Project title:

Best practices effectiveness, prevention and protection measures for control of risk posed by engineered nanomaterials

Project Acronym: **NanoRISK**

Grant Agreement: **LIFE12 ENV/ES/000178**

Deliverable

A1b.Report on the Regulatory Requirements of Engineered Nanomaterials under REACH

Coordinator and Responsible of the Document

ITENE

Date of preparation:
13/01/2013

Nature of the deliverable:
PUBLIC

NanoRISK is funded by DG Environment under the LIFE+ Programme Environmental Policy and Governance (LIFE12 ENV/ES/000178)				
Document Information				
Associated Action	Action A1. Selection and description of the types of nanomaterials			
Coordinator Beneficiary	Instituto Tecnológico del Embalaje, Transporte y Logistica (ITENE)			
Responsible Author	Name	Carlos Fito López	E-mail	cfito@itene.com
	Partner	ITENE	Phone	+34 647 521 544

PROJECT CONSORTIUM INFORMATION

Participants		Contact
PACKAGING, TRANSPORT AND LOGISTICS RESEARCH CENTER		Carlos Fito Email: cfito@itene.com
AVANZARE INNOVACION TECNOLOGICA S.L.		Javier Pérez Email: jperez@avanzare.es
CENTRO RICERCHE PLAST-OPTICA S.P.A		Sara Padovani Email: sara.padovani@magnetimarelli.com Franco Marcori Email:franco.marcori@magnetimarelli.com
INSTITUT VALENCIÀ DE SEGURETAT I SALUT EN EL TREBALL		Juan Uriol Email: uriol_jua@gva.es Paula Beltrán Email: beltran_pau@gva.es
VITO NV- VLAAMSE INSTELLING VOOR TECHNOLOGISCH ONDERZOEK N.V.		Evelien Frijns Email:evelien.frijns@vito.be Patrick Berghmans Email:patrick.berghmans@vito.be

HISTORY CHART

Date	Rev. Nº	Version Nº	Author	Date of Delivery
14/11/13	0	1	Eva Araque Ferrer	03/12/13
04/12/13	1	1	Carlos Fito López	11/01/14

EXECUTIVE SUMMARY

The main objective of this deliverable is to provide a detailed explanation of the application of Regulation (EC) No. 1907/2006 REACH to Nanomaterials, with especial emphasis on the requirements laid down on REACH regulation to evaluate and control the risks resulting from the use of nanomaterials.

Nanomaterials are a challenge for chemicals regulation. Even if they, as substances, basically fall under REACH, the existing regulations are not adequate to deal with their specific features. There are a number of those features which have to be considered when it comes to regulation.

It is generally recognised that **REACH** in its conception, its tools and methods (testing for hazard assessment, risk estimation and risk management measures) **provides the suitable framework of the safe handling of substances in nanoform**. Furthermore many experts consider that the testing requirements, test strategies and test methods under REACH to be in principle applicable to nano-scale substances, if subjected to methodological adaptations.

There is however a **lack of clear specifications regarding the application of several instruments under REACH**, including the registration process , dossier evaluation, substance evaluation, authorization or restriction, and more even in terms of data requirements and documentation that should be presented to ensure a high level of protection of human health and the environment.

NanoRISK project focusses on the registration process where manufacturers and importers are required to **collect or generate data on the substances they manufacture or import**, to use these data to assess the risks related to these substances and to **develop and recommend appropriate risk management measures** (RMMs) to control these risks.

In view of the above, deliverable A1b shows a detailed description of the requirements laid down on REACH regulation that manufacturers and/or downstream users of nanomaterials, as well as manufacturers of articles containing nanomaterials shall meet to ensure a high level of protection of human health and the environment against risks from nanomaterials, hereinafter ENMs.

TABLE OF CONTENTS

1. Scope and Objectives of the deliverable

This deliverable is focussed on the description of the current state of the art concerning the application of the provisions laid down on REACH regulation to substances at the nanometer scale, often called nanomaterials.

This document has been conducted as part of the activities conducted within the LIFE + project NanoRISK, whose main objective is to improve the protection of health and environment from risk posed by chemicals by supporting the European Commission and the European Chemicals Agency in REACH regulation implementation with regard to nanomaterials, assuring the availability of proven and technically feasible prevention and protection measures for mitigating and control the environmental, health and safety (EHS) risks posed by nanomaterials.

Within this deliverable, and as previous step to the definition of proven measures to manage the risk posed by nanomaterials, we present **an extensive review of the requirements established by REACH regulation in order to ensure that risk are adequately controlled**, with special emphasis in those critical information requirements that should be presented in the REACH registration dossiers submitted to the European Chemicals Agency (ECHA) when registering nanomaterials, as substance itself as well as a nanoform of the bulk chemical substance.

The document includes also a brief explanation of the most relevant processes established by REACH for risk assessment purposes, as well as relevant aspects related to the classification and labelling of nanomaterials according with CLP. Moreover, a complete analysis of the current recommendations for nanomaterials published by the European Chemicals Agency (ECHA) have been included.

The main objective of this deliverable is therefore to **provide a clear understanding of how REACH provisions and other relevant pieces of legislations such as CLP apply to nanomaterials**, with special emphasis in the registration process, where registrants have to ensure a high level of protection of human health and the environment from the risks that can be posed by nanomaterials.

2. Introduction to regulatory framework of Nanomaterials

2.1. Overview of the EU Regulation REACH

REACH is a regulation of the European Union, adopted to improve the protection of human health and the environment from the risks that can be posed by chemicals, while enhancing the competitiveness of the EU chemicals industry. It came into force on 1st June 2007 and replaced a number of European Directives and Regulations with a single system

REACH applies to all **chemical substances in whatever size**, **shape** or **physical state** manufactured or imported into the EU in quantities of 1 tonne or more per year. It applies to all individual chemical substances on their own, in preparations or in articles (if the substance is intended to be released during normal and reasonably foreseeable conditions of use from an article).

REACH not only applies to those substances used in industrial processes but also in our day-to-day lives, for example in cleaning products, paints as well as in articles such as clothes, furniture and electrical appliances. Therefore, the regulation has an impact on most companies across the EU.

A major part of REACH is the requirement for manufacturers or importers of substances to register them. **Registration** is a requirement on industry (manufacturers/importers) to collect and collate specified sets of information on the properties of those substances they manufacture or supply at or above 1 tonne per year. This information is used to perform an assessment of the hazards and risks that a substance may pose and how those risks can be controlled. This information and its assessment is submitted to the European Chemicals Agency (**ECHA**).

Registration in therefore a key issue within REACH, where companies **must identify and manage the risks** linked to the substances they manufacture and market in the EU, as well as to **demonstrate how the substance can be safely used** implementing adequate risk management measures (RMMs).

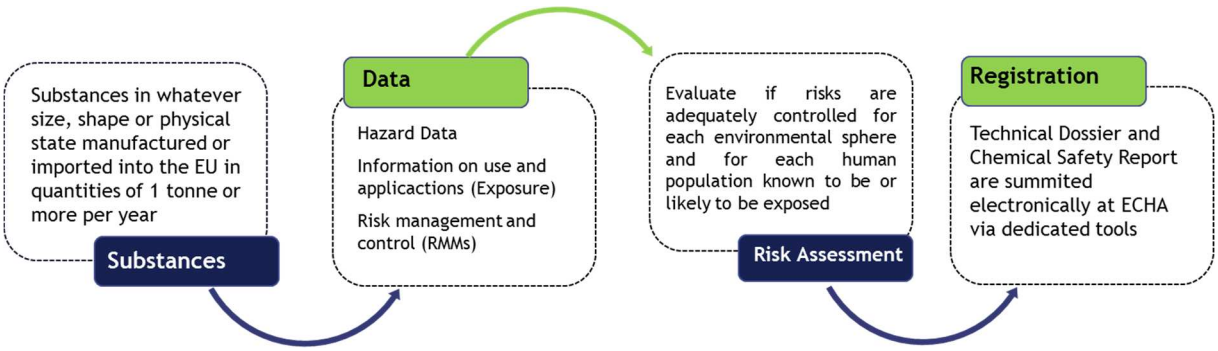


Figure 1. Process flow to REACH registration

2.2. Nanotechnology and chemical safety regulation

European legislation obligates manufacturers and importers to ensure the safety of all products they put on the market. **Although there are no provisions in the European Union legislation that refer explicitly to nanomaterials**, existing legislation on chemicals, worker and environmental protection as well as product specific legislation on medical devices, medicinal products, cosmetics, food, feed, biocides, plant protection products and other products covers in principle the potential health, safety and environmental risks in relation to nanomaterials. Current legislation may however have to be modified as regards thresholds used in some legislation, for example, as new information on nanomaterials becomes available (Commission, 2012).

In relation with the chemical safety regulation, the current legal framework in the EU is based on two main pillars. The first pillar is the legal framework for placing chemicals on the market, and the second is created from specific provisions for health, consumer, occupational safety and environmental protection. The regulatory framework can strongly support safe use of ENM provided that such goal will become a clear regulatory target.

a) According to the information given in the Communication "Regulatory Aspects of Nanomaterials" all nanoparticles in chemical substances must meet the requirements of the **REACH** (Registration, Evaluation and Authorization of Chemicals) (Regulation (EC).

b) General requirements in relation to occupational safety and health of workers at workplaces are presented in the Council Directive 89/391/EC. The aim of this framework directive is to ensure a high level of protection of workers at work. The Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work describes the minimum requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents, including ENM, that are present at the workplace.

The Commission and the relevant EU Agencies have examined and will continue to examine in the future the applicability of legislation and documents supporting its implementation such as standards and technical guidance documents to take into account the special properties of existing and future nanomaterials.

The European Commission emphasized in its communication on Regulatory Aspects of Nanomaterials (COM (2008) 366) that the current legislation in principle covers the potential health, safety and environmental risks in relation to ENM. However, the communication also notes **the lack of knowledge of these issues on engineered nanomaterials** and calls for more research and knowledge.

Based on these needs, later, in 2011, the European Commission published a recommendation on the definition of a nanomaterial, and concluded the following year that **REACH Regulation and Classification and labelling Regulation (CLP) offered the best possible framework for risk management of nanomaterials** occurring as substances or mixtures.

Although **no amendments have been made so** far to the legal text of REACH to incorporate nanomaterials, three new appendices updating Chapters R.7a, R.7b and R.7c of the Guidance on Information Requirements and Chemical Safety Assessment (IR & CSA) were published by ECHA in 2012, to be used as recommendations for registering nanomaterials.

These recommendations are the output of the REACH Implementation Projects on Nanomaterials (**RIP-oNs**), commissioned in 2009 to evaluate the applicability of the existing guidance to nanomaterials and, if needed, develop tailored advice.

ECHA has also set up a webpage aimed specifically at nanomaterials under REACH and CLP, and has updated the IUCLID user manual "Nanomaterials in IUCLID 5" to include instructions on how registrants can report explicitly when a nanoform has been used for testing purposes.

Other important working groups contributing in assuring nanomaterials safety and publishing guidances are the Scientific Committee on Emerging Newly Identified Health Risks (**SCENIHR**), Scientific Committee on Consumer Safety (**SCCS**) and Scientific Committee on Health and Environmental Risks (**SCHER**) to review risk assessment; and a subgroup of the Competent Authorities for Reach and CLP (**CARACAL**) giving advice to the European Commission and ECHA, the Commission Advisory Group (**CASGNano**), working on the need for further policy development for nanotechnology.

At international level, stands out the OCDE Working Party on Manufacturing nanomaterials (**WPMN**), was established in 2006 to advise on emerging policy-relevant issues in science, technology and innovation related to the responsible development and use of nanotechnology.

In view of the above, **ENMs are not treated, nor is it expected to be in the future, differently than any other substances**, as the general hazard and risk patterns do not differ from other chemical substances.

The Commission neither consider appropriate at present to change the rules for when a **chemicals safety assessment** is required.

At the time of writing, the **most common ENMs in terms of tonnage and sales have already been registered**, such as carbon black and amorphous silica, as they are produced in the high tonnage band. However, the Commission has found that many of the existing registration dossiers for nanomaterials do not explain clearly how specific risks of nanomaterials are addressed, for substances which can occur both in nanomaterial and non-nanomaterial forms. Therefore, **it was felt that the regulations need more specific requirements in order to address the properties and risks of these materials**. The European Commission is considering to modify some of the technical provisions in the REACH Annexes; a public consultation to that effect closed on 13 September 2013.

3. Methodology

In order to meet the objectives of the deliverable, a set of specific activities was established. Due to the nature of this deliverable, the tasks conducted were mainly focused on the compilation of the most recent publications on the regulatory aspects of nanomaterials, as well as an in depth review of the current guidelines published by the European Chemicals Agency (ECHA) concerning the chemical safety assessment of nanomaterials.

The main publications reviewed to complete this document are the following:

- EU Communication "Nanomaterials in REACH": 6th Meeting of the REACH Competent Authorities for the implementation of Regulation (EC) 1907/2006 (REACH)
- Second Regulatory Review on Nanomaterials (COM(2012) 572 final)
- COMMISSION RECOMMENDATION of 18 October 2011 on the definition of nanomaterial
- CLP application to nanomaterials: a specific aspect
- Guidance on Information Requirements and Chemical Safety Assessment : recommendations for NMs
- REACH Implementation Projects on Nanomaterials (RIPoN2 Information requirements and RIPoN3 Chemicals safety assessment)

These documents, as well as other related publications were analyzed in depth to understand how the provision of REACH regulation apply to nanomaterials, as well as to identify the current status, trends and opinions of key institution and stakeholders in the regulatory aspects of nanomaterials.

4. Nanomaterials under REACH

4.1. REACH Provisions

The European Community Regulation on chemicals and their safe use (EC 1907/2006), REACH, deals with the Registration[1], Evaluation[2], Authorisation[3] and Restriction[4] of Chemical substances, and entered into force on 1 June 2007.

REACH is very wide in its scope, covering all substances whether manufactured, imported, used as intermediates or placed on the market, on their own, in preparations or in articles. The Regulation exempts certain substances that are adequately regulated under other legislation, like medicinal products, or that generally present such low risks as not to require registration, like water, oxygen, certain noble gases, and cellulose pulp.

Other examples of exemptions are radioactive and subjected to customs supervision substances, or non-isolated intermediates. In other cases, substances occurring in nature such as minerals, ores and ore concentrates, cement clinker, etc. are not required to be registered as long as they are not chemically modified. Polymers are exempted as well from the requirement to register, since they usually are not very hazardous, but monomers in polymers have to be registered. Waste is specifically exempted. Other substances are exempted from parts of REACH, where other equivalent legislation applies, like food, that meets the definition of a substance, on its own or in a preparation, and will be subject to REACH however, such substances are largely exempted from Registration, Evaluation and Authorisation. Finally, Member States may exempt substances used in the interests of defense.

[1] Registration is the submission to the Agency of a technical dossier and, if required, a chemical safety report for a substance being manufactured in or imported into the European Union

[2] There are three types of evaluation within REACH:

- Dossier evaluation performed by the Agency :
  - Compliance check: to examine whether all required information is included in the registration dossier and whether this information is adequate.
  - Checking of testing proposals: to evaluate whether the testing proposals submitted in the registration dossier by the registrant in case further testing is necessary for information specified in Annex IX and X or the Regulation are adequate.
- Substance evaluation performed by a Member State: to clarify any grounds for considering that a substance constitutes a risk to human health or the environment. Member States can also evaluate registered intermediates.

[3] The REACH Regulation sets up a system under which the use of substances with properties of very high concern and their placing on the market can be made subject to an authorisation requirement. This authorisation requirement ensures that risks from the use of such substances are either adequately controlled or outweighed by socio-economic benefits, having taken into account the available information on alternative substances or technologies. Substances requiring authorisation will be included in Annex XIV of the Regulation.

[4] Means any condition for or prohibition of the manufacture, use or placing on the market

The two most important aims of REACH are to improve protection of human health and the environment from the risks of chemicals while enhancing the competitiveness of the EU chemicals industry, increasing transparency and promoting non-animal testing. The Regulation also calls for the progressive substitution of the most dangerous chemicals when suitable alternatives have been identified.

The REACH Regulation places greater responsibility on industry to manage the risks from chemicals and to provide safety information on the substances. Manufacturers and importers that manufacture or import more than one ton of a chemical substance per year are required to gather information on the properties of their chemical substances, which will allow their safe handling, and to register the information in a central database run by the European Chemicals Agency (ECHA). Authorities focus their resources on ensuring industry are meeting their obligations and taking action on substances of very high concern or where there is a need for Community action.

ECHA manages the REACH system: it run the databases necessary to operate the system, evaluates registered information and is building up a public database in which consumers and professionals can find hazard information.

One of the main reasons for developing and adopting the REACH Regulation was that a large number of substances have been manufactured and placed on the market in Europe for many years, and yet there was insufficient information on the hazards that they pose to human health and the environment. There is a need to fill these information gaps to ensure that industry is able to assess hazards and risks of the substances, and to identify and implement the risk management measures to protect humans and the environment. The benefits of the REACH system will come gradually, as more and more substances are phased into REACH.

To achieve its objectives, REACH regulation mainly uses the following instruments:

- ***Pre-Registration* of existing substances** (called phase-in[5] substances): from1st June 2008 to 30th November 2008.

[5] Phase-in substance – synonym existing substance, means a substance which meets at least one of the following criteria: (a) it is listed in the European Inventory of Existing Commercial Chemical Substances (EINECS), (b) it was manufactured in the Community, or in the countries acceding to the European Union on 1 January 1995 or on 1 May 2004, but not placed on the market by the manufacturer or importer, at least once in the 15 years before the entry into force of REACH Regulation, provided that the manufacturer or importer has documentary evidence of this, (c) it was placed on the market in the Community, or in the countries acceding to the European Union on 1 January 1995 or on 1 May 2004, before entry into force of REACH Regulation by the manufacturer or importer and was considered as having been notified in accordance with the first indent of Article 8(1) of Directive 67/548/EEC but does not meet the definition of a polymer as set out in REACH Regulation, provided that the manufacturer or importer has documentary evidence of this. (REACH Article 3 (20))

The pre-registration indicates the intention of the manufacturer / importer to register a substance within 11 years, a delayed registration deadline. A substance that is not pre-registered must be registered immediately, if production/import reaches 1 tonne or more per year.

- ***Registration* of substances manufactured or imported**, on their own, in preparations or intentionally released from articles (substances in articles are potentially subject to a notification scheme or a full registration on a case-by-case basis): This step consists of submission of a technical dossier (the content of the technical dossier is dependent on tonnages) and a Chemical Safety Report (for substances above 10 tonnes per year) to ECHA. Registration requirements depend on the substance amount manufactured or imported by a legal entity, phase-in or non-phase-in status and intrinsic properties resulting in classification leading to prioritization for testing.

- ***Evaluation:*** reviews of the technical registration dossiers by ECHA and the appropriate Member State Competent Authority. It is separated into "dossier evaluation" and "substance evaluation".

- ***Authorisation****:* is applied in two steps: Issuing by ECHA of a "Candidate List of substances of very high concern (SVHC[6])", containing substances liable for Authorisation; and Prioritisation by ECHA of certain substances for inclusion in Annex XIV. Annex XIV includes substances which are banned unless company-specific authorisation is issued. Authorisation can be obtained if the use of a substance is adequately controlled or if no substitutes are available and if the economic and social benefits outweigh the risks, in the case of substances for which no safety threshold applies, for example PBTs[7] or vPvBs[8].

[6] Substances of Very High Concern (SVHC) are defined in Article 57 of Regulation (EC) No 1907/2006 (EC, 2006) and include substances which are: Carcinogenic, Mutagenic or toxic to Reproduction (CMR), meeting the criteria for classification in category 1 or 2 in accordance with Directive 67/548/EEC (This directive was recently replaced by the new EU regulation (EC) No 1272/2008 on classification, labelling and packaging of chemical substances and mixtures, the so-called CLP Regulation. According to the new CLP Regulation these substances shall be classified as 1a or 1b); Persistent, Bioaccumulative and Toxic (PBT) or very Persistent and very Bioaccumulative (vPvB) according to the criteria in Annex XIII of the REACH Regulation); or Identified, on a case-by-case basis, from scientific evidence as causing probable serious effects to human health or the environment of an equivalent level of concern as those above (e.g. endocrine disrupters).

[7] PBT substance - a substance that fulfils all three of the following criteria: 1. Persistence (the half-lives are higher than: 60 days in marine water, or 40 days in fresh- or estuarine water, or 180 days in marine sediment or 120 days in fresh- or estuarine water sediment or in soil, 2. Bioaccumulation (the bioconcentration factor (BCF) is higher than 2,000) 3. Toxicity (the long-term no-observed effect concentration (Noec) for marine or freshwater organisms is less than 0.01 mg/l, or the substance is classified as carcinogenic (category 1 or 2), mutagenic (category 1 or 2) or toxic for reproduction (category 1, 2, or 3), or there is other evidence of chronic toxicity, as identified by the classifications: T, R48, or Xn, R48 according to Directive 67/548/EEC). Additional criteria, based on the case-by-case experts' judgment, have been included in the amendment of Annex XIII of REACH.

[8] vPvB substances - a substance that fulfils the criteria of both: 1. Persistence (the half-lives are higher than 60 days in marine, fresh- or estuarine water, 180 days in marine, fresh- or estuarine water sediment or soil; 2. Bioaccumulation (the bioconcentration factor is greater than 5,000).

Each of those instruments has a different impact on each of the actors involved in the supply chain, production, marketing and use of chemicals. Manufacturers[9] and importers[10] of substances are who have the most direct obligations under REACH, as they shall submit to the ECHA the registration dossier, while downstream users[11] of those substances will be affected by less direct obligations, although the changes that occur in the marketing of substances also cause a clear impact on them.

Basically, the main roles and obligations of downstream users under REACH Regulation are:

- Pre-registration / registration state: They cannot use substances which are nor pre-registered or registered.
- To provide information regarding their uses to suppliers of substances. This enables registrants to include these uses in the chemical safety assessment. It is not a mandatory issue.
- To implement measures specified by their supplier to ensure the safe use of the substance, or to establish safe conditions of use and document these in a downstream user chemical safety report.
- To inform their supplier if they have new information on the hazards of the substance or the risk management advice is not appropriate.
- To comply with the conditions of any restriction which may apply to that substance
- To communicate with their supplier if using a substance included in the Authorisation List.

Exemptions of substances from REACH apply, if any of the following characteristics apply to the substance: used in human/veterinary medicinal products, used in food/feed, used in biocides/pesticides (non-active substances must be registered), non-isolated intermediates that are listed in Annexes IV and V (exempt from registration only).

Specific requirements apply to polymers: they are exempt from registration, but the monomers and other reactants used to produce the polymer need to be registered. There are reduced requirements for isolated and transported isolated substances if only used under strictly controlled conditions.

There are also particular exceptions for R&D and a special notification procedure for uses of substances for Product and Process Orientated R&D (PPORD).

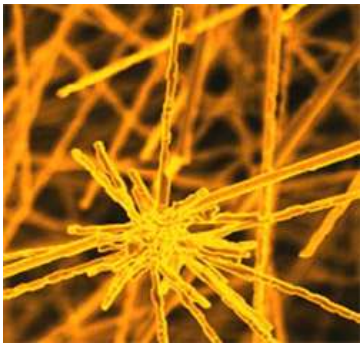
Substances used in cosmetics are not exempt from registration, but Chemical Safety Reports on these substances do not require information on direct risks to human health from final product use. Other effects from the ingredients and the actual product, such as occupational health and human

[9] Means any natural or legal person established within the Community who manufactures a substance within the Community.
[10] Means any natural or legal person established within the Community who is responsible for import
[11] Means any natural or legal person established within the Community, other than the manufacturer or the importer, who uses a substance, either on its own or in a preparation, in the course of his industrial or professional activities. A distributor or a consumer is not a downstream user. A re-importer shall be regarded as a downstream user too.

health via the environment must be included as part of a registration. Substances used in medical devices are not exempt from registration and may trigger a re-assessment of risks already addressed by specific legislation. Uses of substances in medical devices are not subject to the Authorisation procedure under REACH, but could be subject to restrictions.

4.2. REACH Requirements for nanomaterials

REACH regulation, in its Article 3, defines a substance as "a chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition"; a preparation as "a mixture or solution composed of two or more substances"; and an article as "an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition."



There are no provisions in REACH referring specifically to nanomaterials. However, REACH deals with substances, in whatever size, shape or physical state. Substances at the nanoscale are therefore covered by REACH as are covered by those definitions. Then, its provisions apply, as stated by the European Commission (Communities, 2008). Therefore under REACH, manufacturers, importers and downstream users have to ensure that their nanomaterials do not adversely affect human health or the environment.

It is important to note that REACH Regulation was put into force before nanomaterials were considered an issue of safety concern. Although some discussions on the regulatory implications of nanotechnology were already initiated in 2004 (European Commission, Community Health and Consumer Protection, 2004), the knowledge on nano-specific properties was not considered to be sufficient to serve specific regulatory considerations. In a situation when several nanomaterials have already entered the market and exposure for the workers, consumers and environment cannot be excluded, adequate methods to ensure safe use of nanomaterials are essential for sustainable development.

Several critical differences between the nanoforms of substances and their "bulk" (micro or macro-scale) analogues may necessitate additional considerations for REACH regulation and chemicals safety assessment guidance, including clarification of definition and identification of substance, triggers for testing requirements, validation of testing methods, and revision of criteria for authorisation.

4.3. Overview of the Registration dossier

REACH regulation, based on the principle that industry should manufacture, import, use substances or place them on the market in a way that human health and the environment are not adversely affected, establish that manufacturers and importers need to collect or generate data on the substances, and assess how risks to human health and the environment can be controlled by applying suitable risk management measures, as part of the REACH registration process.

The **registration dossier** is the set of information submitted electronically by a registrant for a particular substance. It consists of two main components:

- ✓ a technical dossier, always required for all substances subject to the registration obligations;
- ✓ a chemical safety report, required if the registrant manufactures or imports a substance in quantities of 10 tons or more per year. The chemical safety report is the documentation of the registrant's chemical safety assessment.

The technical dossier contains a set of information about:

- the identity of the manufacturer/importer;
- the identity of the substance;
- information on the manufacture and use of the substance;
- the classification and labeling of the substance;
- guidance on its safe use;
- study summaries of the information on the intrinsic properties of the substance;
- robust study summaries of the information on the intrinsic properties of the substance, if required;
- an indication as to whether the information on manufacture and use, the classification and labeling, the (robust) study summaries and/or, if relevant, the chemical safety report has been reviewed by an assessor;
- proposals for further testing, if relevant;
- for substances registered in quantities between 1 and 10 tones, information on exposure;
- a request as to which information should be considered confidential, including a justification.

According the guidance on registration (ECHA, 2012), the format of the registration dossier must be IUCLID (International Uniform Chemical Information Database). Other IT tools can be used to prepare the dossier as long as they produce the **exact same format**. The last version of this software is IUCLID 5.5.

Each registrant is individually obliged to submit a registration dossier for each of his substances to ECHA in order to register them. The registration dossier must be submitted electronically through the REACH-IT portal of the ECHA website.

Article 10 (a) of REACH, in combination with its Annexes VI to X defines the information to be documented in the technical dossier. Annex XI establishes the rules for the adaptation of the information defined in Annexes VI to X and has to be considered in combination with these annexes. Moreover, Article 10 (b), Article 14 and Annex I set out the general requirements for the CSA and the CSR applicable for substances subject to registration in quantities of ten tones or more per year. The relation between the information to be submitted for registration, as defined in REACH, and the IUCLID 5 sections where it has to be reported is shown in Table 1.

Table 1. Relation between the information requirements in Article10 and the corresponding sections in a IUCLID 5 file **(ECHA, 2012)**.

Information requirements	Article 10	IUCLID 5
(a) Technical dossier	Article 10 (a)	
(i) identity of the manufacturer or	Annex VI section 1	Legal entity & Section 1
(ii) identity of the substance	Annex VI section 2	Section 1
(iii) manufacture and use(s) of the substance and if relevant use and exposure categories	Annex VI section 3	Section 3
(iv) classification and labelling	Annex VI section 4	Section 2
(v) guidance on safe use	Annex VI section 5	Section 11
(vi) study summaries of information derived from the application of Annexes VII to XI	Annex VII to XI	Sections 4, 5, 6 and 7
(vii) robust study summaries of the information derived from the application of Annexes VII to XI if required under Annex I	Annex I, Annex VII to XI	Sections 4, 5, 6 and 7
(viii) indication regarding the review by an assessor of information submitted under (iii), (iv), (vi), (vii) and (b)		Dossier header[12]
(ix) proposals for testing		Sections 4, 5, 6, 7

[12] The dossier header consists of information which is going to be used for administrative purposes and it is completed by the applicant when preparing his dossier from the substance data set.

Information requirements	Article 10	IUCLID 5
(x) exposure information for substances in quantities of 1 to 10 tonnes	Annex VI section 6	Section 3
(xi) request as to which information in Article 119(2) should not be made available on the Internet		All relevant sub sections
(b) Chemical safety report	Article 10 (b) Article 14, Annex 1	Attachment in section 13

4.4. Overview of the Chemical Safety Assessment process

Within REACH regulation, the **chemical safety assessment (CSA)** of substances is the process that identifies and describes the conditions under which the manufacturing and use of a substance is considered to be safe, and hence constitutes the main challenge to achieve a proper implementation of REACH regulation.

In the context of REACH, for all substances that are manufactured or imported in volumes equal to or **greater than 10 tonnes per year**, this Chemical Safety Assessment (CSA) needs to be performed and documented in a Chemical Safety Report (CSR).

The CSR is the key source from which the registrant provides information to all users of chemicals through the exposure scenarios. Under certain circumstances, the CSA does not need to be carried out:

- for a substance present in a preparation in a concentration below certain concentration limits;
- for on-site or transported isolated intermediates;
- for Product and Process Oriented Research and Development (PPORD);
- when the use of the substance is already regulated under specific legislation and the substance is therefore exempted from registration (e.g. biocides, pesticides, pharmaceuticals). For uses in food contact materials and cosmetics, the CSR need not address human health aspects because these are addressed under other legislation.

According with the current guidance on chemical safety assessment, when the registrant manufactures or imports the substance in the nanoform as well as in the bulk form, the registration dossier should include the information of the substance in both the bulk form and the nanoform (ECHA, 2012).

Other actors, different from manufacturers and importers may have to prepare a CSR:

- Downstream users who need or want to make their own CSA /CSR;
- Producers or importers of articles containing substances that are intended to be released from the article, if the substance is not already registered for that use. CSR is required if the substance is present in those articles in volumes above 10 tonnes per year;
- Manufacturers, importers or downstream users prepraring a CSA/CSR as a part of an authorisation application.

Any registrant must identify and apply the appropriate measures to adequately control the risks identified in the CSA, and where suitable, recommend them in the safety data sheets which he supplies. Any registrant, required to conduct a CSA shall keep his chemical safety report available and updated. The chemical safety assessment can be directly applied to nanoamterials and can be split into three major steps. These are:

- **Hazard assessment:** requires the collection and evaluation of all available and relevant information on the substance. This includes information on the intrinsic properties of the substance (physicochemical, toxicological, ecotoxicological properties and fate), on the manufacturing and uses, and on the related emissions and exposures.

  According Article 14 of REACH, if as a result of carrying out the hazard assessment, the registrant concludes that the substance meets the criteria for classification as dangerous in accordance with Directive 67/548/EEC or is assessed to be a PBT or vPvB, the chemical safety assessment shall include two more steps:

- **Exposure assessment**: is the process of measuring or estimating the dose or concentration of the substance to which humans and the environment are or may be exposed, depending on the uses of the substance.

  Within the exposure assessment, the definition of the conditions under which the substance is manufactured and used is critical in order to determine the levels of exposure. The information on the conditions under which a substance is manufactured and used is called **the exposure scenario** under REACH. For each exposure scenario, the exposure levels of humans and the environment need to be determined. The exposure scenarios will cover all identified uses and life stages of the substance.

- **Risk characterization**: the third step in the CSA process is the risk characterization, where the levels of exposure are compared with the threshold levels for each effect. Risks are regarded as controlled under REACH when the exposure levels to the substance are below the threshold levels considered as safe, both for humans and for the environment.

For effects with no threshold levels, emissions and exposures have to be minimised or avoided for risks to be considered to be controlled. If risks are under control, the CSA ends here. If risks are not under control, the CSA has to be refined, either by obtaining more data on the properties of the substance, changing the conditions of manufacturing or use, or making more precise exposure estimations. The process is iterative and will continue until the risks are shown to be under control.

The CSR is a stand-alone document which will be attached in section 13 of IUCLID to the registration dossier and will contain partly information that should already have been reported in the technical dossier. It consists of two parts (ECHA, 2012):

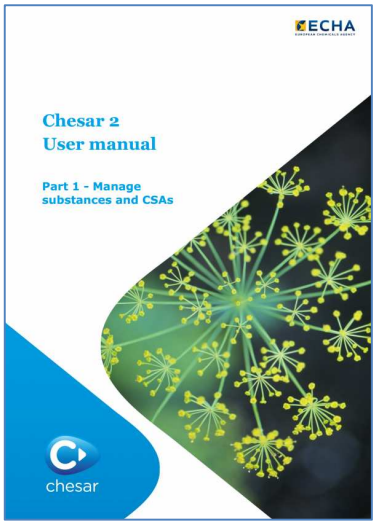
PART A:

1. Summary of risk management measures
2. Declaration that risk management measures are implemented
3. Declaration that risk management measures are communicated

PART B:

1. Identity of the substance and physical and chemical properties
2. Manufacture and uses
3. Classification and labelling
4. Environmental fate properties
5. Human health hazard assessment
6. Human health hazard assessment of physicochemical properties
7. Environmental hazard assessment
8. PBT and vPvB assessment
9. Exposure assessment
10. Risk characterisation

ECHA has developed a tool to help registrants to perform a CSA and generate a CSR named **Chesar**, Chemical safety assessment and reporting tool. The tool provides a structured workflow for carrying out a standard safety assessment for the different uses of a substance and also helps to structure the information needed for the exposure assessment and risk characterisation which will facilitate the generation of a CSR.



To use Chesar the registrant needs to have sufficient information available on the properties of the substance, the uses of the substance, the related tonnages and the conditions under which the uses take place. Based on these inputs the tool calculates exposure estimates that are compared to the predicted no-effect levels.

Workers' exposure estimations provided by CHESAR are calculated using the 'ECETOC TRA worker' tool while environmental exposure estimates are based on the EUSES 2.1 fate model. Chesar also supports the assessments based on other exposure estimation tools or measured data.

Registrants may decide to use other assessment tools instead of CHESAR as long as they are adequate to comply with the REACH requirements.

The ECHA´s Guidance on information requirements and chemical safety assessment helps registrant to undertake a CSA. Based on results from RiP-on 2 project, ECHA published, on 30 April 2012, three new appendices updating **Chapters R.7a, R.7b** and **R.7c** of the Guidance on Information Requirements and Chemical Safety Assessment, recommended when registering nanomaterials.

5. Identification, classification and labeling of nanomaterials

5.1. Identification and naming

When approaching a registration dossier the first issue to be solved in case of a nanomaterial appears to be the substance identification. A correct and consistent identification of a substance is basic on REACH as well as on CLP Regulations.

Similarly, the name and substance identity are the basis for formation of the Substance Information Exchange Forum (SIEFs), data sharing and joint submission of data by multiple registrants. Proper understanding of the identity of a substance is also vital when the Agency receives inquiries relating to a substance.

Moreover, within other REACH processes such as substance evaluation, authorization and restriction, and CLP processes such as notification to the Classification and Labeling inventory and harmonization of Classification and Labeling, discussions on the identity of a substance may occur.

Annex VI, section 2, defines the information on substance identity that shall be included in registration dossiers and states that the information shall be sufficient to enable the substance to be identified. It lists the identifiers that can be included to fulfil this when applicable and appropriate.

These include the name of the substance, chemical identifiers (EC number, CAS name and number, etc.), names (e.g. IUPAC name, chemical name), the molecular and structural formula and its composition (degree of purity, constituents, analytical data, etc.) with a list of spectral and chromatographic requirements that will enable the substance identity to be verified. Mainly, information on substance identification is submitted on IUCLID sections 1.1 Identification, 1.2. Composition and 1.4. Analytical information (Annex VI of REACH).

At this point it is important to note that how information is structured in a registration dossier depends on whether the nanomaterial is a substance or a form of substance. In software IUCLID 5, for completing the registration dossier, from the release of IUCLID 5.4, the options to select “nanomaterial” (when the nanomaterial is registered as a form of a substance instead of as a substance itself), from a list of options in picklists for the “form of the substance”, are in sections 2.1 “Classification and Labelling according to GHS” (directly linked to specific compositions/forms reported in section 1.2) and 4.1. “Appearance/physical state/colour”, as well as in all Endpoint[13]

[13] An endpoint is an information requirement or data point with regard to the physicochemical, ecotoxicological and toxicological properties defined under *Annexes VII* to *X* of the REACH Regulation.

study records[14] where nanomaterial can be selected from a list of options in a picklist for the form of the Test Material for that Endpoint (see Figure).

When a nanomaterial is considered to be a substance itself and the dossier reports a single composition in section 1.2, the registrant can complete the IUCLID dossier as for any other substance.

In addition, other Sections and the relevant fields in IUCLID where labels for substance "nano" form/composition are recommended are:

3.1 *Technological process* – field for the label is "Methods of manufacture".
3.2 *Estimated quantities* - field for the label is "Remarks".
3.6 *Uses advised against* - field for the label is "Brief description".
3.7 *Waste from production and use* - field for the label is "Composition"
3.5 *Identified uses and exposure scenarios* – This section contains two sets of blocks: "*Identified use*" - field for the label is "Brief description" "*Exposure scenario*" - field for the label is "Description".

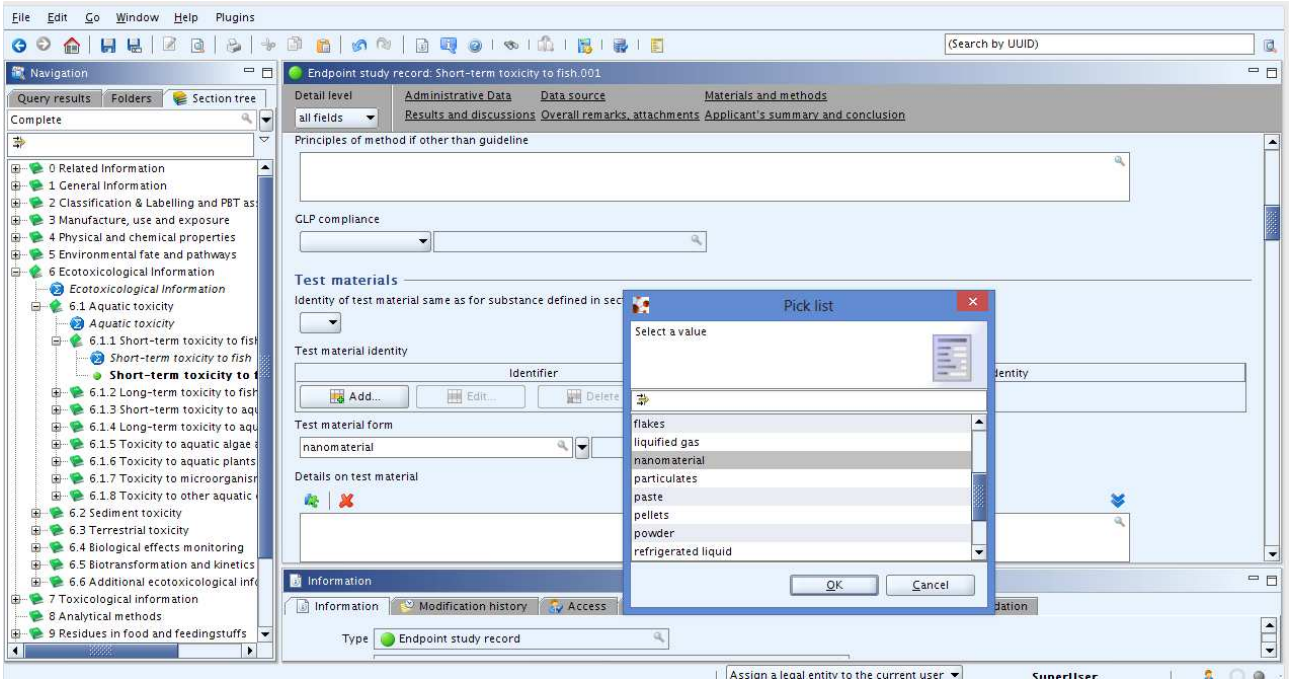


Figure 2. IUCLID screenshot. The picklist for the "test material form" includes nanomaterial in the list of available options.

[14] An endpoint study record provides a standard format for reporting the results of a test on a chemical, with predefined fields and free text prompts which helps the user to summarise a study. The information is entered and stored in the fields provided on the data entry window of IUCLID.

Figure 3. Screenshot of the labelling of the identified uses in section 3.5 **(ECHA, 2013)**

The links between "Identified uses" and "Exposure scenarios" will become visible as it is shown in Figure 3.

The European REACH Implementation Projects on Nanomaterials (RiP-on) launched by the Commission in 2009, evaluated key aspects of the implementation of REACH with regard to nanomaterials concerning Information Requirements and Chemical Safety Assessment. The objective of the project "Substance identification of nanomaterials" (RIP-oN 1) was to evaluate the applicability of existing guidance and, if needed, to develop specific advice on how to establish the substance identity of nanomaterials.

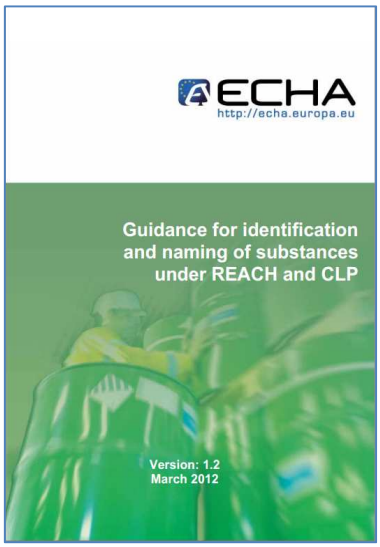
The final report RIP-oN 1 [5], was centred in the Substance Identification of Nanomaterials, studying possible identifiers/characterisers for nanomaterials/nanoforms, by assessing the adequacy of current substance identification parameters laid down in Annex VI, item 2 of REACH and the "Guidance for identification and naming of substances under REACH" (2012). It provided an overview of additional parameters potentially relevant for the identification of nanomaterials. Where consensus amongst the experts could not be reached, report included descriptions of various options for substance identification of nanomaterials in REACH as well as their pros and cons rather than one set of recommendations.

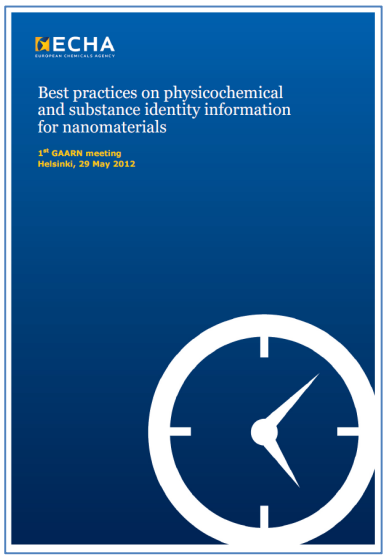
It was not within the scope of RIP-oN 1 specify when changes in the substance identity would, should or could require new information to be generated and/or when or how separate Chemical Safety Assessments should be prepared.

It was concluded that name and molecular structure; chemical composition, purity, impurities/main impurities, additives; and analytical information are all of them relevant as regulatory information requirement for nanomaterials information on these parameters, as for conventional chemicals.

No adaptations are thus far considered relevant for these information requirements. Existing methodologies and guidance for generating information on these parameters are also considered relevant and appropriate for nanomaterials. The chemical composition, purity, impurities/main impurities, additives as well as analytical methods are particularly pertinent in relation to nanomaterials with surface modifications.

To date, the "Guidance for identification and naming of substances under REACH" (2012), related to nanomaterials, concludes that the current state of development is not mature enough to include guidance on the identification of substances in the nanoform in the document. But the IUCLID User Manual for Nanomaterials (ECHA, 2013), published in February 2013, which recompile the instructions for completing a registration dossier with IUCLID 5, mentions at this point that registrants may find useful information in the final report of the REACH Implementation Project on Nanomaterial substance identity (RIP-oN1) (JRC, 2009) where methods suitable for the identification/characterization of nanomaterials were listed and also consider the methods listed in Annex II of the "Guidance Manual For The Testing Of Manufactured Nanomaterials: OECD Sponsorship Programme" (OCDE, 2010).





On the other hand, ECHA published on May 2012 a Best practices guide on physicochemical and substance identity information for nanomaterials (ECHA, 2012) after the 1st GAARN meeting. In relation to the recommendation for the definition of nanomaterials (Commission, 2011), although it is not legally binding, it is a source of information to be legitimately taken into consideration by ECHA, the institutions, Member State competent authorities and registrants. According to that Recommendattion, "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.

There are several analytical techniques that can provide information on primary particle size distribution, as well as aggregate size distribution. However, the results obtained will depend on the

analytical technique used and sample preparation, which leads to a number of assumptions on whether the substance falls within the scope of the current definition for nanomaterials.

Based on the lack of standardised or validated techniques, ECHA stress the convenience of using several analytical techniques for characterising nanoforms (multi-method approach) and explain in detail the method/s used in the dossier.

5.2. Classification and labelling

As in the case of REACH, the regulation (EC) no. 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP) does not contain any specific definition or provision related to nanomaterials nevertheless they are covered by the definition of substance set in the Regulation.

As stated previously, REACH and CLP regulations deal with substances, in whatever size, shape or physical state. Therefore this definition includes all physical states, crystal structures, and dimensions of particles of the substance in powder form or in suspension, even if the particle size would go beyond the nanoscale to individual atoms or molecules. **That means clearly that the classification and labelling of nanomaterials should follow the rules set out in CLP**.

Up to date, it is recognized that different particle sizes or forms of the same substance can have different classification. Thus, if substances are placed on the market both at nanoscale and as bulk, a separate classification and labelling may be required if the available data on the intrinsic properties indicate a difference in hazard class between the two forms.

Besides the above, information on classification and labelling of substances and mixtures as well as **instructions for a safe handling have to be communicated to the supply chain via a Safety Data Sheet (SDS)**. In this regard, since many nanomaterials are not currently classifiable as hazardous, it will be no mandatory to prepare an SDS or include information on label. Anyway, **SDS should reflect current state of knowledge on chemical safety** thus it is extremely important to update it as soon as new information about hazard profile of a nanomaterial is being generated. Further developments of the CLP guidance documents and implementation tools are needed in order to cover nanomaterials more specifically.

Due to the current lack of knowledge, the CLP Regulation has to be modified as regards thresholds applied as soon as new information on nanomaterials becomes available.

6. Required nano-specific information on hazard assessment

The hazard assessment starts with the assessment of the physicochemical, human health and environmental hazards. In addition, the registrant has also to assess whether the substance is persistent, bioaccumulative and toxic or very persistent and very bioaccumulative.

The hazard assessment should be performed on the basis of all available and relevant information which should be reported in the technical dossier. The registrant should rely particularly on the key studies identified in the technical dossier for the relevant endpoints. In addition to these key studies, information available in other studies could also be used by the registrant as supporting information or as part of a weight of evidence approach

All relevant available information on the physicochemical, toxicological, ecotoxicological and environmental fate behavior properties of the substance as specified under Annexes VII to X (and its adaptations according to Annex XI) have to be provided in sections 4 to 7 in IUCLID 5, in the form of study summaries[15] or robust study summaries[16] if required under Annex I[17].

According to REACH, robust study summaries need to be provided only when a chemical safety report is required, i.e. for substances above 10 tons per year, and only for key studies[18]. However, it is recommended to provide robust study summaries for all key studies including for substances manufactured or imported at less than 10 tons per year. This would facilitate the evaluation work to be done by ECHA and eventually Member States in the frame of substance evaluation and may potentially avoid the need for them to request further information.

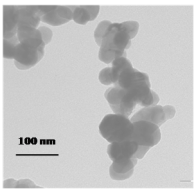
[15] A study summary is a summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an assessment of the relevance of the study.

[16] A robust study summary is a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minmising the need to consult the full study report.

[18] A key study is the study that has been identified as the most suitable to describe an information requirement from the perspective of quality, completeness and representativity of data. When several results are available for given information requirement there can be several key studies. For substances with more than one study available, the study or studies giving rise to the highest concern should normally be used as the key study or studies for the assessment of the substance. In case another study is used as key study this should be fully justified in the technical dossier for the study being used as well as for all studies demonstrating a higher concern.

6.1. Physicochemical properties

The purpose of the physicochemical hazard assessment is to determine the classification and labelling of the substance as well as to assess the potential effects to human health for explosivity, flammability and oxidising potential. Guidance on how to assess physicochemical properties is available in the Chapter R.7 of the Guidance on information requirements and chemical safety assessment in the ECHA´s website[19].



As mentioned previously, a summary of the different effects and at least the explosivity, flammability and oxidising potential must be reported in section 6 of the CSR on the basis of the information available in the endpoint study records.

For the registration of chemicals within REACH, information regarding the physicochemical endpoints showed in Table 2 has to be submitted in the technical dossier.

Table 2. Physicochemical endpoints required in the registration dossier for REACH accomplishment, according the manufactured/imported substance tonnage.

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Physicochemical information				
7.1 State of the substance at 20 °C and 101,3 kPa	X	X	X	X
7.2 Melting/freezing point	X	X	X	X
7.3 Boiling point	X	X	X	X
7.4 Relative density	X	X	X	X
7.5 Vapour pressure	X	X	X	X
7.6 Surface tension	X	X	X	X
7.7 Water solubility	X	X	X	X
7.8 Partition coefficient n-octanol/water (If the test cannot be performed, a calculated value for log P as well as details of the calculation method shall be provided).	X	X	X	X
7.9 Flash-point	X	X	X	X
7.10 Flammability	X	X	X	X
7.11 Explosive properties	X	X	X	X
7.12 Self-ignition temperature	X	X	X	X
7.13 Oxidising properties	X	X	X	X

[19] http://echa.europa.eu/guidance-documents/guidance-on-reach

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Physicochemical information				
7.14 Granulometry	X	X	X	X
7.15. Stability in organic solvents and identity of relevant degradation products Only required if stability of the substance is considered to be critical.			X	X
7.16. Dissociation constant			X	X
7.17. Viscosity			X	X

In IUCLID 5, some other physicochemical endpoints are proposed to be submitted for chemical substances, such as solubility in organic solvents/fat solubility, auto-flammability, oxidation-reduction potential, storage stability and reactivity towards container material, stability (thermal, sunlight and metals), pH and additional physicochemical information.

5.1.2. Existing information requirements applicable for nanomaterials

Information on the physicochemical characterisation of the substance is included in IUCLID sections 4.1 to 4.23. An Endpoint study record can be created for each form of the substance included in the dossier, and each substance form-specific Endpoint study record has the same label as the corresponding substance form/composition.

Current REACH regulations define a "substance" entirely by their chemical composition: "chemical element and its compounds in the natural state or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition". Such definition is inadequate if regulations are to successfully incorporate nanomaterials as has no scope to distinguish nanomaterials from the bulk (micro or macro scale) substance, or different nanoforms from one another.

The most important physical properties of NMs include primary particle characteristics, such as size and shape, as well as other attributes such as aggregation kinetics and dissolution, which will be influenced by the interaction of nanomaterials with each other as well as with their environment.

Below, a description of each of the endpoints applicable to nanomaterials for their physicochemical characterization is presented:

- **Physical appearance** (IUCLID section 4.1, REACH annex VII, 7.1)
  A general description in terms of physical state (solid, liquid or gas), form (e.g. powder, beads, nanomaterial, etc.) and colour should be provided in this endpoint. Data are obtained via visual inspection at 20^0C and 101.3 kPa.

Although this endpoint is not considered as nanospecific (since no differences are detected between bulk and nanoforms in most materials), in some instances (e.g. gold colloids), colour may differ from bulk to nanosize (from dark purple to red wine depending on the size and shape of gold nanocrystals (Daniel, 2004)) and this information should be properly addressed.

- **Melting/freezing point** (IUCLID section 4.2, REACH annex VII, 7.2)
  Melting/freezing temperature (in ^{o}C or K), measured at 101.3 kPa, is provided in this endpoint. Due to their inorganic nature, most of nanomaterials exhibit melting temperatures higher than 300 0C and for some materials this property becomes size-dependent in the nanometric regime (Goldstein, 1992).

  Despite the melting point depression compared to bulk values, melting temperatures remain above 300 0C, and according to REACH (annex VII, column 2, sections 7.2 and 7.3) the study does not need to be conducted for substances which melt in this temperature range.

- **Boiling point** (IUCLID section 4.3; REACH annex VII, 7.3)
  Boiling temperature (in ^{o}C or K), measured at 101.3 kPa, is presented in this endpoint. Again, this measurement can be waived for inorganic nanomaterials as stated in the previous section. Thus, high melting points (above 300 ^{0}C) are used to waive other REACH requirements such as boiling points or vapor pressure (annex VII, section 7.5).

- **Vapor pressure** (IUCLID section 4.6; REACH annex VII, 7.5;)
  Vapor pressure (in Pa) at a given temperature (in ^{0}C or K) can be also waived for substances which melt above 300 ^{0}C (in most if not all nanomaterials) as commented in the previous sections (melting and boiling points). Only if the melting is in the 200-300 ^{0}C range, a limit value based on measurement or a recognized calculation method should be presented.

- **n-octanol/ water partition coefficient** (IUCLID section 4.7; REACH annex VII, 7.8)
  Kow is a coefficient representing the ratio of the solubility of a compound in octanol (a non-polar solvent) to its solubility in water (a polar solvent). The higher the Kow, the more non-polar the compound. In this endpoint logarithm of Kow at a given temperature (in 0C or K) is presented. As stated in REACH (annex VII, column 2, section 7.8) this study does not need to be conducted if the substance is inorganic. However, if nanoparticles have been modified with organic ligands, thus modifying the hydrophobic or hydrophilic character of their surfaces, this endpoint should be taken into account and it becomes nanospecific.

- **Relative density** (IUCLID section 4.4; REACH annex VII, 7.4)
  The ratio of the density (mass of a unit volume, Kg/m^3 or g/cm^3) of a substance to the density of a given reference material (commonly water) at 20 0C is provided in this endpoint. Density of

nanomaterials is an important parameter to be considered, since it affects particle properties like dry sedimentation or deposition in the lung (Schmid, 2007). As the inherent density of nanoparticles is insignificantly affected by size effects, this endpoint cannot be considered as nanospecific.

- **Particle size distribution/Granulometry** (IUCLID section 4.5; REACH annex VII, 7.14)

Granulometry is, as expected, the central nanospecific endpoint. It provides essential information for the definition of any nanomaterial and can be considered as a vital driver for other properties of the substance. The term granulometry not only refers to particle size distribution but also covers other related properties such as nanoparticle crystal structure, shape, and agglomeration degree.

Particle size (in nm) is a fundamental attribute of disperse materials. When a group of particles are of differing sizes, they may be described by a particle size distribution. In this sense, granulometry can be defined as the determination of particle size distribution, thus providing an average particle size accompanied by the standard deviation which describes the width of the corresponding particle size distribution. Electron Microscopy (both TEM and SEM) and Dynamic Light Scattering (DLS) are the most widely used techniques to measure primary particle size and particle size distribution.

Solid particulates/granulates with identical composition can have a variety of well- or ill-defined shapes, including spheres, rods, tubes, fibres and plates, which may have different physical, chemical, and biological properties. Shapes are determined by the way in which the entities are bound together and particles will assume the shape that minimises free energy and is kinetically achievable under given environmental conditions.

Particle shape is an important parameter in the characterisation of some nanoparticles, with contextual value to the assessment of deposition, adsorption kinetics, and hazard assessment in biological media. Knowledge of high aspect ratio particles may inform interpretation of some toxicity test results. Particle shape can be characterised by providing some representative SEM/TEM micrographs.

Furthermore a detailed electron microscopy study should also depict a description of the aggregation/dispersion degree of nanoparticles, showing the formation of aggregates/agglomerates as a result of particle interaction.

Finally the identification of the crystal phase exhibited by studied nanoparticles (usually determined by X-ray and electron diffraction experiments) can be potentially relevant for the identification of the nanomaterials as for any other substance.

- **Water solubility** (IUCLID section 4.8; REACH annex VII, 7.7)
  Solubility (in mg/L, mg/L or g/L) of test substance in water at a given temperature (in 0C or K) may also depend on the particle size, becoming nanospecific. Thus, nanoscale solids can exhibit a significantly increased dissolution rate (Bian, 2011). The effect of surface modification on the water solubility/dispersability must also be considered. In this sense, a distinction between solubility and dispersability has to be made.

- **Solubility in organic solvents/fat solubility** (IUCLID section 4.9)
  Solubility (in mg/L, mg/L or g/L) of test substance in a given organic solvent at 20 0C and substance content in standard fat (mg/100 g fat) at the same temperature are included in this endpoint. As stated in previous sections (partition coefficient and water solubility) surface modification of nanomaterials may enhance their hydrophobicity, thus increasing organic and fat solubilities. In this case both properties can be considered nanospecific.

- **Stability in organic solvents and identity of relevant degradation products** (IUCLID section 4.17; REACH annex VII, 7.15)
  This endpoint is only required if the stability of the substance is considered to be critical and it is generally waived, in most if not all cases, due to the inorganic nature of common nanomaterials. As mentioned in the previous section, the functionalization of nanoparticles with organic groups may modify their interaction with organic solvents, thus affecting their stability, which should be taken into account.

- **Surface tension** (IUCLID section 4.10; REACH annex VII, 7.6)
  Surface tension (in mN/m) at 20 ^{0}C is an endpoint usually waived for inorganic nanomaterials as a result of their low water solubility and the lack of surface activity. Although this endpoint is not considered as relevant or applicable for testing nanomaterials, it should be considered when dealing with surface treated nanoparticles.

- **Flash point** (IUCLID section 4.11; REACH annex VII, 7.9)
  The flash point is defined, generally for liquids, as the lowest temperature (in ^{0}C or K, at 101.3 kPa) at which a substance can vaporize to form an ignitable mixture in air.

  Since most nanomaterials are solids and exhibit high melting points this study does not need to be conducted.

- **Flammability, explosive properties, self-ignition temperature and oxidizing properties** (IUCLID sections 4.13, 4.14, 4.12 and 4.15 respectively; sections 7.10, 7.11, 7.12 and 7.13 respectively, REACH annex VII)

Physical hazard assessment concerns a sub-set of the properties mentioned above, such as whether or not the substance is explosive, oxidizing, extremely flammable, highly flammable, or flammable and self-ignition temperature (in ^{0}C or K, measured at 101.3 kPa). As many nanomaterials are prepared, stored and shipped as powders, there may be some associated risks of explosion of flammability. Furthermore, the results of these tests are known to be size-dependent. In this sense, finer particles are generally more reactive (flammable, explosive and oxidizing) than larger particles and this set of endpoints should be accompanied by particle size distribution data. Then, tests should be performed using the nanoform as the worst case scenario. According to REACH, in some cases, tests can be waived based on chemical structure of nanomaterials (no chemical groups associated with explosive reactions or capable to react with oxygen, metal at the highest oxidation state in metal oxide nanoparticles and so on).

- **Dissociation constant** (IUCLID section 4.21; REACH annex VII, 7.16)

  Ka (commonly expressed as –log Ka or pKa at 20^{0}C) is a specific type of equilibrium constant that measures the propensity of a larger molecule to separate (dissociate) reversibly into smaller components, as when a complex falls apart into its component ligands and ions, or when a salt splits up into its component ions. This endpoint should be taken into consideration when dealing with surface treated nanoparticles and only can be waived when they do not contain functional groups capable of dissociation/ionization at relevant pH ranges.

- **Specific surface area and other relevant surface properties** (IUCLID section 4.23; Not REACH standard information requirements)

  According to OECD (OCDE, 2010), surface area is defined as the area of the exposed surface of a single particle, or more generally, the area of the exposed surface of a certain amount of a material. Surface area as an extensive quantity depends on the amount of the material, and therefore a better comparable characteristic is the ratio of the surface area to the mass of a certain amount of a material.

  This is the so called specific surface area (m^2/g) which is an intensive quantity and thus independent of the amount of the material.

  For particle-based substances, the surface plays an important role in influencing the physical and chemical interactions. As chemical reactions take place at surfaces, a sample of material with a high specific surface area to volume ratio can be expected to have a higher reactivity than a sample of the same material with a low specific surface area to volume ratio.

  Specific surface area is a key parameter in the characterization of nanoparticles, with emerging evidence of quantitative value as a dose metric or descriptor for hazard assessment. The specific

surface area will dictate the surface charge in cases where nanomaterials are surface functionalized. This in turn has direct consequences on (a) nanomaterial interaction (i.e., agglomeration) with other naturally occurring particulate matter (i.e. contaminant vectors); (b) route of exposure as a function of surface ligand-biological interface (i.e. bioaccumulation pathway, bioavailability); and (c) mechanisms of toxicity (e.g. dose response curves normalized for surface area may indicate different results compared to results presented on a per mass basis) (OCDE, 2010) In view of the above, specific surface area is considered as a key nanospecific endpoint, which is vital for the characterization of nanomaterials.

Other relevant surface-related properties are listed as follows:

a. Porosity (mean pore diameter in nm or Å and pore volume in cm^3/g)
b. Photocatalytic activity
c. Zeta potential (in mV)

As porosity is directly related to surface area, it can also be considered a nanospecific endpoint. In the case of porous materials, it is often useful to distinguish between external and internal surface. The external surface is usually regarded as the envelope surrounding the discrete particles or agglomerates, but is difficult to define precisely because solid surfaces are rarely smooth on an atomic scale.

The external surface include all the prominences and also the surface of those cracks which are wider than they are deep; the internal surface comprises the walls of all cracks, pores and cavities which are deeper than they are wide and which are accessible to a test gas (the adsorptive). In practice, the demarcation depends on the methods of assessment and the nature of the pore size distribution; hence accessibility of pores depends on the size and shape of test gas molecules, the area of, and the volume enclosed by, the internal surface as determi
ned by gas adsorption will depend on the adsorptive molecules (molecular sieve effect)

With regard to photocatalytic activity, photocatalysis is the acceleration of a photoreaction in the presence of a catalyst. Some nanomaterials, namely semiconductors, can generate highly reactive free radicals on their surface upon exposure to light. Thus, in photogenerated catalysis, the photocatalytic activity depends on the ability of the catalyst to create electron–hole pairs, which generate free radicals (e.g. hydroxyl radicals: •OH) able to undergo secondary reactions. So that, when dealing with nanoparticles, the photooxidation of propan-2-ol into propan-2-one under UV irradiation, can be employed to evaluate the photocatalytic characteristics of different nanomaterials.

This reaction can be monitored using gas chromatography as reported by Bickley et al (Bickley, 2010). Since photocatalytic activity is size dependent and can be enhanced or completely

switched off by surface treating, it can be considered as a nanospecific endpoint, which is also very relevant for risk assessment.

Zeta potential (in mV) is a measure of the magnitude of the electrostatic or surface charge repulsion or attraction between particles, and is one of the fundamental parameters known to affect stability, thus providing a qualitative understanding of the agglomeration process. It can also be considered as an essential nanospecific endpoint.

- **Viscosity** (IUCLID section 4.22; REACH annex VII, 7.17)
  Dynamic (mPa•s) and static (mm^2/s) viscosities are provided in this endpoint. This endpoint is usually waived with the justification that nanomaterials are solid substances and this is not relevant for solids.

- **Additional physicochemical properties**
  This section encompasses a number of endpoints that are not part of the REACH information requirements such as:
  a. Oxidation reduction potential (in mV, at 20^0C)
  b. pH (at 20^0C)
  c. Storage stability and reactivity towards container material
  d. Stability: thermal, sunlight and metals

  Oxidation reduction potential is a measure of the tendency of a chemical species to acquire electrons and thereby be reduced. Each species has its own intrinsic reduction potential; the more positive the potential, the greater the species affinity for electrons and tendency to be reduced. In nature, redox reactions are an important part of phenomena such as mineral weathering, bacterial respiration, and degradation of pollutants. In terms of nanomaterial toxicity, redox potential is a parameter that has been associated with inducing oxidative stress (Tantra, 2012).
  The measure of the activity (concentration) of the solvated hydrogen ion at 200C, known as pH, should be taken into consideration specially when dealing with surface treated nanoparticles and only can be waived when they do not contain functional groups capable of dissociation/ionization. This endpoint is directly linked to dissociation constant (section 7.16, REACH annex VII; IUCLID section 4.21).

  Finally, storage recommendations should be addressed when dealing with nanomaterials, taking into account their stability/reactivity at the storage conditions (type of container, sunlight exposure, temperature and so on).

5.1.3. Additional Relevant Specific Intrinsic properties for nanomaterials

In IUCLID 5.5 the registrant can already include information on nanoform-specific physicochemical properties in section 4.23., where specific endpoints has been added (4.24 to 4.36), as shown in Figure 2. These nano-specific endpoints adopted from results of RiP-on project are:

- Crystallite and grain size
- Aspect/ratio shape
- Specific surface area
- Zeta potential
- Surface chemistry
- Dustiness
- Porosity
- Pour density
- Photocatalytic activity
- Radical formation potential
- Catalytic activity

6.2. Toxicological Information

In order to identify the intrinsic toxic properties of chemical substances, different tests are required which are quantity-triggered as the tonnage triggered standard information requirements of REACH Annexes VII-X.

The objective of the human health hazard assessment is to determine the classification and labelling of the substance and to define the level of exposure above which humans should not be exposed which known as the derived no-effect level(s) (DNEL). The DNEL, regarded as an exposure level below which an adverse effect will not occur, is derived from toxicity test results using appropriate assessment factors.

While toxicity test results are reported in the technical dossier in the different endpoint study records, the DNEL values and the assessment factors used in their calculation should be reported in the endpoint summary records.

For the registration of chemicals within REACH, information regarding the toxicological endpoints showed in Table 3 has to be submitted in the technical dossier.

Table 3. Toxicological endpoints required in the registration dossier for REACH accomplishment, according the manufactured/imported substance tonnage.

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Toxicological information				
8.1 Skin irritation or skin corrosion				
The assessment of this endpoint shall comprise the following consecutive steps: (1) an assessment of the available human and animal data, (2) an assessment of the acid or alkaline reserve, (3) in vitro study for skin corrosion, (4) in vitro study for skin irritation. Specific Rules: Steps 3 and 4 do not need to be conducted if: — the available information indicates that the criteria are met for classification as corrosive to the skin or irritating to eyes, or — the substance is classified as very toxic in contact with skin, or — an acute toxicity study by the dermal route does not indicate skin irritation up to the limit dose level (2 000 mg/kg body weight).	X	X	X	X
8.1.1 In vivo skin irritation Specific Rules: The study does not need to be conducted if: — the substance is classified as corrosive to the skin or as a skin irritant, or — the substance is a strong acid (pH ≤ 2,0) or base (pH ≥ 11,5), or — the substance is classified as very toxic in contact with skin, or — an acute toxicity study by the dermal route does not indicate skin irritation up to the limit dose level (2 000 mg/kg body weight).		X	X	X
8.2 Eye irritation				
The assessment of this endpoint shall comprise the following consecutive steps: (1) an assessment of the available human and animal data, (2) an assessment of the acid or alkaline reserve, (3) in vitro study for eye irritation. Specific Rule: Step 3 does not need to be conducted if: — the available information indicates that the criteria are met for classification as corrosive to the skin or irritating to eyes.	X	X	X	X
8.2.2 In vivo eye irritation Specific Rules: The study does not need to be conducted if: — the substance is classified as irritating to eyes with risk of serious damage to eyes, or — the substance is classified as corrosive to the skin and provided that the registrant classified the substance as eye irritant, or — the substance is a strong acid (pH ≤ 2,0) or base (pH ≥ 11,5)		X	X	X
8.3 Skin sensitisation				
The assessment of this endpoint shall comprise the following consecutive steps: (1) an assessment of the available human, animal and alternative data, (2) In vivo testing. Specific Rules: Step 2 does not need to be conducted if: — the available information indicates that the substance should be classified for skin sensitisation or corrosivity, or — the substance is a strong acid (pH ≤ 2,0) or base (pH ≥ 11,5) The Murine Local Lymph Node Assay (LLNA) is the first-choice method for in vivo testing. Only in exceptional circumstances should another test be used. Justification for the use of another test shall be provided.	X	X	X	X
8.4. Mutagenicity				
8.4.1 In vitro gene mutation study in bacteria Specific Rule: Further mutagenicity studies shall be considered in case of a positive result.	X	X	X	X

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Toxicological information				
8.4.2 In vitro cytogenicity study in mammalian cells or in vitro micronucleus study Specific Rules: The study does not usually need to be conducted — if adequate data from an in vivo cytogenicity test are available, or — the substance is known to be carcinogenic category 1 or 2 or mutagenic category 1, 2 or 3.		X	X	X
8.4.3 In vitro gene mutation study in mammalian cells, if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. Specific Rule: The study does not usually need to be conducted if adequate data from a reliable in vivo mammalian gene mutation test are available.		X	X	X
Specific Rule: Appropriate in vivo mutagenicity studies shall be considered in case of a positive result in any of the genotoxicity studies in Annex VII or VIII.		X	X	X
Specific Rules: If there is a positive result in any of the in vitro genotoxicity studies in Annex VII or VIII and there are no results available from an in vivo study already, an appropriate in vivo somatic cell genotoxicity study shall be proposed by the registrant. If there is a positive result from an in vivo somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered.			X	X
Specific Rules: If there is a positive result in any of the in vitro genotoxicity studies in Annexes VII or VIII, a second in vivo somatic cell test may be necessary, depending on the quality and relevance of all the available data. If there is a positive result from an in vivo somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered.				X
8.5 Acute toxicity				
Specific Rule: The study/ies do(es) not generally need to be conducted if: — the substance is classified as corrosive to the skin.				
8.5.1 By oral route Specific Rule: The study need not be conducted if a study on acute toxicity by the inhalation route (8.5.2) is available.	X	X	X	X
Specific Rule: In addition to the oral route (8.5.1), for substances other than gases, the information mentioned under 8.5.2 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.		X	X	X
8.5.2. By inhalation Specific Rule: 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.		X	X	X
8.5.3. By dermal route Specific Rule:Testing by the dermal route is appropriate if: (1) inhalation of the substance is unlikely; and (2) skin contact in production and/or use is likely; and (3) the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin.		X	X	X

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Toxicological information				
8.6. Repeated dose toxicity				
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 Specific Rules: 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: (1) inhalation of the substance is unlikely; and (2) skin contact in production and/or use is likely; and (3) 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 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), 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.		X	X	X
Unless already provided as part of Annex VIII requirements or if tests according to Section 8.6.2 of Annex IX is proposed. In this case, Section 3 of Annex XI shall not apply.			X	X
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. Specific Rules: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			X	X

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Toxicological information				
— 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 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. 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), 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).				
8.6.3. Long-term repeated toxicity study (≥ 12 months) Specific Rules: 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.				X
8.6.4. Further repeated dose toxicity studies Specific Rules: 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: — toxicity of particular concern (e.g. serious/severe effects), or — indications of an effect for which the available evidence is inadequate for toxicological evaluation 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), 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 is observed).				X

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Toxicological information				
8.7. Reproductive toxicity				
8.7.1. Screening for reproductive/ developmental toxicity, one species (OECD 421 or 422), if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from in vitro methods that the substance may be a developmental toxicant Specific Rules:This study does not need to be conducted if: — the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or — the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or — relevant human exposure can be excluded in accordance with Annex XI section 3, or — a pre-natal developmental toxicity study (Annex IX, 8.7.2) or a two-generation reproductive toxicity study (Annex IX, Section 8.7.3) is available. If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as Repr Cat 1 or 2: R60, and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for development toxicity must be considered. If a substance is known to cause developmental toxicity, meeting the criteria for classification as Repr Cat 1 or 2: R61, and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered. In cases where there are serious concerns about the potential for adverse effects on fertility or development, either a pre-natal developmental toxicity study (Annex IX, Section 8.7.2) or a two-generation reproductive toxicity study (Annex IX, Section 8.7.3) may be proposed by the registrant instead of the screening study.		X	X	X
Specific Rules:The studies do not need to be conducted if: — the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or — the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or — the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure. If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as Repr Cat 1 or 2: R60, and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for development toxicity must be considered. If a substance is known to cause developmental toxicity, meeting the criteria for classification as Repr Cat 1 or 2: R61, and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered.			X	X
8.7.2. Pre-natal developmental toxicity study, one species, most appropriate route of administration, having regard to the likely route of human exposure (B.31 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 414) Specific Rule:The study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data.			X	X

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Toxicological information				
8.7.2. Developmental toxicity study, one species, most appropriate route of administration, having regard to the likely route of human exposure (OECD 414)				X
8.7.3. Two-generation reproductive toxicity study, one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure, if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues Specific Rule:The study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available date.			X	X
Unless already provided as part of Annex IX requirements				X
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		X	X	X
8.9. Carcenogenicity				
8.9.1. Carcinogenicity study Specific Rules:A carcinogenicity study may be proposed by the registrant or may be required by the Agency in accordance with Articles 40 or 41 if: — the substance has a widespread dispersive use or there is evidence of frequent or long-term human exposure, and — the substance is classified as mutagen category 3 or there is evidence from the repeated dose study(ies) that the substance is able to induce hyperplasia and/or pre-neoplastic lesions. If the substance is classified as mutagen category 1 or 2, the default presumption would be that a genotoxic mechanism for carcinogenicity is likely. In these cases, a carcinogenicity test will normally not be required.				X

In IUCLID 5, some other toxicological endpoints are proposed to be submitted for chemical substances, such as dermal absorption; acute toxicity by routes different from oral, inhalation and dermal; respiratory sensitization; Repeated dose toxicity by routes different from oral, inhalation and dermal and specific investigations (neurotoxicity, inmunotoxicity, and other), exposure related observations in humans (health surveillance data; epidemiological data; direct observations (clinical cases, poisoning incidents and other); sensitisation data (humans); exposure related observations in humans: other data), toxic effects on livestock and pets and other additional toxicological information.

6.2.1. Existing information requirements applicable for nanomaterials

All existing information requirements are relevant for nanomaterials, but it is necessary keep in mind that except some exceptions such as skin and eye irritation, skin sensitisation, in vivo mutagenicity testing for which the OCDE (OCDE, 2010) determined that guidances were valid, no exact guidance is currently available on how to incorporate this type of testing in a testing regime for nanomaterials and thus the use and the need for such *in vitro and in vivo* testing have to be considered on a case-by-case basis.

For many of that assays, measuring methods are available for detection of a nanomaterial and its elemental composition in organs, tissues and other biological samples. In relation to this, labelling methods (radioactive isotopes or fluorescent dyes) are indicated as possible methods. For proper application of labelling methods, it must be ensured that the label is stable and uniquely associated with the nanomaterial.

This would require analyses coupling chemical quantification and confirmation of the nanomaterial in the organs and tissues by imaging techniques such as electron microscopy (Agency, 2013).

6.2.2. Additional Relevant Specific Intrinsic properties for nanomaterials

It is essential for all toxicological testing that the test material be characterized and its physical form monitored during the experiment. In relation with **genotoxicity**, beyond the standard test provided for in Annex VII with respect to in vitro genotoxicity in bacteria, two tests for genotoxicity with mammalian cells in vitro are necessary for nanomaterials (from 1 tn/y).

The standard test to identify the mutagenic potential, as one aspect of genotoxicity, is the Ames test, using bacteria from *salmonella typhimurium* strains. But their bacterial cell wall may interfere with the uptake of nanomaterials into the cell, giving false negative results, so the OECD (OCDE, 2010) recommends that nanomateriasl always be examined with a test battery of three in vitro tests for genotoxicity: the bacterial gene mutations assay (Ames), a mammalian cell-based gene mutations assay (HPRT), and a mammalian cell-based cytogenicity test or micronucleus test, which are validated. Positive results can primarily be expected from the test systems with mammalian cells. The Ames test should nevertheless be included in the test battery because a positive result of this highly specific test is a strong indicator of any mutagenic effect.

In relation with **route of administration**, for the first test to examine acute toxicity as well as all further tests with repeated administration, the inhalation route is the standard administration route for nanomaterials instead of the oral administration route normally used for bulk material.

For insoluble nanomaterials exposure by inhalation is the administration route of highest importance because the major part of nanomaterials contains inhalable or respirable fractions. Oral exposure and dermal exposure towards industrial chemicals in nano form are in principle possible, but in most cases of lower importance compared to exposure by inhalation. It is therefore recommended, taking into account of the most probable type of exposure, so the standard route of administration be changed from oral to inhalation.

As a deviation from the explanations of the OECD test methods and the Test Method Regulation (EC) No 440/2008 concerning **tests with repeated administration**, according ((BfR), 2012) extended exposure-free follow-up phases are necessary for nanomaterials.

Extended follow-up phases serve to identify the distribution of nanomaterials in organs and in the organism which might exhibit a different or delayed pattern compared to the bulk material and also serves to identify possible particle persistence.

Moreover, extended follow-up phases also serve to identify either possible increases in effects or adverse effects, which might occur after a delay. Subacute studies on nanomaterials should include an extended follow-up phase of 28 (instead of 14) days and in the case of subchronic tests this should be 90 (instead of 28) days.

For chronic studies a follow-up phase should to be included. All available data, as well as the life expectancy of the animal species and animal strain and the preceding exposure time have to be taken into account.

As a deviation from the explanations of the OECD test methods and the Test Method Regulation (EC)No. 440/2008 concerning tests with repeated administration, additional study parameters are required for nanomaterals according (BfR, 2012).

These consist of additional clinical-chemistry parameters, additional morphological parameters and/or additional functional-morphological examinations.The extent of the additional study parameters must be in accordance with the actual state of knowledge of the OECD activities (SG4, 2012) concerning the updating of test regulations.

Regarding additional testing requirement for respirable, bio-resistant fibrous nanomaterials, ((BfR), 2012) states that inflammation and a probable carcinogenic effect after inhalation are regarded as relevant health hazards of such nanomaterials. Where fibrous materials are present it must be demonstrated that bio-resistant nano-scale fibres of respirable dimension (WHO fibre dimension >5 µm, diameter <3 µm, length-to-diameter ratio >3:1) are not present.

The corresponding test requirements obtained from the experience with asbestos and man-made mineral fibres can also be applied to fibres of nanomaterials. With the results of these tests it is possible to derive a hazard evaluation concerning carcinogenicity.

Finally, only the ((SCCS), 2012) specifically addresses testing for photoxicity and states that the OECD in vitro test on phototoxicty has not yet been validated for nanomaterials. Issues related to triggering level and adaptation Phototoxicity may be considered as a relevant end-point for nanomaterials used in cosmetics and be triggered in specific other cases with high potential for dermal exposure; however, according to (Agency, 2013) it does not seem appropriate to include this end-point in a standard testing scheme.

6.3. Ecotoxicological Information

The objective of the environmental hazard assessment is to classify and label the substance and to determine a predicted no effect concentration (PNEC) below which adverse environmental effects in the environmental compartments are not expected to occur.

A summary of the different effects on the environmental targeted compartments (aquatic, terrestrial, atmospheric and microorganisms of the sewage treatments systems) shall be reported in the CSR (section 7) on the basis of the information available in the technical dossier under the relevant IUCLID 5 endpoint study record. The result of the assessment, once finalized, should also be reported under the relevant endpoint summaries in IUCLID 5 as well as the calculated PNECs values.

At this point, in addition to information on potential effects on the environment, the registrant has also to document the environmental fate (e.g. degradation, bioaccumulation) of the substance (section 4 of the CSR).

For the registration of chemicals within REACH, information regarding the ecotoxicological endpoints showed in Table 3 has to be submitted in the technical dossier.

Table 4. Ecotoxicological endpoints required in the registration dossier for REACH accomplishment, according the manufactured/imported substance tonnage.

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Ecotoxicological information				
9.1 Aquatic toxicity				
9.1.1 Short-term toxicity testing on invertebrates (preferred species Daphnia) The registrant may consider long-term toxicity testing instead of short-term. Specific Rules: 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, or — 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.	X	X	X	X
9.1.2 Growth inhibition study aquatic plants (algae preferred) Specific Rule: 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.	X	X	X	X
9.1.3. Short-term toxicity testing on fish The registrant may consider long-term toxicity testing instead of shortterm. Specific Rules: 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, or — a long-term aquatic toxicity study on fish is available.		X	X	X

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Ecotoxicological information				
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.				
9.1.4. Activated sludge respiration inhibition testing Specific Rules: 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. 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.		X	X	X
Specific Rule: Long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment.			X	X
9.1.5. Long-term toxicity testing on invertebrates (preferred species Daphnia), (unless already provided as part of Annex VII requirements)			X	X
9.1.6. Long-term toxicity testing on fish, (unless already provided as part of Annex VIII requirements) The information shall be provided for one of the Sections 9.1.6.1, 9.1.6.2 or 9.1.6.3. 9.1.6.1. Fish early-life stage (FELS) toxicity test 9.1.6.2. Fish short-term toxicity test on embryo and sac-fry stages 9.1.6.3. Fish, juvenile growth test			X	X
9.2 Degradation				
9.2.1 Biotic	X	X	X	X
9.2.1.1 Ready biodegradability	X	X	X	X
Specific Rule: Further biotic degradation testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance and its degradation products. The choice of the appropriate test(s) depends on the results of the chemical safety assessment and may include simulation testing in appropriate media (e.g. water, sediment or soil).			X	X
9.2.1.2. Simulation testing on ultimate degradation in surface water Specific Rule: The study need not be conducted: — if the substances is highly insoluble in water, or — if the substance is readily biodegradable.			X	X
9.2.1.3. Soil simulation testing (for substances with a high potential for adsorption to soil) Specific Rule: The study need not be conducted: — if the substance is readily biodegradable, or — if direct and indirect exposure of soil is unlikely.			X	X
9.2.1.4. Sediment simulation testing (for substances with a high potential for adsorption to sediment) Specific Rule: The study need not be conducted: — if the substance is readily biodegradable, or — if direct and indirect exposure of sediment is unlikely.			X	X
Specific Rule: 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. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.		X	X	X

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Ecotoxicological information				
9.2.2. Abiotic 9.2.2.1. Hydrolysis as a function of pH. Specific Rules: The study does not need to be conducted if: — the substance is readily biodegradable, or — the substance is highly insoluble in water.		X	X	X
9.2.3. Identification of degradation products Specific Rule: Unless the substance is readily biodegradable.			X	X
9.3. Fate and behaviour in the environment				
9.3.1. Adsorption/desorption screening Specific Rules: 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.		X	X	X
9.3.2. Bioaccumulation in aquatic species, preferably fish Specific Rules: The study need not be conducted if: — the substance has a low potential for bioaccumulation (for instance a log Kow ≤ 3) and/or a low potential to cross biological membranes, or — direct and indirect exposure of the aquatic compartment is unlikely.			X	X
9.3.3. Further information on adsorption/desorptiondepending on the results of the study required in Annex VIII Specific Rules: The study need not 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 degradation products decompose rapidly.			X	X
9.3.4. Further information on the environmental fate and behaviour of the substance and/or degradation products Specific Rule: Further testing shall be proposed by the registrant or may be required by the Agency in accordance with Articles 40 or 41 if the chemical safety assessment according to Annex I indicates the need to investigate further the fate and behaviour of the substance. The choice of the appropriate test(s) depends on the results of the chemical safety assessment.				X
9.4. Effects on terrestrial organisms				
Specific Rules: 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. 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 or that are very persistent, the registrant shall consider long-term toxicity testing instead of short-term.			X	X
9.4.1. Short-term toxicity to invertebrates			X	X
9.4.2. Effects on soil micro-organisms			X	X
9.4.3. Short-term toxicity to plants			X	X
Specific Rule: Long-term toxicity testing shall be proposed by the registrant if the results of the chemical safety assessment according to Annex I indicates the need to investigate further the effects of the substance and/or degradation products on terrestrial organisms. The choice of the appropriate test(s) depends on the outcome of the chemical safety assessment. These studies do not need to be conducted if direct and indirect exposure of the soil compartment is unlikely.				X

Tonnage level manufactured or imported	≥1 t/a	≥10 t/a	≥100 t/a	≥1000 t/a
Ecotoxicological information				
9.4.4. Long-term toxicity testing on invertebrates, unless already provided as part of Annex IX requirements				X
9.4.6. Long-term toxicity testing on plants, unless already provided as part of Annex IX requirements				X
9.5 Effects on sediment organisms				
9.5.1. Long-term toxicity to sediment organisms Specific Rule: Long-term toxicity testing shall be proposed by the registrant if the results of the chemical safety assessment indicates the need to investigate further the effects of the substance and/or relevant degradation products on sediment organisms. The choice of the appropriate test(s) depends on the results of the chemical safety assessment.				X
9.6. Toxicity to birds				
9.6.1. Long-term or reproductive toxicity to birds Specific Rule: Any need for testing should be carefully considered taking into account the large mammalian dataset that is usually available at this tonnage level.				X

In IUCLID 5, some other ecotoxicological endpoints are proposed to be submitted for chemical substances, such as:

- Toxicity to aquatic plants other than algae
  - EC50/LC50 for freshwater plants
  - EC50/LC50 for marine water plants
  - EC10/LC10 or NOEC for freshwater plants
  - EC10/LC10 or NOEC for marine water plants
- Toxicity to aquatic organisms other than fish, aquatic invertebrates, algae and cyanobacteria
- Toxicity to ground organisms other than soil microorganisms, terrestrial arthropods, plants and birds
- Biological effects monitoring
- Biotransformation and kinetics
- Additional ecotoxicological information

On the other hand, In IUCLID 5, some other environmental fate and pathways different from endpoints stated on RECHA annexes (stability (hydrolysis); biodegradation in water, sediments and soil; bioaccumulation in aquatic/sediment and transport and distribution (adsorption/desorption), are proposed to be submitted for chemical substances, such as:

- Phototransformation in air
- Phototransformation in water
- Phototransformation in soil
- Mode of degaradation in actual use

- Bioaccumultaion: terrestrial
- Henry´s Law Constant
- Distribution modelling
- Monitoring data (in a determined location)
- Field studies
- Additional information on environmental fate and behaviour

6.4. Existing information requirements applicable for nanomaterials

According to (OCDE, 2010), from REACH annexes' requirements, information requirements especially applicable to nanomaterials are:

- Effects on pelagic species (short term/long term)
- Effects on sediment species (short term/long term)
- Effects on soil species (short term/long term)
- Effects on terrestrial species
- Effects on microorganisms
- Effects on activated sludge at waste water treatment plants
- Other relevant information when available

6.5. Additional Relevant Specific Intrinsic properties for nanomaterials

According to ((BfR), 2012), from 1 tonne or more per year of nanomaterial´s manufacture/import, when test programme applies in accordance with Annexes VII and VIII of the REACH Regulation, because of the tendency of nanomaterials to agglomerate and sediment, the sediment is regarded as a particularly relevant exposure route, even at low tonnages. Therefore more information is required. Moreover, in the fish test, a chronic test should be considered instead of an acute one.

On the other hand, the poor water solubility as the only exclusion criterion for ecotoxicological tests cannot justify test waiving for nanomaterials. Rather it must be justified in addition that the nanomaterial is not absorbed and is not capable of penetrating biological membranes. Very good water solubility may justify the waiving of tests of the nanoform if a test is available for the bulkform of the substance. An explanatory note on the remark "if there are mitigating factors indicating that aquatic/microbiological toxicity is unlikely to occur" must be inserted into the preliminary remarks for Annex XVIII or in Annex XI.

As stated also by ((BfR), 2012), from 10 tonnes or more per year of nanomaterial´s manufacture/import, when the test programme from Annex IX apply, in addition as the chronic sediment test from Annex X, identification of the degradation products will remain at 100 tonnes or

more per year because no nanomaterial-specific problem is to be expected and the degradation does not play a crucial role for nanomaterials, except with respect to surface treatment.

The short-time test for terrestrial plants remains at 100 tonnes or more per year. In the case of bioaccumulation, a fish feeding study is to be preferred to the BCF test as the BCF test often fails to give a realistic picture of the accumulation behaviour of NMs.

From 100 tonnes or more per year the test programme from Annex X applies, in addition, the chronic plant tests and reproduction test for birds remain at 1000 tonnes per year. Finally, from 1000 tonnes or more per year chronic plant test and reproduction test for birds apply.

6.6. PBT/ vPvB assessment

The objective of the PBT/vPvB assessment is to determine if the substance fulfils the criteria given in Annex XIII and if so, to characterise the potential emissions of the substance which will be reported as well in the CSR along with conclusion of the PBT, vPvB assessment (section 8).

Relevant information regarding the persistent, bioaccumulative and toxic (PBT) properties of the substance should be already available in the CSR under respectively sections 4 for Persistence and Bioaccumulation and 5 and 7 for Toxicity. In addition further information, like monitoring data might also be useful.

If at the end of the assessment the substance is assessed to be PBT/vPvB, an emission. should be reported in section 8 of the CSR.

7. Required nano-specific information on use, applications and risk controls

According Article 14 of REACH, if as a result of hazard assessment the registrant concludes that the substance meets the criteria for classification as dangerous in accordance with Directive 67/548/EEC or is assessed to be a PBT or vPvB, the chemical safety assessment shall include the following additional steps:

- **Exposure assessment**:
  - Generation of exposure scenario(s) (or the identification of relevant use and exposure categories if appropriate)
  - Exposure estimation
- **Risk characterisation**

The **exposure assessment** consists of determining quantitatively or qualitatively the dose/concentrations of the substance to which humans and the environmental are or may be exposed. The assessment must consider all stages of the **lifecycle** of the substance resulting from the manufacture and identified uses. The exposure assessment includes two main steps : 1) Generation of exposure scenario(s), and 2) Exposure estimation.

On the basis of REACH regulation, an **exposure scenario** is a set of information describing the conditions under which the risks associated with the identified use(s) of a substance can be controlled. It includes operational conditions (for examples the duration and frequency of use or the amount used, the process temperature or the pH) and necessary risk management measures (e.g. local exhaust ventilation or a certain type of glove, waste water and gas treatment).

The description of the exposure scenarios have to be conducted following the structure described in ECHA's tool for Chemical Safety Assessment and Reporting, Chesar 2.0, as well as the guidance on exposure scenario development published by the European Chemicals Agency (ECHA).

The development of these exposure scenarios is a key point within NanoRISK to the extent that if **a manufacturer or importer fails to describe relevant and realistic measures that control risks for a substance in a certain use he can not cover this use in his exposure scenario**, and/or he has to explicitly advise against that use in the safety data sheet.

To support the creation of an exposure scenario according to REACH provisions, chapter D.2 of the ECHA guidance on information requirements and chemical safety assessment describes the core contents of an exposure scenario under REACH. It presents also an overview on the most common determinants of exposure and recommends a standard format for the final exposure scenario.

The exposure scenario format according with this guidance is depicted in the figure below:

1	Short title of the exposure scenario
2	Processes and activities covered by the exposure scenario
Operational Conditions of Use	
3.	Duration and frequency of use *Specify for workers, consumers, environment (where relevant)*
4.1	Physical form of substance or mixture; surface to volume ratio of articles *Gas, liquid, powder, granules, massive solids;* *Surface area per amount of article containing the substance (if applicable);*
4.2	Concentration of substance in mixture or article
4.3	Amount used per time or activity *Specify for workers, consumers, environment (where relevant)*
5	Other relevant operational conditions of use *For example* • *Temperature, pH, mechanical energy input;* • *capacity of receiving environment (e.g. water flow in sewage/river; room volume x ventilation rate);* • *wear and tear with regard to articles (if applicable); conditions related to service-life-time of articles (if applicable);*
Risk Management Measures	
6.1	Risk management measures related to human health (workers or consumers) *Type and effectiveness of single options or combination of options on exposure to be quantified [options to be phrased as instructive guidance]; specify for oral, inhalation and dermal route;*
6.2	Risk management measures related to the environment *Type and effectiveness of single options or combination of options to be quantified [options to be phrased as instructive guidance]; specify for waste water, waste gas, protection of soil;*
7	Waste management measures At the different life cycle stages of the substances (including mixtures or articles at the end of service life);
Information on estimated exposure and DU guidance	
8	Exposure estimation and reference to its source *Estimation of exposure resulting from the conditions described above (entries 3-7 and the substance properties; make reference to the exposure assessment tool applied; specify for routes of exposure; specify for workers, consumers; environment);*
9	Guidance to DU to evaluate whether he works inside the boundaries set by the ES *Guidance how the DU can evaluate whether he operates within the conditions set in the exposure scenario. This may be based on a set of variables (and a suitable algorithm) which together indicate control of risk, but which have some flexibility in the respective values for each variable. Note: This will mostly be specific conditions for a certain type of product; this section may also include a link to a suitable (e.g. easy-to-use) calculation tool.* *Where relevant: Other methods for DU to check whether he works within the boundaries set by the ES may be included here as well.*

Figure 4. Exposure scenario format according with ECHA

A clarification of the contents of the exposure scenario is provided below:

1. Title section

The title section describes which uses and activities with a substance are covered in the exposure scenario. This includes free-text elements and the standardised use descriptors. The following information elements can be included in the standard title section:

- Number of the ES;
- Title of exposure scenario (free text);
- List of all use descriptors related to the life cycle stage and all the uses under it;
- Name of contributing environmental scenario and corresponding Environmental Release categories (ERC);
- List of names of contributing worker/consumer scenarios and corresponding (process categories) PROC or PC/AC (product / articles categories);
- Further explanations (if needed);

2. Conditions of use for controlling risk

The determination of appropriate conditions of use to control risks, including **evaluation of their effectiveness**, is part of the Exposure scenario generation process.

Under the framework of REACH, **information on the mitigating effect of risk management measures is needed for assessing the associated exposure reduction**. Thus, the effectiveness of a measure needs to be expressed in a way that it can be fed into exposure quantification. Since the effectiveness of RMMs is often not a fixed value but a distribution depending on various factors, assumptions on the effectiveness of measures usually need documentation of evidence, which is a key point within NanoRISK project.

This part of the scenario is commonly split into two main section:

a) Conditions affecting environmental exposure

This section includes all operational conditions and risk management measures having been assessed by the registrant as affecting environmental exposure. This also includes municipal waste and waste water treatment, although downstream users do not have much influence on how municipal waste (water) operations are conducted.

The risk management measures controlling risks to the environment are sorted in order of hierarchy, from prevention at source to end-of-the-pipe measures. **For the risk management measures, information on the required/assumed effectiveness is to be reported** (if applicable and relevant).

b) Conditions affecting human health exposure

This section shall include all operational conditions and risk management measures that have been assessed as affecting workers/consumers exposure. These risk management measures controlling risks for workers are sorted in order of the hierarchy specified in the Chemicals Agent Directive.

Each condition of use (OC/RMM) addressed in the Exposure Scenario may be described by a number of information elements. In ECHA's Chemicals Safety Assessment and Reporting Tool Chesar, the following information elements can be reported with regard to one relevant condition of use.

- Name of the condition or measure (e.g. local exhaust ventilation);
- Exposure route and type of effect on which the determinant has an impact in the given case (e.g. short term and long term inhalation, local and systemic effects);
- Value of determinant and effectiveness (e.g. "LEV with hood"; effectiveness 95 % against situation without LEV);
- Further general explanation on the determinant value (e.g. 95 % effectiveness can be achieved with proper installation and regular maintenance by trained personnel);
- Further explanation for the specific CSR (e.g. the LEV is used to minimise residual releases from a rigorously contained process, and thus is part of strictly controlled conditions)

An example of the description of the conditions of use to be conducted in Chesar 2.0 can be observed in the following figures:

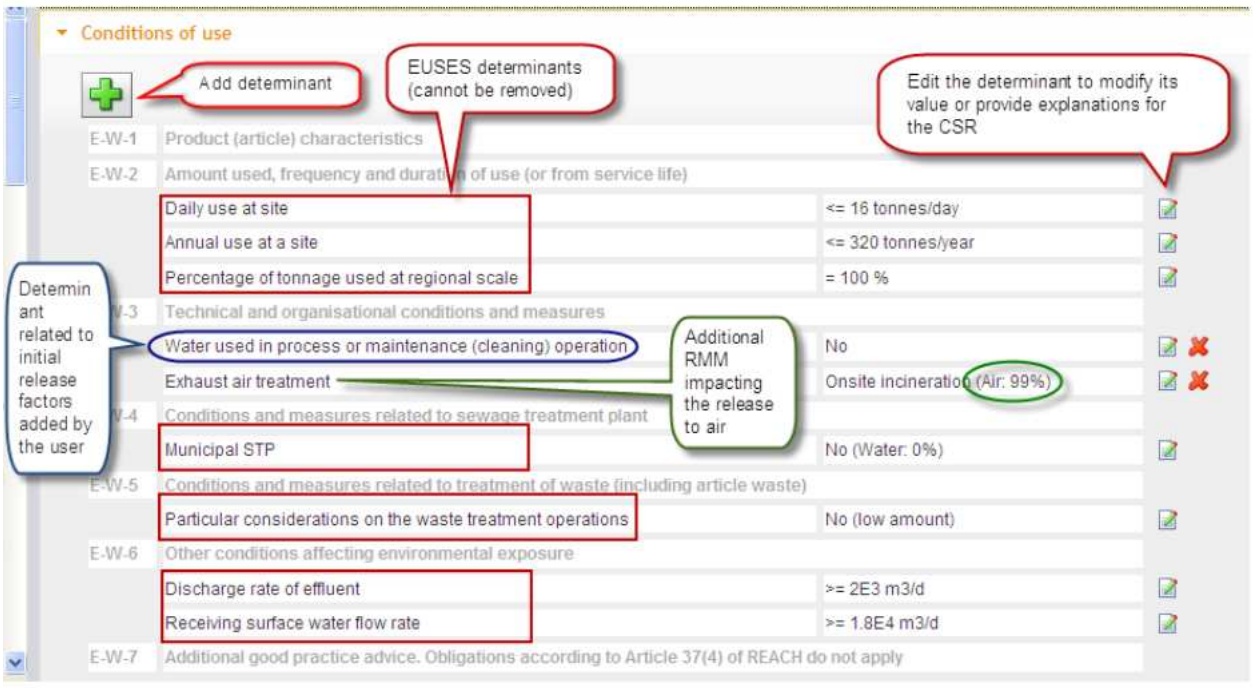
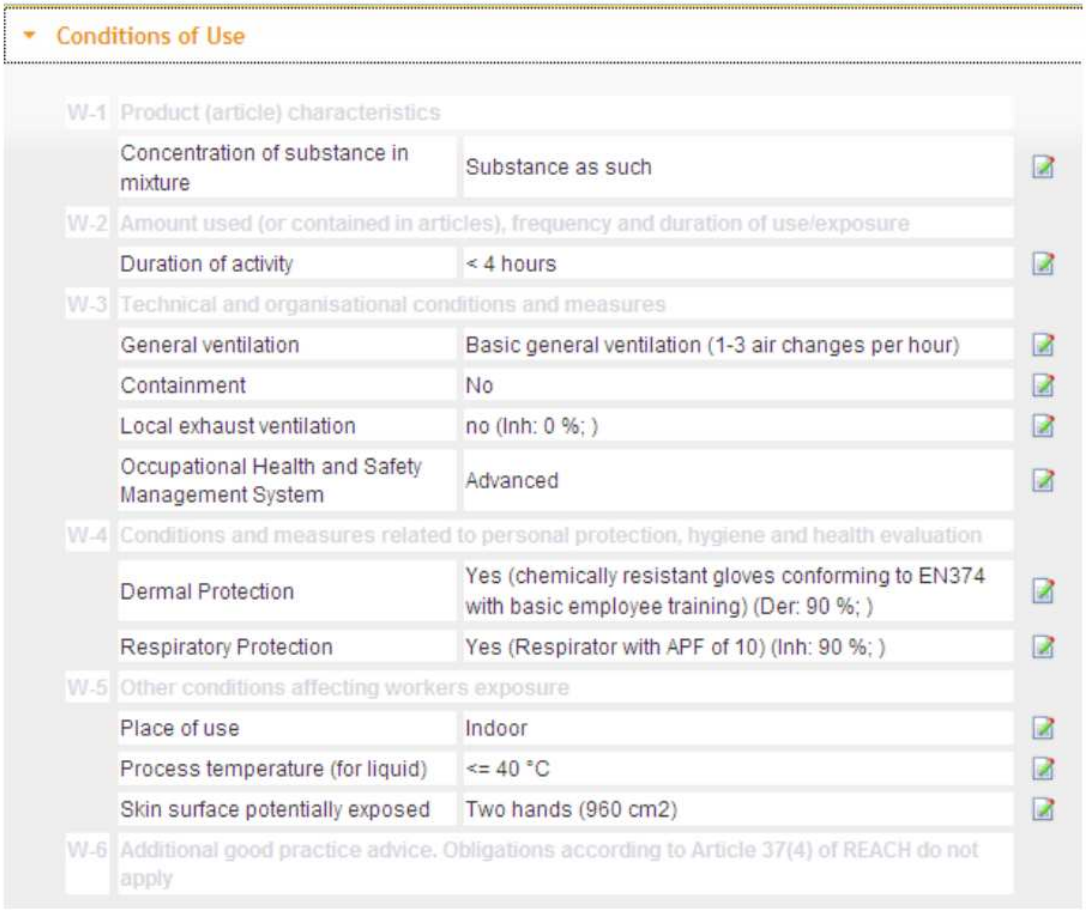


Figure 5a. Example of conditions of use to be reported in Chesar (Environmental Assessment)



Conditions of Use

W-1	Product (article) characteristics	
	Concentration of substance in mixture	Substance as such
W-2	Amount used (or contained in articles), frequency and duration of use/exposure	
	Duration of activity	< 4 hours
W-3	Technical and organisational conditions and measures	
	General ventilation	Basic general ventilation (1-3 air changes per hour)
	Containment	No
	Local exhaust ventilation	no (Inh: 0 %;)
	Occupational Health and Safety Management System	Advanced
W-4	Conditions and measures related to personal protection, hygiene and health evaluation	
	Dermal Protection	Yes (chemically resistant gloves conforming to EN374 with basic employee training) (Der: 90 %;)
	Respiratory Protection	Yes (Respirator with APF of 10) (Inh: 90 %;)
W-5	Other conditions affecting workers exposure	
	Place of use	Indoor
	Process temperature (for liquid)	<= 40 °C
	Skin surface potentially exposed	Two hands (960 cm2)
W-6	Additional good practice advice. Obligations according to Article 37(4) of REACH do not apply	

Figure 5b. Example of conditions of use to be reported in Chesar (Worker Assessment)

3. Information on exposure estimation

This section shall include information of the **exposure resulting from the conditions described in previous sections** of the exposure scenario. The type of information to be reported can include both measured and calculated data, this last considering the use of exposure estimation models that could be used to estimate exposures for the specific purpose of developing an Exposure Scenarios.

For estimation of exposure, the following preferential hierarchy should be applied to exposure data for estimation of exposure levels:

- measured data, including the quantification of key exposure determinants;
- appropriate analogous data, including the quantification of key exposure determinants;
- modelled estimates.

Exposure estimations should be developed by collecting all necessary information (including that obtained from analogous situations or from models); evaluating the information (in terms of its quality, reliability etc.), thus enabling sound estimates of exposure to be derived.

The **risk characterisation** is the final step in the exposure scenario development, where it should be determined whether risks arising from manufacture/import and uses of the substance are controlled. It must be carried out for each exposure scenario for both the human health and the environment.

Risks are regarded as controlled under REACH when **the exposure levels to the substance are below the threshold levels considered as safe**, both for humans and for the environment. For effects with no threshold levels, emissions and exposures have to be minimised or avoided for risks to be considered to be controlled.

The registrant must compare the no effect levels (DNELs) and the predicted no effect concentrations (PNECs) with the calculated exposure concentrations to human and the environment respectively.

4. Advice

A section to communicate particular advice on how to establish whether a downstream user works within the conditions of use set in the exposure scenario is also include. Such advice may be in particular relevant when the measures and conditions contributing to control of risk can be combined in various ways within one exposure scenario.

8. Key Findings

Originally, nanotechnologies and nanomaterials were not included in the scope of the Regulation (EC) No. 1907/2006 REACH. However, there are on-going discussions within the REACH competent authorities and its subgroup on nanomaterials on how REACH applies to nanomaterials. In this regard, It has been agreed that the definition of 'substance' within the regulations is sufficiently broad to encompass NMs (CEC, 2008), and de facto **all REACH provisions apply**.

As key statement, on the basis of the current information launched by the commission, Nanomaterials are regulated by REACH because they are covered by the definition of a chemical "substance" in REACH. The general obligations in REACH therefore apply as for any other substance and there are no provisions referring explicitly to nanomaterials.

In the light of current knowledge and opinions of the EU Scientific and Advisory Committees and independent risk assessors, **nanomaterials are similar to normal chemicals/substances** in that some may be toxic and some may not. Possible risks are related to specific nanomaterials and specific uses. Therefore, **nanomaterials require a risk assessment**, which **should be performed on a case-by-case basis, using pertinent information**. Current risk assessment methods are applicable, even if work on particular aspects of risk assessment is still required.

On the other hand, due to the knowledge GAPs on the properties of the rapidly emerging nanomaterials, it is not yet possible to identify any systematic rules for the toxicological characteristics of all nanomaterials (SCENIHR 2006 and 2007).

The SCENIHR opinion recognised that not all nanomaterials formulations have been found to induce adverse effects, suggesting that the hazard characterization should be carried out on a case by case basis.

On the other hand, an important subject that limits the application of REACH regulation is the adequacy of the current test guidelines to deliver results for hazard classifications of nanomaterials, where important issues in relation to the adequacy of the test guidelines remain unanswered.

Due to the importance of the nanotechnology to the global economy and the need of address the risk posed by the nanomaterials, ECHA has updated the guidance for nanomaterials on the basis of the final reports from REACH Implementation Projects on Nanomaterials (RIPoN2 Information requirements and RIPoN3 Chemicals safety assessment) and the Commission Recommendation on the definition of Nanomaterial .

In addition, ECHA, together with the Member States has also included some substances with nanoforms in the CORAP list of substances to be evaluated in 2012-2014. Furthermore, the Classification and Labelling Inventory and the web portal on Registered substances of ECHA also contain information on substances with nanoforms.

Regarding the last publications of the Commission regarding the implementation of REACH, the following points shall be noticed:

- The Commission concludes on the basis of the Communication of second Regulatory review on Nanomaterials that **REACH sets the best possible framework for the risk management of nanomaterials** when they occur as substances or mixtures but more specific requirements for nanomaterials within the framework have proven necessary.

- The **Commission** envisages modifications in some of the REACH Annexes and **encourages ECHA to further develop guidance for registrations after 2013**.

- The Commission will make an impact assessment of relevant regulatory options, in particular possible amendments of REACH Annexes, to ensure further clarity on **how nanomaterials are addressed and safety demonstrated in registration dossiers**. If appropriate the Commission will come forward with a draft implementing act by December 2013.

Regarding the **information** on the physicochemical, toxicological and ecotoxicological properties are **not sufficient to determine the specific properties of nanomaterials**, nor to assess how these properties affected their behavior and effects in humans and the environment.

The European REACH Implementation Projects on Nanomaterials (RiP-on) launched by the Commission in 2009 together with other European projects focused in that tasks and during 2012 and 2013 ECHA is introducing recommended modifications on registration dossier requirements to be adopted by nanomaterial's registrants, registering nanoforms of substances as well as nanomaterials as such. Therefore, a **set of minimum information requirements should be added when registering nanomaterilas under REACH**, independent of their volume of production and import. These requirements allow a risk assessment of nanomaterials.

In the near future it is expected the publication of the options to be considered for an adaptation of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation when dealing with nanomaterials.

At the time of writing, the results of the European NANO SUPPORT project states that **the total costs for implementing the potential changes in REACH to register nanomaterials range from €11 million to €73 million** as a cumulative effort for all concerned companies for a time period until 2022.

These costs result from extensive application of grouping and read-across approaches under REACH. Without this approach, the costs would multiply up to €100 million and €600 million. The report states: "The overall conclusion of this impact assessment shows that additional costs for companies lead to a reduced uncertainty about potentially adverse effects of nanomaterials to human health and the environment. These may lead to considerable benefits, especially if combined with appropriate risk reduction measures."

9. References

CITATIONS

1. (BfR) The Federal Institute for Risk Assessment N anomaterials and REACH. Background Paper on the Position of German Competent Authorities [Informe]. - 2012.
2. (BSI) British Standards Institution British Standards Institution, Vocabulary – Nanoparticles, PAS 71:2005 [Informe]. - 2005.
3. (OECD) Organisation for Economic Co-operation and Development IMPORTANT ISSUES ON RISK ASSESSMENT OF MANUFACTURED NANOMATERIALS. Series on the Safety of Manufactured Nanomaterials No.33 (ENV/JM/MONO(2012)8) [Informe].
4. (SCCS) Scientific Committee on Consumer Safety Guidance on the Safety Assessment of Nanomaterials in Cosmetics.SCCS/1484/12 [Informe]. - 2012.
5. Agency The Danish Environmental Protection Information Requirements for nanomaterials - IRNANO [Informe]. - 2013.
6. Aitken RA Bassan A, Friedrichs S, Hankin SM, Hansen SF, Holmqvist J, Peters SAK, Poland CA, Tran CL Specific Advice on Exposure Assessment and Hazard/Risk Characterisation forNanomaterials under REACH (RIP-oN 3) – Final Project Report, RNC/RIP-oN3/FPR/1/FINAL [Informe]. - 2011.
7. Bian S.-W., Mudunkotuwa, I. A., Rupasinghe, T. & Grassian, V. H. Aggregation and dissolution of 4 nm ZnO nanoparticles in aqueous environments: Influence of pH, ionic strength, size, and adsorption of humic acid [Publicación periódica] // Langmuir 27, 6059–6068 . - 2011.
8. Bickley R. I. Heterogeneous photocatalysis at liquid–solid interfaces. Oxidative dehydrogenation of propan-2-ol as a method of assessing photocatalytic activity? [Publicación periódica] // Journal of Photochemistry and Photobiology A: Chemistry 216, 256–260 . - 2010.
9. Commission European Commission Recommendation of 18 October 2011 on the definition of nanomaterial (2011/696/EU), OJ L 275/38, 20.10.2011 [Informe]. - 2011.
10. Commission European Commissione staff working paper. Types and uses of nanomaterials, including safety aspects [Publicación periódica]. - 2012.
11. Commission European Second Regulatory Review on Nanomaterials [Publicación periódica]. - 2012.
12. Communities Commission of the European Communication from the Commission to the European Parliament, the council and european economic and social committee regulatory aspects of nanomaterials: Regulatory Aspects of Nanomaterials [Publicación periódica]. - 2008.
13. Daniel M.-C. & Astruc, D. Gold Nanoparticles: Assembly, Supramolecular Chemistry, Quantum-Size-Related Properties, and Applications Toward Biology, Catalysis, and Nanotechnology [Publicación periódica] // Chemical Reviews 104, 293–346. - 2004.

14. ECHA Best practices guide on physicochemical and substance identity information for nanomaterials [Publicación periódica]. - 2012.
15. ECHA Guidance for identification and naming of substances under REACH [Publicación periódica]. - 2007.
16. ECHA Guidance on registration [Publicación periódica]. - 2012.
17. ECHA IUCLID 5 Guidance and support. Nanomaterials in IUCLID 5 [Publicación periódica]. - 2013.
18. European Commission, Community Health and Consumer Protection Nanotechnlogies: A preliminary ris analysis on the basis of a workshop organized in Brussels on 1-2 March 2004 by the Health and Consumer Protection Directorat general of the European Commission [Publicación periódica]. - 2004.
19. Goldstein A. N., Echer, C. M. & Alivisatos, A. P. Melting in semiconductor nanocrystals. Science 256, 1425–1427 [Publicación periódica]. - 1992.
20. Guidance for identification and naming of substances under REACH and CLP. Version 1.2 [Publicación periódica]. - 2012.
21. Hankin SM Peters SAK, Poland CA, Foss Hansen S, Holmqvist J, Ross BL, Varet J, Aitken RJ Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH (RIP-oN2) – Final Project Report, RNC/RIP-oN2/FPR/1/FINAL [Informe]. - 2011.
22. JRC EACH Implementation Project Substance Identification of Nanomaterials (RIP-oN 1) - Advisory Report [Informe]. - 2009.
23. OCDE Guidance Manual For The Testing Of Manufactured Nanomaterials: OECD Sponsorship Programme (ENV/JM/MONO(2009)20/REV) [Publicación periódica]. - 2010.
24. Schmid O., Karg, E., Hagen, D. E., Whitefield, P. D. & Ferron, G. A. On the effective density of non-spherical particles as derived from combined measurements of aerodynamic and mobility equivalent size [Publicación periódica] // Journal of Aerosol Science 38, 431–443 . - 2007.
25. SG4 OECD WPMN Working Objectives for 2012: NM in TG412, TG413 [Informe]. - 2012.
26. Tantra R. ., Cackett, A. ., Peck, R. ., Gohil, D. . & Snowden, J. Measurement of redox potential in nanoecotoxicological investigations [Publicación periódica] // Journal of Toxicology . - 2012.

LIST OF FIGURES

LIST OF TABLES

NanoRISK is partly funded by the European Commission Life+ with grant agreement LIFE12 ENV/ES/178