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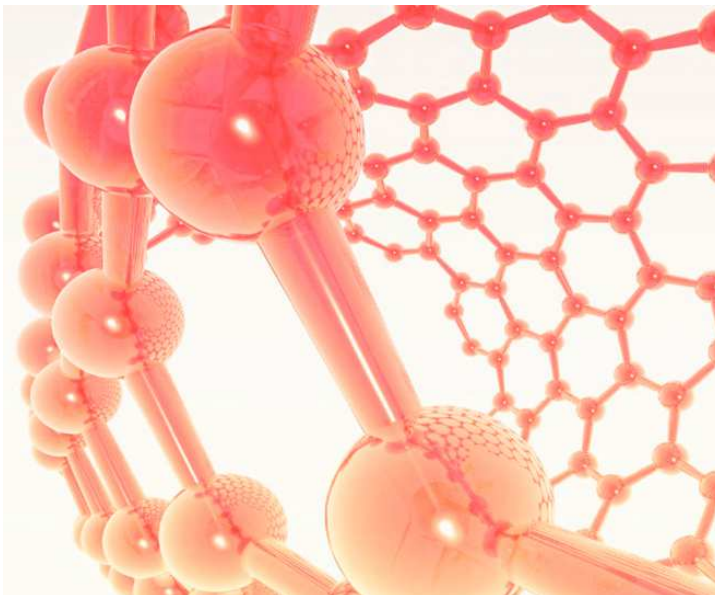
LIFE REACHnano

Development of a web based REACH Toolkit to support the chemical safety assessment of nanomaterials

Guidance on reliable information sources for the characterization of properties of ENMs under REACHsicochemical, toxicological and



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Guidance on reliable information sources for the characterization of the physicochemical, toxicological and ecotoxicological properties of nanomaterials.

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1. Introduction and vision

The Regulation (EC) 1907/2006, mainly known as REACH, concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals, entered into force on 1st June 2007. REACH does not allow placing on the market substances on their own or in mixtures in quantities equal or superior to 1 tonne per year if they have not been registered by every legal entity that manufactures or imports outside the European Union. REACH will be gradually implemented in the European Economic Area[1] through a phased approach with a timeline that extends until June 2018.

The aim of REACH is to ensure a high level of protection of human health and the environment from the risks that can be posed by chemicals as well as promote alternative methods for the assessment of the hazards of substances and ensure the free movement of registered substances along the EEA[2] while enhancing the competitiveness of the EU chemicals industry.

Moreover, REACH and CLP place greater responsibility on industry to manage the risks that chemicals may pose to the health and the environment, as well as to provide sufficient information on the safety of products that would be communicated through the supply chain. Manufacturers and importers will be required to identify and manage risks linked to the substances they manufacture and/or import in quantities of 1 tonne or more per year. To ensure that they actually meet these obligations, registration process should require them to submit a dossier jointly containing this information to ECHA[3]. In addition, communication of technical advice to support risk management should be encouraged throughout the supply chain to downstream users or distributors to meet their responsibility in relation to the management of risks arising from the identified uses of substances. They have to demonstrate to ECHA how the substance can be safely used and they must communicate the risk management measures to the users. The provisions of REACH refer to substances, in whatever size or forms, and also apply to nanomaterials, that are considered either as distinct substances or forms of a substance. However, a degree of uncertainty exists concerning the adequacy of REACH regarding nanomaterials and consequently this is one of the key challenges in relation to adapting REACH to address the properties of nanomaterials. Moreover, there is significant knowledge gaps regarding the properties of nanomaterials due to many of the OECD Test Guidelines are applicable but with conditions, in some cases, and some are not suitable since according to the OECD (2009) review measuring, dosing, delivery and tracking are not reliably accomplished at this stage. Moreover, this revision also considers some other relevant end-points specifically applicable to manufactured nanomaterials. To this end, all available information on physicochemical, toxicological and ecotoxicological properties of nanomaterials has to be gathered, evaluated and selected to be afterwards provided upon registration of substances at nanoscale.

Hence, in the coming years, a remarkable challenge for the nanotechnology industry, the academia and the regulators will be the generation of new data on physicochemical, toxicological and ecotoxicological profile of available ENMs.

[1] REACH applies in all 28 Member States of the European Union, as well as Iceland, Liechtenstein and Norway.
[2] European Economic Area
[3] ECHA: European Chemicals Agency sited in Helsinki.

2. Scope and objectives of the guidance

This guidance document is part of a series of guidance documents that are aimed at helping manufacturers and downstream users of ENMs to perform a complete risk assessment taking into account the requirements laid down on REACH regulation.

The development of the guidance was informed by research and technical activities undertaken as part of the REACHnano project, whose main purpose is to develop a web-based platform to support the chemical safety assessment (CSA) of nanomaterials according to the risk assessment procedures and information requirements laid down on REACH.

Overall, the guidance provided includes a thorough description of relevant information sources that should be taken in consideration for information gathering within the context of REACH, to assist registrants in general, and manufacturers and downstream users of ENMs in particular, meet the information requirements upon registration of nanomaterials by considering all types and sources of information and the reliability of such data for each endpoint. It is aimed at:

- Persons responsible for REACH compliance within companies producing and/or using ENMs;
- Experts from industry associations and other stakeholder organizations informing companies about the requirements for nanomaterials under REACH, especially for risk assessment purposes;
- Researchers from academia, non-profit research organizations and private research institutions.

This guidance contains:

- A brief description of the methodology used to identify relevant information sources and reliability of data;
- A list of identified information sources with indications of which ones are relevant.

To this end, a set of information sources including scientific literature, European projects, databases, and other relevant documents have been studied in order to establish priority sources of information for each of the endpoints and parameters for safety assessment and risk management of nanomaterials. According to figure 1, the methodology has been designed taking the following stepwise approach:

1. Compilation of information sources

Initially information sources to be employed in the data gathering process was compiled. During this first stage, several information sources containing information on physicochemical, toxicological and ecotoxicological properties of nanomaterials were studied. Once identified, the information was compiled into a word document including their specifity, access, scope, pros and limitations.

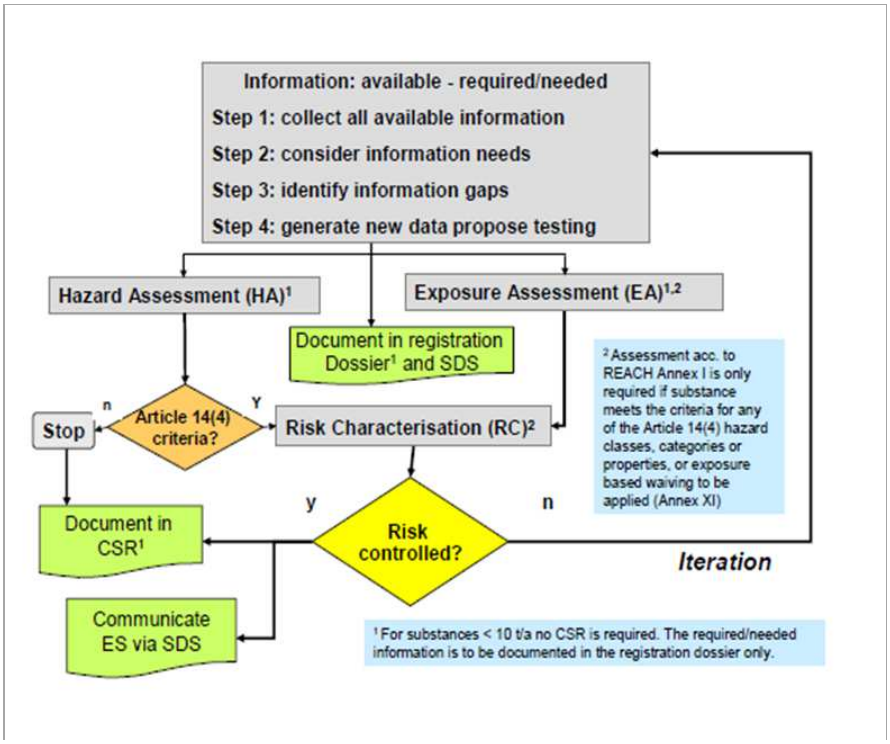

Figure 1. Overall framework of information generation under REACH (Source ECHA: Guidance on information requirements and Chemical Safety Assessment)

2. Evaluation and classification of information sources

Once identified, the sources of information were classified regarding the main areas addressed (identification/characterization and physicochemical properties, toxicological properties, environmental fate & behaviour and ecotoxicological properties), in order to identify the main sources of information for each of the information requirements needed for safety assessment and risk management of nanomaterials. To achieve such objective, each of the sources collected was characterized in terms of relevance for a specific endpoint and reliability of data. Once evaluated, the information sources were organized and classified in order to develop a matrix of information sources.

This guidance can be obtained via the website of the REACHnano project (http://www.lifereachnano.eu). Further guidance documents will be published on this website when they are finalized or updated.

Users are reminded that the information in this document does not constitute legal advice.

3. Methodology approach

The specific information requirements for REACH are detailed in Annexes VI-XI of REACH regulation, so that for each registration the precise information requirements will differ according to tonnage. Annex VII contains the standard requirements for the lowest tonnage level and if a new tonnage level is reached then the information requirements of the corresponding Annex have to be added.

According to REACH, the information gathering strategy has been designed taking the following stepwise approach:

3.1. STEP 1 - Consider information requirements

The first step is to identify all information requirements to perform the chemical safety assessment of nanomaterials in the context of REACH. The specific information requirements detailed in Annexes VI-XI of REACH were identified according to tonnage. The Annex XI allows variation from the standard approach as long as it can be justified. Moreover, recommendations on specific aspects of information requirements concerning materials in nano form (appendices to R7a[4], R7b[5] and R7c[6]) as well as recommendations from the second REACH Implementation Project on Nanomaterials (RIPoN2) addressing a number of domains including physicochemical properties, toxicological and ecotoxicological endpoints which

3.2. STEP 2 – Gather information sources

The second step is to identify and review all relevant information sources in order to establish priority sources of information for each of the endpoints and parameters needed for safety assessment and risk management of nanomaterials.

All existing available information sources containing test data on nanomaterials were gathered regardless whether testing for a given endpoint is required or not at the specific tonnage level. Alternative sources offered by REACH that can replace the results of animal tests such as (Q)SARs[7], read-across, in vitro testing and epidemiological data were also included. All this information will determine whether the generation of further information is needed.

Information source types that are included in this search strategy comprise:

- ✓ **Databases of compiled data**: Databases contain information from original sources (published literature on a substance). It is recommended to supplement with bibliographic databases.
- ✓ **Published literature**: Include papers, review papers, books, monographs and reports. For studies not in the public domain there is the requirement to demonstrate legal title to the information in order to protect intellectual property rights of the data owner.
- ✓ **Internet**: Allow identification of electronic versions of a diverse range of data sources.

The overall assessment of these information sources forms the basis of the information strategy and the identification of the most relevant studies.

[4] Guidance on information requirements and chemical safety assessment. Appendix R7-1 Recommendations for nanomaterials applicable to Chapter R7a Endpoint specific guidance: http://echa.europa.eu/documents/10162/13632/appendix_r7a_nanomaterials_en.pdf

[5] Guidance on information requirements and chemical safety assessment. Appendix R7-1 Recommendations for nanomaterials applicable to Chapter R7b Endpoint specific guidance: http://echa.europa.eu/documents/10162/13632/appendix_r7b_nanomaterials_en.pdf

[6] Guidance on information requirements and chemical safety assessment. Appendix R7-2 Recommendations for nanomaterials applicable to Chapter R7c Endpoint specific guidance: http://echa.europa.eu/documents/10162/13632/appendix_r7c_nanomaterials_en.pdf

[7] ECHA develops and manages, in cooperation with the OECD, the QSAR Toolbox. It is a software application which supports companies to identify data which may be relevant for assessing the hazards of chemical.s

3.3. STEP 3 – Identify information

The specific information requirements needed for the nanomaterial will be compared with the information already available. In the present guidance, a scoring system has been proposed in order to all available data will be relevant and has sufficient quality to fulfil the requirements. If in this step is detected that there is an information gap, new data should be generated according annexes VII and VIII or testing strategies. According to REACH, new tests on vertebrates will be only conducted as a last option when all other data sources have been exhausted. In this case, registrants must give details on their plans for testing on animals to ECHA. The Agency and the Member States authorities need to agree on these so called testing proposals before any higher-tier test can be conducted, avoiding unnecessary animal testing. Moreover, ECHA informs the company and takes any scientifically valid information and studies into account in preparing its decision, sharing the available data and information on testing. For example, the eChemPortal[8] allow the registrants to verify whether information on animal tests is already available from other authorities. Furthermore, ECHA´s dissemination webpage give companies an insight into the information included in registration dossiers.

According to the first step, information requirements have been classified into the three next main areas needed for safety assessment: physicochemical, toxicological and ecotoxicological endpoints. For this purpose, a matrix of information sources to support the information gathering process for nanomaterials has been developed:

- ✓ one matrix for parameters in relation to **identification/characterisation and physicochemical properties**. REACH requires the submission of data on
    - *Name*
    - *Molecular and structural formulae*
    - *Chemical composition*
    - *Purity*
    - *Impurities*
    - *Additives*
    - *Spectral data / HPLC/description of analytical methods enabling reproduction*
    - *Crystal structure (not explicit standard Information requirements in REACH)*
    - *Explicit description of nanoform(s) covered in a dossier (not explicit standard Information requirements in REACH)*
    - *State of the substance*
    - *Melting / freezing point*
    - *Boiling point*
    - *Density*
    - *Particle concentration (not explicit standard Information requirements in REACH)*
    - *Vapour pressure*
        - o *Surface tension of aqueous solution*
        - o *Water solubility*
        - o *Water dissolution kinetics (not explicit standard Information requirements in REACH)*

[8] eChemPortal: The Global Portal to Information on Chemical Substances. More information available on line at: http://www.echemportal.org

- *Dispersion stability in water (not explicit standard Information requirements in REACH)*
- *Partition coefficient n-octanol/water*
- *Fat solubility / solubility in organic solvent (not explicit standard Information requirements in REACH)*
- *Flash point*
- *Flammability*
- *Explosive properties*
- *Self-ignition temperature*
- *Oxidising properties*
- *Granulometry/particle size distribution*
- *Agglomeration/aggregation (not explicit standard Information requirements in REACH)*
- *(Volumen or mass) Specific surface area (not explicit standard Information requirements in REACH)*
- *Morphology/shape/aspect ratio (not explicit standard Information requirements in REACH)*
- *Porosity (not explicit standard Information requirements in REACH)*
- *Surface modifications (surface chemistry/surface functionalisation/surface treatment, coating...) (not explicit standard Information requirements in REACH)*
- *Surface charge/ zeta potential (not standard information requirements in REACH)*
- *Surface structure (not standard information requirements in REACH)*
- *Surface acidity*
- *Surface reactivity (not standard information requirements in REACH)*
- *Surface energy (not standard information requirements in REACH)*
- *Other relevant characterisers (not standard information requirements in REACH)*
- *Stability in organic solvents*
- *Dissociation constant*
- *Viscosity*
- *Catalytic properties (not standard information requirements in REACH)*
- *Photocatalytic properties (not standard information requirements in REACH)*
- *Radical formation potential (not standard information requirements in REACH)*
- *Redox potential (not standard information requirements in REACH)*
- *Dustiness (not standard information requirements in REACH*)

✓ One matrix for information requirements for **toxicological properties**. REACH requires the submission of data on:

- *ADME Dermal absorption (further extended compared to information requirements in REACH)*
- *Acute toxicity (oral, dermal or inhalation)*
- *Skin irritation / corrosion, in vitro*
- *Skin irritation / corrosion, in vivo*
- *Eye irritation, in vitro*
- *Eye irritation, in vivo*
- *Skin sensitization*
- *Mutagenicity in vitro*
- *Mutagenicity in vivo*
- *In vitro toxicological mechanisms (e.g cytotox, oxidative stress, immunotox) (not standard information requirements in REACH)*
- *Photoinduced toxicity (not standard information requirements in REACH)*
- *Repeated dose toxicity 28 days (oral, dermal, inhalation)*

- *Repeated dose toxicity 90 days (oral, dermal, inhalation)*
- *Effects parameters for RDT (e.g cardiovascular, neurotoxic, immunotoxic and inflammatory effects) (not standard information requirements in REACH)*
- *Screening for reproductive /developmental toxicity*
- *Pre-natal developmental toxicity*
- *Two-generation reproductive toxicity study / extended one-generation study*
- *Chronic toxicity study / carcinogenicity*

✓ And finally one matrix for information requirements for **environmental fate & behaviour and ecotoxicological properties**. REACH requires the submission of data on:

- *Hydrolysis as a function of pH*
- *Adsorption/desorption screening*
- *Further information on adsorption /desorption*
- *Ready biodegradability*
- *Further degradation to be considered*
- *Degradation simulation testing (surface water, soil, sediment).ID of degradation products*
- *Further information on degradation*
- *Photodegradation (not standard information requirements in REACH)*
- *Bioaccumulation in aquatic species*
- *Further information on fate and behaviour*
- *Activated sludge respiration inhibition test*
- *Short-term toxicity test invertebrates (daphnia)*
- *Growth inhibition test aquatic plants (algae)*
- *Short-term toxicity fish*
- *Long-term toxicity test invertebrates (daphnia)*
- *Long-term toxicity test fish*
- *Short term toxicity of terrestrial organisms (invertebrates, micro-organisms, plants)*
- *Long term toxicity of terrestrial organisms (invertebrates, plants)*
- *Long term toxicity to sediment organisms*
- *Long term or reproductive toxicity to birds*
- *ADME studies on aquatic organisms (not standard information requirements in REACH)*
- *Population/ecosystem-level studies (not standard information requirements in REACH)*

All the information requirements for chemicals as given in Annexes VI to X of REACH are included in the matrix as well as further relevant information requirements specific for nanomaterials according to the step 1 of this guidance. Initially all information sources identified are provided in Appendix 1. Afterwards, this identified information sources are screened for information requirements according to the proposed matrix of information sources. Based on this approach, each of the information sources has been reviewed identifying “key relevant information sources”. The remaining “further information sources” may still be considered as they contain important background information. The scoring system proposed is based on the degree to which the information source covers a specific information requirement and therefore it will be characterized in terms of relevance of the source.

According to the results of the project IRNANO – Information Requirements for nanomaterials – by the Danish Environmental Protection Agency[9] the same following scores have been used:

+ "key relevant" or "possibly/potentially relevant" information source for a particular Information Requirement

++ Information source under discussion of relevance for a particular Information Requirement

Moreover, attention must be given to establishing the quality of data of such information sources as these sources vary in many aspects. When there is more than one study for each endpoint, the greatest weight is attached to the studies that are the most relevant and reliable. Consequently, a further screening for reliability has been proposed. For traditional chemicals the term "*reliability*" is defined by klimisch et al (1997) as follows (see also OECD, 2005a):

- **Reliability**: Evaluating the inherent quality of a test report or publication relating to preferably standardised methodology and the way the experimental procedure and results are described to give evidence of the clarity and plausibility of the findings. The klimisch codes allows ranking the information focusing on the most relevant ones:

  - **1 = Reliable without restrictions**: "studies or data [...] generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline [...] or in which all parameters described are closely related/comparable to a guideline method."
  - **2 = reliable with restrictions**: "studies or data [...] (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are nevertheless well documented and scientifically acceptable."
  - **3 = not reliable**: "studies or data [...] in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g. unphysiological pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment."
  - **4 = not assignable**: "studies or data [...] which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc.)."

However, currently this classification is not possible for nanomaterials due to there are not a common European approach to the regulatory testing of nanomaterials. Certain projects such as the EU 7th Framework Programme (FP7) NANOREG project, in which ITENE, NIA and LEITAT are also involved, aim towards refinement and establishment of new procedures for nanomaterial characterisation for REACH registration.

[9] Project IRNANO –Information requirements for nanomaterials by the Danish Environmental Protection Agency: http://www2.mst.dk/Udgiv/publications/2013/03/978-87-92903-51-8.pdf

For this reason, a second scoring system has been proposed in order to evaluate the reliability of data when there is more than one study for each endpoint. This second scoring system used for evaluating the data of the identified relevant information sources are based on:

- **I**: if existing OECD test guidelines used for "traditional chemicals" can be successfully applied to NMs
- **II**: If OECD Test Guidelines are applicable but with specific conditions for NMs. Test method development must be adapted and validated (consensus is needed).
- **III**: If OECD Test Guidelines are inadequate for testing Manufactured NMs.

Data that is not reliable may only be used as supporting data.

4. Relevant information sources

This guidance identifies relevant information sources that should be taken in consideration for information gathering within the context of REACH. A list of 19 relevant information sources has been identified in Appendix 1. An initial list was compiled based on scientific literature, European projects, databases and other relevant documents in order to establish priority sources of information for each of the endpoints and parameters for safety assessment and risk management of nanomaterials.

The identification of relevant information sources is based on the proposed scoring system which includes assessment of relevance and reliability of data. From the filled out matrices using the scoring system it can be seen which of these information sources are relevant for the specific information requirement for nanomaterials (scoring **+**) and also to which extent this must be discussed (scoring **++)**.

The detailed outcomes are presented in Appendix 1 and 2.

As a conclusion, it can be stressed that there are significant knowledge gaps with regard to the effective regulation of nanomaterials due to existing methodology test guidelines are not suitable for testing nanomaterials.

5. Best practices recommendations

Summary of some best practices on what type of data should be reported in a registration dossier registering nanoforms in the context of REACH, are reported below. These are by no means exhaustive and should be considered in the context of the further information outlined in compendium of guidelines developed in the framework of the LIFE REACHnano project.

According to the outcomes of REACHNANO project and the current EU legislative framework, the following general actions are recommended:

- **Data related to identification/characterization and physicochemical properties:**

- When the scope of the registered substance involves both nanoforms and bulk forms, it is recommended to provide an updated dossier as soon as possible according to Article 22 of REACH, even if the fraction of nanoforms is below this threshold and only the total tonnage band (for bulk and nanoforms) is > 1000 t/y.

- The absence of a mandated standardized method to determine particle size and distribution need not be considered as a deficiency. ECHA accepts data generated by non-standard methods, provided the conditions of Annex XI are met. For this reason, the absence of standardized methods is not considered as a deficiency. Specifically for physicochemical data, Annex XI 1.1.1 allows registrants to use data generated using non-GLP methods or other test methods than those referred in Article 13 (3) , as long as the information provided is adequate.
- It is stressed that the use of several analytical techniques for characterizing nanoforms (multi-method approach) is favoured due to with current knowledge and the limitations of current analytical techniques, there is no single method that can provide sufficient information on all the physicochemical parameters necessary to characterize nanoforms.

▪ **Data related to information requirements for (eco)toxicological properties:**

- In order to make data useful for regulatory purposes, it is essential that unambiguous information on the physicochemical properties of the nanoform is reported in the studies. In the case of surface treated nanomaterials, coated and uncoated nanomaterials should have separate IUCLID endpoint study records for the different hazard endpoints due to surface modifications may affect the toxicokinetics of nanomaterials.
- In the case of using non-testing data, such as read-across, the basis for the grouping should be established using the similarity rules specified in Annex XI of REACH, and not only based on the chemical composition, in order to define what characteristics a nanoform should have in order to belong a category (Practical Guide 6, ECHA 2009).

The results obtained from in vitro methods can be relevant for hazard identification, however it is worth to note that this type of tests may need adaptation regarding the performance of appropriate sample preparation and adequate controls to check interferences in order to allow an adequate interpretation of this data. It is generally recommended that registrants provide a detailed description of the sample preparation for (eco)toxicological assays, even if it goes beyond the information required in the standard OECD guideline.

6. Appendix

6.1. Identification of information sources

	DATABASE	Access	SPECIFITY	FREE ACCESS	Scope	Pros	Limitations
A	**NHECD**	*http://nhecd.jrc.ec.europa.eu/*	Nanomaterials	Yes	Papers, letters, notes, reviews, books	-Database shows what kind of data is interesting from the health, safety and environmental point of view -Data extracted in the database	Not completely actualized
B	**CEINT protocols**	*http://www.ceint.duke.edu/allprotocols*	Protocols nanomaterials	Yes	Protocols for testing nanomaterials	Research includes all aspects of nanomaterial transport, fate and exposure, as well as ecotoxicological impacts.	Limited at the moment
C	**Nanomaterial Registry**	*https://www.nanomaterialregistry.org/*	Nanomaterials	Yes	Nanomaterials characterization		Only physico-chemical characterization
D	**CaNanoLab**	*https://cananolab.nci.nih.gov/caNanoLab/home.jsp*	Nanobiomedicine	Yes	Protocols, material characterization and literature	Provides support for nanomaterials with characterizations resulting from physico-chemical, in vitro and in vivo assays.	
E	**NBI knowledgebase**	*http://nbi.oregonstate.edu/*	Nanomaterials	Yes	Nanomaterials and biological interaction	-Data extracted in the database	
F	**InterNano**	http://www.internano.org/component/option,com_process/Itemid,146/	Nanomaterials	Yes	Processes	-Data extracted in the database	-Very specific
G	**Google Scholar**	*http://scholar.google.com/*	General	Yes	Papers, letters, notes, reviews, books	If the pdf is freely accessible, it is shown	-Difficult to organize searches, usually organized by Google "relevance"-Everything included: no quality criteria

	DATABASE	Access	SPECIFITY	FREE ACCESS	Scope	Pros	Limitations
H	**PubMed**	*http://www.ncbi.nlm.nih.gov/pubmed/advanced*	General	Yes	Papers, letters, notes, reviews, books	Biomedical literature from MEDLINE, life science journals, and e-books.	
I	**Scopus**	*http://www.scopus.com/home.url;jsessionid=517693122EF8E9BF02C44F7DF2BE4559.kqQeWtawXauCyC8ghhRGJq*	General	No	Papers, letters, notes, reviews, books		
J	**SCIFinder**	*http://www.cas.org/products/scifinder*	General	No	Papers, letters, notes, reviews, books	Search by drawing (organic and organometalic molecules)	Centered in papers for chemists
K	**Web of Science (WoS)**	*http://wokinfo.com/*	General	No	Papers, letters, notes, reviews, books		-Only peer-reviewed journals -Missing papers from new journals
L	**Reaxys**	*https://www.reaxys.com/info/*	General	No	Papers, letters, notes, reviews, books	Search by drawing (organic and organometalic molecules)	Centered in papers for chemists
M	**Google Patents**	*https://www.google.com/?tbm=pts*	General	Yes	Patents: Only US at the moment		
N	**WIPO Patentscope**	*http://patentscope.wipo.int/search/en/search.jsf*	General	Yes	Patents: WO and LATIPAT, EPO, ARIPO and some countries		
O	**USPTO**	*http://www.uspto.gov/*	General	Yes	Patents: US		
P	**EPO**	*http://www.epo.org/searching.html*	General	Yes	Patents: Europe		
Q	**Espacenet**	*http://es.espacenet.com/?locale=en_LP*	General	Yes	Patents: Spain and Latin America		
R	**ECHA´s dissemination webpage**	*http://echa.europa.eu/information-on-chemicals/registered-substances*	General	Yes	Physical Chemical properties, environmental fate and behaviour, ecotoxicity and toxicity of chemicals	ECHA´s dissemination webpage give companies an insight into the information included in registration dossiers.	Information on chemical properties of registered substances is directly accessible via *eChemPortal*

	DATABASE	Access	SPECIFITY	FREE ACCESS	Scope	Pros	Limitations
S	**eChemPortal**	*http://www.echemportal.org*	General	Yes	Physical Chemical properties, environmental fate and behaviour, ecotoxicity and toxicity of chemicals	eChemPortal provides also exposure and use information on chemicals.	

6.2. Appendix 2 – Matrices in support of identified relevant information sources in relation to information requirements for nanomaterials

Matrix 1: **Substance identification, characterization and physicochemical properties**

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Name	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Molecular and structural formulae	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Chemical composition	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Purity	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Impurities	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Additives	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Spectral data /HPLC/ description of analytical methods enabling reproduction	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Crystal structure	Not explicitly required in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Explicit description of nanoform(s) covered in a dossier	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
State of the substance	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Melting/freezing point	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Boiling point	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
(Relative) density	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Particle concentration	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Vapour pressure	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Surface tension of aqueous sol.	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Water solubility	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Water dissolution kinetics	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Dispersion stability in water	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Partition coefficient n-octanol/water	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Fat solubility /solubility in organic solvent	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Flash point	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Flammability	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Explosive properties	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Self-ignition temperature	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Oxidising properties	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Granulometry / particle size distribution	>1tonne	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Agglomeration / aggregation	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Specific surface area	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Morphology /shape/aspect ratio	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Porosity	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Surface modifications (surface chemistry functionalisation / surface treatment, coating…)	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Surface Charge /Zeta potential	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Surface structure	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Surface acidity	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Surface reactivity	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Surface energy	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Other relevant characterisers	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Stability in organic solvents	>100 tonnes	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Dissociation constant	>100 tonnes	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Viscosity	>100 tonnes	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Catalytic properties	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Photocatalytic properties	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Radical formation potential	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Redox potential	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+
Dustiness	Not standard IR in REACH	+	++	+	+	+	++	++	++	+	+	+	+	++	++	++	++	++	+	+

Matrix 2: Toxicological properties

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
ADME Dermal absorption	Further extended compared to IR in REACH	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Acute toxicity -oral -dermal -inhalation	>10 tonnes	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Skin irritation/corrosion, in vitro	>1 tonne	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Skin irritation / corrosion, in vivo	>10 tonnes	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Eye irritation, in vitro	>1 tonne	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Eye irritation, in vivo	>10 tonnes	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Skin sensitization	>1 tonne	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Mutagenicity in vitro	>1 tonne	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Mutagenicity in vivo	May be triggered at all levels	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
In vitro toxicological mechanisms (cytotox, oxidative stress, immunotox)	Not standard IR in REACH	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Repeated dose toxicity 28D -oral / dermal -inhalation	>10 tonnes	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Repeated dose toxicity 90D -oral -dermal -inhalation	>100 tonnes	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Effects parameters for RDT e.g cardiovascular, neurotoxic, immunotoxic and inflammatory elffects	Not standard IR in REACH	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Screening for reproductive / developmental toxicity	>10 tonnes	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Pre-natal developmental toxicity	>100 tonnes	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Two-generation reproductive toxicity study / extended one-generation study	>1000 tonnes	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Chronic toxicity study / carcinocenicity	>1000 tonnes	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Photoinduced toxicity	Not standard IR in REACH	+	++	++	+	+	++	++	+	+	++	+	++	++	++	++	++	++	+	+

Matrix 3: **Environmental fate & behavior and ecotoxicity**

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Hydrolisis as a function of pH	>10 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Adsorption /desorption screening	>10 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Further information on adsorption /desorption	>100 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Ready biodegradability	>1 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Further degradation to be considered	>10 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Degradation simulation testing -surface water -oil -sediment ID of degradation products	>100 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Further information on degradation	>1000 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Photodegradation	Not standard IR in REACH	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Bioaccumulation in aquatic species	>100 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Further information on fate and behaviour	>1000 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Activated sludge respiration inhibition test	>10 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Short-term toxicity test invertebrates (daphnia)	>1 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Growth inhibition test aquatic plants (algae)	>1 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Short-term toxicity fish	>10 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Long-term toxicity test invertebrates (Daphnia)	>100 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Long-term toxicity test fish	>100 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Short term toxicity of terrestrial organisms: -invertebrates -micro-organisms -plants	>100 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Long term toxicity of terrestrial organisms: -invertebrates -plants	>1000 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+

REACH information requirements	Tonnage levels	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
Long-term toxicity to sediment organisms	>1000 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Long-term or reproductive toxicity to birds	>1000 tonnes	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
ADME studies on aquatic organisms	Not standard IR in REACH	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+
Population/ecosystem-level studies	Not standard IR in REACH	+	+	++	++	++	++	++	+	+	++	+	++	++	++	++	++	++	+	+

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