof fulfils or does not fulfil the criteria given in Regulation (EC) No 1272/2008 for classification in the hazard class carcinogenicity

category 1A or 1B, in the hazard class germ cell mutagenicity category 1A or 1B or in the hazard class reproductive toxicity category 1A or 1B.";

(i) Point 1.3.2. is replaced by the following:

"1.3.2. If the information is inadequate to decide whether a substance or, when applicable, nanoforms thereof should be classified for a particular hazard class or category, the registrants shall indicate and justify the action or decision he has taken as a result.";

(j) The second paragraph of subsection 2.2. is replaced by the following:

"If the information is inadequate to decide whether a substance or, when applicable, nanoforms thereof should be classified for a particular hazard class or category, the registrant shall indicate and justify the action or decision he has taken as a result.";

(k) The following sentence is added at the end of point 3.0.2.:

"The assessment shall address nanoforms when they are covered by the registration.";

(l) Point 3.2.1. is replaced by the following:

"3.2.1. The appropriate classification developed in accordance with the criteria in Regulation (EC) No 1272/2008 shall be presented and justified. Any M-factor resulting from the application of Article 10 of Regulation (EC) No 1272/2008 shall be presented and, if it is not included in Part 3 of Annex VI to Regulation (EC) No 1272/2008, justified.

The presentation and justification is applied to nanoforms covered by the registration.";

(m) Point 3.2.2. is replaced by the following:

"3.2.2. If the information is inadequate to decide whether a substance or, when applicable, nanoforms thereof should be classified for a particular hazard class or category, the registrant shall indicate and justify the action or decision he has taken as a result.";

(n) Point 4.0.2. is replaced by the following:

"4.0.2. The PBT and vPvB assessment shall comprise the following two steps, which shall be clearly identified as such in Part B, Section 8 of the Chemical Safety report. The assessment shall address nanoforms when they are covered by the registration:

Step 1 : Comparison with the Criteria.

Step 2 : Emission Characterisation.

The assessment shall also be summarised in the Safety Data Sheet under heading 12.";

(o) Subsection 4.2. is replaced by the following:

"4.2. **Step 2: Emission Characterisation**

If the substance fulfils the criteria or it is considered as if it is a PBT or vPvB in the registration dossier an emission characterisation shall be conducted comprising the relevant parts of the exposure assessment as described in Section 5. In particular it shall contain an estimation of the amounts of the substance released to the different environmental compartments during all activities carried out by the manufacturer or importer and all identified uses, and an identification of the likely routes by which humans and the environment are exposed to the substance. The estimation shall address nanoforms that are covered by the registration.";

(p) The first paragraph of subsection 5.0. is replaced by the following:

"The objective of the exposure assessment shall be to make the quantitative and qualitative estimate of the dose/concentration of the substance to which humans and the environment are or may be exposed. The assessment shall consider all stages of the life-cycle of the substance resulting from the manufacture and identified uses and shall cover any exposures that may relate to the hazards identified in Sections 1 to 4. The assessment shall address nanoforms that are covered by the registration. The exposure assessment shall entail the following two steps, which shall be clearly identified as such in the Chemical Safety Report:";

(q) The following sentence is added at the end of point 5.2.2.:

"When nanoforms are covered by the registration, the emission estimation for these shall, where relevant, take account of situations when the conditions outlined in Annex XI section 3.2 point (c) are fulfilled.";

(r) Point 5.2.3. is replaced by the following:

"5.2.3. A characterisation of possible degradation, transformation, reaction processes, and an estimation of environmental distribution and fate shall be performed.

When nanoforms are covered by the registration, a characterisation of particle aggregation, agglomeration and particle surface chemistry changes shall be included."

2. Annex III to Regulation (EC) No 1907/2006 is amended as follows:

"**CRITERIA FOR SUBSTANCES REGISTERED IN QUANTITIES BETWEEN 1 AND 10 TONNES**

Criteria for substances and, when applicable, for nanoforms thereof, registered between 1 and 10 tonnes, with reference to Article 12(1)(a) and (b):

(a) substances for which it is predicted (i.e. by the application of (Q)SARs or other evidence) that they are likely to meet the criteria for category 1A or 1B classification in the hazard classes carcinogenicity, germ cell mutagenicity or reproductive toxicity or the criteria in Annex XIII;

(b) substances:

(i) with dispersive or diffuse use(s) particularly where such substances are used in consumer mixtures or incorporated into consumer articles; and

(ii) for which it is predicted (i.e. by application of (Q)SARs or other evidence) that they are likely to meet the classification criteria for any health or environmental hazard classes or differentiations under Regulation (EC) No 1272/2008 or for substances with nanoforms, unless those nanoforms are soluble in biological and environmental media."

3. Annex VI to Regulation (EC) No 1907/2006 is amended as follows:

(a) The introductory text under the subtitle 'Guidance note on fulfilling the requirements of annexes VI to XI' is replaced by the following:

"Annexes VI to XI specify the information that shall be submitted for registration and evaluation purposes according to Articles 10, 12, 13, 40, 41 and 46. For the lowest tonnage level, the standard requirements are in Annex VII, and every time a new tonnage level is reached, the requirements of the corresponding Annex have to be added. For each registration the precise information requirements will differ, according to tonnage, use, and exposure. The Annexes shall thus be considered as a whole, and in conjunction with the overall requirements of registration, evaluation and the duty of care.

A substance is defined in accordance with Article 3(1) and identified in accordance with section 2 in this Annex. A substance is always manufactured or imported in at least one form. A substance can also occur in more than one form.

Where a substance being registered is also manufactured or imported in nanoform certain specific information items have to be provided. Nanoforms shall be characterised as provided in this Annex. Furthermore, the registrant of a substance with nanoforms shall justify why the information provided in the joint registration is relevant to cover the information requirements for the registered substances with nanoforms. Information relevant to cover information requirements for such substance can also be submitted separately by individual registrants, where they consider it justified in accordance with Article 11(3).

More than one dataset may be required for one or more information requirements whenever there are significant differences in the properties relevant for the hazard, exposure and risk assessment and management for nanoforms of a substance. The information shall be reported in such a manner that it is clear what information in the joint submission pertains to which nanoform or set of nanoforms of the substance.

The technically and scientifically justified methodologies set out in Annex XI.1.5 shall be used within a registration dossier when two or more forms of a substance are 'grouped' for the purposes of one, more or possibly all the information requirements.

Guidance note on nanoforms:

In accordance with the Commission Recommendation of 18 October 2011 on the definition of nanomaterial[1], 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, is a nanoform of a substance. The term 'nanoform', when it is referred to in the other Annexes, shall relate to a nanoform or a set of nanoforms that has been characterised in accordance with section 2.4 below. A substance may have one or more different nanoforms, based on differences in the parameters in points 2.4.2 to 2.4.5.

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[2].

The requirements specific to nanoforms apply without prejudice to requirements applicable to other forms of a substance. The term 'nanoform', when it is referred to in the other Annexes, shall relate to an individual nanoform or a set of nanoforms when one has been defined in accordance with section 2.4 below.";

(b) Step 1 is replaced by the following:

"STEP 1 – GATHER AND SHARE EXISTING INFORMATION

The registrant should gather all existing available test data on the substance to be registered, this would include a literature search for relevant information on the substance.

Wherever practicable, registrations should be submitted jointly, in accordance with Articles 11 or 19. This will enable test data to be shared, thereby avoiding unnecessary testing and reducing costs. The registrant should also collect all other available and relevant information on the substance including on nanoforms of the substance when they are covered by the registration, regardless whether testing for a given endpoint is required or not at the specific tonnage level. This should include information from alternative sources (e.g. from (Q)SARs, read-across from other substances, *in vivo* and *in vitro* testing, epidemiological data) which may assist in identifying the presence or absence of hazardous properties of the substance and which can in certain cases replace the results of animal tests.

In addition, information on exposure, use and risk management measures in accordance with article 10 and this Annex should be collected. Considering all this information together, the registrant will be able to determine the need to generate further information.";

(c) Step 3 is replaced by the following:

"STEP 3 – IDENTIFY INFORMATION GAPS

The registrant shall then compare the information needs for the substance with the information already available and the extent to which currently available information can be applied to nanoforms covered by the registration and identify where there are gaps.

It is important at this stage to ensure that the available data is relevant and has sufficient quality to fulfil the requirements.";

(d) Step 4 is replaced by the following:

"STEP 4 – GENERATE NEW DATA/PROPOSE TESTING STRATEGY

In some cases it will not be necessary to generate new data. However, where there is an information gap that needs to be filled, new data shall be generated (Annexes VII and VIII), or a testing strategy shall be proposed (Annexes IX and X), depending on the tonnage. New tests on vertebrates shall only be conducted or proposed as a last resort when all other data sources have been exhausted.

The above approach shall also apply if there is a gap of available information for one or more nanoforms of the substance included in the jointly submitted registration dossier.

In some cases, the rules set out in Annexes VII to XI may require certain tests to be undertaken earlier than or in addition to the standard requirements.

NOTES

Note 1: If it is not technically possible, or if it does not appear scientifically necessary to give information, the reasons shall be clearly stated, in accordance with the relevant provisions.

Note 2: The registrant may wish to declare that certain information submitted in the registration dossier is commercially sensitive and its disclosure might harm him commercially. If this is the case, he shall list the items and provide a justification.";

(e) The introductory text in Section 2 Identification of the substance is replaced by the following:

"For each substance, the information given in this section shall be sufficient to enable each substance to be identified and the different nanoforms to be characterised. If it is not technically possible or if it does not appear scientifically necessary to give information on one or more of the items below, the reasons shall be clearly stated.";

(f) Subsection 2.3. is replaced by the following:

"2.3. Composition of each substance. Where a registration covers one or more nanoforms, these nanoforms shall be characterized pursuant to section 2.4 of this Annex.

2.3.1. Degree of purity (%)

2.3.2. Nature of impurities, including isomers and by-products

2.3.3. Percentage of (significant) main impurities

2.3.4. Nature and order of magnitude (… ppm, … %) of any additives (e.g. stabilising agents or inhibitors)

2.3.5. Spectral data (ultra-violet, infra-red, nuclear magnetic resonance or mass spectrum)

2.3.6. High-pressure liquid chromatogram, gas chromatogram

2.3.7. Description of the analytical methods or the appropriate bibliographical references for the identification of the substance and, where appropriate, for the identification of impurities and additives. This information shall be sufficient to allow the methods to be reproduced.

2.4. Characterisation of nanoforms of a substance: For any of the characteristics, the information provided may be applicable to individual nanoforms or sets of similar nanoforms provided that the boundaries of the sets are clearly specified. A justification shall be provided to demonstrate why the sets are appropriate for the hazard assessment, exposure assessment and risk assessment of the individual nanoforms that are manufactured and placed on the market.

The information in points 2.4.2 – 2.4.5 shall be clearly assigned to the different nanoforms or sets of similar nanoforms identified in point 2.4.1.

2.4.1. Names or other identifiers of the nanoforms or sets of similar nanoforms of the substance

2.4.2. Particle number size distribution with indication of the number fraction of constituent particles in the size range 1 nm – 100 nm.

2.4.3. Description of surface functionalization or treatment and identification of each agent including IUPAC name and CAS or EC number.

2.4.4. Shape, aspect ratio and other morphological characterisation; information on assembly structure including e.g. shell like structures or hollow structures, if appropriate

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

2.4.6. Description of the analytical methods or the appropriate bibliographical references for the identification of the information elements in this sub-section. This information shall be sufficient to allow the methods to be reproduced.";

(g) In section 3, the following introductory text is added after the title 'INFORMATION ON MANUFACTURE AND USE(S) OF THE SUBSTANCE(S)':

"Where a substance being registered is manufactured or imported in one or several nanoforms, the information on manufacture and use under 3.1-3.7 shall include separate information on the different nanoforms or sets of similar nanoforms as characterised in subsection 2.4.";

(h) In section 5, the introductory text is replaced by the following:

"This information shall be consistent with that in the Safety Data Sheet where such a Safety Data Sheet is required according to Article 31.

Where a substance being registered is also manufactured or imported in one or several nanoforms, the information pursuant to this Section shall address the different nanoforms or sets of similar nanoforms as characterised in subsection 2.4 where relevant.";

(i) In section 6, the following introductory text is added after the title 'INFORMATION ON EXPOSURE FOR SUBSTANCES REGISTERED IN QUANTITIES BETWEEN 1 AND 10 TONNES PER YEAR PER MANUFACTURER OR IMPORTER':

> "Where a substance being registered is manufactured or imported in one or several nanoforms, the information pursuant to this Section shall address the different nanoforms or sets of similar nanoforms as characterised in subsection 2.4 separately."

4. Annex VII to Regulation (EC) No 1907/2006 is amended as follows:

(a) "In the introductory text, the following text is added after the third paragraph:

"Without prejudice to the information submitted for other forms, any relevant physicochemical, toxicological and ecotoxicological information shall include characterisation of the nanoform tested and test conditions. Where QSARs are used or evidence is obtained by means other than testing, a description shall be provided of the range of material characteristics/properties to which the evidence can be applied.";

(b) Subsection 7.7 is replaced by the following:

7.7. Water solubility	7.7. The study does not need to be conducted where: – the substance is hydrolytically unstable at pH 4, 7 and 9 (half-life less than 12 hours), or – the substance is readily oxidisable in water. Where the substance appears 'insoluble' in water, a limit test up to the detection limit of the analytical method shall be performed. For nanoforms the potential confounding effect of dispersion shall be assessed when conducting the study.

(c) Subsection 7.8 is replaced by the following:

7.8. Partition coefficient n-octanol/water	7.8. The study does not need to be conducted if the substance is inorganic. If the test cannot be performed (e.g. the substance decomposes, has a high surface activity, reacts violently during the performance of the test or does not dissolve in water or in octanol, or it is not possible to obtain a sufficiently pure substance), a calculated value for log P as well as details of the calculation method shall be provided.] For nanoforms the potential confounding effect of dispersion in octanol and water shall be assessed.

(d) After subsection 7.14., the following is added:

7.14 bis Dustiness Only for nanoforms	7.14 bis. The study does not need to be conducted if exposure to granular form of the substance during its life-cycle can be excluded.

(e) Point 8.4.1. is replaced by the following:

8.4.1. *In vitro* gene mutation study in bacteria	8.4.1. The study does not need to be conducted if it is not appropriate for some nanoforms. In such case other studies involving one or more in vitro mutagenicity study(ies) in mammalian cells (Annex VIII, sections 8.4.2. and 8.4.3 or other internationally recognised methods) shall be provided.

(f) Point 8.5.1 is replaced by the following:

8.5.1. By oral route	8.5.1. The study need not be conducted if a study on acute toxicity by the inhalation route (8.5.2) is available. For nanoforms, if any of the routes in Annex VIII 8.5.2 or 8.5.3 is the more appropriate route of exposure that study may be conducted instead.

(g) Point 9.1.1. is replaced by the following:

9.1.1. Short-term toxicity testing on invertebrates (preferred species *Daphnia)* The registrant may consider long-term toxicity testing instead of short-term.	9.1.1. The study does not need to be conducted if: - there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes. Moreover, for nanoforms high insolubility in water alone cannot serve as justification for waiving the test; - a long-term aquatic toxicity study on invertebrates is available, or - adequate information for environmental classification and labelling is available. The long-term aquatic toxicity study on *Daphnia* (Annex IX, section 9.1.5.) shall be considered if the substance is poorly water soluble.

(h) Point 9.1.2. is replaced by the following:

9.1.2. Growth inhibition study aquatic plants (algae preferred)	9.1.2. The study does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes. Moreover, for nanoforms high insolubility in water alone cannot serve as justification for waiving the test.

5. Annex VIII to Regulation (EC) No 1907/2006 is amended as follows:

(a) "In the introductory text, the following text is added after the first paragraph:

"Without prejudice to the information submitted for other forms, any relevant physicochemical, toxicological and ecotoxicological information shall include characterisation of the nanoform tested and test conditions. Where QSARs are used or evidence is obtained by means other than testing, a description shall be provided of the range of material characteristics/properties to which the evidence can be applied.";

(b) Subsection 8.5. is replaced by the following:

8.5. Acute toxicity	8.5. The study/ies do(es) not generally need to be conducted if: - the substance is classified as corrosive to the skin. In addition to the oral route (8.5.1.) or to the more appropriate route as indicated in Annex VII for nanoforms, for substances other than gases, the information mentioned under 8.5.1. to 8.5.3. shall be provided for at least one other route. The choice for the second route will depend on the nature of the substance and the likely route of human exposure. If there is only one route of exposure, information for only that route need be provided.

(c) Point 8.6.1 is replaced by the following:

8.6.1. Short-term repeated dose toxicity study (28 days), one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure.	8.6.1. The short-term toxicity study (28 days) does not need to be conducted if: - a reliable sub-chronic (90 days) or chronic toxicity study is available, provided that an appropriate species, dosage, solvent and route of administration were used, or - where a substance undergoes immediate disintegration and there are sufficient data on the cleavage products, or - relevant human exposure can be excluded in accordance with Annex XI Section 3. The appropriate route shall be chosen on the following basis: Testing by the dermal route is appropriate if: – inhalation of the substance is unlikely; and – skin contact in production and/or use is likely; and – the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin. Testing by the inhalation route is appropriate if exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or

	droplets of an inhalable size. For nanoforms a histopathological determination of brain and lung tissues, as well as an examination of relevant parameters in bronchoalveolar lavage (BAL) fluid, kinetics, where relevant, and recovery period shall be considered when conducting the test, taking into account the relevant technical guidance at the international level. The sub-chronic toxicity study (90 days) (Annex IX, Section 8.6.2) shall be proposed by the registrant if: the frequency and duration of human exposure indicates that a longer term study is appropriate; and one of the following conditions is met: - other available data indicate that the substance may have a dangerous property that cannot be detected in a short-term toxicity study, or - appropriately designed toxicokinetic studies reveal accumulation of the substance or its metabolites in certain tissues or organs which would possibly remain undetected in a short-term toxicity study but which are liable to result in adverse effects after prolonged exposure. Further studies shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41 in case of: - failure to identify a NOAEL in the 28 or the 90 days study, unless the reason for the failure to identify a NOAEL is absence of adverse toxic effects, or - toxicity of particular concern (e.g. serious/severe effects), or - indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation. In such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects (e.g. immunotoxicity, neurotoxicity, and for nanoforms - indirect genotoxicity as a result of persistent inflammation), or - the route of exposure used in the initial repeated dose study was inappropriate in relation to the expected route of human exposure and route-to-route extrapolation cannot be made, or - particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity to humans may be expected), or - effects shown in substances with a clear relationship in molecular structure with the substance being studied, were not detected in the 28 or the 90 days study.

(d) Subsection 8.8. is replaced by the following:

8.8. Toxicokinetics	
8.8.1. Assessment of the toxicokinetic behaviour of the substance to the extent that can be derived from the relevant available information.	For nanoforms a toxicokinetics study shall be proposed or may be required by the Agency in accordance with Article 40 or 41 in case such an assessment cannot be performed on the basis of the relevant available information, including from the study conducted in accordance with 8.6.1. The choice of the study will depend on the remaining information gaps and the results of the chemical safety assessment.

(e) Point 9.1.3 is replaced by the following:

9.1.3. Short-term toxicity testing on fish: the registrant may consider long-term toxicity testing instead of short-term.	9.1.3. The study does not need to be conducted if: - there are mitigating factors indicating that aquatic toxicity is unlikely to occur, for instance the substance is highly insoluble in water or the substance is unlikely to cross biological membranes, or - a long-term aquatic toxicity study on fish is available. For nanoforms high insolubility in water alone cannot serve as an indication that aquatic toxicity is unlikely to occur. Long-term aquatic toxicity testing as described in Annex IX shall be considered if the chemical safety assessment according to Annex I indicates the need to investigate further effects on aquatic organisms. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment. The long-term aquatic toxicity study on fish (Annex IX, Section 9.1.6) shall be considered if the substance is poorly water soluble.

(f) Point 9.1.4. is replaced by the following:

9.1.4. Activated sludge respiration inhibition testing	9.1.4. The study does not need to be conducted if: - there is no emission to a sewage treatment plant, or - there are mitigating factors indicating that microbial toxicity is unlikely to occur, for instance the substance is highly insoluble in water, or - the substance is found to be readily biodegradable and the applied test concentrations are in the range of concentrations that can be expected in the influent of a sewage treatment plant. For nanoforms high insolubility in water alone cannot serve as an indication that microbial toxicity is unlikely to occur. The study may be replaced by a nitrification inhibition test if

	available data show that the substance is likely to be an inhibitor of microbial growth or function, in particular nitrifying bacteria.

(g) Subsection 9.2. is replaced by the following:

9.2. Degradation	9.2. Further degradation testing shall be considered if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance. For nanoforms such test(s) shall consider morphological transformation (e.g. irreversible changes in particle size, shape and surface properties, loss of coating), chemical transformation (e.g. oxidation, reduction) and other abiotic degradation (e.g. photolysis).The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.

(h) Section 9.2.2 is replaced by the following:

9.2.2. Abiotic 9.2.2.1. Hydrolysis as a function of pH.	9.2.2.1. The study does not need to be conducted if: - the substance is readily biodegradable, or - the substance is highly insoluble in water. For nanoforms high insolubility in water alone cannot serve as a justification for waiving.

(i) Point 9.3.1. is replaced by the following:

9.3.1. Adsorption/desorption screening	9.3.1. The study does not need to be conducted if: - based on the physicochemical properties the substance can be expected to have a low potential for adsorption (e.g. the substance has a low octanol-water partition coefficient), or - the substance and its relevant degradation products decompose rapidly. For nanoforms, the Octanol-Water Partition Coefficient (Kow) or Soil Adsorption Coefficient (Koc/Kd) parameters shall only be used in the waiving with an adequate justification of their relevance for the adsorption potential of the nanoforms covered.

6. Annex IX to Regulation (EC) No 1907/2006 is amended as follows:

(a) "In the introductory text, the following text is added after the second paragraph:

"Without prejudice to the information submitted for other forms, any relevant physicochemical, toxicological and ecotoxicological information shall include characterisation of the nanoform tested and test conditions. Where QSARs are used or evidence is obtained by means other than testing, a description shall be provided of the range of material characteristics/properties to which the evidence can be applied.";

(b) After subsection 7.17, the following is added:

7.18. Further information on physicochemical properties Only for nanoforms	Further testing for nanoforms covered by the registration shall be considered by the registrant or may be required by the Agency in accordance with Article 41, if there is an indication that specific additional particle properties significantly influence hazard of or exposure to those nanoforms and only if these are relevant in toxicological, ecotoxicological or risk characterisation.

(c) Point 8.6.2 is replaced by the following:

8.6.2. Sub-chronic toxicity study (90-day), one species, rodent, male and female, most appropriate route of administration, having regard to the likely route of human exposure.	8.6.2. The sub-chronic toxicity study (90 days) does not need to be conducted if: – a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure; or – a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used; or – a substance undergoes immediate disintegration and there are sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake); or – the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day "limit test", particularly if such a pattern is coupled with limited human exposure. The appropriate route shall be chosen on the following basis: Testing by the dermal route is appropriate if: (1) skin contact in production and/or use is likely; and

	(2) the physicochemical properties suggest a significant rate of absorption through the skin; and (3) one of the following conditions is met: – toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test; or – systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies; or – in vitro tests indicate significant dermal absorption; or – significant dermal toxicity or dermal penetration is recognised for structurally-related substances. Testing by the inhalation route is appropriate if: – exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size. For nanoforms a histopathological determination of brain and lung tissues, as well as an examination of relevant parameters in bronchoalveolar lavage (BAL) fluid, kinetics, where relevant, and recovery period shall be considered when conducting the test, taking into account the relevant technical guidance at the international level. Further studies shall be proposed by the registrant or may be required by the Agency in accordance with Articles 40 or 41 in case of: – failure to identify a NOAEL in the 90 days study unless the reason for the failure to identify a NOAEL is absence of adverse toxic effects; or – toxicity of particular concern (e.g. serious/severe effects); or – indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation. In such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects (e.g. immunotoxicity, neurotoxicity, and for nanoforms - indirect genotoxicity as a result of persistent inflammation), or – particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity to humans may be expected).

(d) Point 9.2.1.2. is replaced by the following:

9.2.1.2. Simulation testing on ultimate	9.2.1.2. The study need not be conducted if :

degradation in surface water	the substances is highly insoluble in water, or the substance is readily biodegradable. For nanoforms high insolubility in water alone cannot serve as a justification for waiving.

(e) Subsection 9.3. is replaced by the following:

9.3. Fate and behaviour in the environment	
9.3.2. Bioaccumulation in aquatic species, preferably fish	9.3.2. The study need not be conducted if: the substance has a low potential for bioaccumulation (for instance a log Kow $\leq$ 3) and/or a low potential to cross biological membranes, or direct and indirect exposure of the aquatic compartment is unlikely. For nanoforms, the Octanol-Water Partition Coefficient (Kow) or Soil Adsorption Coefficient (Koc/Kd) parameters shall not be used without adequate justification for waiving based on the low potential for bioaccumulation or the unlikely direct and indirect exposure of the aquatic compartment .
9.3.3. Further information on adsorption/desorption depending on the results of the study required in Annex VIII	9.3.3. The study need not be conducted if: based on the physicochemical properties, can be expected to have a low potential for adsorption, or the substance and its degradation products decompose rapidly. For nanoforms, the physicochemical properties shall not be used without adequate justification for waiving based on the low potential for adsorption.

(f) Subsection 9.4 is replaced by the following:

9.4. Effects on terrestrial organisms	9.4. These studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely. In the absence of toxicity data for soil organisms, the equilibrium partitioning method may be applied to assess the hazard to soil organisms. If applying the equilibrium partitioning method to nanoforms covered by the registration, this shall be scientifically justified. The choice of the appropriate tests depends on the outcome of the chemical safety assessment. In particular for substances that have a high potential to adsorb to soil (e.g. some nanoforms) or that are very persistent, the registrant shall consider long-term toxicity testing instead of short-term.

7. Annex X to Regulation (EC) No 1907/2006 is amended as follows:

(a) "In the introductory text, the following text is added after the second paragraph:

> Without prejudice to the information submitted for other forms, any relevant physicochemical, toxicological and ecotoxicological information shall include characterisation of the nanoform tested and test conditions. Where QSARs are used or evidence is obtained by means other than testing, a description shall be provided of the range of material characteristics/properties to which the evidence can be applied.";

(b) Point 8.6.3. is replaced by the following:

	8.6.3. A long-term repeated toxicity study (≥ 12 months) may be proposed by the registrant or required by the Agency in accordance with Articles 40 or 41 if the frequency and duration of human exposure indicates that a longer term study is appropriate and one of the following conditions is met: - serious or severe toxicity effects of particular concern were observed in the 28-day or 90-day study for which the available evidence is inadequate for toxicological evaluation or risk characterisation, or - effects shown in substances with a clear relationship in molecular structure with the substance being studied were not detected in the 28-day or 90-day study, or - the substance may have a dangerous property that cannot be detected in a 90-day study. If nanoforms are covered by the registration, physicochemical characteristics as well as molecular structure shall be taken into consideration when determining if one of the conditions above are met.

8. Annex XI to Regulation (EC) No 1907/2006 is amended as follows:

(a) "In the introductory text, the following text is added after the last paragraph:

The requirements specific to nanoforms in this Annex are without prejudice to requirements applicable to other forms of a substance.";

(b) Point 1.1.3. is replaced by the following:

"1.1.3. *Historical human data*

Historical human data, such as epidemiological studies on exposed populations, accidental or occupational exposure data and clinical studies, shall be considered.

The strength of the data for a specific human health effect depends, among other things, on the type of analysis and on the parameters covered and on the magnitude and specificity of the response and consequently the predictability of the effect. Criteria for assessing the adequacy of the data include:

(1) – the proper selection and characterisation of the exposed and control groups;

(2) –adequate characterisation of exposure ;

(3) – sufficient length of follow-up for disease occurrence;

(4) –valid method for observing an effect;

(5) –proper consideration of bias and confounding factors; and

(6) – a reasonable statistical reliability to justify the conclusion.

In all cases adequate and reliable documentation shall be provided.

When nanoforms are covered by the registration the above approach shall address the nanoforms separately.";

(c) Subsection 1.2. is replaced by the following:

"1.2. **Weight of evidence**

There may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion.

There may be sufficient weight of evidence from the use of newly developed test methods, not yet included in the test methods referred to in Article 13(3) or from an international test method recognised by the Commission or the Agency as being equivalent, leading to the conclusion that a substance has or has not a particular dangerous property.

Where sufficient weight of evidence for the presence or absence of a particular dangerous property is available:

further testing on vertebrate animals for that property shall be omitted,

further testing not involving vertebrate animals may be omitted.

In all cases adequate and reliable documentation shall be provided.

When nanoforms are covered by the registration the above approach shall address the nanoforms separately.";

(d) Subsection 1.3. is replaced by the following:

"1.3. **Qualitative or Quantitative structure-activity relationship ((Q)SAR)**

Results obtained from valid qualitative or quantitative structure-activity relationship models ((Q)SARs) may indicate the presence or absence of a certain dangerous property. Results of (Q)SARs may be used instead of testing when the following conditions are met:

-– results are derived from a (Q)SAR model whose scientific validity has been established,

– the substance falls within the applicability domain of the (Q)SAR model,

– results are adequate for the purpose of classification and labelling and/or risk assessment, and

– adequate and reliable documentation of the applied method is provided.

The Agency in collaboration with the Commission, Member States and interested parties shall develop and provide guidance in assessing which (Q)SARs will meet these conditions and provide examples.

When nanoforms are covered by the registration the above approach shall address the nanoforms separately.";

(e) The last paragraph in Section 1.4 is replaced by the following:

"Such confirmation may be waived if the following conditions are met:

(1) results are derived from an *in vitro* method whose scientific validity has been established by a validation study, according to internationally agreed validation principles;

(2) results are adequate for the purpose of classification and labelling and/or risk assessment; and

(3) adequate and reliable documentation of the applied method is provided.

When nanoforms are covered by the registration the above approach in Points (1) to (3) shall address the nanoforms separately.";

(f) The first paragraph in Section 1.5 is replaced by the following:

"Substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint. The Agency, after consulting with relevant stakeholders and other interested parties, shall issue guidance on technically and scientifically justified methodology for the grouping of substances sufficiently in advance of the first registration deadline for phase-in substances.

When nanoforms are covered by the registration the above approach shall address the nanoforms separately. For grouping different nanoforms of the same substance the molecular structural similarities alone cannot serve as a justification.

If nanoforms covered by a registration are grouped or placed in a 'category' with other forms, including other nanoforms, of the substance in the same registration the obligations above shall apply in the same manner."

9. Annex XII to Regulation (EC) No 1907/2006 is amended as follows:

(a) The introductory text is replaced by the following:

"INTRODUCTION

The purpose of this Annex is to set out how downstream users are to assess and document that the risks arising from the substance(s) they use are adequately controlled during their use for a use not covered by the Safety Data Sheet supplied to them and that other users further down the supply chain can adequately control the risks. The assessment shall cover the life-cycle of the substance, from its receipt by the downstream user, for his own uses and for his identified uses further down the supply chain. The assessment shall consider the use of the substance on its own, in a mixture or in an article.

The assessment shall address nanoforms when they are covered by the registration. Justifications and conclusions drawn from the assessment shall be relevant to the nanoforms.

In carrying out the chemical safety assessment and producing the Chemical Safety Report, the downstream user shall take account of information received from the supplier of the chemical in accordance with Article 31 and 32 of this Regulation.

When nanoforms of the substance are covered by his own use or identified uses down the supply chain, an appropriate metric for the assessment and presentation of the results in steps 1-6 of the chemical safety assessment under 0.6.1 and 0.6.2 shall be considered, with the justification included in the chemical safety report and summarised in the safety data sheet. A multiple metric presentation is preferable, ensuring availability of mass metric information.

Where available and appropriate, an assessment carried out under Community legislation, (e.g. risk assessments completed under Regulation (EEC) No 793/93) shall be taken into account in the chemical safety assessment and be reflected in the Chemical Safety Report. Deviations from such assessments shall be justified. Assessments carried out under other international and national programmes may also be taken into account.

The process which the downstream user goes through in carrying out the chemical safety assessment and in producing his Chemical Safety Report, involves three steps:";

(b) Under Step 2, the following text is added after the first paragraph:

"When nanoforms of the substance are covered by his own use or identified uses down the supply chain, the assessment shall cover the hazard, PBT and vPvB assessment of nanoforms(s) as used.";

(c) Under Step 2, the third paragraph is replaced by the following:

"In those cases where the downstream user considers that information, in addition to that provided by the supplier, is necessary for producing his Chemical Safety Report, the downstream user shall gather this information. Where this information can only be obtained by testing on vertebrate animals, he shall submit a proposal for a testing strategy to the Agency in accordance with Article 38. He shall explain why he considers that additional information is necessary. While waiting for results of further testing, he shall record in his chemical safety report the risk management measures intended to manage the risks being explored that he has put in place. The above record taking shall address nanoforms when they are covered by his own uses or identified uses down the supply chain. Such information shall be relevant to the nanoforms."