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NANoREG harmonised terminology for environmental health and safety assessment of nanomaterials

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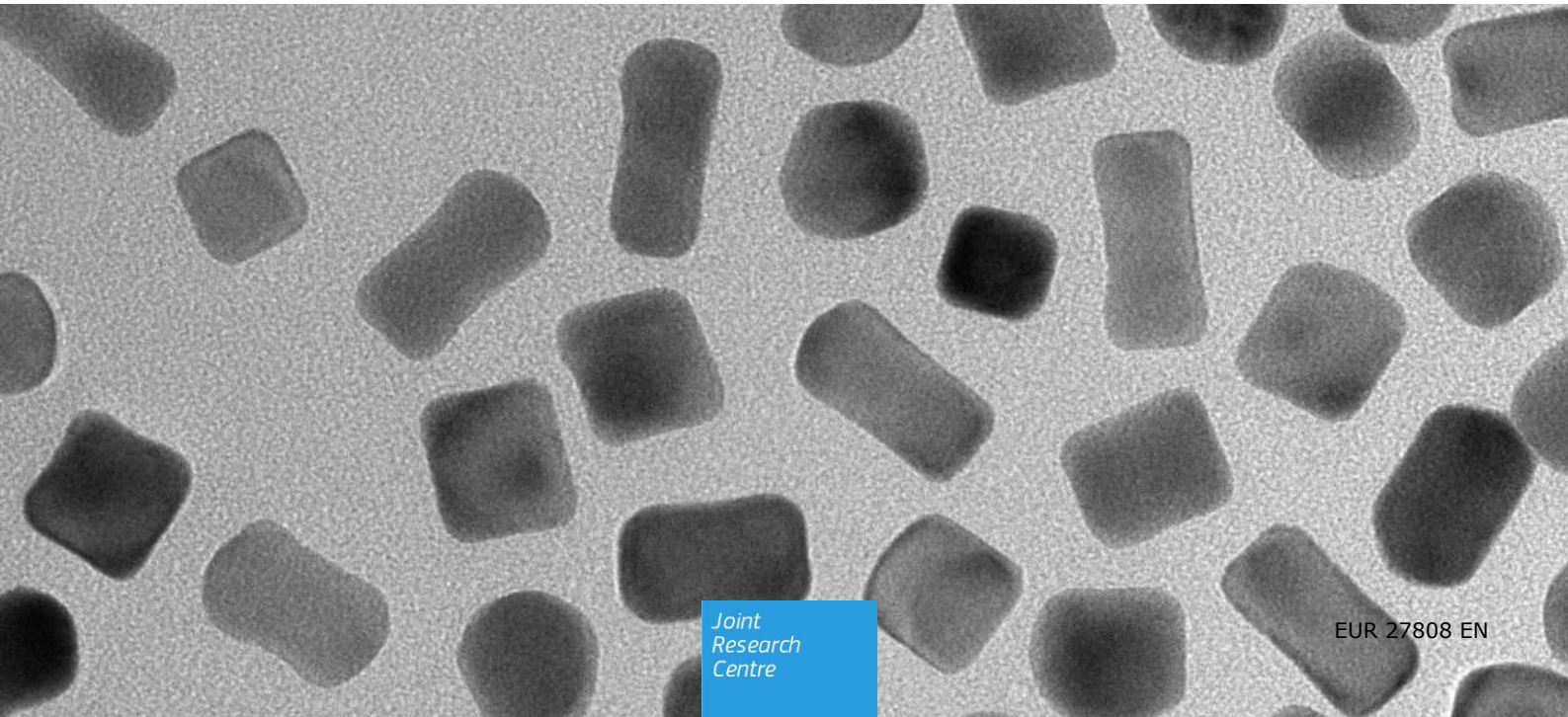

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Foreword

The present report has been developed within the NANoREG project: "A common European approach to the regulatory testing of nanomaterials", funded by the European Union's 7th Framework Programme, under grant agreement no. 310584 (http://cordis.europa.eu/project/rcn/107159_en.html, www.nanoreg.eu).

It represents the project attempt at bringing common understanding and consistency in the use of key terms important in the field of environmental health and safety (EHS) assessment of nanomaterials. It is at the same time a contribution to the on-going (global) debate on the meaning of some of those words in this field. The NANoREG partners, including JRC, believe in the usefulness of this terminology review for scientific experts and stakeholders, such as regulatory authorities, industry and consumers.

This report has been shared with the participants to the OECD Expert Meeting on 'Grouping and read-across for the hazard assessment of manufactured nanomaterials' hosted by the European Commission's Directorate-General for the Environment (DG ENV) and scientifically organised by JRC in Brussels on 13-14 April 2016.

The content of the report has been considered in the development of a scientific document on *Usage of (eco)toxicological data for bridging data gaps between and grouping of nanoforms of the same substance. Elements to consider*, jointly prepared by RIVM, ECHA and JRC. It is available for download from the ECHA website (https://echa.europa.eu/documents/10162/13630/eco_toxicological_for_bridging_grouping_nanoforms_en.pdf).

For a direct access to the 'NANoREG Harmonised Terminology', go to Section 3.

Acknowledgements

Contributions to intermediate versions of this document were received from several NANoREG partners, including:

- National Agency for New Technologies, Energy and Sustainable Economic Development (ENEA, Italy),
- ECAMRICERT, Italy (at that time VenetoNanotech, Italy),
- National Institute for Public Health and the Environment (RIVM, The Netherlands),
- Norwegian Institute for Air Research (NILU, Norway),
- Institute for Soldering and Quality (ISQ, Portugal),
- National Research Centre for the Working Environment (NRCWE, Denmark),
- Austrian Institute of Technology (AIT, Austria), and
- European Chemicals Agency (ECHA, Finland).

The final draft version of this terminology was reviewed by some project partners:

- BioNanoNet Research Society (BioNanoNet, Austria),
- ENVICAT Consulting (ENVICAT, Belgium),
- Karolinska Institute (KI, Sweden), and
- Foundation SINTEF (SINTEF, Norway).

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Abstract

Several terms in the field of environmental health and safety (EHS) assessment of chemicals and nanomaterials (hereinafter NMs) have been defined or used by the scientific community and different organisations, including international bodies, European authorities, and industry associations. This is also true for multidisciplinary projects such as NANoREG, which aims at supporting regulatory authorities and industry in dealing with EHS issues of manufactured NMs.

The objective of the present JRC technical report is to publish the harmonised terminology that has been developed and used within NANoREG. It has been agreed upon and adopted by all project partners in their activities and related documents. The report specifically includes: i) the methodology used to select key terms that form the harmonised terminology and to develop harmonised definitions; ii) the existing literature definitions that have been used as a starting point to develop for each key term a harmonised definition; and iii) the reason(s) behind the choices that have been made in drafting a definition. As far as possible, the harmonised definition is reproducing (an) already existing definition text(s), thus avoiding the creation of new and unwelcome information.

The discussion on the key terms to be considered for the harmonised terminology led to the selection of 43 key terms. The list includes terms with international regulatory relevance, such as those defined at OECD level, as well as terms that have a specific meaning and use under REACH.

The 'NANoREG Harmonised Terminology' has already proven very useful in the context of the OECD work, as support document to the April 2016 OECD Expert Meeting on 'Grouping and read-across for the hazard assessment of manufactured nanomaterials', and in a regulatory context, as support document to the work recently released by RIVM, ECHA and JRC on using (eco)toxicological data for bridging data gaps between nanoforms of the same substance (March 2016).

For quick access, the 'NANoREG Harmonised Terminology' is reported in Section 3.

1. Introduction

Consistent use of terminology is important in any field of science and technology to ensure common understanding of concepts and tools among experts and different stakeholders, such as regulatory authorities, industry and consumers.
Several terms in the field of environmental health and safety (EHS) assessment of nanomaterials (hereinafter NMs) have been indeed defined or used by the scientific community and various organisations, including international bodies, European authorities, and industry associations.

This is true for multidisciplinary projects such as NANoREG, which aims at supporting regulatory authorities, and industry, in dealing with EHS issues of manufactured NMs ('nanoEHS') (http://cordis.europa.eu/project/rcn/107159_en.html, www.nanoreg.eu).
Terminology thus plays an important role in NANoREG's internal process of producing diverse types of output with regulatory relevance (e.g. physicochemical characterisation and test protocols, grouping and read-across approaches, exposure models, a framework for safety assessment of NMs, etc.). The process takes place in a collaborative effort across several NANoREG work packages or tasks, involving quite a few partners. Moreover, the different types of NANoREG output ('deliverables') are addressed to a large audience of scientists, industry and regulatory bodies, extending beyond Europe. Hence, a coordinated initiative has been undertaken by the Joint Research Centre (JRC) to harmonise the use of specific wording within NANoREG.

The objective of this JRC report is to disseminate the harmonised terminology that has been developed and used within NANoREG. This collection of key terms has been agreed upon by all project partners and adopted in their activities and related documents, as recommended by the NANoREG internal Guidance Document.

Accordingly, Section 2 of the report illustrates the methodology used i) to select key terms that form the 'NANoREG Terminology', ii) to develop harmonised 'NANoREG Definitions', and iii) it also explains the thinking that led to the choices made in drafting a definition. In Section 3, those definitions, adopted by the project Consortium, are reported in a table format and constitute the 'NANoREG Harmonised Terminology'. Section 4 summarises the existing literature definitions that have been used as starting point to elaborate, for each key term, a NANoREG Definition. It also shortly discusses the reason(s) behind the choices that have been made in drafting a definition.

2. Methodology

The NANoREG Harmonised Terminology illustrated in this report is not a 'dictionary' that collects a long list of well-known, well-defined scientific and/or regulatory terms relevant to the field of nanoEHS. Rather, the NANoREG Harmonised Terminology focuses on a relatively short list of key terms that may be interpreted in various ways, depending on where the reader is located on the globe or on the reader's scientific area of expertise. Moreover, it focuses on few terms that are specifically relevant in a REACH context, which represents the regulatory framework of reference for NANoREG.

The first step was therefore to agree with all project partners on a relatively short list of key terms that are considered relevant to the nanoEHS field and, more specifically, to the various tasks performed within NANoREG (Section 3).

The second step was to retrieve from different types of information sources existing definitions for each of those key terms (Section 4). Highest priority was given to guidelines and standards from international organisations (e.g. OECD, ISO) and official documents from European bodies, including text from relevant legislation (e.g. REACH) and guidance/opinions from agencies and committees (e.g. ECHA, SCCS). Official documents from US and Canadian bodies were also considered to discern possible definition differences in comparing with the European perspective. Then, publicly available documents that are widely used and cited were consulted. This includes reports

from European national authorities, reports from industrial associations (e.g. ECETOC) and, with the lowest priority, peer-reviewed/non peer-reviewed scientific literature.

The relevant sources that have been accessed for each key term do not represent an exhaustive list. Due to time and resources constraints, the sources of existing definitions were not selected through an extensive literature search, but rather by using the available knowledge within NANoREG's Task 1.4 [1]. The Task 1.4 partners include scientists of varying expertise (e.g. physicochemical characterisation, ecotoxicity, exposure, regulatory risk assessment, safe-by-design, grouping and read-across, life cycle assessment and data management). This has guaranteed that the most relevant sources per key term could be reviewed in a relatively short time period (about 5 months). It is therefore recognised that some sources may have been neglected in the process. Nevertheless, this is seen as a minor gap, hence not influencing the overall elaboration of the harmonised definitions. The existing definitions that have been collected in this second step are reported as quotations of original text (Section 4).

The third step was to elaborate and reach consensus on a proposal of a harmonised NANoREG Definition for each key term (Section 3 and 4). A NANoREG Definition is, as often as possible, a copy-paste from an existing definition reported in a high-priority source with regulatory relevance and/or broad consensus at international level (e.g. OECD, ISO), thus avoiding the creation of new and unwelcome information. However, in some cases, it is a compromise between existing definitions from various relevant sources, for instance if the existing definitions are conflicting or complementary).

The whole 3-steps process was coordinated by JRC. The Task 1.4 partners were involved in each step. They were periodically informed on the progress of the document and asked to contribute at each step, from the selection of the key terms to the collection of the existing definitions, up to the discussion on how to formulate the harmonised NANoREG Definitions. In the last step of the process, the document was circulated among *all* NANoREG partners to reach the widest possible consensus within the Consortium.

In chronological order, JRC has gathered the existing definitions for a preliminary list of 43 key terms. It circulated a first draft version of the document among T1.4 partners on 24 June 2015. T1.4 partners were asked to provide input to the document and, more specifically, i) to indicate if there were key terms that needed to be added to or removed from the list and ii) if there were additional definitions that should have been studied.
An updated draft version of the terminology was circulated on 13 July 2015 for further comments by the T1.4 partners. JRC coordinated the collection of additional input, received from ENEA, ECAMRICERT (at that time VenetoNanotech, Italy), RIVM, NILU, ISQ, and NRCWE. JRC then drafted a proposal of a 'NANoREG Definition' for each key term in a third draft version of the terminology that was circulated in Task 1.4 on 31 August 2015. The partners were asked to comment in order to find consensus on the most suitable definition for each key term. JRC revised and consolidated the proposed definitions according to the received feedback (AIT, ENEA, and ECHA). The final draft version of the terminology, still *proposing* NANoREG Definitions, was sent to the NANoREG Project Officer on 29 September 2015 and, through him, to all project partners, with 23 October 2015 as deadline for comments. The document was reviewed by some partners (BIONANONET, ENVICAT, KI, and SINTEF) and the final version was released for 'internal to NANoREG use' by JRC on 30 October 2015.
On 11 November 2015 the NANoREG Management Committee adopted the 'NANoREG Harmonised Terminology' as new deliverable of the project. It agreed to its public dissemination in the form of a JRC Report, upon JRC's proposal. The expected date of publication of the report by JRC was March 2016.

[1] Task 1.4: 'Framework Development'

3. NANoREG Harmonised Terminology and Definitions

In Table 3.1, the 43 terms identified by the NANoREG partners as 'key' in the field of nanoEHS and relevant to the project tasks are listed in alphabetical order.

This list constitutes the 'NANoREG Harmonised Terminology'. For each key term, a harmonised definition, adopted by consensus within the whole Consortium is reported. This is the 'NANoREG Definition' of the term.

Table 3.1 NANoREG Harmonised Terminology and Definitions in the field of environmental health and safety assessment of nanomaterials with focus on the European REACH regulatory context.

KEY TERM	NANoREG DEFINITION
ADAPTATION	The term 'adaptation' is used in the context of REACH (EP and EC 2006; EC 2009) to indicate all types of deviation from the standard information requirements at the actual tonnage level to avoid unnecessary animal testing. Adaptation types mostly include testing omission, triggering, and replacement (ECHA 2011a). The rules for adaptation are laid down in Annex XI to REACH (EC 2009) and include: 1) testing does not appear scientifically necessary and is substituted by use of existing data, weight of evidence, QSARs, in vitro methods, grouping and/or read-across; 2) testing is technically not possible as a consequence of the properties of the substance; 3) substance-tailored exposure-driven testing (see 'Adaptation based on exposure'). More specifically, the term 'omission' or 'waiving' is used when testing can be avoided and no other information needs to be supplied (e.g. when there is no significant exposure to the substance in any scenario). The term 'replacement' is used when alternative test methods rather than animal testing may be used for fulfilling the information requirements (e.g. read-across if one or more analogues exist, in vitro studies). The term 'triggering' is used when additional animal testing is needed to investigate further the effects on humans or the environment.
ADAPTATION BASED ON EXPOSURE	The term 'adaptation based on exposure' is used in the context of REACH (EP and EC 2006; EC 2009) to indicate a deviation from the standard information requirements at the actual tonnage level based on exposure arguments (ECHA 2011a). According to REACH Annex XI (EC 2009) and ECHA guidance (ECHA 2011a), exposure based adaptations may be appropriate under the following conditions: – Exposure is absent (i.e. exposure is excluded) or not significant throughout the whole life cycle of the substance for manufacture and all identified uses; or – When strictly controlled conditions apply throughout the life cycle of the substance for manufacture and all identified uses; and – No releases from the article life cycle stage (and subsequent waste life stage) are to be expected and consequently there is a negligible likelihood of exposure (this situation only applies to substances incorporated into articles). The same principles apply to nanomaterials as long as the 'no release' or 'no leaching out' during the life cycle statement is supported by analytical/experimental data and documentation (ECHA 2012a; 2014a).
ADVERSE OUTCOME PATHWAY (AOP)	OECD defines an Adverse Outcome Pathway (AOP) as a linear sequence of key events (or pathway) from the exposure of an individual or population to a chemical substance through to a final adverse (toxic) effect (or adverse outcome) at the individual level (for human health) or population level (for ecotoxicological endpoints) (OECD 2013a). An AOP can therefore be seen as a conceptual way to assemble the existing knowledge on the link between a molecular initiating event caused by a chemical reaching an initial key target and a series of subsequent processes that are triggered at the subcellular, cellular, tissue, organ, whole animal, and population level, which result in an adverse effect (OECD 2013a). The key events/processes in an AOP should be definable and make sense from a physiological and biochemical point of view (OECD 2013a). An AOP should be built upon all documented, plausible and testable existing knowledge (OECD 2014a).

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
	Different pathways can result in the same adverse outcome, and each constitutes an individual AOP (OECD 2014a). Although initially developed for use in ecotoxicology (Ankley et al 2010), the AOP concept is also applicable to human health effects (Schultz 2010).
ALTERNATIVE TEST METHOD	OECD defines an 'alternative test method' as a test that reduces the number of animals required; refines procedures to lessen or eliminate pain or distress to animals, or enhance animal well-being; or fully replaces animals with non-animal systems or with non-sentient species (OECD 2005). This definition follows the principle of the 3Rs, i.e. to Replace, Reduce and Refine the use of animals in (eco)toxicity testing. In the EU, the development and validation of alternative approaches to animal testing is explicitly encouraged in Directive 2010/63/EU (EP and EC 2010) and REACH (EP and EC 2006). In Directive 2010/63/EU it is also specified that alternative test methods should provide the same or higher levels of information as those obtained in procedures using animals (EP and EC 2010). Alternative test methods are typically based on either in vitro systems or computer-based models. In vitro systems are experimental methods that use (reconstructed) tissues, whole cells or parts of cells. Computer-based models (often termed 'in silico' or 'non-testing methods') refer to any non-experimental methods that can be used to predict data for the assessment of chemicals based on their intrinsic properties. The development and application of these approaches is based on the similarity principle, i.e. the hypothesis that similar compounds should have similar biological activities (ECHA 2008a). According to OECD (2014a) and ECHA (2008a), non-testing data can be generated by three main approaches: – Grouping and read-across; – Trend analysis and use of computational methods based on internal models; – Use of computational models based on external models. In more general terms, non-testing methods can be divided into comprehensive (global) methods (also called 'expert systems') and specific (local) ones (including (Q)SARs) (ECHA 2008a; Raunio 2011).
ANALOGUE(S)	OECD considers two techniques for grouping of chemicals: the formation of a 'chemical category' (referred to as 'category approach') and the identification of 'analogues' (referred to as 'analogue approach') (OECD 2014a). More specifically, OECD defines an 'analogue' as a chemical whose intrinsic physicochemical, environmental or toxicological properties are likely to be similar to those of another chemical based upon a number of potential properties including structural and physicochemical properties (OECD 2014a). The term 'analogue approach' is used when the grouping involves a very limited number of chemicals and trends or regular patterns in properties are not apparent. In this case, the focus of the assessment is on filling data gaps for one or few more individual chemical(s) using data from one or few more similar individual chemical(s) that are considered as analogues. The OECD terminology is reflected in ECHA guidance for the implementation of REACH (ECHA 2008a) and in guidance by industry (ECETOC 2012). As far as nanomaterials are concerned, OECD states that it is premature to develop guidance on grouping for nanomaterials, as research first needs to pave the way for it (OECD 2014a), and has not developed any recommendation on how the grouping concepts and approaches previously developed for chemicals need to be adapted to take MNs' specificities into account. At European level, ECHA has not yet developed official guidance on how to implement grouping concepts and approaches for nanomaterials in the context of REACH. Until now, the existing guidance (ECHA 2008a) has been considered in principle applicable to nanomaterials. The use of data between analogues in registration dossiers is supported for nanomaterials and should be performed in line with the similarity rules in Annex XI to REACH (ECHA 2013a).

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
	In the US, no specific recommendation has been developed for nanomaterials. However, given that for many nanomaterials the available information is insufficient, US EPA has made use of analogues from existing chemical categories to assess the potential hazard of some nanomaterials, e.g. carbon nanotubes (US EPA 2014a). Despite the lack of official guidance at international and European level, experts seem to agree that identifying analogues for nanomaterials introduces additional challenges, compared to traditional chemicals: similarity cannot be based on structural or chemical composition only, but needs to consider a wider spectrum of physicochemical properties determining identity and behaviour of nanomaterials, including e.g. impurities, surface treatment, surface area, surface charge and shape (RIVM 2015; OECD 2014b; ECHA 2013b). Moreover, some researchers underline that physicochemical properties are not sufficient for categorization of nanomaterials, and that indicators of both hazard and exposure potential need to be included (Godwin et al 2015). Arts and colleagues suggest that all aspects of the nanomaterials life cycle need to be considered in a grouping approach, i.e. physicochemical properties, biophysical interactions, intended use, external exposure, uptake and internal exposure, biokinetics and early biological and apical effects (Arts et al 2014).
ASSESSMENT FACTOR (AF)	International organisations, such as IPSC and OECD, define an 'assessment actor' as a numerical adjustment used to extrapolate from experimentally determined (dose-response) relationships to estimate the agent exposure below which an adverse effect unlikely to occur (IPSC 2004; OECD 2003). In the REACH context (EP and EC 2006), the exposure level to a substance below which an adverse effect unlikely to occur is called Derived No Effect Level (DNEL) for human health and Predicted No Effect Level (PNEC) for the environment (ECHA 2008b; 2012b). The biological starting points to derive these levels are the dose descriptors obtained from long-term or short-term animal experiments (e.g. NOEC, EC10, BMD, EC50). To account for the uncertainty and variability associated with extrapolation from individual test animals to human population or whole ecosystems, a set of assessment factors is applied to the initial dose descriptors. In establishing the size of the assessment factors to be applied a number of aspects need to be considered. Both ECHA (2012b) and US EPA (2002) identify the following sources of uncertainty and variability: – Interspecies differences; – Intraspecies differences; – Differences in duration of exposure; – Issues related to dose-response; – Quality of the whole database. Preferably, the value for each individual assessment factor is based on substance-specific information, i.e. a 'substance-specific assessment factor' is derived. However, 'default assessment factors', usually 10-fold, need most often to be used to compensate for lack of data (e.g. human data) and information (e.g. on toxicodynamics) (ECHA 2012b).
CATEGORISATION	The term 'categorisation' is used in the scientific literature to indicate the organisation of nanomaterials into 'groups' or 'categories' based on criteria that could either consider their structural and physicochemical similarities (e.g. Godwin et al 2015) or their similarities in terms of exposure route, physicochemical properties and/or mode of action (e.g. Gebel et al 2014). In both cases, the term 'categorisation' seems to resemble the concept of 'grouping' and 'chemical category', which are terms well-defined at OECD level, and in both US and EU legislation on chemicals. In the Canadian legislation on chemicals, the term 'categorisation' refers to the identification of substances that i) may present the greatest potential for human exposure or ii) are persistent, bioaccumulative and inherently toxic to human beings or non-human organisms (CEPA 1999). This process resembles the 'hazard classification' required by UN (2003) and EU (EP and EC 2008) for chemicals (see 'classification') and the 'PBT assessment' required by EU under REACH. In all cases, substances tend to be evaluated and grouped based on their hazard or exposure potency without consideration of their structural/physicochemical similarities.

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
CHEMICAL CATEGORY	OECD considers two techniques for grouping of chemicals: the formation of a 'chemical category' (referred to as 'category approach') and the identification of 'analogues' (referred to as 'analogue approach') (OECD 2014a). More specifically, OECD defines a 'chemical category' as a group of chemicals for which physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity (OECD 2014a). This definition was initially proposed by US EPA (1999), which has so far developed 56 chemical categories to be used to assess new chemicals under the Toxic Substances Control Act (US EPA 2010). The same definition is also used by ISO (2014). At EU level, a similar definition is included in Annex XI to REACH, where the use of categories is considered among the rules for adaptation of the standard testing regime (EP and EC 2006; EC 2009). The OECD terminology is reflected in ECHA guidance for the implementation of REACH (ECHA 2008a) and in guidance by industry (ECETOC 2012). A 'chemical category' usually encompasses a large number of chemicals, which are often related by a trend in a property for a given endpoint (OECD 2014a). As the number of chemicals in a category increases, the potential for developing hypotheses and generalisations about the trends within the category also increases (ECHA 2008a). If the available test results show that the chemicals in a category behave in a similar or predictable manner, then interpolation and/or extrapolation may be used to assess the chemicals instead of conducting additional testing (US EPA 1999) (see 'interpolation' and 'extrapolation'). This allows the properties of the individual chemicals in the category to be assessed on the basis of the evaluation of the category as a whole, rather than based on measured data for each individual chemical (OECD 2014a). As far as nanomaterials are concerned, OECD states that it is premature to develop specific guidance on this subject for nanomaterials as research first needs to pay the way for it (OECD 2014a). At European level, ECHA has not developed any official guidance on the development and use of the category approach for nanomaterials in the context of REACH. Until now, the existing guidance for chemicals (ECHA 2008a) has been considered in principle applicable to nanomaterials. However, the ECHA Group Assessing Already Registered Nanomaterials (GAARN) has clarified that the use of data from chemical categories in REACH registration dossiers is supported for nanomaterials and should be performed in line with the similarity rules specified in Annex XI to REACH (ECHA 2013a). In the US, no specific category has been developed for nanomaterials. However, given that for many nanomaterials the available information is insufficient, US EPA has made use of data from existing chemical categories to assess the potential hazard of some nanomaterials, e.g. carbon nanotubes (US EPA 2014a). Despite the lack of official guidance at international and European level, experts seem to agree that developing categories for nanomaterials introduce additional challenges compared to traditional chemicals: similarity cannot be based on structural or chemical composition only, but a wider spectrum of physicochemical properties determining identity and behaviour of nanomaterials including e.g. impurities, surface treatment, surface area, surface charge and shape (RIVM 2015; OECD 2014b; ECHA 2013a) needs to be considered. Some experts underline that physicochemical properties are not sufficient for categorization of nanomaterials and indicators of both hazard and exposure potential needs to be included (Godwin et al 2015). Arts and colleagues suggest that all aspects of the nanomaterials' life cycle need to be considered in a grouping approach, i.e. physicochemical properties, biophysical interactions, intended use, external exposure, uptake and internal exposure, biokinetics and early biological and apical effects (Arts et al 2014).
CHEMICAL SAFETY ASSESSMENT (CSA)	The term Chemical Safety Assessment (CSA) has a specific meaning in the context of the REACH (EP and EC 2006). It indicates the process that identifies and describes the conditions under which the manufacturing and use of a substance is considered to be safe (ECHA 2009). There are three major steps in the CSA process under REACH and are: – Hazard assessment, – Exposure assessment, – Risk characterisation.

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
	The goal of the assessment is not to establish whether or not there is a risk, but to identify and describe the conditions under which the risks are controlled (ECHA 2011b). Risks are regarded as controlled when the estimated exposure levels do not exceed the predicted no effect levels (DNEL or PNEC). For substances for which such no-effect levels cannot be determined, the risk characterisation may consist of semi-quantitative or qualitative assessment of the likelihood that adverse effects are avoided (ECHA 2011b).
CLASS OF SUBSTANCES	At UN level and in the EU legislation on chemicals, substances are assigned to the same 'hazard class' when they share the same physicochemical (e.g. explosiveness), health (e.g. carcinogenicity) or environmental (e.g. aquatic acute toxicity) hazard potential (UN 2003, EP and EC 2008), without the condition of structural similarity. The assignation is based on the results of a standard test method for a specific endpoint and is most commonly used for classification and labelling purposes (NIEHS 1997). As far as nanomaterials are concerned, the US and Canada have developed the 'Joint Nanomaterials Classification Scheme' for regulatory purposes (RCC 2013). The scope is not to assign nanomaterials to hazard classes for labelling purposes but to group them based on similarities in chemical composition for read-across (RCC 2013). The concept of 'class' in this document is therefore different from the one in UN/EU documents and more similar to the concept of 'grouping' and 'chemical category' used at OECD and EU level. The document indeed specifies that the term 'classification' is not intended to be similar to its use in other regulatory/policy documents in Canada, the US or internationally (RCC 2013). Since a clear and unique definition of the term 'class of substances' at international and/or European level could not be found, in NANoREG both terms 'class of substances' and 'classification' are used in line with UN/EU documents and practices (UN 2003, EP and EC 2008).
CONTROL BANDING (CB)	ISO defines Control Banding (CB) as a pragmatic approach that can be used for the control of workplace exposure to possibly hazardous agents with unknown or uncertain toxicological properties and for which quantitative exposure estimations are lacking (ISO 2014). It may complement the traditional quantitative methods based on air sampling and analysis with reference to Occupational Exposure Levels (OELs) when they exist (ISO 2014). CB is a risk assessment approach in a context of uncertainty using the generally accepted risk paradigm, where risk is a function of severity of impact (hazard) and the anticipated probability of that impact (exposure) (Brouwer 2012). It is a qualitative approach where both hazard and exposure are graded into two to five different levels, usually referred to as 'bands'. It is based on expert judgment and combined, most often in a matrix, resulting into control or risk bands (Brouwer 2012). A range of control techniques (e.g. general ventilation, containment) is associated to each control or risk band. CB has frequently been used in risk management guidance for particles and chemicals (ISO 2012) and its possible application to nanomaterials has been recently debated (Brouwer 2012).
DATA GAP	OECD defines a 'data gap' as a physical-chemical, environmental fate, ecotoxicological, or mammalian toxicological/human health endpoint for which data is not available when required for an assessment (OECD 2014a). A data gap can be related to either a regulatory requirement that is not fulfilled (and may be fulfilled via animal testing or alternative test methods) or a need for some specific information that is deemed crucial for a certain type of assessment.
DATA GAP FILLING	OECD defines 'data gap filling' as the process of providing data to inform upon a particular endpoint by whatever means is scientifically justified, including direct animal testing and alternative test methods (OECD 2014a).

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
ENDPOINT	OECD defines an 'endpoint' as a broad description of a specific environmental or toxicological property of a chemical, e.g. acute oral toxicity or water solubility, which can be assessed though any type of test method (OECD 2005; 2014a).
EXPOSURE SCENARIO (ES)	In risk assessment, an 'exposure scenario' can be defined as a set of facts, assumptions and inferences that describe how exposure to a chemical may occur under certain conditions (US EPA 1992, OECD 2003, IPSC 2004). According to US EPA (1992), these conditions include: – The physical setting where exposure takes place (exposure setting); – The exposure pathway(s) from source(s) to exposed individual(s) (exposure pathways); – The characterization of the chemical, i.e., amounts, locations, time variation of concentrations, source strength, environmental pathways from source to exposed individuals, fate of the chemical in the environment, etc. (characterization of the chemical); – Identification of the individual(s) or population(s) exposed, and the profile of contact with the chemical based on behaviour, location as a function of time, characteristics of the individuals, etc. (characterization of the exposed population); and – If the dose is to be estimated, assumptions about the transfer of the chemical across the boundary, i.e., ingestion rates, respiration rates, absorption rates, etc. (intake and uptake rates). In risk assessment, the exposure scenario is the basis for quantification and evaluation of exposure levels of an individual (for human health) or population (for the environment) to a chemical (OECD 2003, IPSC 2004). Under REACH, an 'exposure scenario' not only characterises the set of conditions that describes how the substance is manufactured or used during its life cycle and how exposures of humans and the environment may occur, but also those actions by which the manufacturer or importer controls – or recommends downstream users to control – exposures (EP and EC 2006). Thus, an 'exposure scenario' under REACH specifies those operational conditions and risk management measures that need to be implemented to ensure that the use of the substance is safe (ECHA 2011b).
EXTRAPOLATION	OECD defines 'extrapolation' as the estimation of a value for a member of a chemical category that is near or at the boundary of the chemical category using measured values from members that are internal to that chemical category (OECD 2014a). In general, confidence in the prediction is enhanced when available experimental data from members of the chemical category allows for interpolation rather than extrapolation, as extrapolation is perceived to be more uncertain and therefore less reliable (OECD 2014a) (see 'interpolation').
FRAMEWORK	A set of elements (e.g. ideas, best practices, regulatory provisions) organised in a conceptual manner, which constitute a frame of reference for a certain topic or issue.
GROUPING	OECD (2014a) defines 'grouping' as the general approach for considering more than one chemical at the same time. The rationale underpinning grouping may be based on the following: – Common functional group(s); – Common constituents or chemical classes, similar carbon range numbers; – A common mode or mechanism of action or adverse outcome pathway; – The likelihood of common precursors and/or breakdown products via physical or biological processes that result in structurally similar chemicals; – An incremental and constant change across the category. According to OECD, grouping may include formation of a 'chemical category' or identification of (a) 'chemical analogue(s)' (OECD 2014a). The terms 'category approach' and 'analogue approach' are therefore used to describe techniques for grouping of chemicals, whilst the term 'read-across' is reserved for a technique of data gaps filling in either approach.

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
	The OECD terminology is reflected in guidance for the implementation of REACH by ECHA (2008a) and industry (ECETOC 2012). Structural similarity is a prerequisite for any grouping approach under REACH (EC 2009, ECHA 2015a). In the US and Canada, the term 'categorization' is more often used to indicate the organisation of chemicals into 'groups' or 'categories' based on structural similarities for regulatory purposes (Godwin et al 2015). As far as nanomaterials are concerned, OECD states that it is premature to develop guidance on grouping for nanomaterials, as research first needs to pave the way for it (OECD 2014a), and has not developed any recommendation on how the grouping and read-across concepts and approaches previously developed for chemicals need to be adapted to take NMs' specificities into account. At European level, ECHA has not developed yet any official guidance on how to implement grouping and read-across for nanomaterials in the context of REACH. Until now, the existing guidance (ECHA 2008a) has been considered in principle applicable to nanomaterials. However, the ECHA Group Assessing Already Registered Nanomaterials (GAARN) has clarified that the use of grouping and read-across in REACH registration dossiers is supported for nanomaterials and should be performed in line with the similarity rules specified in Annex XI to REACH (ECHA 2013a). However, while read-across commonly involves substances with different chemical composition but structural similarity, read-across of nanomaterials largely involves different nanoscale materials of the same chemical composition, i.e. different nanoforms of a certain substance addressed within the same REACH registration dossier (ECHA 2013a) (see 'nanoform'). Despite the lack of official guidance at international and European level, experts seem to agree that grouping and read-across of nanomaterials introduce additional challenges compared to traditional chemicals: similarity cannot be based on structural or chemical composition only, but needs to consider a wider spectrum of physicochemical properties determining identity and behaviour of nanomaterials including e.g. impurities, surface treatment, surface area, surface charge and shape (RIVM 2015; OECD 2014b; ECHA 2013a). Physicochemical characterisation is therefore a prerequisite of any grouping and read-across approach for nanomaterials (ECHA 2013a). Some experts underline that physicochemical properties are not sufficient for categorization of nanomaterials and that indicators of both hazard and exposure potential need to be included (Godwin et al 2015). Arts and colleagues suggest that all aspects of the nanomaterials' life cycle need to be considered in a grouping approach, i.e. physicochemical properties, biophysical interactions, intended use, external exposure, uptake and internal exposure, biokinetics and early biological and apical effects (Arts et al 2014). The RCC Nanotechnology Initiative has developed a Canada-US 'Joint Classification Scheme for nanomaterials', where the term 'classification' is used in place of 'grouping' but with the same meaning (RCC 2013). The scheme has been developed for regulatory purposes and its rationale is based only on similarity of chemical composition. For each class, the scheme provides a list of physicochemical properties to be considered at a subsequent step for identification of analogues that could be used for read-across.
HARMONISATION	The term 'harmonisation' can be defined as the establishment of a common and coherent basis in a certain field/activity or for a certain scope. At OECD level, 'harmonisation' means establishing a common and coherent basis for chemical testing in safety assessment. OECD focuses on harmonisation of Test Guidelines for chemicals in order to ensure the generation of reliable and reproducible data, which can be shared among OECD countries under the Mutual Acceptance of Data (MAD) agreement. At UN level, 'harmonisation' means establishing a common and coherent basis for chemical hazard classification and communication (UN 2003).
INFORMATION REQUIREMENT	The term 'information requirement' can be defined as the entry in a legal text requiring information on e.g. physicochemical properties, (eco)toxicological effects, fate and behaviour of a chemical (Danish EPA 2013).

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
INTERPOLATION	OECD defines 'interpolation' as the estimation of a value for a member of a chemical category using measured values from members that are on both sides of that member within the spectrum of that chemical category (OECD 2014a). In general confidence in the prediction is enhanced when available experimental data from members of the chemical category allows for interpolation rather than extrapolation, as extrapolation is perceived to be more uncertain and therefore less reliable (OECD 2014a) (see 'extrapolation'). Annex XI to REACH explicitly requires interpolation (EC 2009).
LIFE CYCLE	ISO defines the 'life cycle' of a product system as the consecutive and interlinked stages of a product system, from raw material acquisition or generation from natural resources to final disposal (i.e. cradle-to-grave) (ISO 2006). Under EU REACH Regulation (EP and EC 2006) the safe use of a substance during the whole life cycle needs to be ensured. ECHA identifies different stages during the life cycle of a substance, including manufacture, formulation, use by industrial workers, professional workers and consumers and end-use or service life (ECHA 2010a; ECHA 2011b).
LIFE CYCLE ASSESSMENT (LCA)	ISO defines Life Cycle Assessment (LCA) as the compilation and evaluation of the inputs, outputs and the potential environmental impacts (e.g. use of resources and the environmental consequences of releases) of a product system throughout its life cycle, from raw material acquisition through production, use, end-of-life treatment, recycling and final disposal (i.e. cradle-to-grave) (ISO 2006). LCA is therefore a comprehensive tool for environmental sustainability assessment that evaluates the overall impacts of a product system on human health and natural resources (Som et al 2010). With regard to nanomaterials, LCA can be used for comparing a product that includes nanomaterials with similar products without nanomaterials and, thus, to assess the relative environmental performance of products containing nanomaterials in comparison with their conventional equivalents (Som et al 2010).
MODE OF ACTION	OECD defines 'mode of action' as the functional or anatomical change at cellular level resulting from the exposure of a living organism to a chemical (OECD 2014a). In comparison, 'mechanism of action' is defined as the change at molecular level (OECD 2014a).
NANOFORM	For the term 'nanoform', there is no internationally agreed definition. At European level, the term is not officially defined. However, in the context of REACH (EP and EC 2006), the term appears in several documents (EC 2008a; JRC and ECHA 2012) and refers to a form of a substance that meets the criteria of the EC Recommendation for the definition of a nanomaterial 2011/696/EU (EC 2011), here subsequently referred to as the EC Definition, as opposed to a 'bulk form' or 'non-nanoform' of the same substance, i.e. a form of the same substance not meeting the criteria of the EC Definition.
(QUANTITATIVE) STRUCTURE-ACTIVITY RELATIONSHIP ((Q)SAR)	OECD defines a Structure-Activity Relationship (SAR) as a qualitative relationship that relates a chemical (sub)structure to the presence or absence of a property or activity of interest (OECD 2014a). The chemical substructure may consist of adjacently bonded atoms, or an arrangement of non-bonded atoms that are collectively associated with the property or activity (OECD 2014a). A Quantitative Structure-Activity Relationship (QSAR) is a mathematical model (often a statistical correlation) relating one or more quantitative parameters derived from chemical structure to a quantitative measure of a property or activity (e.g. a (eco)toxicological endpoint) (OECD 2014a). QSARs are quantitative models yielding a continuous or categorical result (OECD 2014a). (Q)SAR is an expression used to consider, simultaneously, SARs and QSARs (OECD 2005).

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
(Q)SAR MODEL VALIDATION	The conventional use of the terms 'reliability' and 'relevance' for test methods can be extended to the validation process for (Q)SAR models (see 'Test method validation' and 'Validation'). However, because (Q)SAR models are derived from experimental data, the concepts of reliability and relevance for test guideline purposes are necessary but not necessarily sufficient for validation of (Q)SAR models and need to be expanded (OECD 2007). OECD (2007) specifies that for a (Q)SAR model to be accepted for regulatory purposes, it should be associated with the following information: – A defined endpoint; – An unambiguous algorithm; – A defined domain of applicability; – Appropriate measures of goodness-of-fit, robustness and predictivity; – A mechanistic interpretation, if possible. 'Goodness-of-fit' and 'robustness' indicate the internal performance of a (Q)SAR model, determined by using a training set (OECD 2007). The 'predictivity' of a (Q)SAR model is determined by using an appropriate test set (OECD 2007). A 'validated' (Q)SAR is a model considered to be reliable for a particular purpose based on the results of the validation process in which the domain of application and the level of uncertainty required is defined (OECD 2007). A 'valid' (Q)SAR is a model considered to be adequate for the intended purpose because either reliability has been demonstrated by historical use, or by a validation process (OECD 2007).
READ-ACROSS	OECD defines 'read-across' as a technique to fill in data gaps where the test information concerning a certain endpoint for one chemical, referred to as source chemical, is used to predicted the test information concerning the same endpoint for another chemical, referred to as target chemical, which is considered to be similar based on a scientific justification (OECD 2014a). Theoretically, read-across can be applied to retrieve test information concerning any type of endpoint i.e. physicochemical properties, environmental fate, human health effects, and ecotoxicity (OECD 2014a). For any of them, read-across can be performed in a qualitative or quantitative manner (OECD 2014a). The aim of any read-across approach is to provide a prediction that is (more or less) equivalent to the omitted standard animal study and hence be acceptable for regulatory purposes (Schultz et al 2015). Read-across is mentioned in Annex XI to REACH as one of the rules for adaptation of the standard testing regime (EC 2009). The OECD terminology is reflected in ECHA guidance for the implementation of REACH (ECHA 2008a) and in guidance by industry (ECETOC 2012). As far as nanomaterials are concerned, OECD states that it is premature to develop guidance on grouping and read-across for nanomaterials, as research first needs to pave the way for it (OECD 2014a), and has not developed yet any recommendation on how the grouping and read-across concepts and approaches previously developed for chemicals need to be adapted to take MNs' specificities into account. At European level, ECHA has not developed any official guidance on how to implement grouping and read-across approaches for nanomaterials in the context of REACH. Until now, the existing guidance (ECHA 2008a) and the Read-Across Assessment Framework (RAAF) (ECHA 2015a) have been considered in principle applicable to nanomaterials. However, the ECHA Group Assessing Already Registered Nanomaterials (GAARN) has clarified that the use of data from grouping and read-across in REACH registration dossiers is supported for nanomaterials and should be performed in line with the similarity rules specified in Annex XI to REACH (ECHA 2013a). ECHA GAARN has also clarified that while read-across commonly involves substances with different chemical composition but of structural similarity, read-across of nanomaterials largely involves different nanoscale materials of the same chemical composition, i.e. different nanoforms of a certain substance addressed in the same REACH registration dossier (ECHA 2013a) (see 'nanoform').

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
	Despite the lack of official guidance at international and European level, experts seem to agree that grouping and read-across of nanomaterials introduce additional challenges, compared to traditional chemicals: similarity cannot be based on structural or chemical composition only, but a wider spectrum of physicochemical properties determining identity and behaviour of nanomaterials, including e.g. impurities, surface treatment, surface area, surface charge and shape (RIVM 2015; OECD 2014a; ECHA 2013a) needs to be considered. Physicochemical characterisation is therefore a prerequisite of any grouping and read-across approach for nanomaterials (ECHA 2013a).
READ-ACROSS ASSESSMENT FRAMEWORK (RAAF)	The Read-Across Assessment Framework (RAAF) is a structured tool developed by ECHA to facilitate the assessment of read-across cases in REACH registration dossiers by ECHA evaluators (ECHA 2012c). The RAAF provides a framework and guidance for consistent evaluation of the scientific aspects of a proposed read-across case, resulting in an output which is suitable for subsequent regulatory consideration of the read-across case (ECHA 2015a). It is thus not meant to serve as guidance for registrants (ECHA 2012c).
REGULATORY ACCEPTANCE	The 'regulatory acceptance' of a test method is its formal acceptance by regulatory authorities indicating that the test method may be used to provide information to meet a specific regulatory requirement (OECD 2005). This includes, but is not limited to, a formal adoption of a test method by EU and/or OECD and included in the EU Test Methods Regulation (EC 2008b) and/or as an OECD Test Guideline, respectively (EURL ECVAM 2015). In general, regulatory acceptance depends upon the outcome of the validation process. The process has generally been on a case-by-case basis. Regulatory authorities have the option to accept results generated using a test method that has not undergone what today would be considered formal validation (e.g., methods used in mechanistic studies that could help underpin or explain results derived from other tests). However, the regulatory acceptance of tests that have not been subjected to prevailing validation processes is discouraged. In cases in which validation is not considered necessary or appropriate, a written justification should be available (OECD 2005).
SAFE-BY-DESIGN	The 'safe by design' concept aims at reducing potential health and environmental risks at an early phase of the innovation process. Such concept aims at creating an integrated research strategy. This enables the consideration of safety aspects for humans and the environment in the design process of a product/material, to eliminate or minimise the risk of adverse effects during its life cycle including construction, use, maintenance and deconstruction. Within the safe-by-design concept the functionality of a nanomaterial and its toxicity/safety are therefore considered in an integrated way. Such an approach maximises resources use and expedites the development of products containing nanomaterials and new nanomaterials that are safer by design.
STANDARDISATION	ISO defines 'standardisation' as the activity of establishing provisions for common and repeated use of a certain tool aimed at achievement of the optimum degree of order in a given context (ISO 2015a). An ISO/CEN 'standard' is a document that provides requirements, specifications, guidelines or characteristics that can be used consistently to ensure that materials, products, processes and services are fit for their purpose (ISO 2015b; CEN 2015).
STANDARD OPERATING PROCEDURE (SOP)	OECD defines a Standard Operating Procedure (SOP) for a laboratory as a formal, written procedure that describes in detail how to perform specific routine and test-specific laboratory operations (e.g. a specific measurement or sampling operation) (OECD 2005). The purpose of a SOP is to carry out the operations correctly and always in the same manner (FAO 1998). A SOP should be available at the place where the work is done (FAO 1998).

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
	A SOP is a compulsory instruction; if deviations from this instruction are allowed, then the conditions for these deviations should be documented (including who can give permission and what exactly the complete procedure will be) (FAO 1998). SOPs are required by Good Laboratory Practice (OECD 2005).
SUBSTANCE	At EU level, the term 'substance' is defined 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 (EP and EC 2006; EP and EC 2008). The same definition is included in the Globally Harmonised System (UN 2003).
TEST METHOD	OECD defines a 'test method' as an experimental system that can be used to obtain a range of information about a certain chemical, from intrinsic properties to adverse effects in a living organism or population (OECD 2005). The term 'test method' may be used interchangeably with 'assay' for both ecotoxicity and human health studies (OECD 2005). OECD defines 'testing' as applying a test method (OECD 2005).
TEST METHOD VALIDATION	OECD defines 'test method validation' as a process based on scientifically sound principles by which the reliability and relevance of a particular test method are established for a specific purpose (OECD 2005). The 'reliability' of a test method is defined as the extent of reproducibility of results from a test method within and among laboratories over time, when performed using the same standardised protocol (OECD 2005). The 'relevance' of a test method describes the relationship between the test and the effect in the target species and whether the test method is meaningful and useful for a defined purpose, with the limitations identified (OECD 2005). Regulatory need, usefulness and limitations of the test method are aspects of its relevance (OECD 2005). New and updated test methods need to be both reliable and relevant i.e. validated (OECD 2005).
TIERED TESTING STRATEGY	OECD defines a 'tiered testing strategy' as a stepwise testing strategy where all existing information on a test substance is reviewed, in a specified order, using a weight of evidence process at each tier to determine if sufficient information is available for a hazard classification decision, prior to progression to the next tier (OECD 2013b). A tiered approach usually progresses from a review of existing literature and data to a review of data for related chemicals or formulations, to perhaps a (Q)SAR analysis, to simple in vitro screening assays, to the use of more complex in vitro three-dimensional models, to testing in lower species, to the traditional animal test (Ferrario et al 2014).
TOOL	A 'tool' is an experimental or computerised procedure used to generate, collect and/or store a certain type of output.
TREND ANALYSIS	OECD defines 'trend analysis' as a data gap filling method for quantitative endpoints. Trend analysis can be applied to fill data gaps in a chemical category when the members are related by a trend such that the properties of the category members change in a predictable manner and there is a pattern in the changing potency of the properties across the category (e.g. increasing, decreasing, or constant) (OECD 2014a).
VALIDATION	At international level, the term 'validation' is defined as a process by which the reliability and relevance of a particular approach, method, procedure, or assessment is established for a defined purpose (IPSC 2004; OECD 2005).

Table 3.1 ***(cont.)***

KEY TERM	NANoREG DEFINITION
	Different parties define 'reliability' as establishing the reproducibility of the outcome of the approach, method, procedure, or assessment over time, and 'relevance' as establishing the meaningfulness and usefulness of the approach, method, procedure, or assessment for the defined purpose (IPSC 2004). A 'validated method' is therefore a test method for which the reliability and relevance for a specific purpose have been established in one or more validation studies (NIEHS 1997). A 'valid method' is a test method determined to be acceptable for a specific use and application (NIEHS 1997).
VALUE CHAIN	The 'value chain' describes the full range of activities which are required to bring a product or service from conception, through the different phases of production (involving a combination of physical transformation and the input of various producer services), delivery to final consumers and final disposal after use (Kaplinsky and Morris 2001). While the 'life cycle' is a series of ordered phases through which an object and its different forms passes, the 'value chain' begins with an intellectual process and focuses on the activities to bring that object from conception to use and disposal (including e.g. design, production, marketing, distribution). Within NANoREG, 'safety value chain case studies' for some nanomaterials are performed. These case studies add value to the normal linear process of describing the fate of a material/product and how its value increases or decreases along the value chain by integrating aspects related to safety and performing risk assessment when appropriate.
WAIVING	See 'adaptation'.
WEIGHT OF EVIDENCE (WoE)	The term 'weight of evidence' is not a scientifically well-defined term or an agreed formalised concept (ECHA 2011c). In the context of hazard assessment, several international and European bodies define 'weight of evidence' as the process of considering the strengths and weaknesses of various pieces of information in reaching and supporting a conclusion concerning the hazard potential of a substance (ECHA 2010b, SCENHIR 2012, OECD 2012a, OECD 2013b, Ferrario et al 2014). In this process, relevance and reliability of each piece of available information is assessed and weighed using expert judgment (ECHA 2011c). All pieces of information and related weights are then compared to each other and integrated to draw a conclusion (ECHA 2011d).

4. Literature definitions collected for the key terms

In this section, the original definitions that have been collected from the literature and used to develop the NANoREG Definitions are reported and discussed. Each key term is addressed by a dedicated sub-section where a table summarises the literature definitions that have been considered, in chronological order and starting from the most recent one. Moreover, the text briefly discusses the sources and types of definitions that are available, what has been or not been taken into account for the NANoREG Definition elaboration and gives the reasons for these choices. As far as possible, the NANoREG Definition is reproducing (an) already existing definition text(s), thus avoiding the creation of new and unwelcome information.

4.1 Adaptation

Table 4.1 shows the original definitions of the term 'adaptation', which have been collected from the literature and used to develop the NANoREG Definition. The term

'adaptation' is mainly used in REACH legal text (EP and EC 2006) and in principle applies to all substances including NMs. Definitions could only be found in ECHA official guidance documents for implementation of REACH (ECHA 2010c, 2011a). Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by ECHA.

Table 4.1 Literature definitions collected for the key term 'adaptation' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'adaptation'
EU BODIES	
ECHA 2011a Adaptations to information requirements	The terminology 'adaptation' comprises all types of modifications of the standard information requirements, including omissions, triggering, replacement or other adaptations. The term 'omission' (=waiving) is used when on the basis of specific rules in Annex XI, section 3, or the sections in column 2 of Annex VII-X testing may be omitted. Contrary to adaptation, additional testing can be triggered if the chemical safety assessment indicates the need to investigate further the effects on humans or the environment […]
ECHA 2010c How to report data waiving	[…] the adaptation of the standard information requirements means the use of non-standard methods for fulfilling the information requirements. This includes the adaptation options outlined in Annex XI sections 1.1-1.5: the use of existing data, including historical human data, the use of a Weight of Evidence (WoE) approach, information generated using Quantitative Structure Activity Relationships (QSAR), in vitro tests methods, and grouping of substances and read-across. These adaptation options can be used either individually or combined together (e.g. use of (Q)SAR and information from read-across). In all cases the data used must be adequate, reliable and relevant for the particular endpoint(s), and must follow the criteria set out in Annex XI for each method of adaptation.
EP and EC 2006; EC 2009 REACH Annex XI	[…] a registrant may adapt the standard testing regime in accordance with the general rules set out in Section 1 of this Annex. […] 1. TESTING DOES NOT APPEAR SCIENTIFICALLY NECESSARY 2. TESTING IS TECHNICALLY NOT POSSIBLE 3. SUBSTANCE-TAILORED EXPOSURE-DRIVEN TESTING

4.2 Adaptation based on exposure

Table 4.2 shows the original definitions of the term 'adaptation based on exposure', which have been collected from the literature and used to develop the NANoREG Definition. The term 'adaptation based on exposure' is mainly used in REACH legal text (EP and EC 2006) and in principle applies to all substances including NMs. Definitions could only be found in ECHA official guidance documents for implementation of REACH (ECHA 2011a). Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by ECHA. The NANoREG Definition also includes those considerations made by ECHA Group Assessing Already Registered Nanomaterials (GAARN) with regard to the application of this concept to NMs (ECHA 2012a; 2014a).

Table 4.2 Literature definitions collected for the key term 'adaptation based on exposure' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'adaptation based on exposure'
EU BODIES	
ECHA 2014a Third GAARN meeting Best practice for REACH registrants	[…] they have to provide analytical and/or experimental data to demonstrate and support their "no release" statement.
ECHA 2012a First GAARN meeting Best practice for REACH registrants	If registrants are able to show (by measurement and documentation) that particles form strong aggregates that will not leach out nanoparticles during the lifecycle of the substance, then this may be an exposure-based argument that no further testing (beyond size) is necessary.
ECHA 2011a Adaptations to information requirements	REACH provides for the option that information requirements may be adapted based on the justification – that exposure is absent or not significant (Annex XI, section 3.2(a) (i); Annex VIII column 2 section 8.6.1 and 8.7.1) or unlikely (Annex IX column 2 section 9.4) or, – that strictly controlled conditions (Annex XI section 3.2 (b)) apply for the whole life cycle1 of the substance (including the waste stage), – and for substances incorporated into an article that the substance is not released during the whole life cycle and that the likelihood of exposure of man or the environment is negligible (Annex XI section 3.2 (c) (i) and 3.2 (c) (ii)). These provisions were included to avoid unnecessary animal testing. Based on adequate information on exposure, release and fulfilment of strictly controlled conditions, a decision can be taken whether it is possible to omit certain testing, or if further testing should be proposed, or if more stringent risk management measures (RMMs)/operational conditions (OCs) need to be introduced. Exposure based adaptation (EBA) in this context is defined as a deviation from the standard information requirement at the actual tonnage level based on exposure arguments. Exposure based adaptations may be appropriate under the following conditions: – exposure is absent (= exposure excluded) or not significant throughout the whole life cycle of the substance for manufacture and all identified uses or – when strictly controlled conditions apply throughout the life cycle of the substance for manufacture and all uses and – no releases from the article life cycle stage (and subsequent waste life stage) is to be expected and consequently there is a negligible likelihood of exposure. Situation iii) only applies to substances incorporated into articles. Annex XI section 3.2 (a) requires that the absence or insignificance of exposure is underpinned by the derivation of a risk characterisation ratio (quantitative assessment). If the justification is based on Annex XI section 3.2 (b) or (c) a qualitative assessment is expected to include three elements: the description of operational conditions and risk management measures in all related exposure scenarios; the quantification of the resulting release/exposure for all routes; and a qualitative statement why the release is low enough. […] a high level of confidence is needed to demonstrate *no or no significant exposure or no release*.

Table 4.2 *(cont.)*

Source	Original definition of the term 'adaptation based on exposure'
EP and EC 2006; EC 2009 REACH Annex XI	Testing in accordance with Sections 8.6 and 8.7 of Annex VIII and in accordance with Annex IX and Annex X may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report. […] The justification shall be based on a through and rigorous exposure assessment in accordance with section 5 of Annex I and shall meet one of the following criteria: (a) […] (i). the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5; (ii). a DNEL or a PNEC can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes (*); (iii). the comparison of the derived DNEL or PNEC with the results of the exposure assessment shows that exposures are always well below the derived DNEL or PNEC; (b) where the substance is not incorporated in an article the manufacturer or importer demonstrates and documents for all relevant scenarios that throughout the life cycle strictly controlled conditions as set out in Article 18(4)(a) to (f) apply; (c) where the substance is incorporated in an article in which it is permanently embedded in a matrix or otherwise rigorously contained by technical means, it is demonstrated and documented that all of the following conditions are fulfilled: (i). the substance is not released during its life cycle; (ii). the likelihood that workers or the general public or the environment are exposed to the substance under normal or reasonably foreseeable conditions of use is negligible; and (iii). the substance is handled according to the conditions set out in Article 18(4)(a) to (f) during all manufacturing and production stages including the waste management of the substance during these stages.

4.3 Adverse Outcome Pathway (AOP)

Table 4.3 shows the original definitions of the term 'Adverse Outcome Pathway (AOP)', which have been collected and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2011, 2013a, 2014a) and peer-reviewed scientific literature (Ankley et al 2010, Schultz 2010, Watanabe et al 2011, Villeneuve and Garcia-Reyero 2011). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.3 Literature definitions collected for the key term 'Adverse Outcome Pathway (AOP)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'Adverse Outcome Pathway (AOP)'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	[…] the documented, plausible, and testable processes by which a chemical induces molecular and the associated biological responses that describe how the molecular perturbations cause effects at the subcellular, cellular, tissue, organ, whole animal, and population levels of observation. The pathway approach is based on the concept that toxicity results from a chemical first reaching and then interacting with an initial key target (e.g., membrane, receptor) in the organism; this is defined as the primary molecular initiating event. Subsequent to this primary interaction begins a series of events that can individually be documented and tested, resulting in an adverse outcome (e.g., reproductive failure, neurotoxicity). […] several pathways can result in the same adverse outcome, and each constitutes an individual AOP.
OECD 2013a Developing and assessing AOPs	An AOP can be defined in the context of Figure 1. An AOP is a sequence of events from the exposure of an individual or population to a chemical substance through a final adverse (toxic) effect at the individual level (for human health) or population level (for ecotoxicological endpoints). The key events in an AOP should be definable and make sense from a physiological and biochemical perspective. AOPs incorporate the toxicity pathway and mode of action for an adverse effect. AOPs may be related to other mechanisms and pathways as well as to detoxification routes. […] an AOP may describe a pathway initiated via non-specific interactions (e.g. a toxicant physically residing in a bio-membrane), as well as more specific ligand-receptor interactions leading to adverse effects. Although developed for use in ecotoxicology, the AOP concept is also applicable to human health effects (Schultz, 2010). In an AOP, it is important to integrate all of the known information. The approach is based on the concept that toxicity results from the chemical first reaching and then interacting with an initial target or targets in the organism. As such, an AOP is the sequential progression of events from the molecular initiating event (MIE) to the in vivo outcome of interest (Fig. 1). Generally, it refers to a broader set of pathways that would: 1) proceed from the MIEs, in which a chemical interacts with a biological target (e.g. DNA binding, protein oxidation etc.), 2) continue on through a sequential series of biological activities (e.g. gene activation, or altered tissue development etc.), and 3) ultimately culminate in the final adverse effect relevance to human or ecological risk assessors (e.g. mortality, disrupted reproduction, cancer, or extinction, etc.) (OECD 2011) […]
OECD 2012b Collection of working definitions	[…] it relates to a linear sequence of events from the exposure of an individual to a chemical substance through to an understanding of the adverse (toxic) effect at the individual level (for human health) or population level (for ecotoxicological endpoints). The key events in an AOP should be definable and make sense from a physiological and biochemical perspective. AOPs incorporate the toxicity pathway and mode of action. AOPs may be related to other mechanisms and pathways as well as detoxification routes.
OECD 2011 Mechanistic information in forming chemical categories	[…] existing knowledge concerning the linkage between at the molecular initiating event and an adverse outcome at the individual or population levels (Ankley, Bennett et al. 2009). As such, AOPs by definition span multiple levels of biological organization. AOPs often start out being depicted as linear processes, however, the amount of detail and linearity characterizing the pathway between a molecular initiating event and an adverse outcome within an AOP can vary substantially, both as a function of existing knowledge and risk assessment needs. […] Linking molecular initiating events to the in vivo outcomes […] Qualitative means of establishing causal linkages. Conceptual framework for organising information at different levels of biological organisations, characterising the weight of evidence.

Table 4.3 *(cont.)*

Source	Original definition of the term 'Adverse Outcome Pathway (AOP)'
PEER-REVIEWED SCIENTIFIC LITERATURE	
Villeneuve and Garcia-Reyero 2011 Predictive ecotoxicology testing in the 21st century	A conceptual framework that links a molecular-level initiating event with adverse effects relevant for risk assessment.
Watanabe et al 2011 Defining and modelling known adverse outcome pathways	The sequence of events between cellular response and adverse outcome on an individual organism or population of organisms is an AOP.
Schultz 2010 Adverse outcome pathways	Each adverse outcome pathway is a set of chemical, biochemical, cellular, physiological, behavioural, etc. responses which characterise the biological effects cascade resulting from a particular MIE. The term "adverse outcome pathway" has been selected so not to cause confusion with the term "Toxicity Pathway", which is used by the US National Research Council in its document, Toxicity Testing in the Twenty-first Century: A Vision and a Strategy, where the focus is on omics and high throughput *in vitro* data (Schultz 2010).
Ankley et al 2010 Adverse outcome pathways: a conceptual framework	Representation of existing knowledge concerning the linkage between the molecular initiating event and an adverse outcome at the individual or population levels.

4.4 Alternative test method

Table 4.4 shows the original definitions of the term 'alternative test method', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2005; 2014a), in documents from European bodies including REACH legal text (EP and EC 2006), ECHA official guidance for implementation of REACH (ECHA 2008a, 2012d, 2014b), in legal text of Directive on protection of animals used for scientific purposes (EP and EC 2010), and EURL ECVAM webpage (EURL ECVAM 2015), as well as in peer-reviewed scientific literature (Raunio 2011). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.4 Literature definitions collected for the key term 'alternative test method' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'alternative test method'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	[…] non-testing methods for filling data gaps: – Read-across; – Trend analysis and use of computational methods based on internal models; – Use of computational methods based on external models. In principle the above-listed non-testing techniques can be used to indicate either the presence or the absence of an effect or an estimated value (e.g., a relevant toxicity value such as a LOAEL) for an analogue or a group of substances. However, this is highly dependent on the substance under consideration, the endpoint, the level of information already available, the regulatory purpose, and the confidence that can be derived from its interpretation.
OECD 2005 Test methods for hazard assessment	A test that: reduces the numbers of animals required; refines procedures to lessen or eliminate pain or distress to animals, or enhance animal well-being; or replaces animals with non-animal systems or with non-sentient species.
EUROPEAN BODIES	
EURL ECVAM 2015 Glossary	Alternative test methods The term "alternative" is generally associated with the Principles of the 3Rs, - Replacement, Reduction and Refinement - of animal testing. In this context an alternative method serves to fully replace an animal test, to reduce the number of animals needed in a test, or to refine an animal testing procedure in order to reduce pain and suffering. Alternative test methods that are developed to reduce or replace animal experiments are typically based on either in vitro systems or on computer-based models. In vitro test methods use (reconstructed) tissues, whole cells or parts of cells. Recent advances in cell-based research include the development of two-dimensional and three-dimensional cell (co)-cultures which mimic very closely cells and tissues in the human body. The growing use of 'omics' technologies (e.g. transcriptomics, proteomics and metabonomics) in combination with in vitro test systems allows a comprehensive analysis of the impact of a chemical at the molecular level and can indicate potential toxicity pathways that may lead to adverse health effects. Computer-based approaches (often termed in silico or non-testing methods) are becoming increasingly powerful and can be used effectively to predict the toxicity of a chemical from its basic properties. Computer models are also an important tool for efficiently integrating toxicological information derived from complimentary in vitro and in silico methods. A non-testing approach frequently used in the safety assessment of industrial chemicals, for example, is called 'read-across' technique where toxicological effects for one chemical are predicted using data for the same toxicological effect from another chemical, which is considered to be similar in terms of chemical structural, physico-chemical properties, or bioactivity.
ECHA 2014b Use of alternatives to testing on animals for REACH	By contrast to animal test methods; in the context of REACH this mainly relates to the use of in vitro methods, (Q)SAR, grouping and read-across (Article 13(1)): "Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met. In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, in vitro methods or qualitative or quantitative structure-activity relationship models or from information from structurally related substances (grouping or read-across)." Alternative test methods can also be in vivo tests, but which use fewer animals and/or causes less suffering.

Table 4.4 *(cont.)*

Source	Original definition of the term 'alternative test method'
ECHA 2012d Non-testing methods under REACH	[…] "non-test method" refers to any non-experimental method or approach that can be used to provide data for the assessment of chemicals. Data, produced by a non-test method, are called "non-test data". Non-test methods include QSAR models and read-across/grouping approaches and can be used to predict in a quantitative or a qualitative manner the physicochemical, biological, i.e. (eco)toxicological, and environmental fate properties of substances from knowledge of their chemical structure and other properties. Both QSARs and read-across/grouping approaches are based on the principle that the properties of substances, including their biological activities, depend on their chemical structure and hence can be predicted from it (similar substances have similar properties).
ECHA 2008a QSARs and grouping of chemicals	Non-testing data can be generated by three main approaches: a) grouping approaches, which include read-across and chemical category formation; (quantitative) structure-activity relationships ((Q)SARs); and c) expert systems. The development and application of all kinds of non-testing methods is based on the similarity principle, i.e. hypothesis that similar compounds should have similar biological activities. […] non-testing techniques for filling data gaps: – read-across, – trend analysis and use of computational methods based on internal models, – use of computational methods based on external models.
EP and EC 2010 Directive 2010/63/EU Protection of animals used for scientific purposes	The Commission and the Member States shall contribute to the development and validation of alternative approaches which could provide the same or higher levels of information as those obtained in procedures using animals, but which do not involve the use of animals or use fewer animals or which entail less painful procedures, and they shall take such other steps as they consider appropriate to encourage research in this field.
EP and EC 2006 REACH	The Commission, Member States, industry and other stakeholders should continue to contribute to the promotion of alternative test methods on an international and national level including computer supported methodologies, in vitro methodologies, as appropriate, those based on toxicogenomics, and other relevant methodologies.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Raunio 2011 In silico toxicology, non-testing methods	In more general terms, non-testing methods can be divided into two main classes, i.e., comprehensive (global) and specific (local) ones. Comprehensive methods, also called expert systems, mimic human reasoning and formalise existing knowledge. Expert systems have an advantage over QSAR methods in that prediction is related to specific mechanisms. Specific systems generally apply to a narrow range of targets, e.g., specific receptors or enzymes. Specific methods can be divided into ligand-based and target-based techniques. Ligand-based modelling such as QSAR involves active ligands without considering the 3-dimensional (3D) structure of the protein and the possible sites of interaction. Target-based methods calculate atomic interactions between ligands and their target macromolecules. They require 3D structures of both ligands and macromolecules and need more computational power.

4.5 Analogue(s)

Table 4.5 shows the original definitions of the term 'analogue(s)', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2014a) and ISO (2014), documents from European bodies such as ECHA official guidance for

implementation of REACH (ECHA 2008a, 2012c, 2013b, 2015a), documents from US bodies (US EPA 2014a), reports from industry associations (CEFIC-LRI 2012, ECETOC 2012), and in peer-reviewed scientific literature (van Leeuwen et al 2007, 2009, Patlewicz et al 2014). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. These definitions are reflected in ECHA official guidance documents for implementation of REACH and in reports by industry, and in principle apply to all chemicals including NMs. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD. The NANoREG Definition also includes those considerations made by several organisations (OECD, ECHA GAARN, RIVM) and authors in the peer-reviewed scientific literature with regard to the application of this concept to NMs (ECHA 2013b, OECD 2014a, Arts et al 2014, Godwin et al 2015, RIVM 2015).

Table 4.5 Literature definitions collected for the key term 'analogue(s)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'analogue(s)'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	In the analogue approach where comparisons are made between a very limited number of chemicals, endpoint information for one chemical is used to predict the same endpoint for another chemical, which is considered to be "similar" in some way (usually on the basis of structural similarity and similar properties and/or activities). When the focus of the assessment is on filling data gaps for one specific chemical, empirical data from one or more similar chemical(s) ("the analogue(s)") or "source" chemical can be used to predict the same endpoint for the "target" chemical, which is considered to be "similar". This analogue approach is useful when the target and source chemicals share a known common mode (and/or mechanism) of action, and the adverse effects resulting from this mode (and/or mechanism) of action is evaluated. The analogue approach could also be used in the absence of effects or when no specific mode (and/or mechanism) of action is expected and toxicokinetic behaviour is not expected to differ significantly. In such case, more evidence, or more lines of evidence, should support the assessment. […] comparisons are made between a very limited number of chemicals, endpoint information for one chemical is used to predict the same endpoint for another chemical, which is considered to be "similar" in some way (usually on the basis of structural similarity and similar properties and/or activities). An analogue is a chemical whose intrinsic physical-chemical, environmental or toxicological properties are likely to be similar to another chemical based upon a number of potential properties, including structural, physical-chemical and toxicological. […] in addition to structural similarity and similar physical-chemical properties between the source chemical(s) and the target chemical, criteria such as common functional group, biochemical processes and mode (and/or mechanism) of action, or environmental fate come into play for judging the suitability of source chemical(s). In principle the above-listed non-testing techniques can be used to indicate either the presence or the absence of an effect or an estimated value (e.g., a relevant toxicity value such as a LOAEL) for an analogue or a group of substances. However, this is highly dependent on the substance under consideration, the endpoint, the level of information already available, the regulatory purpose, and the confidence that can be derived from its interpretation. *NB. Figure 2 (p. 65) Stepwise approach to an analogue approach*

Table 4.5 *(cont.)*

Source	Original definition of the term 'analogue(s)'
INTERNATIONAL BODIES	
ISO 2014 Use of the control banding approach	analogous material material of the same chemical category, with a similar composition and/or crystalline phase and documented similar physicochemical properties (metal oxides, graphite, ceramics, etc.)
EUROPEAN BODIES	
ECHA 2015a Read-Across Assessment Framework	The term 'analogue approach' is used when read-across is employed between a small number of structurally similar substances; there is no trend or regular pattern on the properties. As a result of the structural similarity, a given toxicological property of one substance (the source) is used to predict the same property for another substance (the target) to fulfil a REACH information requirement. The outcome of a study conducted with the source substance is read-across for all investigated parameters to the target substance. A worst-case approach may also be used. In the context of the RAAF as describe in this document, the simplest case of an analogue approach is considered: read-across from a single source substance to a target substance. If an analogue approach uses more than one source or target substance, the assessment of the read-across approach has to be repeated for each source and/or target substance.
ECHA 2013b Grouping of substances and read-across approach	The term *analogue approach* is used when read-across is employed within a group of a very limited number of substances for which trends are not apparent: i.e. the simplest case is read-across from a single source substance to a target substance.
ECHA 2012c An introduction to the assessment of read-across in ECHA	[…] is concerned with read-across between two or among a few analogues.
ECHA 2008a QSARs and grouping of chemicals	The term analogue approach is used when the grouping is based on a very limited number of chemicals, where trends in properties are not apparent. The simplest example of the category approach is a comparison between two chemicals. This form of evaluation is often called a read-across approach, and this is the term used in Annex XI of REACH. […] In order to avoid confusion, evaluations of a very limited number of chemicals using largely read-across to fill data gaps is described in this guidance as the analogue approach. The term read-across is therefore limited to the technique for filling data gaps. *NB. Figure R.6-5 (p. 95) Stepwise procedure to the analogue approach*
US BODIES	
US EPA 2014a Nanomaterials under TSCA Presentation at ECHA workshop	Given the lack of data, EPA uses analogs to make determinations. For many nanoscale materials where there are insufficient data, EPA uses data for the category "Respirable, Poorly Soluble Particulates" to assess potential hazard. Category is limited to effects on the lung as a result of inhaling particles < 10 um in diameter.

Table 4.5 *(cont.)*

Source	Original definition of the term 'analogue(s)'
INDUSTRY ASSOCIATIONS	
CEFIC-LRI 2012 Experts Workshop on Read-across assessment	[…] comparisons are made between a very limited number of substances. Endpoint information on the source substance(s) is used to predict the same endpoint for the target substance, which is considered to be 'similar' in some way (usually on the basis of structural similarity and similar properties and/or activities). Potential source substances need to be reasonably data-rich from which comparisons can be made.
ECETOC 2012 Category approaches, read-across, (Q)SAR	In this report, the term 'category approach' and 'analogue approach' are used to describe techniques for grouping chemicals, whilst the term 'read-across' is reserved for a technique of filling data gaps in either approach. […] Analogue approach is often used when the grouping is based on a very limited number of chemicals, typically two substances.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Patlewicz et al 2014 Read-across approaches	[…] the analogue approach, which is based on a chemical group with a very limited number of structurally similar substances (usually a target and source substance), […]
Van Leeuwen et al 2009 Using chemical categories to fill data gaps in hazard assessment	Read-across has been proposed to estimate missing data from a single or restricted number of compounds using the analogue approach […].
Van Leeuwen et al 2007 Intelligent Testing Strategies	[…] the identification of a chemical substructure that is common to the two substances (which are therefore analogues).

4.6 Assessment Factor (AF)

Table 4.6 shows the original definitions of the term 'Assessment Factor (AF)', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2003), IPSC (2004), and IUPAC (Duffus et al 2007), in documents from European bodies such as ECHA official guidance for implementation of REACH (ECHA 2008b; 2012d), in documents from US bodies such as US EPA (1998, 2002, 2014b), in reports from industry associations (ECETOC 2010), and in peer-reviewed scientific publications (Ferrario et al 2004). The definitions that are reported in official guidance documents by OECD and IPSC are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD and IPSC and complements them with elements provided by ECHA and US EPA.

Table 4.6 Literature definitions collected for the key term 'Assessment Factor (AF)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'Assessment Factor (AF)'
INTERNATIONAL BODIES	
Duffus et al 2007 IUPAC Recommandations	Uncertainty factor (UF): 1. In assay methodology, confidence interval or fiducial limit used to assess the probable precision of an estimate. 2. In toxicology, value used in extrapolation from experimental animals to man (assuming that man may be more sensitive) or from selected individuals to the general population. For example, a value applied to the no-observed-effect-level (NOEL) or no-observed-adverse-effect-level (NOAEL) to derive an acceptable daily intake (ADI) or tolerable daily intake (TDI). Note: The NOEL or NOAEL is divided by the value to calculate the ADI or TDI. See also Modifying factor, Safety factor.
IPSC 2004 Risk Assessment Terminology	Assessment factor: Numerical adjustment used to extrapolate from experimentally determined (dose–response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur. Related terms: Safety factor, Uncertainty factor.
OECD 2003 Key generic terms	Assessment factor: Numerical adjustment used to extrapolate from experimentally determined (dose-response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur. Related terms: Safety Factor, Uncertainty Factor.
EUROPEAN BODIES	
ECHA 2012b Characterisation of dose-response for human health	The term assessment factor is used because of it being a neutral term. However, these factors can in the DMEL approach also be viewed as 'correction factors' and 'uncertainty factors'. The next step in the calculation of a DNEL is to address uncertainties in the extrapolation of experimental data to the real human exposure situation, taking into account variability and uncertainty. These uncertainties concern, e.g., differences between animals and humans in anticipated sensitivity towards the toxicity of the substance. All these uncertainties/differences are individually addressed by so-called assessment factors (AFs), that together result in an overall AF that is applied to the corrected dose descriptor to account for all these uncertainties. Preferably, the value for each individual assessment factor is based on substance-specific information. However, although sound in principle, in practice the approach has limitations (data are often scarce, especially toxicodynamic data, and human data) and, therefore, default assessment factors most often need to be used. Each step in the process, including any choice for an assessment factor value, whether substance-specific or default should be explained as transparently as possible, with a qualitative narrative in the chemical safety report (CSR). Assessment factors are numerical values. They are used to address the differences between the experimental data and the human situation, taking into account the uncertainties in the extrapolation procedure and in the available data set. In principle, all data on a specific substance need to be reviewed thoroughly in order to use, as far as possible, substance-specific information for the establishment of appropriate values for the various assessment factors. When substance-specific information is not available, data on analogues, which act with the same mode of action as the chemical under consideration, should be taken into account. However, when the available data do not allow the derivation of substance-specific or analogue-specific assessment factors, default assessment factors should be applied. Although very often necessary to rely upon, the default assessment factors represent a fall-back position rather than the starting point.

Table 4.6 *(cont.)*

Source	Original definition of the term 'Assessment Factor (AF)'
	Several aspects are involved in the extrapolation of experimental data to the human situation, inter alia, from the variability in the experimental data and from intra- and inter-species variation, the nature and severity of the effect, and the sensitivity of the human (sub-)population (REACH Annex I, Section 1.4.1). These aspects will be discussed under the following headings; – Interspecies differences; – Intraspecies differences; – Differences in duration of exposure; – Issues related to dose-response; – Quality of whole database.
ECHA 2008b Characterisation of dose-response for environment	The general principle of these methods is that the result from a laboratory test is divided by an appropriate assessment factor. The sparser the available data, the higher is the assessment factor which is applied. PNECs are estimated by division of the lowest value for the toxicity with the relevant assessment factor. Results of long-term tests (expressed as EC10 or NOEC for a sublethal parameter) are preferred to those of short-term tests (EC/LC50), because such results give a more realistic picture of effects on the organisms during their entire life cycle. In establishing the size of these assessment factors, a number of uncertainties have been addressed to extrapolate from single-species laboratory data to a multi-species ecosystem. These areas comprise: – Intra- and inter-laboratory variation of toxicity data; – Intra- and inter-species variations (biological variance); – Short-term to long-term toxicity extrapolation; – Laboratory data to field impact extrapolation.
US BODIES	
US EPA 2014b Guidance for applying quantitative data to develop data-derived extrapolation factors	In deriving reference concentrations (RfCs) and reference doses (RfDs), the Agency has historically used default uncertainty factors (UFs) to compensate for a lack of information (U.S. EPA, 2002b). As science has advanced, however, there has been a growing effort to increase reliance on available data to modify the values for these UFs (IPCS, 2005). The default UFs were developed to address data gaps in the development of RfDs and RfCs, but when appropriate data are available for an assessment, those data are given precedence over standard default values (U.S. EPA, 2004a). This guidance describes an approach for identifying and using pertinent information for developing data-derived extrapolation factors (DDEFs) for the purposes of developing RfDs, RfCs, or related metrics/approaches (e.g., hazard index, margin of exposure).
US EPA 2002 Review of reference dose and reference concentration processes	Reference values are derived in a way that attempts to account for both the uncertainty and the variability in the data available […] Uncertainty/Variability Factor: One of several, generally 10-fold, default factors used in operationally deriving the RfD and the RfC from experimental data. The factors are intended to account for (1) the variation in sensitivity among the members of the human population (i.e., inter-individual variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies uncertainty); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation when the database is incomplete. Modifying Factor (MF): A factor used in derivation of a reference dose or reference concentration. The magnitude of the MF reflects the scientific uncertainties of the study and database not explicitly treated with standard uncertainty factors (e.g., the completeness of the overall database). A MF is greater than zero and less than or equal to 10, and the default value for the MF is1. [Current definition in IRIS; this report recommends that its use be discontinued.]

Table 4.6 *(cont.)*

Source	Original definition of the term 'Assessment Factor (AF)'
US EPA 1998 Guidelines for ecological risk assessment	Uncertainty factors are used to ensure that measures of effects are sufficiently protective of assessment endpoints. Uncertainty factors are empirically derived numbers that are divided into measure of effects values to give an estimated stressor level that should not cause adverse effects to the assessment endpoint. Uncertainty factors have been developed most frequently for chemicals because extensive ecotoxicologic databases are available, especially for aquatic organisms. Uncertainty factors are useful when decisions must be made about stressors in a short time and with little information. Uncertainty factors have been used to compensate for assessment endpoint/effect measures differences between endpoints (acute to chronic effects), between species, and between test situations (e.g., laboratory to field). Typically, they vary inversely with the quantity and type of measures of effects data available (Zeeman, 1995). […] Despite their usefulness, uncertainty factors can also be misused, especially when used in an overly conservative fashion, as when chains of factors are multiplied together without sufficient justification. Like other approaches to bridging data gaps, uncertainty factors are often based on a combination of scientific analysis, scientific judgment, and policy judgment (see section 4.1.3). It is important to differentiate these three elements when documenting the basis for the uncertainty factors used. Empirical data can be used to facilitate extrapolations between species, genera, families, or orders or functional groups (e.g., feeding guilds) (Suter, 1993a).
INDUSTRY ASSOCIATIONS	
ECETOC 2010 Guidance on assessment factors to derive DNEL	The biological starting point for DNEL are dose descriptors such as the no observed adverse effect levels (NOAEL) or benchmark doses (BMD) that are expected to be mostly obtained from animal experiments. The dose descriptors are adapted to human exposure periods and life time (in relation to the experimental setting), and extrapolated to human populations by means of physiological scaling factors and a number of assumptions which are considered into a system of standardised assessment factors (AF). Both the REACH TGD and ECETOC recognise that when substance- or category-specific information is available there may be a scientific justification for deviating from default guidance. ECETOC has introduced the term 'informed' AF to address these alternative AF. The term 'default' AF is, in contrast, conceived for those cases where little else other than the experimental dose descriptor is known about a compound (or category) and other aspects of the toxicological profile, mode of action (MOA), toxicokinetics and species variability are unknown.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Ferrario et al 2004 Glossary of reference terms	Assessment factor (safety factor, uncertainty factor): Numerical adjustment used to extrapolate from experimentally determined (dose/concentration-response) relationships to estimate the agent exposure below which an adverse effect is not likely to occur (OECD, 2004b).

4.7 Categorisation

Table 4.7 shows the original definitions of the term 'categorisation', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from Canadian bodies such as CEPA legal text (CEPA 1999) and in peer-reviewed scientific literature (Gebel et al 2014, Godwin et al 2015). The term 'categorisation' is not defined in European legal acts and not used by European bodies. One definition with regulatory relevance is present in CEPA legal text for chemicals (CEPA 1999) and applies to the Canadian regulatory context. The definitions reported in the peer-reviewed literature seems to be quite general: Godwin and colleagues (2015) defines 'categorisation' as a synonymous of 'grouping' for both chemicals and NMs whereas Gebel and colleagues (2014) uses the term 'categorisation'

of NMs in a way that is similar to the concept of 'chemical category' and 'category approach' as defined by OECD. Accordingly, no harmonised definition of the term 'categorisation' has been adopted in NANoREG and project partners have concluded that the terms 'chemical category' and 'category approach' are preferred (see 'chemical category').

Table 4.7 Literature definitions collected for the key term 'categorisation' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'categorisation'
CANADIAN BODIES	
CEPA 1999 Canadian Environmental Protection Act	PRIORITY SUBSTANCES AND OTHER SUBSTANCES Categorization of substances on Domestic Substances List 73. (1) The Ministers shall, within seven years from the giving of Royal Assent to this Act, categorize the substances that are on the Domestic Substances List by virtue of section 66, for the purpose of identifying the substances on the List that, in their opinion and on the basis of available information, (a) may present, to individuals in Canada, the greatest potential for exposure; or (b) are persistent or bioaccumulative in accordance with the regulations, and inherently toxic to human beings or to non-human organisms, as determined by laboratory or other studies.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Godwin et al 2015 Nanomaterial Categorization	Categorization refers to the grouping of chemicals. […] Categorization strategies may include grouping, ranking, and read-across as examples of types of categorization. […] In the context of nanomaterials, additional factors could be considered such as grouping by mechanisms of action at the nano/biointerface. Categorization strategies are needed to enable regulators and industry either to predict ENM risk better or to allow prioritization of the testing (hazard, exposure, physicochemical) needed to estimate their potential risk while minimizing time-consuming and costly *in vivo* studies or traditional risk assessments. The "holy grail" of this field is to be able to categorise the risk potential of ENMs based on their physicochemical properties because such as approach would allow manufacturers and regulators to make rapid decisions without requiring costly and time-consuming *in vivo* and/or *in vitro* data. […] constructive guidance on how to improve and to expedite categorization of ENMs according to risk potential: – Physicochemical properties are not currently sufficient for ENM categorization for regulatory purposes. – Categorisation methods for regulatory purposes should include indicators of both hazard and exposure potential. – Alternative testing strategies (ATS) may provide a useful means for expedited hazard screening for ENMs. – Decision-tree approaches for categorizing CNTs according to their risk potential post-manufacturing could facilitate decision-making in the EPA' New Chemicals program and in other frameworks. – Targeted cross-comparison of ATS with standard assays may be needed for ATS to be incorporated as an accepted component of categorization strategies in some regulatory contexts.
Gebel et al 2014 Manufactured nanomaterials categorization	[…] it seems reasonable to categorise nanomaterials according to their route of exposure, physicochemical properties and mode of action.

4.8 Chemical category

Table 4.8 shows the original definitions of the term 'chemical category', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2014a) and ISO (2014), in documents from European bodies such as REACH legal text (EC 2009), ECHA official guidance for implementation of REACH (ECHA 2008a, 2012c, 2013a, 2014b, 2015a, 2015b), and JRC reports (JRC 2005), in documents from US bodies such as TSCA legal text (TSCA 2002) and US EPA guidance (US EPA 1999), in reports from industry associations (CEFIC-LRI 2012, ECETOC 2012), and in peer-reviewed scientific literature (van Leeuwen et al 2007, van Leeuwen et al 2009, Godwin et al 2015). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. These definitions are reflected in ECHA official guidance for implementation of REACH and in reports by industry, and in principle apply to all chemicals including NMs. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD. The NANoREG Definition also includes those considerations made by several organisations (OECD, ECHA GAARN, RIVM, US EPA) and scientists with regard to the application of this concept to NMs (ECHA 2013b, OECD 2014a, Arts et al 2014, RIVM 2015, Godwin et al 2015).

Table 4.8 Literature definitions collected for the key term 'chemical category' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'chemical category'
INTERNATIONAL BODIES	
ISO 2014 Use of the control banding approach	[…] group of chemicals whose physicochemical and human health and/or ecotoxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern, usually as a result of structural similarity
OECD 2014a Guidance on grouping of chemicals	Chemicals whose physical-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of chemicals. […] the properties of the individual chemicals within a category are assessed on the basis of the evaluation of the category as a whole, rather than based on measured data for any one particular chemical alone. For (a) category member(s) that lacks data for one or more endpoints, the data gap can be filled in a number of ways, including by read-across from one or more other category members. Within a chemical category, the members are often related by a trend in an effect for a given endpoint, and a trend analysis can be carried out through deriving a model based on the data for the members of the category. An advantage of a chemical category assessment approach is that identification of consistent patterns of effects within a category in itself increases confidence in the reliability of the results for all the individual chemicals in the category, compared to evaluation of data purely on a chemical-by-chemical basis. A category of chemicals will often show the presence and absence of a particular effect among the members of the category, based on a common functional group, physical-chemical properties, common reactivity, metabolism, and a presumed mode (and/or mechanism) of action based on a similar structure. However, a modulation of effects could appear as a result of a constant pattern in changing chemical structure or physical-chemical properties across the category. A chemical category approach may be suitable for more toxicological endpoints or other endpoints, since the structural changes across the category may affect changes in physical-chemical properties or other molecular descriptors or profilers that would cause changes of several toxicological properties or other endpoints of the individual category members in a coherent and consistent manner.

Table 4.8 *(cont.)*

Source	Original definition of the term 'chemical category'
	However, it may only be possible to identify the trends and changes for some, and not all, of the endpoints of potential interest. Hence, it may not be possible to use a category approach for all relevant hazard endpoints. In principle the above-listed non-testing techniques can be used to indicate either the presence or the absence of an effect or an estimated value (e.g., a relevant toxicity value such as a LOAEL) for an analogue or a group of substances. However, this is highly dependent on the substance under consideration, the endpoint, the level of information already available, the regulatory purpose, and the confidence that can be derived from its interpretation. NB. Figure 3 (p. 77) Stepwise approach to category development
EUROPEAN BODIES	
ECHA 2015b Regulatory challenges of nanomaterials workshop proceedings	In a category approach, a group of substances whose properties are likely to be similar or follow a regular pattern is constructed.
ECHA 2015a Read-Across Assessment Framework	The term category approach is used when read-across is employed between several substances that have structural similarity. These substances are grouped together on the basis of defined structural similarity and differences between the substances. As a result of the structural similarity, the toxicological properties will either all be similar or follow a regular pattern. Predictions should cover all parameters as required in the respective REACH information requirements. It may be possible to make predictions within the group for the target substance(s) on the basis of a demonstrable regular pattern. Alternatively, whenever there is more than one source substance in the category and no regular pattern is demonstrated for the property under consideration, the prediction may be based on a read-across from a category member with relevant information in a conservative manner (worst case). The basis for the prediction must be explicit.
ECHA 2014b Use of alternatives to testing on animals for REACH	Group of substances with physicochemical, toxicological and ecotoxicological properties that are likely to be similar or follow a regular pattern as a result of structural similarity.
ECHA 2013a Grouping of substances and read-across approach	[…] with a higher number of substances in a group the term *category approach* is used.
ECHA 2012c An introduction to the assessment of read-across in ECHA	[…] involves a larger group of substances and is supported by regular patterns in this group for the endpoint that has to be read across.
ECHA 2008a QSARs and grouping of chemicals	A chemical category is a group of chemicals whose physico-chemical and human health and/or environmental toxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity (or other similarity characteristic).

Table 4.8 *(cont.)*

Source	Original definition of the term 'chemical category'
	In principle, more members are generally present in a chemical category, enabling the detection of trends across endpoints. As the number of possible chemicals being grouped into a category increases, the potential for developing hypotheses for specific endpoints and making generalisations about the trends within the category will also increase, and hence increase the robustness of the evaluation. NB. Figure R.6-6 (p. 97) Stepwise procedure to category development
EC 2009 REACH Annex XI	Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances.
JRC 2005 Chemical categories and read-across	A chemical category is a group of chemicals whose physicochemical and toxicological (including ecotoxicological) properties are likely to be similar or follow a regular pattern as a result of structural similarity. These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and/or human health effects. The similarities may be based on the following: – a common functional group (e.g., aldehyde, epoxide, ester, etc.) related to specific – activity; or – the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals (e.g., the "family – approach" of examining related chemicals such as acid/ester/salt); and – an incremental and constant change across the category (e.g., the methylene group difference between adjacent members of the alpha-olefins). Within a category different members may be selected for the endpoint desired. If the available test results show that the chemicals in a category behave in a similar or predictable manner, then interpolation and/or extrapolation may be used to assess the chemicals instead of conducting additional testing.
US BODIES	
US EPA 2014a Nanomaterials under TSCA Presentation at ECHA workshop	Given the lack of data, EPA uses analogs to make determinations. – For many nanoscale materials where there are insufficient data, EPA uses data for the category "Respirable, Poorly Soluble Particulates" to assess potential hazard. – Category is limited to effects on the lung as a result of inhaling particles < 10 um in diameter.
US EPA 1999 Chemical categories	A chemical category, for the purposes of the Challenge Program, is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and/or human health effects. The similarities should be based on the following: – a common functional group (e.g., aldehyde, epoxide, ester, etc.); or – the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals (e.g., the "family approach" of examining related chemicals such as acid/ester/salt); and – an incremental and constant change across the category (e.g., the dimethylene group difference between adjacent members of the alpha-olefins – see Appendix). Within a category different members can be selected for the endpoint desired - i.e., those selected for a category approach for environmental effects endpoints may not be suitable for assessing human health effect endpoints. […]

Table 4.8 *(cont.)*

Source	Original definition of the term 'chemical category'
	If these test results show that the chemicals in the category behave in a similar or predictable manner, then interpolation and/or extrapolation can be used to assess the chemicals in lieu of conducting additional screening-level testing.
TSCA 2002 US Toxic Substances Control Act	The term "category of chemical substances" means a group of chemical substances the members of which are similar in molecular structure, in physical, chemical, or biological properties, in use, or in mode of entrance into the human body or into the environment, or the members of which are in some other way suitable for classification as such for purposes of this Act, except that such term does not mean a group of chemical substances which are grouped together solely on the basis of their being new chemical substances.
INDUSTRY ASSOCIATIONS	
CEFIC-LRI 2012 Experts workshop on read-across assessment	[…] is a group of substances whose physico-chemical and human health and/or environmental toxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity. In principle, more members are generally present in a chemical category, enabling the evaluation of trends within endpoints.
ECETOC 2012 Category approaches, read-across, (Q)SAR	In this report, the term 'category approach' and 'analogue approach' are used to describe techniques for grouping chemicals, whilst the term 'read-across' is reserved for a technique of filling data gaps in either approach. […] A chemical category describes a group of chemicals whose physicochemical and human health/environmental toxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity (or other similar characteristic). The category approach is, by its very nature, a weight of evidence approach (WoE), since it typically integrates both estimated and experimental data, and involves expert judgment. […] also provides a mean of strategic testing.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Godwin et al 2015 Nanomaterial categorization	[…] a chemical category is a group of chemicals whose physicochemical and human health and/or ecotoxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern, usually as a result of structural similarity.
Van Leeuwen et al 2009 Using chemical categories to fill data gaps in hazard assessment	Although the legal definitions of a chemical category may vary and will evolve through use, a chemical category is generally considered to be a group of chemicals whose properties are likely to be similar or follow a regular pattern as a result of mechanism, mode of toxic action or structural similarity. These similarities may create a predictable pattern in all or only some of the following parameters: physicochemical properties, quantum chemical properties, environmental fate, environmental effects and/or human health effects. The problem is there is no generally accepted method for measuring similarity. The similarities may be based on: – a common functional group (e.g. aldehyde, epoxide, ester) related to specific activity; – the likelihood of common precursors and/or breakdown products, via physical or toxicological processes, which result in structurally similar chemicals (e.g. the 'family approach' of examining related chemicals such as acid/ester/salt); – an incremental and constant change of key physicochemical properties across the category which determines other properties such as biological and (eco)toxicological effects (e.g. the methylene group difference between adjacent members of the alpha-olefins).

Table 4.8 *(cont.)*

Source	Original definition of the term 'chemical category'
	Within a category, different members may be selected for the endpoint to be assessed. If the available test results show that the chemicals in a category behave in a similar or predictable manner, then interpolation and/or extrapolation may be used to assess the untested chemicals instead of conducting additional testing. Chemical categories are 'designed' on the basis of scientific considerations such as mechanistic or behavioural similarity to enable reliable data gap filling using read-across, trend analysis, structural alerts and QSAR models.
Van Leeuwen et al 2007 Intelligent testing strategies	A chemical category is a group or "family" of chemicals whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. These structural similarities may create a predictable pattern in all or the following parameters: physicochemical properties, environmental fate, environmental effects, and/or human health effects. The similarities may be based on: – A common functional group (e.g., aldehyde, epoxide, ester) related to specific activity. – The likelihood of common precursors and/or breakdown products, via physical or toxicological processes, which result in structurally similar chemicals (e.g., the "family approach" of examining related chemicals such as acid/ester/salt). – An incremental and constant change of key physicochemical properties across the category which determines other properties such as biological and (eco)toxicological effects (e.g., the methylene group difference between adjacent members of the alphaolefins). Within a category, different members may be selected for the endpoint desired. If the available test results show that the chemicals in a category behave in a similar or predictable manner, then interpolation and/or extrapolation may be used to assess the chemicals instead of conducting additional testing.

4.9 Chemical Safety Assessment (CSA)

Table 4.9 shows the original definitions of the term 'Chemical Safety Assessment (CSA)', which have been collected from the literature and used to develop the NANoREG Definition. The term 'Chemical Safety Assessment (CSA)' is mainly used in REACH legal text and in principle applies to all substances including NMs (EP and EC 2006). Definitions could only be found in documents from European bodies such as REACH (EP and EC 2006) and Cosmetic Products Regulation (EP and EC 2008) legal texts, and ECHA official guidance for implementation of REACH (ECHA 2009, 2011b). Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by ECHA.

Table 4.9 Literature definitions collected for the key term 'Chemical Safety Assessment (CSA)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'Chemical Safety Assessment (CSA)'
EUROPEAN BODIES	
ECHA 2011b Introduction to the guidance document	The goal of the assessment is not to establish whether or not there is a risk, but to identify and describe the conditions under which the risks are controlled. Risks are regarded as controlled when the estimated exposure levels do not exceed the predicted no effect levels (DNEL or PNEC). For substances for which such no-effect levels cannot be determined, the risk characterisation consists of semi-quantitative or qualitative assessment of the likelihood that adverse effects are avoided.

Table 4.9 *(cont.)*

Source	Original definition of the term 'Chemical Safety Assessment (CSA)'
ECHA 2009 Guidance in a nutshell chemical safety assessment	Is the process that identifies and describes the conditions under which the manufacturing and use of a substance is considered to be safe. There are three major steps in the CSA process. These are: – Hazard assessment – Exposure assessment – Risk characterisation
EP and EC 2009 Cosmetic Products Regulation	In order to demonstrate that a cosmetic product complies with Article 3, the responsible person shall, prior to placing a cosmetic product on the market, ensure that the cosmetic product has undergone a safety assessment on the basis of the relevant information and that a cosmetic product safety report is set up in accordance with Annex I.
EP and EC 2006 REACH	A chemical safety assessment of a substance shall include the following steps: a) Human health hazard assessment b) Physicochemical hazard assessment c) Environmental hazard assessment d) Persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) assessment If, […] the registrant concludes that the substance meets the criteria for classification as dangerous […] or is assessed to be a PBT or vPvB, the chemical safety assessment shall include the following additional steps: a) Exposure assessment including the generation of exposure scenario(s) (or the identification of relevant use and exposure categories if appropriate) and exposure estimation; b) Risk characterisation.

4.10 Class of substances

Table 4.10 shows the original definitions of the term 'class of substances', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as UN (2003), in documents from European bodies such as CLP Regulation legal text (EP and EC 2008), and in documents from US/Canadian authorities including a report by NIESH (1997), CEPA legal text (CEPA 1999), and a report by RCC (2013). The term 'class of substances' is used with a different meaning in the considered sources. The harmonised definition adopted in NANoREG reflects the definitions provided by UN and considered in EU legislation, which in principle apply to all chemicals including NMs.

Table 4.10 Literature definitions collected for the key term 'class of substances' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'class of substances'
INTERNATIONAL BODIES	
RCC 2013 Joint Nanomaterials Classification Scheme	[…] the term "classification scheme" will refer to the organization of nanomaterials for regulatory purposes. The word 'classification' is not intended to be similar to its use in other regulatory/policy documents in Canada, the US or internationally. […] to establish criteria for identifying key characteristics of nanomaterials and subsequently determining which nanomaterials are sufficiently different from their non-nano counterparts to warrant a closer examination for environmental, human health, and

Table 4.10 *(cont.)*

Source	Original definition of the term 'class of substances'
	safety endpoints (those of concern); and which nanomaterials are sufficiently similar to their non-nano counterparts to be considered as traditional chemicals for regulatory purposes (those of no-concern). […] a classification scheme for nanomaterials based on similarities in chemical composition that will support the use of analogue/read across information.
UN 2003 Globally Harmonised System	Hazard class means the nature of the physical, health or environmental hazard, e.g. flammable solid, carcinogen, oral acute toxicity; […] the hazard classification process refers principally to the hazards arising from the intrinsic properties of the substances and mixtures […]
EUROPEAN BODIES	
EP and EC 2008 CLP Regulation	'hazard class' means the nature of the physical, health or environmental hazard;
US BODIES	
NIEHS 1997 Validation of alternative methods	Hazard classification: Assignment of a chemical or product hazard into a category of severity based on the results of a standard test method for a specific toxic endpoint; most commonly used for labelling purposes.
CANADIAN BODIES	
CEPA 1999 Canadian Environmental Protection Act	[…] "class of substances" means any two or more substances that (a) contain the same portion of chemical structure; (b) have similar physico-chemical or toxicological properties; or (c) for the purposes of sections 68, 70 and 71, have similar types of use.

4.11 Control Banding (CB)

Table 4.11 shows the original definitions of the term 'Control Banding (CB)', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as ISO (2012, 2014), in documents from US bodies (NIOSH 1999), and in peer-reviewed scientific literature (Brouwer 2012, Hoehener and Hoeck 2013). The definitions that are reported in ISO standards are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by ISO. The NANoREG harmonised definition also includes those considerations made in a recent peer-reviewed scientific publication (Brouwer 2012) with regard to the application of this concept to NMs.

Table 4.11 Literature definitions collected for the key term 'Control Banding (CB)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'Control Banding (CB)'
INTERNATIONAL BODIES	
ISO 2014 Use of the control banding approach	Control banding is a pragmatic approach which can be used for the control of workplace exposure to possibly hazardous agents with unknown or uncertain toxicological properties and for which quantitative exposure estimations are lacking. It may complement the traditional quantitative methods based on air sampling and analysis with reference to OELs when they exist. It can provide an alternative risk assessment and risk management process, by grouping occupational settings in categories presenting similarities of hazards and/or exposure, while incorporating professional judgment and monitoring. This process applies a range of control techniques (such as general ventilation or containment) to a specific chemical, considering its range (or band) of hazard and the range (or band) of exposure. In general, control banding is based on the idea that while workers can be exposed to a diversity of chemicals, implying diversity in risks, the number of common approaches to risk control is limited. These approaches are grouped into levels based on how much protection the approach offers (with "stringent" controls being the most protective). The greater the potential for harm, the greater the levels of protection needed for exposure control.
ISO 2012 Occupational risk management applied to engineered nanomaterials	Control banding (CB) is an approach by which control methods are selected based on knowledge or assumptions about the hazardous nature of the materials being used and the exposure potential of the situation. CB has frequently been used in risk management guidance for other particles and chemicals and is usually based on a matrix having the axes exposure and hazard into which various control approaches are placed. CB therefore requires the user to have knowledge of, or make judgments concerning, the relative hazard of the materials being used and/or the relative exposure potential of the material and situation. Paik et al.[30] have described the development of a pilot control banding tool for NOAAs. ISO/TS 12901- 2 describes a specific tool based on control banding to further support the implementation of good practice in this area.
US BODIES	
NIOSH 2009 Control banding	A strategy that groups workplace risks into control categories or bands based on combinations of hazard and exposure information. The following four main CBs have been developed for exposure to chemicals by inhalation: Band 1: Use good industrial hygiene (IH) practice and general ventilation. Band 2: Use local exhaust ventilation. Band 3: Enclose the process. Band 4: Seek expert advice. This qualitative strategy to assess and manage risk focuses resources on exposure controls and describes how strictly a risk needs to be managed.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Hoehener and Hoeck 2013 Consolidated framework EHS draft	In the absence of occupational exposure limits and definitive knowledge of toxicity, control banding is a qualitative strategy for classifying and handling chemicals and hazards associated with chemical exposures in the workplace, as well as for assessing potential risks for consumers and the environment.
Brouwer 2012 Control banding for nanomaterials	Basically, it is a risk assessment approach in a context of uncertainty using the generally accepted risk paradigm, where risk is a function of severity of impact (hazard) and the anticipated probability of that impact (exposure). Both hazard and exposure are graded into two to five different levels, usually referred as bands. The two sets of bands are combined, most often in a matrix, resulting into control or risk bands.

4.12 Data gap

Table 4.12 shows the original definitions of the term 'data gap', which have been collected from the literature and used to develop the NANoREG Definition. One definition could be found (OECD 2014a). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definition provided by OECD.

Table 4.12 Literature definitions that have been collected for the key term 'data gap' and have been considered to develop the NANoREG Definition.

Source	Original definition of the term 'data gap'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	A data gap is a physical-chemical, environmental fate, ecotoxicological, or mammalian toxicological/human health endpoint for which data are not available when required for an assessment.

4.13 Data gap filling

Table 4.13 shows the original definitions of the term 'data gap filling', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (OECD 2014a), in document from EU bodies such as ECHA official guidance for implementation of REACH (ECHA 2008a), and in reports from industry associations (ECETOC 2012). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.13 Literature definitions collected for the key term 'data gap filling' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'data gap filling'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	[…] is the process of providing data to inform upon a particular endpoint by whatever means is scientifically justified including alternative techniques to direct testing. […] non-testing methods for filling data gaps: – Read-across; – Trend analysis and use of computational methods based on internal models; – Use of computational methods based on external models.
EUROPEAN BODIES	
ECHA 2008a QSARs and grouping	Non-testing data can be generated by three main approaches: a) grouping approaches, which include read-across and chemical category formation; (quantitative) structure-activity relationships ((Q)SARs); and c) expert systems.

Table 4.13 *(cont.)*

Source	Original definition of the term 'data gap filling'
	The development and application of all kinds of non-testing methods is based on the similarity principle, i.e. hypothesis that similar compounds should have similar biological activities. Within a chemical category, data gaps may be filled by read-across, trend analysis and QSARs. […] non-testing techniques for filling data gaps: – read-across – trend analysis and use of computational methods based on internal models – use of computational methods based on external models
INDUSTRY ASSOCIATIONS	
ECETOC 2012 Category approaches, read-across, (Q)SAR	Whenever a category is formed, data gaps may be filled in using read-across (qualitative or quantitative), trend analysis (local (Q)SAR) and external (Q)SAR models and expert systems.

4.14 Endpoint

Table 4.14 shows the original definitions of the term 'endpoint', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (OECD 2005, 2012a, 2014a), in documents from EU bodies such as ECHA official guidance for implementation of REACH (ECHA 2014b, 2015a), and in reports from European national authorities (Danish EPA 2013). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.14 Literature definitions collected for the key term 'endpoint' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'endpoint'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	An endpoint refers to a broad description of a specific environmental or toxicological property, for example acute oral toxicity, or water solubility.
OECD 2012b Collection of working definitions	The recorded observation coming from an *in chemico* method, an *in vitro* assay or an *in vivo* assay. The measurement of a biological effect, e.g. LC50 or EC50. A large number of endpoints are used in regulatory assessments of chemicals. These include lethality, carcinogenicity, immunological responses, organ effects, developmental and reproductive effects, etc. In QSAR analysis, it is important to develop models for individual toxic endpoints.

Table 4.14 *(cont.)*

Source	Original definition of the term 'endpoint'
OECD 2005 Validation of new or updated test methods	The biological or chemical process, response, or effect, assessed by a test.
EUROPEAN BODIES	
ECHA 2015a Read-Across Assessment Framework	The word "endpoint" has different meanings depending on the context in which it is used and so can lead to misunderstandings. In the context of the REACH information requirements, endpoints are listed in column 1 of the standard information requirements (Annex VI to X) and are described either as a property itself (e.g. skin irritation) and/or as a type of study (e.g. carcinogenicity study). Other hazardous properties of a substance partially/not covered by the column 1 information requirements (e.g. immunotoxicity) may also be relevant to understanding the hazards and risks a substance may present. Due to the different complexities (e.g. key parameters, biological targets) of each endpoint, a read across must be specific to the endpoint or property under consideration. In the context of this document, preference is given to the term "property", which is used to describe the outcome of a relevant study used to fulfil a REACH information requirement.
ECHA 2014b Use of alternatives to testing on animals for REACH	Observable or measurable inherent property/data point of a chemical substance. It may refer to a physical-chemical property (such as vapour pressure), or to degradability, or to a biological effect that a given substance has on human health or the environment (e.g. carcinogenicity, irritation, or aquatic toxicity).
EUROPEAN NATIONAL AUTHORITIES	
Danish EPA 2013 IRNANO	An endpoint or parameter defines more precisely what the outcome investigated during the testing is, e.g. mortality or behavioural changes in (eco-)toxicity studies. Thus, toxicological testing often looks at several endpoints/parameters within a given test.

4.15 Exposure Scenario (ES)

Table 4.15 shows the original definitions of the term 'Exposure Scenario (ES)', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2003) and IPSC (2004), in documents from EU bodies such as REACH legal text (EP and EC 2006) and ECHA official guidance for REACH implementation (ECHA 2011b), and in documents from US bodies such as US EPA (1992, 1998). Several organisations (i.e. IPSC, OECD and US EPA) propose a generic definition of ES in risk assessment. In the context of REACH, a specific definition of ES is used. The harmonised definition adopted in NANoREG includes and discusses both types of definition.

Table 4.15 Literature definitions collected for the key term 'Exposure Scenario (ES)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'Exposure Scenario (ES)'
INTERNATIONAL BODIES	
IPCS 2004 Risk assessment terminology	A set of conditions or assumptions about sources, exposure pathways, amounts or concentrations of agent(s)involved, and exposed organism, system, or (sub)population (i.e., numbers, characteristics, habits) used to aid in the evaluation and quantification of exposure(s) in a given situation. A combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur. These may include the source, the exposed population, the time frame of exposure, microenvironment(s), and activities. Scenarios are often created to aid exposure assessors in estimating exposure.
OECD 2003 Key generic terms	A set of conditions or assumptions about sources, exposure pathways, amount or concentrations of agent(s) involved, and exposed organism, system, or (sub) population (i.e., numbers, characteristics, habits) used to aid in the evaluation and quantification of exposure(s) in a given situation.
EUROPEAN BODIES	
ECHA 2011b Introduction to guidance document	[…] identify and document the conditions of manufacture and use which are needed for controlling the risks to human health and the environment. This includes operational conditions (OC) and risk management measures (RMM). In REACH this set of information is called "exposure scenario" (ES). The goal of the assessment is not to establish whether or not there is a risk, but to identify and describe the conditions under which the risks are controlled.
EP and EC 2006 REACH Regulation	[…] means the set of conditions, including operational conditions and risk management measures, that describes how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment. These exposure scenarios may cover one specific process or use several processes or uses as appropriate; […]
US BODIES	
US EPA 1998 Guidance on ecological risk assessment	A set of assumptions concerning how an exposure may take place, including assumptions about the exposure setting, stressor characteristics, and activities that may lead to exposure.
US EPA 1992 Guidance on exposure assessment	In exposure scenario evaluation, the assessor attempts to determine the concentrations of chemicals in a medium or location and link this information with the time that individuals or populations contact the chemical. The set of assumptions about how this contact takes place is an exposure scenario. An exposure scenario is the set of information about how exposure takes place. An exposure scenario generally includes facts, data, assumptions, inferences, and sometimes professional judgment about the following: – The physical setting where exposure takes place (exposure setting). – The exposure pathway(s) from source(s) to exposed individual(s) (exposure pathways). – The characterization of the chemical, i.e., amounts, locations, time variation of concentrations, source strength, environmental pathways from source to exposed individuals, fate of the chemical in the environment, etc. (characterization of the chemical). – Identification of the individual(s) or population(s) exposed, and the profile of contact with the chemical based on behaviour, location as a function of time, characteristics of the individuals, etc. (characterization of the exposed population).

Table 4.15 *(cont.)*

Source	Original definition of the term 'Exposure Scenario (ES)'
	– If the dose is to be estimated, assumptions about the transfer of the chemical across the boundary, i.e., ingestion rates, respiration rates, absorption rates, etc. (intake and uptake rates). Exposure scenario - A set of facts, assumptions, and inferences about how exposure takes place that aids the exposure assessor in evaluating, estimating, or quantifying exposures.

4.16 Extrapolation

Table 4.16 shows the original definitions of the term 'extrapolation', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2014a), in documents from European bodies such as a report by JRC (2005), and in reports from industry associations (CEFIC-LRI 2012). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.16 Literature definitions collected for the key term 'extrapolation' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'extrapolation'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	[…] the process where data from category members at one side of the category is used to predict the hazards of those members at the other side. Of course, it could also be said that an analogue approach itself is by default an extrapolation, unless there are analogues identified that bracket the target chemical. […] refers to the estimation of a value for a member that is near or at the category boundary using measured values from internal category members. There is a preference for the use of interpolation rather than extrapolation, because extrapolation is perceived to be more uncertain and therefore less reliable.
EUROPEAN BODIES	
JRC 2005 Chemical categories and read-across	[…] extrapolation refers to the estimation of a value for a member that is near or at the category boundary using measured values from internal category members […] In general, interpolation between category members is preferred to extrapolation. However, in certain cases, such as where toxicity does not change among tested category members, extrapolation to other category members may be acceptable.
INDUSTRY ASSOCIATIONS	
CEFIC-LRI 2012 Experts workshop on read-across assessment	It is intuitive that confidence in the read-across prediction is enhanced when experimental data for structural analogues allows for interpolation rather than extrapolation. For analogue approaches the interpolation/extrapolation distinction is perhaps less meaningful. An analogue approach by default is an extrapolation since the target chemical compared to the source either possesses the toxicity-determining features to a lesser degree (target predicted less potent than source) or a greater degree (target predicted more potent than source).

4.17 Framework

Table 4.17 shows the original definitions of the term 'framework', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in online dictionaries (Merriam-Webster 2015) and in peer-reviewed scientific literature (Hristozov et al 2012). Accordingly, the harmonised definition adopted in NANoREG combines elements of these definitions and proposes a suitable one for the project.

Table 4.17 Literature definitions collected for the key term 'framework' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'framework'
ONLINE DICTIONARIES	
Merriam-Webster 2015	1 /a : a basic conceptional structure (as of ideas) /b : a skeletal, openwork, or structural frame 2: frame of reference 3: the larger branches of a tree that determine its shape"
PEER-REVIEWED SCIENTIFIC LITERATURE	
Hristozov et al 2012	A "framework" is a set of practices, organised in a conceptual manner that constitute a policy;

4.18 Grouping

Table 4.18 shows the original definitions of the term 'grouping', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (OECD 2014a; 2014b, Igarashi 2014), in documents from European bodies such as REACH legal text (EP and EC 2006, EC 2009) and ECHA official guidance for implementation of REACH (ECHA 2008a; 2013a; 2013b; 2015a), in reports from European national authorities (RIVM 2015), in reports from industry associations (ECETOC 2012), and in peer-reviewed scientific literature (Walser and Studer 2015, Arts et al 2014). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. These definitions are reflected in ECHA official guidance documents for implementation of REACH and in guidance by industry and apply to all chemicals including NMs. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD. The NANoREG harmonised definition also includes those clarifications made by several organisations (OECD, ECHA GAARN, RIVM) and scientists with regard to the application of this concept to NMs (ECHA 2013b; OECD 2014a; Arts et al 2014; RIVM 2015; Godwin et al 2015).

Table 4.18 Literature definitions collected for the key term 'grouping' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'grouping'
INTERNATIONAL BODIES	
Igarashi T 2014 Expert meeting on categorisation of manufactured nanomaterials OECD member countries' approaches to grouping, read-across, equivalence of nanomaterials	Concept of grouping: This may be a category approach or an analogue approach, where nanomaterials are grouped based on their physical-chemical properties; […] Grouping should take into account, that some nanomaterials show very different physico-chemical properties, only depending on minor surface modifications. Therefore, grouping shall not be based on a chemical composition approach alone. Until nano-specific practices are developed, if needed, the OECD Guidance on Grouping of Substances provides a set of useful approaches that are generally applicable to nanomaterials.
OECD 2014b Expert meeting on categorisation of manufactured nanomaterials Background document	While the grouping of chemicals, particularly for purposes of hazard assessment, is used in many jurisdictions, nanomaterials introduce additional challenges, due to intrinsic and extrinsic differences in physical and chemical properties and differences among nano-forms of a chemical species, and between nano and non-nano forms. Further, they often do not exist as distinct species; rather the populations of the materials can consist of distinct species and agglomerates and aggregates and their properties are dependent upon the medium in which they are found. Thus, in looking at how to group nanomaterials, in addition to chemical composition and shape there are also considerations of properties, such as surface charge, which add complexity to the exercise. The context of this OECD Expert Meeting is regulatory, and regulators typically distinguish substances under their respective laws based on a molecular identity (material) focus as opposed to only a properties focus. Thus, while a consideration of properties should also be considered in developing the scheme, any categories being proposed at the workshop should also be based on molecular identity. Specifically, the framework of the categorization scheme should start with molecular identity as shown in the categorization scheme below.
OECD 2014a Guidance on grouping of chemicals	The way in which grouping is undertaken to predict properties of some members of the group depends on the purpose of the prediction, e.g., for commercial decision-making, screening and priority-setting of chemicals for further evaluation, hazard identification for risk assessment and classification and labelling, filling information requirements in different regulatory schemes. Therefore, the administrative practice, standard of proof, and degree of scientific certainty in the assessment will all vary depending on the purpose of the prediction. If grouping is applied, not every chemical needs to be tested for every required endpoint. Rather, the data for chemicals and endpoints that have been tested can be used to estimate the corresponding properties for the untested chemicals and endpoints. Grouping of chemicals can lead to the application of a category or an analogue approach. The general approach for considering more than one chemical at the same time. It can include formation of a chemical category or identification of (a) chemical analogue(s) with the aim of filling data gaps as appropriate. […] makes it possible to extend the use of measured data to similar untested chemicals. […] reliable estimates that are adequate for classification and labelling and/or risk assessment can be made without further testing. […] an alternative to testing individual chemicals and as a result should lead to a decrease in the use of animal testing. The rationale underpinning the analogue approach and the category approach may be based on the following: – Common functional group(s) […]; – A common mode or mechanism of action or adverse outcome pathway; – Common constituents or chemical classes, similar carbon range numbers […]; – The likelihood of common precursors and/or breakdown products via physical or biological processes that result in structurally similar chemicals […]; – An incremental and constant change across the category […].

Table 4.18 *(cont.)*

Source	Original definition of the term 'grouping'
	While a category may in principle be based on one of these rationales, in practice endpoint justifications and supporting information will be multifaceted. All pre-existing experimental or other (e.g., from the literature) evidence that can support the category needs to be addressed. This could be similar effects in lower-tier studies where these exist, availability of "bridging" studies that are not necessarily endpoint related (e.g., common results in in vitro or other types of screening studies), evidence from computational and non-computational theoretical models, common bioavailability, metabolism and reactivity profiles, common mode and/or mechanism of action (MOA), or adverse outcome pathway (AOP). The definition of a group starts with structural similarity and allowed structural differences and then continues with investigating the hypothesis for common mode of action. The possibility to confirm a common mode (and/or mechanism) of action within a chemical category has been further investigated in the last years at OECD via the development of the concept of adverse outcome pathways (AOPs). In principle the above-listed non-testing techniques can be used to indicate either the presence or the absence of an effect or an estimated value (e.g., a relevant toxicity value such as a LOAEL) for an analogue or a group of substances. However, this is highly dependent on the substance under consideration, the endpoint, the level of information already available, the regulatory purpose, and the confidence that can be derived from its interpretation. At present, it seems premature to develop guidance on grouping specifically for nanomaterials. Nevertheless, research efforts will pave the way for common approaches and frameworks to grouping nanomaterials for purpose of hazard assessment in the future. In addition, expand further on why certain properties tend to elicit certain effects in vitro or in vivo and where opportunities may exist to group nanomaterials together to rationalize testing. Section 6.9 will be amended as accepted principles for grouping and read-across of nanomaterials arise from these activities.
EUROPEAN BODIES	
ECHA 2015a Read-Across Assessment Framework	Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. Structural similarity is a pre-requisite for any grouping and read-across approach under REACH. These similarities may be due to a number of factors: – Common functional group (i.e. chemical similarity within the group), – Common precursors and/or likelihood of common breakdown products via physical and/or biological processes which result in structurally-similar degradation products (i.e. similarity through (bio)transformation), or – A constant pattern in the changing of the potency of the properties across the group (i.e. of physico-chemical and/or biological properties).
ECHA 2013b Second GAARN meeting Best practices for REACH registrants	A basis for grouping the nanoforms/nanomaterials of interest (in terms of their similarity) should be established using the similarity rules specified in Annex XI of the REACH Regulation. The hypothesis, or basis for the grouping, should be used to define what characteristics a nanoform/nanomaterial should have in order to belong to a category. The similarity rules (which could also be called criteria or principles) might be used individually and are case-dependent. However, a category (and similarity) may be justified on more than one basis, as multiple justifications usually increase the confidence in the category. The hypothesis will help to show if the grouping applies to the category members for either environmental or toxicological endpoints or both, and if it is adequate for all routes of exposure and duration of effects (Practical Guide 6, ECHA 2009). The registration dossier should contain a comprehensive physicochemical characterisation of the registered nanoform(s) (First GAARN meeting best practices report). Only when well-characterised nanoforms are reported in the dossier, can a read-across approach or use of existing data (e.g. weight of evidence) be considered for the purpose of hazard assessment. Generating data on toxicokinetics might also be considered for grouping substances in relation to read-across approaches, or extrapolating from in vitro to in vivo situations.

Table 4.18 *(cont.)*

Source	Original definition of the term 'grouping'
ECHA 2013a Grouping of substances and read across approach	Substances that are structurally similar with physicochemical, toxicological, ecotoxicological and/or environmental fate properties that are likely to be similar or to follow a regular pattern may be considered as a *group* of substances. These similarities may be due to a number of factors: – Common functional group (i.e. chemical similarity within the group) – Common precursors and/or likely common breakdown products via physical and/or biological processes which result in structurally-similar degrading chemicals – A constant pattern in the properties across the group […]
ECHA 2008a QSARs and grouping of chemicals	[…] describes the general approach to assessing more than one chemical at the same time. It can include formation of a chemical category or identification of a chemical analogue for which read-across may be applied. The similarities may be based on the following: – Common functional group(s) […]; – A common mode or mechanism of action or adverse outcome pathway; – Common constituents or chemical classes, similar carbon range numbers […]; – The likelihood of common precursors and/or breakdown products via physical or biological processes that result in structurally similar chemicals […]; – An incremental and constant change across the category […].
EP and EC 2006; EC 2009 REACH Annex XI	Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. The similarity may be based on: (1). A common functional group; (2). The common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or (3). A common pattern in the changing of the potency of the properties across the category.
EUROPEAN NATIONAL AUTHORITIES	
RIVM 2015 Grouping nanomaterials	Scientists have determined many ways in which changing the size of a particle can change the properties of a material and have identified many of the other important variables that influence the behaviour of a nanomaterial […]. The results of research to date do not allow for tightly defined algorithms for grouping nanomaterials. They do allow, as described in this report, for drawing some "read-across" conclusions based on the weight of evidence. Some physicochemical data are so essential to characterising a nanomaterial that they should be compiled during the initial step in the process. These data include chemical composition, surface characteristics, impurities and surface area.
INDUSTRY ASSOCIATIONS	
ECETOC 2012 Category approaches, Read-across, (Q)SAR	In this report, the term 'category approach' and 'analogue approach' are used to describe techniques for grouping chemicals, whilst the term 'read-across' is reserved for a technique of filling data gaps in either approach.

Table 4.18 *(cont.)*

Source	Original definition of the term 'grouping'
PEER-REVIEWED SCIENTIFIC LITERATURE	
Walser and Studer 2015 Nanomaterial sameness and grouping schemes	A grouping scheme is therefore required which allows for bundling similar nanomaterials into *clouds* with underlying test strategies. A cloud may be constructed on the basis of modes of action (MOA), which can lead via adverse outcome pathways (AOP) to impacts such as chronic toxicity, reproductive toxicity, genotoxicity, etc. (OECD 2014). […] Clouds can accommodate nanomaterials of different entities (and hence different physicochemical properties) as long as their hazard is based on the same AOPs. In addition, test results can be transferred from one to another cloud if the underlying AOPs are the same for a specific endpoint (read across). […] the clouds and the entities are complementary concepts to be combined in the regulatory hazard assessment of nanomaterials. The grouping of unlimited identities into entities allows us (i) to distinguish different nanomaterials and (ii) to unify similar nanomaterials. Hence, it provides an interpretation of ''sameness'' based on physico-chemical properties. The grouping strategy helps industry, research and regulatory authorities to decide on a new notification or to identify a similar nanomaterial of the same entity already notified.
Arts et al 2014 Critical appraisal grouping nanomaterials	[…] This grouping concept implies that some, if not all, information on the hazard of a NM can be derived from the respective bulk material, from molecules or ions of its constituents, or from similar NMs. […]NM grouping should not be restricted to the determination of nanostructure–activity relationships, but should take into account all aspects of the substance's entire life cycle. These aspects include the NM's material properties (e.g. size, shape, crystallinity) and biophysical interactions (e.g. generation of oxidative species), its intended use (and hence incorporation into the respective product and possible release therefrom), the 'external exposure' to the NM (i.e. the dose level and physicochemical form of the NM exposure outside the body), NM uptake and 'internal exposure' (referring to the NM's concentration and physico-chemical form at the site of action in the organism), and, finally, its biokinetics and possible early biological and apical effects.

4.19 Harmonisation

Table 4.19 shows the original definitions of the term 'harmonisation', which have been collected from the literature and used to develop NANoREG Definition. Definitions could be found in documents and webpages from international organisations such as UN (2003) and OECD (2015). The term is defined at UN and OECD level with different scope/meaning. Accordingly, the harmonised definition adopted in NANoREG includes a generic definition of the term 'harmonisation' and considers OECD and UN activities as examples of such a process.

Table 4.19 Literature definitions collected for the key term 'harmonisation' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'harmonisation'
INTERNATIONAL BODIES	
OECD 2015 Testing of chemicals	OECD assists countries in harmonising test methods for chemical safety and good laboratory practice, in order to ensure high quality and reliable data and for countries and industry to fully benefit from the OECD agreement on Mutual Acceptance of Data and avoid duplicative testing. Under the Mutual Acceptance of Data system, results from a chemical safety test conducted in OECD countries shall be accepted by other OECD and adhering countries if the test was carried out according to OECD Test Guidelines and GLP Principles.
UN 2003 Globally Harmonised System	[…] harmonisation means establishing a common and coherent basis for chemical hazard classification and communication, from which the appropriate elements relevant to means of transport, consumer, worker, and environment protection can be selected; […]

4.20 Information requirement

Table 4.20 shows the original definitions of the term 'information requirement', which have been collected from the literature and used to develop the NANoREG Definition. No definitions in documents from international organisations could be found. Definitions could only be retrieved from documents prepared by European bodies such as REACH legal text (EP and EC 2006) and reports from national authorities (Danish EPA 2013). Accordingly, the harmonised definition adopted in NANoREG reflects the definition provided by Danish EPA as the text of this definition is generic enough to cover any type of information on chemicals required by any legal text including REACH.

Table 4.20 Literature definitions collected for the key term 'information requirement' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'information requirement'
EUROPEAN BODIES	
EP and EC 2006 REACH Annex VI	Annexes VI to XI specify the information that shall be submitted for registration and evaluation purposes according to Articles 10, 12, 13, 40, 41 and 46. […] what information is required for registration.
EUROPEAN NATIONAL AUTHORITIES	
Danish EPA 2013 IRNANO	An information requirement is generally understood as the entry in a legal text requiring information on e.g. physicochemical, toxicological and ecotoxicological properties.

4.21 Interpolation

Table 4.21 shows the original definitions of the term 'interpolation', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2014a) and IUPAC (Duffus et al 2007), in documents from European bodies such as JRC (2005), and

reports from industry associations (CEFIC-LRI 2012). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. These definitions are taken on board by industry in their guidance documents and in principle apply to all chemicals including NMs. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.21 Literature definitions collected for the key term 'interpolation' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'interpolation'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	Within a category where trends in toxicity or factors influencing toxicity have been identified and the category members arranged in line with the trend as illustrated in Figure 1, interpolation can be described as the process whereby data from category members on either side of a datapoor category member is used to predict its hazards. […] the estimation of a value for a member using measured values from other members on "both sides" of that member within the defined category spectrum There is a preference for the use of interpolation rather than extrapolation, because extrapolation is perceived to be more uncertain and therefore less reliable.
Duffus et al 2007 IUPAC recommandations	Estimation of a value between two known data points.
EUROPEAN BODIES	
JRC 2005 Grouping and read-across approaches	Interpolation is the estimation of a value for a member using measured values from other members on "both sides" of that member within the defined category spectrum. In general, interpolation between category members is preferred to extrapolation. However, in certain cases, such as where toxicity does not change among tested category members, extrapolation to other category members may be acceptable. Interpolation can be performed with a certain confidence when the series of values is monotonic (all increasing or decreasing), but guidance is needed in the case that one or more values are outliers to the trend.
INDUSTRY ASSOCIATIONS	
CEFIC-LRI 2012 Expert workshop on read-across assessment	It is intuitive that confidence in the read-across prediction is enhanced when experimental data for structural analogues allows for interpolation rather than extrapolation. For analogue approaches the interpolation/extrapolation distinction is perhaps less meaningful. An analogue approach by default is an extrapolation since the target chemical compared to the source either possesses the toxicity-determining features to a lesser degree (target predicted less potent than source) or a greater degree (target predicted more potent than source). The legal text expressly stipulates interpolation.

4.22 Life cycle

Table 4.22 shows the original definitions of the term 'life cycle', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as ISO (2006) and in documents from European bodies such as ECHA official guidance for implementation of REACH (ECHA 2010b; 2011b). The definitions that are reported in ISO standards are

given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. However, these definitions are generic and applicable to any product system. Since REACH provisions for chemicals and NMs are extensively discussed within NANoREG, the definition of the term 'life cycle of a substance' provided by ECHA needs also to be considered. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by both OECD and ECHA.

Table 4.22 Literature definitions collected for the key term 'life cycle' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'life cycle'
INTERNATIONAL BODIES	
ISO 2006 Life cycle assessment	[…] consecutive and interlinked stages of a product system, from raw material acquisition or generation from natural resources to final disposal
EUROPEAN BODIES	
ECHA 2011b Introduction to the guidance document	The exposure assessment needs to cover manufacture and all identified uses of the substance and to consider all life-cycle stages resulting from the manufacture and identified uses. It needs to cover all relevant human and environmental exposure routes and populations. […] life cycle stages subsequent to identified uses (releases from articles and releases from waste life stage). […] information on manufacture (if within EU), use, handling and disposal of the substance or of articles containing the substance (i.e. covering its whole life cycle), […] The exposure assessment shall cover manufacture and all identified uses of the substance and the life cycle stages resulting from these identified uses. This includes, where relevant, service-life of articles and the waste life stages of the substance on its own, in mixtures or in articles.
ECHA 2010a Use descriptor system	Seven main groups of actors play a role during the life cycle of the substance: Manufacturers and importers of chemical substances (including metals and minerals), companies mixing and blending chemicals (formulators) to produce mixtures, distributors, industrial end-users, professional end-users and consumers. The life cycle stage at which a use takes place (manufacture, formulation or end-use), […] […] life cycle stages (manufacture, formulation, end-use or service life) […] "Stages" include one or more uses at a certain life cycle stage which are being characterised by similar conditions of use with i) regard to the environment and ii) the main user group. There are 3 main user groups and 4 stages. For the stages "manufacture" and "formulation" it is assumed that they always take place under industrial conditions.

4.23 Life Cycle Assessment (LCA)

Table 4.23 shows the original definitions of the term 'Life Cycle Assessment (LCA)', which have been collected from the literature and used to develop a harmonised definition in NANoREG. Definitions could be found in documents from international organisations such as ISO (2006), in documents from European bodies such as JRC (2010) and in peer-reviewed scientific literature (Som et al 2010, SETAC 1993). The definitions that are reported in ISO standards are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. However, these definitions are generic and applicable to any product system. A specific

definition of LCA for chemicals and/or NMs could not be found. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by ISO and also considers those considerations made by scientists in peer-reviewed scientific literature with regard to the application of this concept to NMs (Som et al 2010).

Table 4.23 Literature definitions collected for the key term 'Life Cycle Assessment (LCA)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'life cycle assessment (LCA)'
INTERNATIONAL BODIES	
ISO 2006 Life cycle assessment	Compilation and evaluation of the inputs, outputs and the potential environmental impacts of a product system throughout its life cycle. LCA addresses the environmental aspects and potential environmental impacts (e.g. use of resources and the environmental consequences of releases) throughout a product's service life cycle from raw material acquisition through production, use, end-of-life treatment, recycling and final disposal (i.e. cradle-to-grave).
EUROPEAN BODIES	
JRC 2010 ILCD Handbook	Life Cycle Assessment (LCA) is a structured, comprehensive and internationally standardised method. It quantifies all relevant emissions and resources consumed and the related environmental and health impacts and resource depletion issues that are associated with any goods or services ("products"). Life Cycle Assessment takes into account a product's full life cycle: from the extraction of resources, through production, use, and recycling, up to the disposal of remaining waste. Critically, LCA studies thereby help to avoid resolving one environmental problem while creating others: This unwanted "shifting of burdens" is where you reduce the environmental impact at one point in the life cycle, only to increase it at another point. Therefore, LCA helps to avoid, for example, causing waste-related issues while improving production technologies, increasing land use or acid rain while reducing greenhouse gases, or increasing emissions in one country while reducing them in another. Life Cycle Assessment is therefore a vital and powerful decision support tool, complementing other methods, which are equally necessary to help effectively and efficiently make consumption and production more sustainable.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Som et al 2010 Life cycle concepts in safe nanoproducts	The wording —life cycle assessmentǁ stands exclusively for a clearly defined methodological framework that has been developed in the early 1990ʻs as reported e.g. in the ISO 14040/14044 standards. LCA is essentially a comprehensive tool for environmental sustainability assessment. In theory, it takes into account all inputs (i.e. materials, energy, chemicals, land use etc) and all outputs (i.e. emissions, solid waste, products etc.) throughout the life-cycle of a product – from the extraction of the resources to the final disposal of the product. LCA evaluates thereby the overall impacts of a product system on natural environment, human health, natural resources, and man-made environment. LCA can be used for comparing a product that includes ENMs with similar products without ENMs and thus to assess the relative environmental performance of nanoproducts in comparison with their conventional equivalents. The main contribution of LCA is often towards impact categories like resource use, global warming, acidification, ecotoxicity, human welfare and other. Whereas risk assessment of nanomaterials focuses on the toxic impacts, LCA provides a more comprehensive overview of the potential environmental impacts of nanoproducts, including all other substances used during manufacturing of the product.
SETAC 1993 Guidelines for LCA	LCA is a way of assessing the environmental burdens associated with the whole life cycle of a product or service, from its cradle to its grave

4.24 Mode of action

Table 4.24 shows the original definitions of the term 'mode of action', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2011; 2012a; 2014a) and reports from industry associations (ECETOC 2007). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.24 Literature definitions collected for the key term 'mode of action' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'mode of action'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	A mode of action describes a functional or anatomical change, at the cellular level, resulting from the exposure of a living organism to a chemical. In comparison, a mechanism of action describes such changes at the molecular level. A mechanism of action denotes the sequence of events leading from the absorption of an effective dose of a chemical to the production of a specific biological response in the target organ. Understanding a chemical's mechanism requires appreciation of the causality and temporal relationships between the steps leading to a particular toxic endpoint, as well as the steps that lead to an effective dose of the chemical at the relevant biological target(s).
OECD 2012b Collection of working definitions	[…] it relates to the events including, and downstream of, the toxicity pathway. These could lead to an adverse effect in an individual. The MoA starts with the molecular initiating event. Unlike AOP, it does not (usually) include consideration of exposure or effects at higher levels than the individual.
OECD 2011 Mechanistic information in forming chemical categories	The sequence of key events and cellular and biochemical events (measurable parameters), starting with the interaction of an agent with the target cell, through functional and anatomical changes, resulting in cancer or other adverse health effects (USEPA 2005; Boobis, Doe et al. 2008). Mode of action differs from mechanism, in that the latter implies a more detailed understanding of the molecular basis of the toxic effect (Seed et al. 2005).
INDUSTRY ASSOCIATIONS	
ECETOC 2007 Mode of action approach for specifically acting chemicals	A common set of physiological and behavioural signs that characterise a type of adverse biological response, where the major (but not all) biochemical steps are understood.

4.25 Nanoform

Table 4.25 shows the original definitions of the term 'nanoform', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could not be found in documents from international organisations. The term is used in several documents from European bodies (EC 2008a, JRC and ECHA 2012, ECHA 2012a, ECHA 2013a, SCCS 2013, SCCS 2015) and in reports from industry associations (ETUC 2010), and is often used as a synonymous of 'nanomaterial' (EC 2011). Accordingly, the harmonised definition adopted in NANoREG takes inspiration from the definition reported

in two documents prepared by European bodies (EC 2008a; JRC and ECHA 2012) and linked to REACH. The NANoREG harmonised definition has been developed in agreement with ECHA and is in line with the definition of the term 'nanomaterial' developed by the European Commission (EC 2011).

Table 4.25 Literature definitions collected for the key term 'nanoform' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'nanoform'
EUROPEAN BODIES	
SCCS 2015 Factsheet on silica in nanoform	Something is in 'nanoform' when particles of that substance are less than 100 nm in size.
SCCS 2013 Opinion on carbon black (nano-form)	[…] nanomaterial […] the material in its nano form […]
ECHA 2013a Second GAARN meeting Best practice for REACH registrants	The registration dossier should contain a comprehensive physicochemical characterisation of the registered nanoform(s) (First GAARN meeting best practices report). Only when well-characterised nanoforms are reported in the dossier, can a read-across approach or use of existing data (e.g. weight of evidence) be considered for the purpose of hazard assessment.
ECHA 2012a First GAARN meeting	When the scope of the registered substance involves both nanoforms and bulk forms […]
JRC and ECHA 2012 NANO-SUPPORT final report	Finally, the term 'nanomaterial' has in this report been used for dossiers addressing nanomaterials only whereas the term 'nanoform' has been used for dossiers that (seem to) also address other forms (e.g. bulk). Thus, a nanoform registered 'alone' (not along with non-nanoforms) would be a nanomaterial. In essence, the terms therefore cover the same, but a distinction was found useful for reporting the results in this project.
EC 2008a Regulatory aspects of nanomaterials	The term "nanoform" will be useful in cases where reference is made to particular forms of a substance with nanomaterial properties, as opposed to the "bulk form" of the same substance, i.e. (the) form(s) of the substance without nanomaterial properties.
EUROPEAN NATIONAL AUTHORITIES	
ETUC 2010 Regulatory definition of a substance in the nanoform	For regulatory purposes a substance in the nanoform: – Is defined when it is a solid at room temperature; and – Its PPSDn av or d<100 of the production process shows that more than 80% of the (number-) fraction is below 100 nm. (In case the number fraction below 100 nm is less than 10% the substance is fully in the bulk. In between 80% and 10% the substance is called a multi-constituent substance between its nanoform and bulk). When the surface area of the primary particles is treated chemically by more than 20%, the untreated substance in the nanoform is different from the treated one.

4.26 (Quantitative) Structure-Activity Relationship ((Q)SAR)

Table 4.26 shows the original definitions of the term '(Quantitative) Structure-Activity Relationship ((Q)SAR)', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2005, 2014a) and in documents from European bodies such as ECHA official guidance for implementation of REACH (ECHA 2008a; 2014b). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. These definitions are reflected in ECHA official guidance for implementation of REACH and in principle apply to all chemicals including NMs. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.26 Literature definitions collected for the key term '(Quantitative) Structure-Activity Relationship ((Q)SAR)' and considered to develop the NANoREG Definition.

Source	Original definition of the term '(Quantitative) Structure-Activity Relationship ((Q)SAR)'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	A SAR is a qualitative relationship that relates a (sub)structure to the presence or absence of a property or activity of interest. The substructure may consist of adjacently bonded atoms, or an arrangement of non-bonded atoms that are collectively associated with the property or activity. SARs can be helpful in the qualitative evaluation of the analogues identified as belonging to a category. A (Q)SAR is a mathematical model (often a statistical correlation) relating one or more quantitative, parameters derived from chemical structure to a quantitative measure of a property or activity (e.g. a (eco)toxicological endpoint). (Q)SARs are quantitative models yielding a continuous or categorical result.
OECD 2005 Validation of new and updated test methods	(Q)SAR [(Quantitative) Structure-Activity Relationship]: An expression used to consider, simultaneously, SARs and QSARs. SAR (Structure-Activity Relationship): A theoretical model for making predictions of physicochemical properties, environmental fate parameters, or biological effects (including toxic effects in environmental and mammalian species). SARs are qualitative relationships in the form of structural alerts that incorporate molecular substructures or fragments related to the presence or absence of activity. QSAR (Quantitative Structure-Activity Relationship): A QSAR is a theoretical model for making predictions of physicochemical properties, environmental fate parameters, or biological effects (including toxic effects in environmental and mammalian species). QSARs relate quantitative measures of chemical structure to continuous or categorical variables describing the property to be predicted.
EUROPEAN BODIES	
ECHA 2014b Use of alternatives to testing on animals for REACH	Theoretical models that can be used to predict in a quantitative or qualitative manner the physicochemical, biological (e.g. (eco) toxicological) and environmental fate properties of compounds from knowledge of their chemical structure. A SAR is a qualitative relationship that relates a (sub)structure to the presence or absence of a property or activity of interest. A (Q)SAR is a mathematical model relating to one or more quantitative parameters, which are derived from the chemical structure, to a quantitative measure of a property or activity.
ECHA 2008a QSARs and grouping of chemicals	SARs and QSARs, collectively referred to as (Q)SARs, are theoretical models that can be used to predict in a qualitative or quantitative manner the physico-chemical, biological (e.g. toxicological) and environmental fate properties of compounds from a knowledge of their chemical structure.

Table 4.26 *(cont.)*

Source	Original definition of the term '(Quantitative) Structure-Activity Relationship ((Q)SAR)'
	A SAR is a qualitative relationships that relates a (sub)structure to the presence or absence of a property or activity of interest. The substructure may consist of adjacently bonded atoms, or an arrangement of non-bonded atoms that are collectively associated with the property or activity. A QSAR is a mathematical model (often a statistical correlation) relating one or more quantitative parameters derived from chemical structure to a quantitative measure of a property or activity (e.g. a (eco)toxicological endpoint). QSARs are quantitative models yielding a continuous or categorical result.

4.27 (Quantitative) Structure-Activity Relationship ((Q)SAR) model validation

Table 4.27 shows the original definitions of the term '(Quantitative) Structure-Activity Relationship ((Q)SAR) model validation', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in one document from OECD (2007). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.27 Literature definitions collected for the key term '(Quantitative) Structure-Activity Relationship ((Q)SAR) model validation' and considered to develop the NANoREG Definition.

Source	Original definition of the term '(Quantitative) Structure-Activity Relationship ((Q)SAR) model validation'
INTERNATIONAL BODIES	
OECD 2007 Validation of QSAR models	To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information: 1. a defined endpoint; 2. an unambiguous algorithm; 3. a defined domain of applicability; 4. appropriate measures of goodness-of-fit, robustness and predictivity; 5. a mechanistic interpretation, if possible. […] a) the internal performance of a model (as represented by goodness-of-fit and robustness), determined by using a training set; and b) the predictivity of a model, determined by using an appropriate test set. The conventional OECD uses of the terms "reliability" and "relevance" can be extended to the validation process for (Q)SAR models. However, because (Q)SAR models are derived from experimental data, the concepts of reliability and relevance for test guideline purposes are necessary but not necessarily sufficient for validation of (Q)SAR models. This guidance document for (Q)SAR validation expands the concepts of reliability in a manner that retains that from a test method as the "maximum reliability" which can be expected from (Q)SAR model. Since few test methods have documented the reproducibility between laboratories for a single chemical, the validation of (Q)SAR models based on experimental data from different laboratories incorporates this implicit, but not often documented, reproducibility of the experimental test methods along with other important performance elements of the (Q)SAR model.

Table 4.27 *(cont.)*

Source	Original definition of the term '(Quantitative) Structure-Activity Relationship ((Q)SAR) model validation'
	In particular, the assessment of (Q)SAR reliability places greater emphasis on the accuracy of the (Q)SAR predictions with respect to many different chemicals than on the reproducibility of the (Q)SAR within and between laboratories. Moreover, reliability is more often described for an entire group of tested chemicals than as the reproducibility of individual endpoint estimations. Likewise, the term "relevance" must be extended for the validation of (Q)SAR models because biological effects (endpoints) measured by test methods may appear to be similar for different chemicals but result of different molecular interactions and pathways. Consequently, even though the relevance of a test endpoint in regulatory assessments may be established, an additional assessment of the (Q)SAR model relevance must be made with respect to the expected molecular interactions and pathways by which each causes the biological effect. This important distinction between experimental test methods and (Q)SAR models is sometimes expressed by the extent to which each can be applied to the chemicals being regulated. The more reliable test methods tend to be more globally applicable to measuring the same endpoint for many different chemicals whereas the more reliable (Q)SAR models of major toxicity pathways reflected in a given endpoint tend to be relevant for specific classes of chemicals.
Cross-validation	Cross-validation refers to the use of one or more statistical techniques in which different proportions of chemicals are omitted from the training set (e.g. leave-one-out [LOO], leave-many-out [LMO]). The QSAR is developed on the basis of the data for the remaining chemicals, and then used to make predictions for the chemicals that were omitted. This procedure is repeated a number of times, so that a number of statistics can be derived from the comparison of predicted data with the known data. Cross-validation techniques can be used to assess the robustness of the model (stability of model parameters), and to make estimates of predictivity.
External validation	External validation refers to a validation exercise in which the chemical structures selected for inclusion in the test set are different to those included in the training set, but which should be representative of the same chemical domain. The QSAR model developed by using the training set chemicals is then applied to the test set chemicals in order to verify the predictive ability of the model. Many QSAR practitioners regard external validation to be the most stringent form of validation, provided that sufficient experimental data are available, and the test structures are selected judiciously, in order to allow for a sufficient coverage of the applicability domain of the model. In the ideal validation process, the results of external validation will be used to supplement the results obtained by internal validation. However, in practice, there may be insufficient data to perform an external validation.
Internal validation	Internal validation refers to a validation exercise in which one or more statistical methods are applied to the training set of chemicals. Internal validation results in one or more measures of goodness-of-fit, robustness of model parameters, and estimates of predictivity. Many QSAR practitioners regard internal validation to be an essential, but not sufficient, aspect of statistical validation, which should ideally be supplemented by external validation.
Model performance	The performance of a (Q)SAR model refers to its goodness-of-fit, robustness and predictive ability in relation to a defined applicability domain. Model performance is established by using the techniques of statistical validation.
Validated vs valid	A validated (Q)SAR is a model considered to be reliable for a particular purpose based on the results of the validation process in which the domain of application and the level of uncertainty required is defined. A valid (Q)SAR is a model considered to be adequate for the intended purpose either because reliability has been demonstrated by historical use or by a validation process.

4.28 Read-across

Table 4.28 shows the original definitions of the term 'read-across', which have been collected and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2014a), in documents from European bodies such as REACH legal text (EP and EC 2006, EC 2009), ECHA official guidance for implementation of REACH (ECHA 2008a), other ECHA scientific reports (ECHA 2012c, 2013a, 2013b, 2014b, 2015a, 2015b), and SCCS guidance (SCCS 2012), on US EPA official website (US EPA 2015), in a report by US/Canada RCC (2013), in reports from industry associations (ECETOC 2012), and in peer-reviewed scientific literature (van Leeuwen et al 2007, van Leeuwen et al 2009, Cronin 2013, Godwin et al 2015, Schultz et al 2015). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. These definitions are reflected in ECHA official guidance for implementation of REACH along with guidance by industry and in principle apply to all chemicals including NMs. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD. The NANoREG Definition also includes those considerations made by several organisations (OECD, ECHA GAARN, RIVM) and scientists with regard to the application of the 'read-across' concept to NMs (ECHA 2013a; OECD 2014a; Arts et al 2014; RIVM 2015; Godwin et al 2015).

Table 4.28 Literature definitions collected for the key term 'read-across' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'read-across'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	The principle of the read-across technique is that endpoint or test information for one chemical is used to predict the same endpoint or test for another chemical, which is considered to be similar by scientific justification. A chemical used to make an estimate can be referred to as a source chemical, and a chemical for which an endpoint is estimated can be referred to as a target chemical. Theoretically, the technique of read-across can be applied to characterise physical-chemical properties, environmental fate, human health effects and ecotoxicity. For any of these areas, read-across may be performed in a qualitative or quantitative manner. Within a group of chemicals, read-across can be performed in the following ways to fill data gaps: – One-to-one (one analogue used to make an estimation for a single chemical); – Many-to-one (two or more analogues used to make an estimation for a single chemical); – One-to-many (one analogue used to make estimations for two or more chemicals); or – Many-to-many (two or more analogues used to make estimations for two or more chemicals). In qualitative read-across, the presence (or absence) of a property/activity for the target chemical is inferred from the presence (or absence) of the same property/activity for one or more source chemicals. Qualitative read-across gives a "binary" or "yes/no" answer. In quantitative read-across, the known value(s) of a property for one or more source chemicals is used to estimate the unknown value of the same property for the target chemical. Quantitative read-across is used to obtain a quantitative value for an endpoint, such as a dose-response relationship […]. The purpose of the read-across can be to replace the results of a standard experimental study entirely (i.e. standalone read-across), or may have supporting role.

Table 4.28 *(cont.)*

Source	Original definition of the term 'read-across'
	To increase confidence in the read-across approach when applied to analogues or a category, evidence must be provided to underpin the hypothesis on which the read-across is based. This can be done by adding new elements to reinforce and develop the initial hypothesis, or by providing new scientific evidence that the category parameter is behaving as expected. The most compelling evidence in support of a read-across hypothesis is information on a common mode of action of the substances and a mechanistic rationale for their common biological behaviour. […] read-across can only be used on a case-by-case basis by providing a hypothesis on which the read-across is based.
RCC 2013 Joint Nanomaterials Classification Scheme	That is, identification of a chemical analogue to the nanomaterial in question and allocation of known characteristics from that analogue to the new nanomaterial. […] to select appropriate analogue/read-across information within a class of nanomaterials. The physicochemical parameters listed (in the white boxes) represent the intrinsic physicochemical parameters which must be similar between two nanomaterials for them to be considered for analogue/read-across information.
EUROPEAN BODIES	
ECHA 2015b Regulatory challenges nanomaterials workshop proceedings	In a read-across approach, endpoint information from one or many chemicals is used to predict the same endpoint, either qualitatively or quantitatively, for one or many other chemicals. For predictions of nanomaterial properties using read-across or categories, three main possible scopes of prediction are conceivable: 1. from bulk to all nano-forms, 2. from bulk to specific nano-forms, 3. from one or many nano-forms to one or many nano-forms (of the same chemical identity but with differences in physicochemical characteristics, differently coated nano-forms, or nano-forms of different chemical identity). Read-across is recognised as one of the key issues in finding a pragmatic way to bridge existing data gaps in the hazard characterisation of nanomaterials. Therefore, there is a push from both academia and policy makers, to find a way forward in agreeing on key issues within read-across and categorisation of nanomaterials; for example, establishing criteria for when and how read-across may be acceptable. Currently, in several FP7 projects, read-across is an identified deliverable and the issue is also discussed at a global level in an OECD context. Any read-across and category approach applied for nanomaterials in a regulatory context must not compromise the insurance of the safe use of the substance and thus must be based on a robust scientific justification. The approach should identify and consider the properties or parameters that drive the endpoint in question.
ECHA 2015a Read-Across Assessment Framework	The application of the grouping concept described above means that REACH information requirements for physicochemical, human health and/or environmental properties may be predicted from information from tests conducted on reference substance(s) within the group, referred to in this document as source substance(s), by interpolation to other substances in the group, referred to as target substance(s), and this is called read-across. Thus, in principle, read-across is regarded as a technique for predicting endpoint information for one substance (target substance), by using data from the same endpoint from (an)other substance(s), (source substance(s)).

Table 4.28 *(cont.)*

Source	Original definition of the term 'read-across'
ECHA 2014b Use of alternatives to testing on animals for REACH	Read-across is an approach for filling data gaps, either by using a category or an analogue approach. For the purposes of the REACH Regulation (Article 13(1)), read-across is considered by ECHA to be an alternative method.
ECHA 2013a Second GAARN meeting Best practice for REACH registrants	The use of non-testing data, such as data generated by read-across, is supported for nanomaterials as for any other substance. When considering reading across to another nanoform or a counterpart bulk material, a solid scientific justification should be provided in the IUCLID dossier of the registered substance. It is insufficient to justify the use of data for read-across based only on the chemical composition of a nanomaterial, and further physicochemical parameters such as aspect ratio, shape, form, solubility, surface area, charge, surface treatment etc. should provide a reliable dataset to support a sound scientific interpretation of the similarities or differences among (nano)forms. The registration dossier should contain a comprehensive physicochemical characterisation of the registered nanoform(s) (First GAARN meeting best practices report). Only when well-characterised nanoforms are reported in the dossier, can a read-across approach or use of existing data (e.g. weight of evidence) be considered for the purpose of hazard assessment. Generating data on toxicokinetics might also be considered for grouping substances in relation to read-across approaches, or extrapolating from in vitro to in vivo situations.
ECHA 2013b Grouping of substances and read-across approach	Within a group of substances, a data gap might be filled by *read-across* [….] […] REACH information requirements for physicochemical properties, human health effects and/or environmental effects may be predicted from tests conducted on *reference substance(s)* within the group, referred to as *source substance(s)*, by interpolation to other substances in the group, referred to as target substance(s), and this is called *read-across*. Thus, read-across is regarded as a technique for predicting endpoint information for one substance (*target substance*), by using data from the same endpoint from (an)other substance(s), (*source substance(s)*). […] endpoint-by-endpoint basis […]
ECHA 2012c An introduction to the assessment of read-across in ECHA	The framework is only to deal with read-across that is aimed at meeting specific information requirements for substances (i.e. studies from Annex VII to Annex X of the REACH Regulation). The starting point is a study with a 'source substance' (i.e. the 'analogue'). The core of the read-across consists of the explanation by the registrant why the result of this study can also be applied to the 'target substance', so that the prediction can be used to meet the REACH information requirement for the target substance (i.e. the registered substance). It should be noted that the RAAF is to assess read-across of study results, not of classifications of the source substance or of hazardous properties of the source substance predicted by nonstandard methods or by means of a weight-of-evidence approach. The REACH guidance distinguishes two types of read-across: analogue-approach read-across and grouping/category-approach read-across. The first type is concerned with read-across between two or among a few analogues, the second type involves a larger group of substances and is supported by regular patterns in this group for the endpoint that has to be read across. The RAAF covers both, analogue-approach and grouping/category-approach read-across. (The broader approach to chemical categories or grouping used in some other regulatory schemes or for other purposes should not be confused with the specific purpose for REACH information requirements examined in the RAAF.)

Table 4.28 *(cont.)*

Source	Original definition of the term 'read-across'
ECHA 2008a QSARs and grouping of chemicals	Read-across is a technique used to predict endpoint information for one chemical by using data from the same endpoint from another chemical which is considered to be similar in some way (on the basis of structural similarity and similar properties and/or activities). While read-across is a technique for data gap filling within the context of a category approach, it is also a useful tool for data gap filling in cases where comparisons are based on a very limited number of chemicals. Theoretically, the technique of read-across can be applied to characterise physical-chemical properties, environmental fate, human health effects and ecotoxicity. For any of these areas, read-across may be performed in a qualitative or quantitative manner. In qualitative read-across, the presence (or absence) of a property/activity for the target chemical is inferred from the presence (or absence) of the same property/activity for one or more source chemicals. Qualitative read-across gives a "binary" or "yes/no" answer. In quantitative read-across, the known value(s) of a property for one or more source chemicals is used to estimate the unknown value of the same property for the target chemical. Quantitative read-across is used to obtain a quantitative value for an endpoint, such as a dose-response relationship […]. […] comparison between two chemicals. This form of evaluation is often called a read-across approach, and this is the term used in Annex XI of REACH.
EP and EC 2006; EC 2009 REACH Annex XI	[…] physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint.
SCCS 2012 Safety assessment of nanomaterials in cosmetics	In view of the current insufficient level of scientific understanding, and the high level of uncertainties over the potential deviations in the properties, behaviour, and effects of nanomaterials compared to conventional equivalents, the SCCS is of the view that the use of a read-across or categorisation approach based on inter- or intra- nanomaterial extrapolation for risk assessment of nanomaterials is currently not possible. This means that risk assessment shall be carried out on a case-by-case basis, using a precautionary approach where necessary – in terms of requirement for further testing, or by taking a conservative approach in the application of assessment factors.
US BODIES	
US EPA 2015 Glossary	Read Across from Analogs/Categories – "Read across" is a technique of filling data gaps. To "read across" is to apply data from a tested chemical for a particular property or effect (cancer, reproductive toxicity, etc.) to a similar untested chemical. The read across technique is often applied within groups of similar chemicals assembled for assessment using either analog approach (grouping based on a very limited number of chemicals) or category approach (grouping based on a larger number of chemicals). In an analog/category approach, not every chemical needs to be tested for every endpoint.
INDUSTRY ASSOCIATIONS	
ECETOC 2012 Category approaches, read-across, (Q)SAR	In this report, the term 'category approach' and 'analogue approach' are used to describe techniques for grouping chemicals, whilst the term 'read-across' is reserved for a technique of filling data gaps in either approach. Endpoint information for one chemical is used to predict the same endpoint for another chemical, which is considered to be similar in some way (usually on the basis of structural similarity or same mode of action or other properties). Qualitative read-across is similar to the use of a SAR […]

Table 4.28 *(cont.)*

Source	Original definition of the term 'read-across'
PEER-REVIEWED SCIENTIFIC LITERATURE	
Godwin et al 2015 Nanomaterial categorization	Read across refers to the process where endpoint information for one chemical (the source chemical) is used to predict the same endpoint for another chemical (the target chemical), which is considered to be "similar" in some way (usually on the basis of similarities in physicochemical properties that are deemed to be indicative of risk, hazard, or exposure potential).
Schultz et al 2015 A strategy for read-across	The underlying philosophy of read-across is that substances which are similar in chemical structure will have similar properties and thereby, have similar toxicokinetic and toxicodynamic properties. Therefore, experimentally-derived toxicological properties from one substance, often referred to as the source chemical, can be read across to fill the data gap for a second substance, the target chemical, which has a similar chemical structure and for which a toxicology study may be lacking. […] the aim of the read-across is to provide a prediction(s) that is (more or less) equivalent to the omitted standard animal study and hence be acceptable for regulatory purposes. […] Whilst no consensus has been reached by stakeholders and users, there is growing agreement that when read-across is applied to make predictions to fulfil information requirements, this must be done on an endpoint-by-endpoint basis, i.e. for the particular toxicology study to be predicted. This approach to apply to endpoints individually is due, even when there is an over-arching category hypothesis, to different applicability domains, different source chemicals and/or different Weights-of-Evidence (WoE) which may apply to making predictions for different endpoints. Obviously, there will be occasions where one or more endpoints will be closely related and knowledge may be transferable, thus allowing read-across arguments to build, partially, on each other. […] Within the applicability domain of a chemical category, read-across can be performed to fill data gaps with a number of approaches which can be summarised into the following four techniques: (1) one-to-one read-across (i.e., one source substance used to make a prediction for a single target chemical), (2) many-to-one read-across (i.e., two or more source substances used to make a prediction for a single target chemical), (3) one-to-many read-across (i.e., one source substance used to make a prediction for two or more target chemicals), or (4) many-to-many read-across (i.e., two or more source substances used to make predictions for two or more target chemicals). Techniques 3 and 4 may be considered as being multiple simultaneous applications of techniques 1 and 2, respectively. Given limited data availability, the ‘‘one-to-one’’, or analogue approach, is often the only viable option. Ideally, however, the ‘‘many-to-one’’ or category approach is preferred as it inherently possesses a greater WoE in that each analogue in the category supports the others.
Cronin 2013 Chemical grouping, categories and read-across	If a compound belongs to a group of compounds with a well categorised toxicological profile, it can be possible to interpolate its activity. These interpolations, (predictions) of toxicity may, when utilised properly, provide hazard information that can be used in the assessment procedure described above. The process of prediction is termed ‘‘read-across’’ as it assumes that activities, toxicities or properties can be read across between compounds within a category.

Table 4.28 *(cont.)*

Source	Original definition of the term 'read-across'
van Leeuwen et al 2009 Using chemical categories to fill data gaps in hazard assessment	In read-across, one or more properties of a chemical of interest are inferred by comparison to a chemical that is similar in structure and interaction mechanisms for which the properties of interest are known (Figure 1). These properties may include physicochemical properties, environmental fate or toxic effects. An assessment of similarity underpins the approach. The basic assumption is that similarity in chemical structure implies similarity in their activities or properties. Read-across has been proposed to estimate missing data from a single or restricted number of compounds using the analogue approach [14]. In this approach, endpoint information for a tested substance is used to predict the same endpoint for a similar but untested substance. In its simplest form, qualitative read-across, the presence or absence of an activity for the untested chemical of interest can be inferred from the presence or absence of the same activity for the tested analogue(s). The key to success in using read-across to predict toxicity is selecting the analogous set of chemicals based on the likelihood that each member of the set will show a common behaviour or a consistent trend for the toxicological effect in question [13]. An advantage of the analogue read-across approach is that the identification of consistent patterns of measured effects within an analogues category increases confidence in both the measured and predicted results for the individual chemicals within the category. In the case of quantitative read-across, the value of a particular parameter for tested analogue(s) is used to estimate the toxicity for the untested chemical with the assumption that the potency of the effect of interest is shared by both the tested and untested analogue. Quantitative read-across works best for homologous series of chemicals where the metric needed to extrapolate from one substance to another can be linked to a particular property of the category. However, when the members of the category are not simple homologues, it is essential that some parameter that scales the trend in toxicity across the members of the category be established in order to better use measured toxicity values to predict the missing value of an untested compound.
van Leeuwen et al 2007 Intelligent testing strategies	In read-across, one or more properties of a chemical of interest are inferred by comparison to a similar chemical or chemicals, for which the properties of interest are known (Figure 11.4). These properties may include physicochemical properties, environmental fate, toxicity and ecotoxicity. An assessment of similarity underpins the approach. The basic assumption is that similarity in structure implies similarity in activities or properties. The read-across can be qualitative or quantitative: 1. Qualitative read-across can be regarded as an application of SAR. The process involves: (a) the identification of a chemical substructure that is common to the two substances (which are therefore analogues) and (b) the assumption that the presence (or absence) of a property/activity for a substance can be inferred from the presence (or absence) of the same property/activity for an analogous substance. This assumption implies that analogues behave qualitatively similarly, and is usually the result of an expert judgement evaluation. 2. Quantitative read-across involves the identification of a chemical substructure that is common to the two substances (which are therefore analogues), and the assumption that the known value of a property for one substance can be used to estimate the unknown value of the same property for another substance. This assumption implies that the potency of an effect shared by different analogous substances is similar, and is also usually the result of an expert judgement evaluation [25, 26].

4.29 Read-Across Assessment Framework (RAAF)

Table 4.29 shows the original definitions of the term 'Read-Across Assessment Framework (RAAF)', which have been collected from the literature and used to develop the NANoREG Definition. The term 'Read-Across Assessment Framework (RAAF)' is used in the context of REACH and in principle applies to all substances including NMs. Definitions could only be found in scientific documents prepared by European bodies such as ECHA (2012c, 2014c, 2015a) and in reports from industry associations (CEFIC-LRI 2012). Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by ECHA.

Table 4.29 Literature definitions collected for the key term 'Read-Across Assessment Framework (RAAF)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'Read-Across Assessment Framework (RAAF)'
EUROPEAN BODIES	
ECHA 2015a Read-Across Assessment Framework	ECHA is therefore in the process of codifying a systematic approach to assessing those read-across cases that are encountered in its dossier evaluation activities. This systematic approach is called 'The Read-Across Assessment Framework', or RAAF. The RAAF provides a framework and guidance for consistent evaluation of the scientific aspects of a proposed read-across case, resulting in an output which is suitable for subsequent regulatory consideration of the read-across case.
ECHA 2014c Workshop on the RAAF	[…] a systematic approach to the assessment of read-across cases […] […] a structured method for the assessment of read-across cases by ECHA evaluators.
ECHA 2012c An Introduction to the assessment of read-across in ECHA	'The Read-Across Assessment Framework', or RAAF. This framework is meant to present a structured tool for the assessment of read-across cases by the ECHA evaluators. It is thus not meant to serve as guidance for registrants, […] The RAAF consists of a two-tiered assessment scheme.
INDUSTRY ASSOCIATIONS	
CEFIC-LRI 2012 Expert workshop on read-across assessment	The RAAF is a tiered systematic approach, developed by ECHA to facilitate its internal evaluation of read-across.

4.30 Regulatory acceptance

Table 4.30 shows the original definitions of the term 'regulatory acceptance', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2005) and on European bodies' websites (EURL ECVAM 2015). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. These definitions are reflected in the EURL ECVAM Glossary and in principle apply to all chemicals including NMs. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD.

Table 4.30 Literature definitions collected for the key term 'regulatory acceptance' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'regulatory acceptance'
INTERNATIONAL BODIES	
OECD 2005 Test methods for hazard assessment	The formal acceptance of a test method by regulatory authorities indicating that the test method may be used to provide information to meet a specific regulatory requirement. Regulatory acceptance is dependent upon the outcome of the validation […] The regulatory acceptance process has generally been on a case-by-case basis, and regulatory authorities have the option to accept results generated using a test method that has not undergone what today would be considered formal validation (e.g., methods used in mechanistic studies that could help underpin or explain results derived from other tests). However, acceptance of a test method by a specific regulatory authority does not necessarily indicate universal acceptance by other authorities. Acceptance policies differ from country to country and even, at times, among regulatory authorities within a country. Harmonisation of international regulatory acceptance of adequately validated test methods may be achieved by considering the guidance provided in this document. The regulatory acceptance of tests that have not been subjected to prevailing validation processes is discouraged. In cases in which validation is not considered necessary or appropriate, a written justification should be available. After a test method has undergone formal validation and is considered acceptable for specific proposed uses, a recommendation may be made that it be adopted as an OECD Test Guideline. As mentioned earlier in this document, regulatory acceptance would be greatly facilitated by the involvement, as early as possible in the validation process, of the regulatory agencies to which test results derived from the validated method will be submitted.
EUROPEAN BODIES	
EURL ECVAM 2015 Glossary	Regulatory acceptance of a test method is its formal acceptance by regulatory authorities indicating that the test method may be used to provide information to meet a specific regulatory requirement. This includes, but is not limited to, a formal adoption of a test method by EU and/or OECD as an EU test method and included in the EU Test Methods Regulation (EC, 2008) and/or as an OECD Test Guideline, respectively.

4.31 Safe-by-design

Table 4.31 shows the original definitions of the term 'safe-by-design', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be retrieved from peer-reviewed scientific literature (Ariëns 1980, Behm 2005, Anastas and Warner 2005, Kelty 2009, Sealy 2011, Sips et al 2013, Lynch et al 2014, Movia et al 2014, Burello and Worth 2015, Zimmerman and Anastas 2015). Most of publications discuss the concept of safe-by-design in the field of material/chemical engineering. Some of them attempt to adapt the concept to the field of nanotechnology and synthesis of NMs but none provides a comprehensive and clear definition. The harmonised definition adopted in NANoREG takes inspiration from the definition of 'safe-by-design' as proposed in NANoREG Deliverable 6.3 on *"Comparison on toxicity testing in drug development and in present MNMs safety testing"* (submitted on 3 December 2014), which is also used in the context of ProSafe and NANoREG II.

Table 4.31 Literature definitions collected for the key term 'safe-by-design' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'safe-by-design'
PEER-REVIEWED SCIENTIFIC LITERATURE	
Zimmerman and Anastas 2015 Designing safer chemicals	[…] how do we design future substances to eliminate the need for engineered control systems.
Burello and Worth 2015 A rule for designing safer nanomaterials	All these information point towards the emergence of an effective rule for designing safer nanomaterials, that is to design nanomaterials that do not interfere with the redox equilibrium of the cell. Although currently there is no clear and structured safe-by-design strategy, at TNO we are developing a number of rules to support the synthesis of safer nanomaterials. The key element is to align functionality and safety, and, in essence, understand how we could modify certain properties which make a nanomaterial appealing for its use – but also possibly hazardous for the environment, health and safety domains, while preserving its functionality.
Lynch et al 2014 A basis for safer-by-design NMs	Identification of critical properties (physicochemical descriptors) that confer the ability to induce harm in biological systems is crucial, enabling both prediction of impacts from related NMs (via quantitative nanostructure-activity relationships (QNARs) and read-across approaches) and development of strategies to ensure these features are avoided or minimised in NM production in the future ("safety by design"). A number of challenges to successful implementation of such a strategy exist, including: (i) the lack of widely available systematically varied libraries of NMs to enable generation of sufficiently robust datasets for development and validation of QNARs; (ii) the fact that many physicochemical properties of pristine NMs are inter-related and thus cannot be varied systematically in isolation from others (e.g. increasing surface charge may impact on hydrophobicity, or changing the shape of a NM may introduce defects or alter the atomic configuration of the surface); and (iii) the effect of ageing, transformation and biomolecule coating of NMs under environmental or biological conditions.
Movia et al 2014 Safe-by-design	Such approach finds his routes in the concept of safe-by-design nanomaterials, where efforts are focused on characterizing the physical, chemical and biological properties of the core material, followed by "layering" as a method to produce safe nano-enabled theranostics [16].
Sips et al 2013 Safer-by-design	Safe(r) by design aims at an integrated and iterative process where safety and functionality are weighed. This concept seems by nature plausible for many stakeholders. It is thought to reduce the necessity for risk management activities, which can be beneficial both for industry and for upholding authorities. On the other hand, it might require larger investments in research and development. This already implies that the development in iterative loops between safety and functionality needs to be done very efficiently.
Sealy 2011 Safe-by-design nanoparticles	Now researchers from the US and Germany have taken a 'safe-by-design' approach to reduce the in vivo toxicity of ZnO nanoparticles by doping with Fe. The results demonstrate that it is possible to design and synthesize a widely used nanomaterial as a less toxic nanoparticle […] An understanding of hazardous nanomaterial properties is essential for safe design from both the lifecycle as well as the biological perspective […]
Kelty 2009 The story of safety by design	[…] 'safety by design' idea, the idea that you can study implications and from that go back and engineer materials and processes to be safer and to have less of the impact that you don't want them to have […] The outcome of this arrangement is the story we tell here, the attempt to make 'safety' a fundamental property of new nanomaterials: 'safety by design.'

Table 4.31 *(cont.)*

Source	Original definition of the term 'safe-by-design'
	[…] a kind of strategic working over of the demand for responsibility, into a form of science that is both application and implication at once, both concern and control: it was an attempt to define safety as a fundamental property of materials. […] it presumed that safety was an issue of design, not a feature of the established risk framework of hazard levels and exposure routes; […] Rather, it creates a new mode of veridiction—a new set of truth claims about safety as a fundamental property of matter, claims that might be made about wide classes of materials and their uses and ultimately replace one version of risk analysis ('is it safe?') with another and quite different version ('how do you engineer towards safety?').
Anastas and Warner 2005 Hazard reduction as a chemical design criterion in green chemistry	Green chemistry seeks to incorporate hazard reduction *ab initio*, in other words, as an integral part of the design process. […] green chemistry's goal is to prevent adverse consequences of the design of chemicals by making informed design choices that minimize hazard. As a design criterion, hazard reduction would occupy equal status with the other physicochemical attributes associated with chemical structure and function. Hazard should be considered a design flaw and efforts need to be made in the designing phase to minimize or eliminate it.
Behm 2005 Design for construction safety concept	The design for construction safety concept is defined as the consideration of construction site safety in the design of a project.
Ariëns 1980 Design of safer chemicals	The goals are not to cure but to prevent, implying efforts to design safer chemicals. […] Design involves control of potentially toxic actions of chemical agents by molecular manipulation, which requires an insight into the chemical mechanisms of toxic action, and therewith an insight into the relationship between structure and toxic action.

4.32 Standardisation

Table 4.32 shows the original definitions of the term 'standardisation', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be retrieved from webpages of international organisations such as ISO (2015a, 2015b) and CEN (2015). As both ISO and CEN are standardisation organisations the harmonised definition adopted in NANoREG reflects these definitions.

Table 4.32 Literature definitions collected for the key term 'standardisation' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'standardisation'
INTERNATIONAL BODIES	
ISO 2015a Glossary	Standardization: Activity of establishing, with regard to actual or potential problems, provisions for common and repeated use, aimed at the achievement of the optimum degree of order in a given context (from ISO/IEC Guide 2:2004, definition 1.1).
ISO 2015b Homepage	A standard is a document that provides requirements, specifications, guidelines or characteristics that can be used consistently to ensure that materials, products, processes and services are fit for their purpose.

Table 4.32 *(cont.)*

Source	Original definition of the term 'standardisation'
	ISO International Standards ensure that products and services are safe, reliable and of good quality. For business, they are strategic tools that reduce costs by minimizing waste and errors and increasing productivity. They help companies to access new markets, level the playing field for developing countries and facilitate free and fair global trade.
CEN 2015 Homepage	Standards are documents that set out specifications and other technical information with regard to various kinds of products, materials, services and processes. Standards provide a basis for mutual understanding among individuals, businesses, public authorities and other kinds of organizations. They facilitate communication, commerce, measurement and manufacturing. European Standards bring benefits to businesses and consumers in terms of reducing costs, enhancing performance and improving safety. They also help to ensure the compatibility of different components, products and services. European Standards can be used to enhance safety and performance, improve energy efficiency, and protect consumers, workers and the environment. They complement European and national policies, and make it easier for businesses and other actors to respect relevant legislation. European Standardization is a key instrument for consolidating the Single Market and facilitating cross-border trade – within Europe and also with the rest of the world. It is a valuable tool for strengthening the competitiveness of European companies, thereby creating the conditions for economic growth.

4.33 Standard Operating Procedure (SOP)

Table 4.33 shows the original definitions of the term 'Standard Operating Procedure (SOP)', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could found in documents from international organisations such as OECD (2005) and FAO (1998), in reports from European national authorities (NILU 2013), and in documents prepared by US bodies such as US EPA (1992). Accordingly, the harmonised definition developed in NANoREG combines elements from each of these definitions.

Table 4.33 Literature definitions collected for the key term 'Standard Operating Procedure (SOP)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'Standard Operating Procedure (SOP)'
INTERNATIONAL BODIES	
OECD 2005 Validation of new and updated test methods	A formal, written procedure that describes in detail how specific routine and test-specific laboratory operations should be performed. SOPs are required by Good Laboratory Practice.
FAO 1998 Guidelines for quality management in soil and plant laboratories	An important aspect of a quality system is to work according to unambiguous Standard Operating Procedures (SOPs). A SOP for a laboratory can be defined as follows: *"A Standard Operating Procedure is a document which describes the regularly recurring operations relevant to the quality of the investigation. The purpose of a SOP is to carry out the operations correctly and always in the same manner. A SOP should be available at the place where the work is done".*

Table 4.33 *(cont.)*

Source	Original definition of the term 'Standard Operating Procedure (SOP)'
	A SOP is a compulsory instruction. If deviations from this instruction are allowed, the conditions for these should be documented including who can give permission for this and what exactly the complete procedure will be. The original should rest at a secure place while working copies should be authenticated with stamps and/or signatures of authorized persons. Several categories and types of SOPs can be distinguished.
EUROPEAN NATIONAL AUTHORITIES	
NILU 2013 Good laboratory practice system	Standard Operating Procedures means documented procedures, which describe how to perform tests or specific activities.
US BODIES	
US EPA 1992 Guidelines for exposure assessment	Standard operating procedure (SOP) - A procedure adopted for repetitive use when performing a specific measurement or sampling operation.

4.34 Substance

Table 4.34 shows the original definitions of the term 'substance', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be retrieved from different pieces of legislation on chemicals including UN Globally Harmonised System (UN 2003), European REACH legal text (EP and EC 2006) and CLP Regulation (EP and EC 2008), US TSCA (TSCA 2002) and CEPA (1999). Accordingly, the harmonised definition developed in NANoREG reflects the definition provided in European law such as REACH and CLP Regulation (EP and EC 2006, 2008). The same definition is used in the UN Globally Harmonised System (UN 2003).

Table 4.34 Literature definitions collected for the key term 'substance' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'substance'
INTERNATIONAL BODIES	
UN 2003 Globally Harmonised System	Substance means chemical elements and their compounds in the natural state or obtained by production process including any additive necessary to preserve the stability of the product and any impurities deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition;
EUROPEAN BODIES	
EP and EC 2008 CLP Regulation	'substance' means 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;

Table 4.34 *(cont.)*

Source	Original definition of the term 'substance'
EP and EC 2006 REACH Regulation	[…] means 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.
US BODIES	
TSCA 2002 US Toxic Substances Control Act	[…] the term "chemical substance" means any organic or inorganic substance of a particular molecular identity, including— (i) any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and (ii) any element or uncombined radical. (B) Such term does not include— (i) any mixture, (ii) any pesticide (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act) when manufactured, processed, or distributed in commerce for use as a pesticide, (iii) tobacco or any tobacco product, (iv) any source material, special nuclear material, or byproduct material (as such terms are defined in the Atomic Energy Act of 1954 and regulations issued under such Act), (v) any article the sale of which is subject to the tax imposed by section 4181 of the Internal Revenue Code of 1954 (determined without regard to any exemptions from such tax provided by section 4182 or 4221 or any other provision of such Code), and (vi) any food, food additive, drug, cosmetic, or device (as such terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act) when manufactured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device
CANADIAN BODIES	
CEPA 1999 Canadian Environmental Protection Act	"substance" means any distinguishable kind of organic or inorganic matter, whether animate or inanimate, and includes (a) any matter that is capable of being dispersed in the environment or of being transformed in the environment into matter that is capable of being so dispersed or that is capable of causing such transformations in the environment, (b) any element or free radical, (c) any combination of elements of a particular molecular identity that occurs in nature or as a result of a chemical reaction, and (d) complex combinations of different molecules that originate in nature or are the result of chemical reactions but that could not practicably be formed by simply combining individual constituents, and, except for the purposes of sections 66, 80 to 89 and 104 to 115, includes (e) any mixture that is a combination of substances and does not itself produce a substance that is different from the substances that were combined, (f) any manufactured item that is formed into a specific physical shape or design during manufacture and has, for its final use, a function or functions dependent in whole or in part on its shape or design, and (g) any animate matter that is, or any complex mixtures of different molecules that are, contained in effluents, emissions or wastes that result from any work, undertaking or activity.

4.35 Test method

Table 4.35 shows the original definitions of the term 'test method', which have been collected from the literature and used to develop the NANoREG Definition. One definition could be found in a document by OECD (2005). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definition provided by OECD.

Table 4.35 Literature definitions collected for the key term 'test method' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'test method'
INTERNATIONAL BODIES	
OECD 2005 Test methods for hazard assessment	[…] an experimental system that can be used to obtain a range of information from chemical properties through the adverse effects of a substance. The term 'test method' may be used interchangeably with 'assay' for ecotoxicity as well as for human health studies. …'. Testing means applying a test method.

4.36 Test method validation

Table 4.36 shows the original definitions of the term 'test method validation', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2005) and in documents prepared by European bodies such as ECHA (2014b). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definition provided by OECD.

Table 4.36 Literature definitions collected for the key term 'test method validation' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'test method validation'
INTERNATIONAL BODIES	
OECD 2005 Test methods for hazard assessment	Test method validation is a process based on scientifically sound principles by which the reliability and relevance of a particular test, approach, method or process are established for a specific purpose. Reliability is defined as the extent of reproducibility of results from a test within and among laboratories over time, when performed using the same standardised protocol. The relevance of a test method describes the relationship between the test and the effect in the target species and whether the test method is meaningful and useful for a defined purpose, with the limitations identified. In brief, it is the extent to which the test method correctly measures or predicts the (biological) effect of interest, as appropriate. Regulatory need, usefulness and limitations of the test method are aspects of its relevance. New and updated test methods need to be both reliable and relevant i.e. validated. A validated test method [...] a test method for which validation studies have been completed to determine the relevance (including accuracy) and reliability for a specific purpose. It is important to note that a validated test method may not have sufficient performance in terms of accuracy and reliability to be found acceptable for the proposed purpose.
EUROPEAN BODIES	
ECHA 2014b Use of alternatives to testing on animals for REACH	Process by which the reliability and relevance of a test method are evaluated for the purpose of supporting a specific use.

4.37 Tiered testing strategy

Table 4.37 shows the original definitions of the term 'tiered testing strategy', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2013b) and in peer-reviewed/non peer-reviewed scientific literature (Stone et al 2013, Ferrario et al 2014). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definition provided by OECD.

Table 4.37 Literature definitions collected for the key term 'tiered testing strategy' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'tiered testing strategy'
INTERNATIONAL BODIES	
OECD 2013b Ocular corrosives and severe irritants	A stepwise testing strategy where all existing information on a test substance is reviewed, in a specified order, using a weight of evidence process at each tier to determine if sufficient information is available for a hazard classification decision, prior to progression to the next tier. If the irritancy potential of a test substance can be assigned based on the existing information, no additional testing is required. If the irritancy potential of a test substance cannot be assigned based on the existing information, a step-wise sequential animal testing procedure is performed until an unequivocal classification can be made.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Ferrario et al 2014 Glossary of reference terms	Tiered test scheme: Testing approaches based on sequential assessments, where a result at one tier is used to determine the next step, if any. It is usually a decision-tree type of testing; after each step, the information is assessed to determine whether a prediction for the toxicity endpoint can be made or whether further testing/analysis needs to be done. A tiered approach usually progresses from a review of existing literature and data to a review of data for related chemicals or formulations, to perhaps a SAR/(Q)SAR analysis, to simple in vitro screening assays, to the use of more complex in vitro three-dimensional models, to testing in lower species, to the traditional animal test.
Stone et al 2013 ITS-NANO final report	Sets of a structured approach to assessing the fate and effects of NMs, where test in higher tiers may be required depending upon the results of tests at earlier stages (i.e. lower tiers). Under a tiered structure, for example, data requirements for effects testing might progress from acute to chronic laboratory studies to field studies.

4.38 Tool

Table 4.38 shows the original definitions of the term 'tool', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be retrieved from online dictionaries (Merriam-Webster 2015) and peer-reviewed scientific literature (Hristozov et al 2012). The harmonised definition adopted in NANoREG takes inspiration from the definition provided by Hristozov et al (2012) but is adapted to the context of the project.

Table 4.38 Literature definitions collected for the key term 'tool' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'tool'
ONLINE DICTIONARIES	
Merriam-Webster 2015	– a handheld device that aids in accomplishing a task; – something (as an instrument or apparatus) used in performing an operation or necessary in the practice of a vocation or profession; – an element of a computer program (as a graphics application) that activates and controls a particular function; – a means to an end.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Hristozov et al 2012 Risk assessment of engineered nanomaterials	A "tool" is a procedure used to generate certain type of output (e.g., data).

4.39 Trend analysis

Table 4.39 shows the original definitions of the term 'trend analysis', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2014a) and in documents prepared by European bodies such as ECHA official guidance for implementation of REACH (ECHA 2008a). The definitions that are reported in OECD official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. These definitions are reflected in ECHA official guidance for implementation of REACH and in principle apply to all chemicals including NMs. Accordingly, the harmonised definition adopted in NANoREG reflects the definition provided by OECD.

Table 4.39 Literature definitions collected for the key term 'trend analysis' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'trend analysis'
INTERNATIONAL BODIES	
OECD 2014a Guidance on grouping of chemicals	Trend analysis refers to a data-gap filling method for "quantitative endpoints" (e.g., 96h-LC50 for fish) if a number of analogues (at least 3) with experimental results are identified. For a given category endpoint, the category members are related by a trend such that the properties of the category members change in a predictable manner and there is a pattern in the changing potency of the properties across the category. A chemical that identifies a turning point in a trend is called a breakpoint chemical. Category members falling at the opposite extremes of a trend and between which interpolations are considered reliable are called sentinel or boundary chemicals.

Table 4.39 *(cont.)*

Source	Original definition of the term 'trend analysis'
EUROPEAN BODIES	
ECHA 2008a QSARs and grouping of chemicals	For a given category endpoint, the category members are often related by a trend (e.g. increasing, decreasing or constant) in an effect, and a trend analysis can be carried out using a model based on the data for the members of the category.

4.40 Validation

Table 4.40 shows the original definitions of the term 'validation', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as OECD (2005) and IPSC (2004), in European bodies' webpages (EURL ECVAM 2015), and in reports from US bodies (NIEHS 1997). The definitions that are reported in OECD and IPSC official guidance documents are given higher priority as they have regulatory relevance and are the result of a broad consultation at international level. Accordingly, the harmonised definition adopted in NANoREG reflects the definitions provided by OECD and IPSC.

Table 4.40 Literature definitions collected for the key term 'validation' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'validation'
INTERNATIONAL BODIES	
IPCS 2004 Risk assessment terminology	Process by which the reliability and relevance of a particular approach, method, process, or assessment is established for a defined purpose. Different parties define "Reliability" as establishing the reproducibility of the outcome of the approach, method, process, or assessment over time. "Relevance" is defined as establishing the meaningfulness and usefulness of the approach, method, process, or assessment for the defined purpose.
OECD 2005 Validation of test methods	The process by which the reliability and relevance of a particular approach, method, process, or assessment is established for a defined purpose.
EUROPEAN BODIES	
EURL ECVAM 2015 Glossary	Validation is the process by which the reliability and relevance of a procedure are established for a specific purpose.
US BODIES	
NIEHS 1997 Validation and regulatory acceptance of test methods	Valid method: A method determined to be acceptable for a specific use and application. Validated method: A test method for which the reliability and relevance for a specific purpose have been established in one or more validation studies.

4.41 Value chain

Table 4.41 shows the original definitions of the term 'value chain', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from European national authorities (BSR 2010), in reports from industry associations (WBCSD 2011), in universities' websites (Duke University 2015), and in peer-reviewed scientific literature (Kaplinsky and Morris 2001). There is no internationally agreed definition of the term 'value chain'. The definition formulated by Kaplinsky and Morris (2001) is clear and underlines the importance of considering the "full range of activities" in a value chain, from the very beginning of an intellectual process to disposal of a product or a service. Accordingly, the harmonised definition adopted in NANoREG reflects the definition formulated by Kaplinsky and Morris (2001). The NANoREG harmonised definition also explains the difference between the terms 'life cycle' and 'value chain' and what is meant by 'safety value chain case study' within the project.

Table 4.41 Literature definitions collected for the key term 'value chain' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'value chain'
EUROPEAN NATIONAL AUTHORITIES	
BSR 2010 Responsible supply chain management	A series of activities undertaken by a company that generate and add value to products. These activities include inbound logistics, operations, outbound logistics, marketing and sales, and services, and they are supported by activities including firm infrastructure, human resources management, technology development and procurement. A company's value chain is part of a larger value system that includes the value chains of upstream suppliers and downstream channels and customers. (See Michael Porter, Competitive Advantage: Creating and Sustaining Superior Performance. New York: Free Press, 1980.)
INDUSTRY ASSOCIATIONS	
WBCSD 2011 A value chain approach	A value chain refers to the full life cycle of a product or process, including material sourcing, production, consumption and disposal/recycling processes.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Kaplinsky and Morris 2001 A handbook for value chain research	The value chain describes the full range of activities which are required to bring a product or service from conception, through the different phases of production (involving a combination of physical transformation and the input of various producer services), delivery to final consumers, and final disposal after use.
NON PEER-REVIEWED SCIENTIFIC LITERATURE	
Duke University 2015 The global value chains initiative	The value chain describes the full range of activities that firms and workers do to bring a product from its conception to its end use and beyond. This includes activities such as design, production, marketing, distribution and support to the final consumer. The activities that comprise a value chain can be contained within a single firm or divided among different firms. Value chain activities can produce goods or services, and can be contained within a single geographical location or spread over wider areas.”

4.42 Waiving

Table 4.42 shows the original definitions of the term 'waiving', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from European bodies such as ECHA official guidance for implementation of REACH (ECHA 2010c; 2011a). Accordingly, the harmonised definition adopted in NANoREG reflects the definition provided by ECHA. See the term 'adaptation'.

Table 4.42 Literature definitions collected for the key term 'waiving' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'waiving'
EUROPEAN BODIES	
ECHA 2010c How to report data waiving	[…] waiving of the information requirements for an endpoint means that the submission of the standard information for the particular endpoint is not considered necessary in a specific case.
ECHA 2011a Adaptations to information requirements	The term 'omission' (=waiving) is used when on the basis of specific rules in Annex XI, section 3, or the sections in column 2 of Annex VII-X testing may be omitted.

4.43 Weight of Evidence (WoE)

Table 4.43 shows the original definitions of the term 'Weight of Evidence (WoE)', which have been collected from the literature and used to develop the NANoREG Definition. Definitions could be found in documents from international organisations such as UN (2003) and OECD (2012a, 2013b), in documents prepared by European bodies such as REACH legal text (EC 2009), ECHA official guidance for implementation of REACH (ECHA 2010b, 2011c, 2011d), and documents prepared by SCENIHR (2012), in US bodies' official guidance documents (US EPA 1998, NRC 2009) and in peer-reviewed scientific literature (Weed 2005, Linkov et al 2009, Hope and Clarkson 2013, Ferrario et al 2014, Rhomberg 2014). International and European bodies (i.e. OECD, SCENHIR and ECHA) tend to use the term WoE in the context of hazard assessment and propose the same definition. Accordingly, the harmonised definition adopted in NANoREG reflects this definition and integrates it with features specified in other sources.

Table 4.43 Literature definitions collected for the key term 'Weight of Evidence (WoE)' and considered to develop the NANoREG Definition.

Source	Original definition of the term 'Weight of Evidence (WoE)'
INTERNATIONAL BODIES	
UN 2003 Globally Harmonised System	This means that all available information bearing on the determination of toxicity is considered together, including the results of valid in vitro tests, relevant animal data, and human experience such as epidemiological and clinical studies and well-documented case reports and observation.

Table 4.43 *(cont.)*

Source	Original definition of the term 'Weight of Evidence (WoE)'
OECD 2014a Guidance on grouping of chemicals	Weight of evidence refers to a positive expert opinion that considers available evidence from different independent sources and viewpoints on a particular issue, coming to a considered view of the available, oftentimes conflicting, data. It is preferred when every source does not provide sufficient information individually.
OECD 2012a; OECD 2013b	The process of considering the strengths and weaknesses of various pieces of information in reaching and supporting a conclusion concerning the hazard potential of a substance.
EUROPEAN BODIES	
SCENIHR 2012 Weighing of evidence and uncertainty	The process of considering the strengths and weaknesses of various pieces of information in reaching and supporting a conclusion concerning the hazard potential of a substance.
ECHA 2011c Hazard assessment	The weight of evidence (WoE) approach is not a scientifically well-defined term or an agreed formalised concept. It involves assessing the relevance, reliability and adequacy of each piece of available information, holding the various pieces of information up against each other and reaching a conclusion on the hazard. This process always involves expert judgement. It is important to document and communicate how the evidence-based approach was used in a reliable, robust and transparent manner.
ECHA 2011d Evaluation of available information	[…] is a component of the decision-making procedure on substance properties and thus an important part of the chemical safety assessment. […] An evidence based approach involves an assessment of the relative values/weights of different pieces of available information that has been retrieved and gathered in previous steps. […] An evidence based approach may imply formalised decision schemes where explicit rules for weighing information elements have been established. After having assessed/ranked the quality of the individual components the next step should be the integrating, comparing and putting together all information pieces with their relative values or weights and drawing a conclusion. This often includes expert judgment.
ECHA 2010b How to report weight of evidence	The process of considering the strengths and weaknesses of various pieces of information in reaching and supporting a conclusion concerning the hazard potential of a substance.
EC 2009 REACH Annex XI	There may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion.
US BODIES	
NRC 2009 Science and decisions, advancing risk assessment	The phrase weight of evidence (WOE) is used by EPA and other scientific bodies to describe the strength of the scientific inferences that can be drawn from a given body of evidence. In its most common applications in EPA, WOE is used to characterize the hazardous (toxic or carcinogenic) properties of chemicals on the basis of an integrated analysis of all relevant observational and experimental data. It is increasingly used to describe the strength of evidence supporting particular modes of (toxic) action (MOAs) and dose-response relationships. Because scientific evidence used in WOE evaluations varies greatly among chemicals and other hazardous agents in type, quantity, and quality, it is not possible to describe the WOE evaluation in other than relatively general terms. It is thus not unexpected that WOE judgments in particular cases can vary among experts and that consensus is sometimes difficult to achieve.

Table 4.43 *(cont.)*

Source	Original definition of the term 'Weight of Evidence (WoE)'
US EPA 1998 Guidance on ecological risk assessment	The development of lines of evidence provides both a process and a framework for reaching a conclusion regarding confidence in the risk estimate. It is not the kind of proof demanded by experimentalists (Fox, 1991), nor is it a rigorous examination of weights of evidence. (Note that the term "weight of evidence" is sometimes used in legal discussions or in other documents, e.g., Urban and Cook, 1986; Menzie et al., 1996). The phrase lines of evidence is used to de-emphasize the balancing of opposing factors based on assignment of quantitative values to reach a conclusion about a "weight" in favor of a more inclusive approach, which evaluates all available information, even evidence that may be qualitative in nature. It is important that risk assessors provide a thorough representation of all lines of evidence developed in the risk assessment rather than simply reduce their interpretation and description of the ecological effects that may result from exposure to stressors to a system of numeric calculations and results.
PEER-REVIEWED SCIENTIFIC LITERATURE	
Ferrario et al 2014 Glossary	The process of considering the strengths and weaknesses of various pieces of information in reaching and supporting a conclusion concerning the hazard potential of a substance.
Rhomberg 2014 Hypothesis-driven WoE	"weight-of-evidence" evaluation—the application of professional judgment to consider the strengths and weaknesses of individual studies, to compare and contrast their findings, and to try and reconcile or explain inconsistencies so as to arrive at a characterization of what potential toxicological properties are sufficiently supportable to justify the regulatory decisions that will be made. The challenge is for such a process to be sufficiently flexible to apply to a wide variety of arrays of data and patterns of agreement and disagreement, and at the same time sufficiently prescribed so that the results will not be seen as arbitrary, having consistent application of principles and standards of proof from case to case, applied in a way that is seen as transparent and objective.
Hope and Clarkson 2013 WoE methods in ecological risk assessments	The term "weight of evidence" (WOE) has been mathematically defined for over a century and is used in studies of decision-making in humans and other primates (Good 2003; Gold and Shadlen 2007). It has not, however, been practically defined, in terms of tools and procedures, for use in predictive risk assessments (Weed 2005). WOE is basically the process of considering the strengths and weaknesses of various pieces of information in order to inform a decision being made among competing alternatives. An evidence-based approach involves an assessment of the relative weights of different pieces of available information. To this end, a weight is assigned to each piece of information, in either an objective way using a formalized procedure or expert judgment. The weight given to available evidence will be influenced by factors such as data quality, consistency of results, nature and severity of effects, and relevance of the information to the decision context. In the context of an ecological risk assessment (ERA), a WOE approach integrates outcomes from two or three lines of evidence (LOEs) to estimate the probability (i.e., chance) of an adverse outcome for an assessment endpoint.
Linkov et al 2009 Review of WoE approaches	Weight of evidence (WOE) can be defined as a framework for synthesizing individual lines of evidence, using methods that are either qualitative (examining distinguishing attributes) or quantitative (measuring aspects in terms of magnitude) to develop conclusions regarding questions concerned with the degree of impairment or risk. In general, qualitative methods include presentation of individual lines of evidence without an attempt at integration, or integration through a standardized evaluation of individual lines of evidence based on qualitative considerations. Quantitative methods include integration of multiple lines of evidence using weighting, ranking, or indexing as well as structured decision or statistical models.
Weed 2005 WoE: a review of concepts and methods	"Weight of evidence" typically refers either to the interpretative methods of risk assessment or to claims about risk that emerge from their use. The central role that this concept plays in the practice of risk assessment makes it imperative that the many stakeholders be clear about its definition, its uses, and its implications.

Table 4.43 *(cont.)*

Source	Original definition of the term 'Weight of Evidence (WoE)'
	"Weight of evidence" has at least three characteristic uses: metaphorical, methodological (with several subcategories), and theoretical, roughly in order of their relative prevalence. The most common use of the phrase "weight of evidence" is to refer to a body of scientific evidence that has been examined for some purported risk, without reference to any interpretative methodology. "Weight of evidence" in this context can therefore be considered symbolic or metaphorical; the phrase could be replaced by the words "summary interpretation of the evidence" or "synthesis of the evidence." The second category in Table I is methodological. In this literature, the phrase "weight of evidence" is sometimes used to refer to a methodological approach with a fairly simple premise: that all available evidence should be examined and interpreted.

5. Closing remarks

The development of the NANoREG harmonised terminology in the field of nanoEHS was a very useful initiative in that it facilitated mutual understanding among partners during meetings and improved coherence of project documents. The benefit has been particularly evident in those activities coordinated by JRC, where partners with very different types of expertise worked together aiming at producing multidisciplinary and integrated outputs, such as the NANoREG Framework and the associated Toolbox.

The discussion on the key terms to be considered for the NANoREG Terminology led to the selection of 43 key terms. The list includes terms with international regulatory relevance such as those defined at OECD level (e.g. Adverse Outcome Pathway, alternative test method, grouping, read-across) as well as terms that have a specific meaning and use under REACH (e.g. Chemical Safety Assessment, nanoform). They represent the main regulatory reference for all project activities and deliverables. Most of the selected key terms have been already defined for chemicals. Either they have been considered as appropriate for NMs, too, or they have been discussed and slightly modified to account for NM specificities.

The relevant sources for the development of the harmonised definitions were selected through an extensive literature search, but based on the expert judgment of the project partners. The references do not represent an exhaustive list of sources and hence it cannot be excluded that other definitions may be available in other guidance documents, legal texts or scientific publications. However, this possible source of uncertainty has been considered as minor and acceptable, taking into account the short time schedule available to serve the NANoREG project and the available human resources.

This report is to be considered solely as a project document that does not have any regulatory consequences and does not represent the official position of the European Commission.

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List of abbreviations and definitions

ADI	Acceptable Daily Intake
AF	Assessment Factor
AIT	Austrian Institute of Technology
AOP	Adverse Outcome Pathway
ATS	Alternative Testing Strategy
BMD	Benchmark Dose
CB	Control Banding
CEFIC-LRI	European Chemical Industry Council-Long-range Research Initiative
CEN	European Committee for Standardisation
CEPA	Canadian Environmental Protection Act
CLP	Classification Labelling Packaging
CNTs	Carbon Nanotubes
CSA	Chemical Safety Assessment
CSR	Chemical Safety Report
DDEF	Data-Derived Extrapolation Factor
DG ENV	Directorate-General for the Environment
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
EC	European Council
EC10	Effect Concentration 10%
EC50	Effect Concentration 50%
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EHS	Environmental Health and Safety
ENEA	National Agency for New Technologies, Energy and Sustainable Economic Development
ENM	Engineered Nanomaterial
EP	European Parliament
EPA	Environmental Protection Agency
ERA	Ecological Risk Assessment
ES	Exposure Scenario
EU	European Union
EURL ECVAM	European Union Reference Laboratory for alternatives to animal testing
FAO	Food and Agriculture Organization of the United Nations
GAARN	Group Assessing Already Registered Nanomaterials
GLP	Good Laboratory Practice
IPSC	International Programme on Chemical Safety
ISO	International Standardisation Organisation
ISQ	Institute for Soldering and Quality
IUPAC	International Union of Pure and Applied Chemistry
JRC	Joint Research Centre
KI	Karolinska Institute
LCA	Life Cycle Assessment
LOAEL	Lowest Observed Adverse Effect Level
LoE	Line of Evidence
MAD	Mutual Acceptance of Data
MF	Modifying Factor
MIE	Molecular Initiating Event
MOA	Mode of Action
NANoREG	A common European approach to the regulatory testing of nanomaterials
NIEHS	National Institute of Environmental Health Sciences
NILU	Norwegian Institute for Air Research
NM	Nanomaterial

NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NRCWE	National Research Centre for the Working Environment
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
PBT	Persistent Bioaccumulative Toxic
PNEC	Predicted No Effect Concentration
QNAR	Quantitative Nanostructure-Activity Relationship
(Q)SAR	(Quantitative) Structure-Activity Relationship
RAAF	Read-Across Assessment Framework
RCC	Regulatory Cooperation Council
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfC	Reference Concentration
RfD	Reference Dose
RIVM	National Institute for Public Health and the Environment
SAR	Structure-Activity Relationship
SCCS	Scientific Committee on Cosmetics Safety
SCENHIR	Scientific Committee on Emerging and Newly Identified Health Risks
SOP	Standard Operating Procedure
TDI	Tolerable Daily Intake
TGD	Technical Guidance Document
TNO	Netherlands Organization for applied scientific research
TSCA	Toxic Substances Control Act
UF	Uncertainty Factor
UN	United Nations
US EPA	United States Environmental Protection Agency
US	United States
vPvB	very Persistent very Bioaccumulative
WoE	Weight of Evidence

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