

NANoREG

Grant Agreement Number 310584

Deliverable D 2.05

Protocol for characterization and categorization of MNM in powders and liquid dispersions

Due date of deliverable: 2015/12/30

Actual submission date: 2016/01/21

Author(s) and company:	Rambabu Atluri (NRCWE) Christian Micheletti (VN) Keld Alstrup Jensen (NRCWE)
Work package/task:	WP2 / Task 2.2c
Document status:	draft / <u>final</u>
Confidentiality:	confidential / restricted / <u>public</u>
Key words:	

DOCUMENT HISTORY

Version	Date	Reason of change
1	2015/11/23	Draft update and circulated to VN for comments
2	2015/12/14	Draft update after comments from VN
3	2015/12/15	Review and acceptance of Keld Alstrup Jensen
4.	2016/01/20	Final comments and draft update, JRC
5.	2016/04/24	First author revision and draft update, NRCWE
6.	2016/06/01	WP leader final revision, NRCWE
7.	2017/03/07	Project Office harmonized lay-out
8.	2017/06/01	Project Office changed picture formats in order to avoid blackening in PDF/A

This work is licensed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-sa/4.0/> or send a letter to Creative Commons, PO Box 1866, Mountain View, CA 94042, USA.

Lead beneficiary for this deliverable: NRCWE; 4

Owner(s) of this document	
Owner of the content	NRCWE 4
Co-Owner 1	VN 41

Table of Content

1	DESCRIPTION OF TASK	4
2	DESCRIPTION OF WORK & MAIN ACHIEVEMENTS	4
2.1	SUMMARY	4
2.2	BACKGROUND OF THE TASK	5
2.3	DESCRIPTION OF THE WORK CARRIED OUT	6
2.3.1	Review existing nomenclature and procedures for substance ID and reporting	6
2.3.2	Evaluate the suitability of existing MNM categorization paradigms (case studies)	6
2.3.3	Establish proposals for suitable nomenclature and categorization paradigm for MNM	7
2.4	RESULTS	7
2.4.1	Review existing nomenclature and procedures for substance ID and reporting	7
2.4.2	Evaluate the suitability of existing MNM categorization paradigms (case studies)	8
2.4.3	Establish proposal for suitable nomenclature and categorization paradigm for MNM	11
2.4.3.1	NM nomenclature:	15
2.4.3.2	Evaluation and conclusions	21
3	DEVIATIONS FROM THE WORK PLAN	22
4	REFERENCES / SELECTED SOURCES OF INFORMATION	22
5	ANNEXES	23
5.1	ANNEX I	24
	Review of the existing nomenclature and procedures for substance ID and reporting	24
5.1.1.1	A long-lasting definition of “Nanomaterial”	24
5.1.1.2	Classification and Categorization of Nanomaterials	30
5.1.1.3	Substance identification: Substances at Nanoscale	33
5.1.1.4	Information requirements for reporting of Nanomaterials	36
5.2	ANNEX II	40
5.2.1.1	Introduction	40
5.2.1.2	MNM case studies	40
5.2.1.3	Case studies	44
5.2.1.4	Conclusions	49
5.2.1.5	Supporting info	50
5.3	ANNEX III	53
	Examples	53

1 Description of task

Task 2.2 (Identification of Manufactured nanomaterials (MNM) according to the EC regulatory definition) has been split in several subtasks, one of which is Task 2.2c: Substance identification, NM categorization, and nomenclature for reporting NM in REACH, whose contributing partners are NRCWE, and VN.

As from the description of work (DoW) for Task 2.2c, the nomenclature and procedures for substance identification and reporting of various MNM in REACH will be evaluated (D2.5). Focus will be set on description and categorization of MNMs such as fullerene, carbon nanotubes, graphene, as well as surface-modified “old” MNM, including organoclays, cosmetics and pharmaceutical derivatives. The evaluation will consider the already proposed and used ISO and scientific nomenclature and should finally by a set of generically applicable neutral terms with a foreseeable future application. Suitable methods and procedures for a definition of primary particle, aggregate, and agglomerate size will be selected based on comparative testing.

2 Description of work & main achievements

2.1 Summary

As part of WP2, one of the objectives (D2.5, and Task 2.2) is to recommend a categorization of different manufactured nanomaterials (MNM) and their chemical derivatives. To derive the physicochemical-(Phys-chem)-based categorization and nomenclature for MNMs, three consecutive steps were followed, namely:

Part 1: Review existing nomenclature and procedures for substance ID and reporting (for REACH);

Part 2: Evaluate the suitability of existing MNM categorization paradigms (case studies);

Part 3: Establishment of a proposal for a suitable nomenclature and categorization paradigm for MNM.

The first part of the deliverable concisely summarizes the developments in the last few years on the issues such as a definition of nanomaterial, nanoscale size limits, natural vs. man-made nanomaterials, classification and categorization of nanomaterials, information requirements for substance identification and reporting of nanomaterials, naming a substance with nanoscale properties, etc. The report is a reasoned review of existing scientific publications and reports published by various international organizations (ANNEX I).

In the second part of the deliverable, the suitability of existing categorization paradigms was evaluated. A range of nanomaterial's as case studies were selected among the materials available in NANoREG repository. The selected case studies are characterized by a variety of physical-chemical properties, to cover a reasonable range of physicochemical parameter values. Both the ISO and Regulatory Cooperation Council (RCC) approaches have been applied for selected nanomaterials (ANNEX II).

In the final part of the deliverable, a new categorization scheme is proposed as an outcome of reviewing and processing already existing paradigms. The scheme also considers the specific aims of the NanoDefine, taking into account REACH naming and identification guidance. The user will be

able to identify/classify any substance or mixture according to the proposed scheme. The material categorization is discussed in the following chapter and the details on the nomenclature of different types of materials are discussed in the subsequent parts.

2.2 Background of the task

In the past few decades, there has been a strong interest in the research community for the development of products containing nanomaterials. The word "Nanomaterial" is broadly used to refer to a substance whose constituent particles are in the 1 to 100 nm size range. As a result of the dimension alone, nanomaterials may exhibit additional or different properties and behaviours as compared to macroscopic materials with the same chemical composition. Not only size-dependent properties but also surface properties make nanomaterials promising candidates for various applications.

A large number of nanomaterials have been developed in the last years [1], including carbon-based nanomaterials (e.g. fullerenes), organic nanoparticles (e.g. dendrimers, nanocapsules, and lipids), metal and metal oxide nanomaterials (e.g. gold, silver, silica, titanium dioxide, and semiconductor nanoparticles), or quantum dots such as cadmium sulphide. Together with the number of NMs that have been developed, also the number of publications in public and scientific domains has grown steadily in the period 2000 - 2014 (Figure 1). The data extracted by searching with a keyword "nanomaterial* as a " title" in Web of Sciences resulted more than 7800 articles, while using the same keyword as a topic, resulted more than 37000 publications.

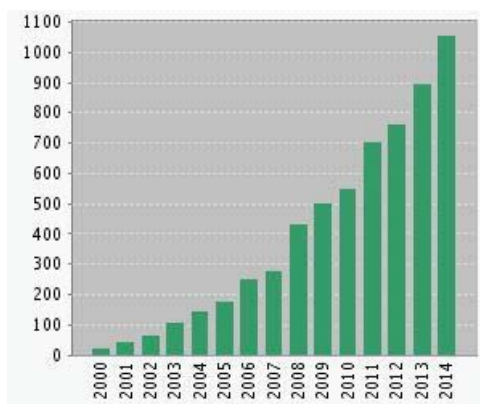


Figure 1: Number of articles / year between 2000 -2014, searched in Web of Sciences with a key word "Nanomaterial*" in the Title.

Concerns about identification and reporting of nanomaterials have also been raised due to their safety and possible associated health effects. The European Commission has set an action plan for immediate implementation of integrated and responsible approach for nanoscience and nanotechnology. To support the regulation and defining a proper regulation for products containing nanomaterials EU has spanned out a number of projects such as, ENNSATOX, NANOMMUNE, ENPRA, EuroNanoTox, HINAMOX, InLiveTox, INSTANT, ITS-NANO, MARINA, MembranenanoPart, MODERN , NanoPolyTox, NanoPUZZLES, NanosafePACK, NanoStair, NanoSustain, NanoValid, Nanogenotox, NanoDefine, and NANoREG, to name a few. Some of them are completed, and some of them are still on-going [4].

In addition to peer-reviewed articles [5,6], an overwhelming number of documents were published by the European Commission and ECHA as well as other stakeholders that describes Nanomaterials in REACH [7], Guidance on information requirements and chemical safety

assessment [8], Physical chemical properties of Manufactured nanomaterials, Identification and naming of substances under REACH and CLP [9], Scientific and technical support on assessment of nanomaterials in REACH registration dossiers and adequacy of available information, the EU commission recommendation on the definition of nanomaterial [10], scientific basis for the definition of the term " nanomaterial" , Risk assessment of products of Nanotechnologies, REACH implementation projects [11,12] substance identification of nanomaterials, specific advice on fulfilling information requirements for nanomaterials under REACH, Specific advice on exposure assessment and hazard/risk characterization for nanomaterials under REACH, Considerations on a definition of a nanomaterial for regulatory purposes [13] Nanomaterials impact assessment report etc., to name a few. However, there are still concerns and clarity is needed on specific issues such as a definition of nanomaterial, nanoscale size limits, natural vs. man-made nanomaterials, classification and categorization of nanomaterials, information requirements for substance identification and reporting of nanomaterials, naming a substance in the nanoscale etc.

Herein, a nomenclature and procedure for substance identification and reporting of various MNM is proposed. Adoption of this proposal can be a considerable improvement of the REACH guidance.

2.3 Description of the work carried out

2.3.1 Review existing nomenclature and procedures for substance ID and reporting

The European Commission and related agencies (e.g. EFSA, ECHA) has been active for issuing policies that regulate substances at the nanoscale and issued different advisory reports. However, there are some uncertainties and partially unclear guidelines for issues such as the definition of nanomaterial, nanoscale size limits, natural vs. man-made nanomaterials, classification and categorization of nanomaterials, information requirements for substance identification and reporting of nanomaterials, naming a substance contain nanoscale properties. To improve the suitability of the existing methods, schemes, and procedures for the MNM categorization and naming, a review of grouping/identifying MNM approaches are summarized, to identify gaps and strength, as the basis for the development of the NANoREG proposal. More details of the work can be found at ANNEX I.

2.3.2 Evaluate the suitability of existing MNM categorization paradigms (case studies)

The goal of this document is to establish a method to categorize a range of nanomaterials on the basis of physical and chemical properties, by applying two existing categorization schemes. The selected case studies are characterized by a variety of physical-chemical properties, to cover a reasonable range of physicochemical parameter values. The exercise allowed identifying issues in the application of the two schemes, as a first step toward the formulation of the NANoREG proposal.

Categorization and grouping are two terms that are used as synonyms. According to OECD, 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. However, in this report, we consider the identification and naming procedure applied in line with the chemical registration as per the REACH guidance document. Consequently, it is important to highlight that the categorization and naming approach discussed here only considers the physicochemical grouping. Hence, the aim is to identify physicochemical properties that are suitable for the MNM Identification and naming (ANNEX II). Potential links between physicochemical properties and risk and specific hazard

properties are not taken into consideration for grouping, but aims to ease the identification of nanomaterials that likely have special properties.

2.3.3 Establish proposals for suitable nomenclature and categorization paradigm for MNM

In the final part of the deliverable, a new categorisation scheme is proposed, taking into account the issues identified in ANNEX II, and keeping in mind the specific scope of Task 2.2. As a starting point, the NanoDefine [14] approach was considered. However, In the NanoDefine project a categorisation approach is suggested to help the user to conduct a proper characterisation of the NM with the final aim to identifying whether the material is a NM according to the EC Recommended Definition. The proposal here in D2.5 has a different goal, linked to nomenclature. The user will be able to categorise and name any substance or mixture according to the schemes discussed herein. The material classification is further discussed in section, §2.4.3.

As a proposal for a nomenclature for MNMs, a simple system was developed with a minimum set of descriptors. Our chemical nomenclature system is NOT generic and considers chemical constituents such as metals, metal oxides, carbon, organics, etc., as an individual case. As examples, we herein particularly focused on metal oxides (MOs) and carbon nanotubes (CNTs) to define their naming and compatibility with the classification scheme.

At the end of the document (ANNEX III), a few examples are given to illustrate how the classification and nomenclature could be used. The MNM examples are selected from the NANoREG MNM and associated NANoREG technical data sheets to fill in for each of the requested characteristics. Both mono- and multi-constituent types of MNM were chosen and processed through the classification scheme. Users are advised to follow the scheme with the available data to classify MNM.

2.4 Results

2.4.1 Review existing nomenclature and procedures for substance ID and reporting

Materials exist in different forms and sizes depending on the source and manufacturing process. In nature, there is a large number of nano-sized materials with properties that are distinct and relatively comparable to man-made nanomaterials. Man-made nanomaterials are defined as either manufactured nanomaterials or engineered nanomaterials or synthetic nanomaterials or modified nanomaterials. Either bottom-up or top-down process can be used to produce man-made nanomaterials. Ideally, Mono-disperse particles with spherical shape are a simple way to imagine a “nanomaterial”. However, in reality, the nanoparticles, irrespective of their morphologies, are not 100% uniform. This problem is particularly evident in industrially relevant larger-scale productions. Moreover, nanoparticles have a great tendency to agglomerate and some occur in aggregates, which also can agglomerate and lead to even μm -size particles. Unfortunately, there is no measurable parameter that offers a specific threshold value for us to generically define the transition between micro- and nanomaterials. Therefore, it is not easy to introduce a simple and meaningful definition term for nanomaterials to be used for regulatory purposes. Optimally, the nanomaterial term should be as clear and simple as possible and should be understandable by end-users. So far, several international organizations and committees, as well as a few governmental institutions, have proposed scientific and administrative definitions of nanomaterials. Therefore, we start this section by reviewing the existing definitions of nanomaterials. See ANNEX I and Table 1 for an overview of existing working definitions for the term “nanomaterial”.

Further, we reviewed the parameters proposed for classification and categorization of nanomaterials including size, location, and complexity of the nanostructure. However, not all nanomaterials can be classified based on size alone: other potential parameters must also take into account, for example, surface chemistry. Indeed, we also discussed pre-requisite for substances at nano-scale and their identification. It is argued that substances at the nanoscale must be considered as special substances and evaluated in a case-by-case approach. A common scheme for substance identification may not work for all nanomaterials. Size could be a primary identifier that distinguishes nanomaterial from a bulk material, but a clear, and a concise additional identifier should also be reported that indicates the specificity of the nanomaterial.

Finally, the status of the information requirements set by different organizations has also been reviewed. All organizations consider that particle size, shape, and surface area the key parameters to consider when reporting substances at the nanoscale. However, different organizations have different guidelines and reporting requirements. For simplicity, it is necessary, or at least highly beneficial, to develop a harmonized system for identification, reporting and labelling of substances at the nanoscale.

2.4.2 Evaluate the suitability of existing MNM categorization paradigms (case studies)

In order to evaluate the suitability of existing chemical and nanomaterial categorization schemes, several case studies were considered. The MNM to be used for the case studies should be accompanied by a proper physical-chemical characterization, carried out according to standardized or at least harmonized procedures. Therefore, case studies were selected among the MNM included in the NANoREG project, of which some have already been extensively characterized following well-described standard operation procedures. The case studies MNMs cover a variety in chemical composition, shape, and size. The detailed physicochemical characterization is reported in the technical data sheets (TDS) available from the NANoREG NIWO system (www.nanoreg.eu). For practical testing of existing categorization procedures, these MNMs are categorized following two schemes. The first one is the ISO Nano Tree, as reported in the Technical Report ISO/TR 11360, published in 2010 [15]. The other approach is the categorization scheme recently drafted by the RCC of USA and Canada. The two methods were selected because they rely on different physicochemical parameters. For example, ISO starts with the size and shape as main parameters, while RCC is based on chemical composition. A full description of the categorization schemes and validation procedures is included in ANNEX II of this report.

The ISO Nano Tree Approach:

ISO proposed a “nano-tree,” as a globally harmonized methodology for classifying various nanomaterials. The document (ISO/TR 11360:2010) is published as Nanotechnologies – Methodology for the classification and categorization of nanomaterials [15]. The classification system utilizes 1) special dimension (D), and 2) quantum confinement as the basis for classifying wide range of nanomaterials including nano-objects, nanostructures and nanocomposites. As per the technical report ISO/TR 11360:2010, the “nano-tree” consists of four columns (C1 – C4) that describe a nanomaterial including Dimension, Internal/external structure and type of nanomaterials, Chemical Nature/identity and Properties/behaviour. A detailed description of the ISO Nano Tree approach is discussed in the ANNEX I.

The application of the ISO Nano Tree was performed following the so-called C1-C4 column order in ISO/TR 11360 using the information available in the NANoREG Technical Data Sheets (TDS). Some

of the TDSs are still incomplete, but the data available were sufficient to assess the performance of the categorization systems. One can access the TDS documents at www.nanoreg-materials.eu.

The first column (C1) defines the minimum size of the nano-object being <100 nm. The TDS reported size measurement using different methods, and it allowed to identify 1D, 2D, 3D classes of MNM. For example, JRCNM02000a / NM-200, is an amorphous Silica having an average size of around 50 ± 55 nm can be classified as a 3D MNM, while NM-400 / JRCNM04000a, a carbon nanotube with a diameter around 18 nm and a length around 850 nm, is a 2D MNM. However, in the case of a sample of MNM with two distinct size-populations and different morphologies, it is hard to identify a single class. A tentative procedure to solve this issue was done for NM-111 / JRCNM01101a, a surface-modified ZnO, where both 3D and 2D classes were identified, especially by aspect ratio, which, for population 2, was ranging from 2 to 8.5. With a size within 10 and 450 nm, population 2 could be classified as a 2D MNM. Another possibility is to quantify the percentage of each population (by number in accord with the recommended EC definition of a NM), and define a percentage threshold for which a population is relevant, or not, in the sample (i.e., if it is a population or "impurities").

The second column (C2 and C2S) is dedicated to the structure of the nano-objects. Considering our MNM case studies, an uncoated MNM is to be considered as a single component MNM (see JRCNM02000a and JRCNM04000a), while /JRCNM01101a is a multi-constituent nano-object since it is coated with triethoxycapryl silane, an organic coating. The C2S column is dedicated to the identification of the type of nano-object. JRCNM02000a is a nanoparticle. JRCNM04000a is a nanotube and a classification of JRCNM04000a as a HARN can be useful here, even if not reported in the Nano Tree. The HARN concept is different from the fibre concept since a nanotube has a very high aspect ratio, but it can be shorter than 5 μm , and it is thus not a fibre of concern according to the WHO definition [16]. This point is also relevant for the shape parameter, which is not clearly described in the C2S column. It can be probably added as a C2SS column, but up to now there is no specification of shape in the ISO/TR 11360. The 3D JRCNM01101a can be classified either as a nanoparticle or core-shell nano-object because of the coating. A definition of core-shell is not reported in the ISO technical report, and coated particles are not available as a choice. It is our understanding that the shell in core-shell nano-objects normally is considered to be hard materials and not a molecular coating. The 2D JRCNM01101a can be classified as a nanorod, but also here the coating is not mentioned and not available as a choice. It is shown in the "multi-component nano-object" that the structure of the nano-object is not simple, but the reference to chemical composition is not specified in C2. In consequence, a multi-component nano-object is generally not specified in the ISO nano-Tree scheme.

The third column (C3) is referring to the chemical composition, and in this column the chemical composition of all the different constituents of the nano-objects is included. The available classes, as provided, do not cover the conventional chemical compositions of MNM. For example, metal oxides are missing, while ceramics are included. Anyway, JRCNM02000a was classified as semi-metallic, JRCNM04000a as carbon-based, and JRCNM01101a as metallic for the core (metal oxides is missing as a choice) and organic for the coating.

Column 4 (C4) is for the inclusion of the properties of the nano-objects. The list of possible choices, even if not exhaustive, is long, and it covers several classes of properties, also linked to the specific uses (e.g. magnetic properties, elastic properties). However, the properties in the Nano Tree are seen more as descriptors than as grouping parameters.

In addition, the commonly measured physicochemical properties are not explicitly included in the list, and sometimes it is hard to decide where to put the measured property. For example, the crystalline structure is not included in the Nano Tree at the moment. The crystalline structure is important for some MNM, because different crystalline structures lead to different physicochemical properties. In our view, the Nano Tree can accommodate the crystalline structure in the Chemical properties group (C4), since solid state chemicals can be specified by composition and crystalline structure, which to a great extent are interlinked. The zeta-potential can be included in Electric properties in C4. It is an important property defining the interaction of MNM with the specific surrounding environment. Zeta-potential is not strictly an inherent property, but it can be used to predict the behaviour of the MNM and used properly, it can be valuable in a categorization scheme. Finally, dustiness is an essential property of MNM in powder form applied in industries to consider the risk of dust explosions and risk of occupational exposure. It is a measurable end-point and even-though the results are method dependent, it should be part of the mandatory reporting for risk assessment using existing or emerging standard procedures. Dustiness can be included in the Mechanical properties (C4).

In general, during the application of the Nano Tree, it emerged that the ISO scheme is structured to identify categories of MNM on the basis of size, shape, and chemical composition, in this order. The properties included in C4, which are not ranked according to priority and relevance, are considered physicochemical descriptors rather than grouping parameters. It is not clear how and when two MNM, even in the same class (e.g., 3D, Metals), are considered similar. Similarity can be defined as two MNM having the same (or close) value for a given set of (in this case) physicochemical parameters. The Similarity between two MNM can allow read-across, i.e. the inference of similar behaviour, but the Nano Tree does not specify MNM for this purpose. There is no indication of what similarity means, and there are no criteria given to measure the similarity of MNM.

RCC approach:

The test application of the RCC approach highlighted that a comparison of MNM similarity within each chemical group can be done only on the basis of the physicochemical properties. Contrary to the Nano Tree, the RCC approach is limiting the number of properties to be measured for each chemical composition class. In some cases, some parameters are known, such as surface reactivity, and it can be measured by using different methods, as well as proxy parameters. In our case, the specific surface area can be a proxy, but more direct measurements can be also useful. The system reflects that it has been developed for regulatory purposes, which is not the case for the ISO Nano Tree.

To identify similar MNM in the chemical classes, the RCC approach suggests that there has to be a significant similarity between the values of the measured properties. It is also true that similarity can be relative to a specific MNM behaviour, and thus refer to a set of parameters such as toxicity, persistence, bioaccumulation in organisms, and so on. However, for this exercise we selected different MNM to cover different aspects of the categorization approaches, and expected to be not similar in properties. For example, JRCNM01100a and JRCNM01101a, both metal oxides, show close values for almost all measured parameters (e.g. size distribution, core chemical composition, specific surface area). However, JRCNM01101a is coated, while JRCNM01100a is uncoated. Since the surface properties determine at least the initial interactions between the MNM and the biotic and abiotic environment, it is not immediately possible to put these two MNM into the same group. The same is the case for JRCNM04000a and JRCNM04001a, where one MN is capped and shorter, and the other is uncapped and longer. However, the impression is that the RCC approach

has more rationale and is suitable to define MNM categories on the basis of physical-chemical properties.

2.4.3 Establish proposal for suitable nomenclature and categorization paradigm for MNM

The MNM categorization scheme proposed herein is based on considerations of the reviewed previous paradigms and it serves as a possible procedure for a range of nanomaterials. The categorization scheme introduces relevant physicochemical properties of nanomaterials by subgrouping them into 1) Structure/Chemical composition, 2) Shape/Porosity, and 3) Specific Physicochemical properties. The detailed description of each subgroup is discussed in the subsequent sections, and the applicability of the proposed scheme was assessed by selecting specific NANoREG core-nanomaterials and available TDS. The proposed classification scheme seems to fit well with the majority of the nanomaterials, and after further testing it could be proposed as a tool for MNM classification.

In addition, we also proposed a system of nomenclature for nanomaterials on the basis of physical and chemical properties. The NM nomenclature provides a minimum set of descriptors that enables one to immediately understand the chemical composition and structural relationships of a substance. Though, our approach for naming is generic, each chemical component such as metals, metal oxides, carbon, organics etc., is considered as individual cases. Hence, to give examples, we particularly focused on metal oxides and carbon nanotubes, to define their naming and compatibility to the classification scheme.

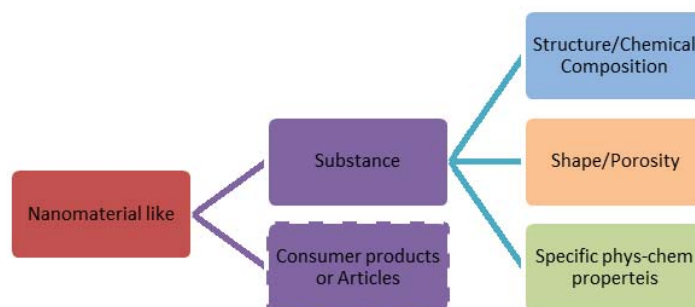


Figure 2. Important Phys-chem characteristics used for categorisation of MNMs

Figure 2 shows the general criteria for categorization of MNMs using the system developed in the NANoREG project. This is a rational approach to synthesize the information, and to use the information to establish a proper MNM nomenclature. In the first part we give an explanation about the scheme structure. In the following parts, each section of the system will be discussed in detail. Unless otherwise stated, the terminologies used in the scheme are coherent with Regulation (EC) No 1907/2006 (REACH) and ISO standards. In addition, the scheme is validated with a set of data available with in NANoREG and the examples are included in the ANNEX III.

The main assumption of the scheme is that we deal with a nanomaterial according to a regulatory definition accepted by EU authorities, whatever this definition could be. Since the scope is MNM categorization and naming, we will consider only substances as defined by REACH. Consumer products and articles are instead more relevant for risk assessment, which is out of the scope of this exercise.

For any MNM, three important groups of characteristics are identified:

- Structure/Chemical composition,
- Shape/porosity,
- Specific physicochemical properties.

For each group, validated methods to measure the MN properties are needed to allow a proper categorization. In NANoREG Deliverable 2.4, methods enabling identification and quantitative analysis of both inorganic and organic surface coatings of manufactured nanomaterials are provided. In Deliverable 2.10, SOPs for the quantitative size and shape analysis of manufactured nanomaterials using TEM were developed and validated by inter- and intra-laboratory comparison. Finally, in Deliverable 2.11, a procedure for determination of the volume specific surface area (VSSA) is developed and discussed as a reliable, simple tool to support the identification of nanomaterials.

1) Structure/Chemical composition

The main assumption in this group of properties is that we already know the chemical composition of the MNM as well as its structure. There are standardized protocols that can be used to define both characteristics, also among the NANoREG WP2 work. The scheme is a rational approach to synthesize the information, and to use the information to establish the proper MNM nomenclature.

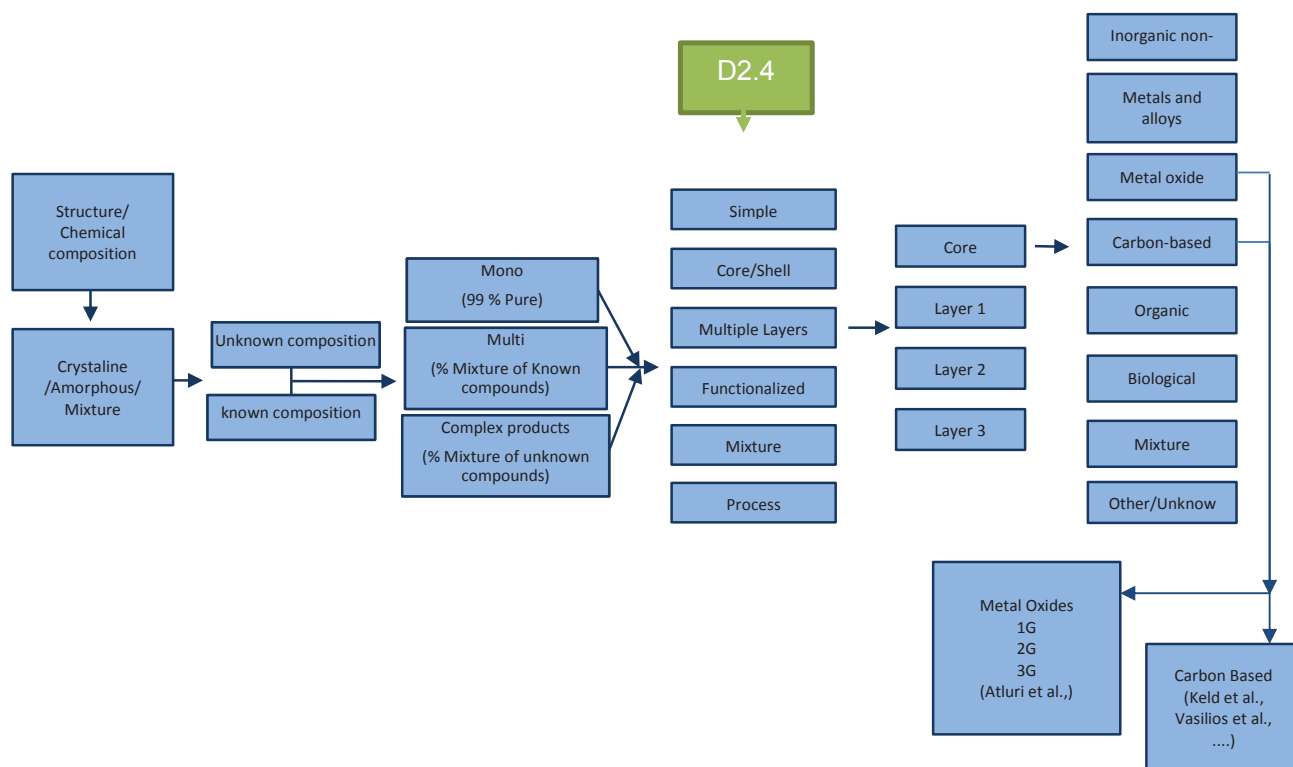


Figure 3: Structure/Chemical composition based characteristics for categorisation of MNMs

As shown in Figure 3 structure/chemical composition part, the first criteria is to know if the sample is crystalline, amorphous, or a mixture of them. The following aspect is the chemical composition, which is defined in accordance with REACH as mono- or multi- constituent, or as a Substance of Unknown or Variable composition (UVCB). As per the REACH terminology, a mono-constituent substance is defined by its composition, in which the main constituent is present at least at 80% (w/w). However, in the chemical composition of MNM, even a component with a 1% fraction can be really important for a functional aspect,

thus influencing the properties of the resulting material. Therefore, the 1% should be reflected in the categorization and naming. In this scheme, it is proposed that for a MNM to be a proper mono-constituent substance, the fraction of the main constituent should be at least 99.9%. Unfortunately, there are arguments/comments within the NANoREG consortium that which say that it may not be practical to assume such a high purity and recommends a considerable level of “acceptable impurities”. These impurities can be the result of processing, on purpose or unavoidable. The level of “acceptable impurities” depends on the nanomaterial type, processing method and application area. For example, heavy metal content of synthetic amorphous silica is <0.1%, although it has been considered as a highly pure substance under food and pharma grade. Likewise, carbon nanotubes with traceable amounts of metal ions from the production /cleaning process and which cannot be avoidable. Therefore, the acceptable impurities and their level are going to be considered in the scheme as a specification for each part of the MNM structure. But, to define the mono-constituent in the scheme in a generic term, we assigned 99% purity of nanomaterials.

If the user does not know the composition, the sample will be ranked in the "mixture - or complex composition". In case of UVCB, the focus is on the variability of the composition, as can be envisaged with the synthesis of some new MNM.

The next layer of the first group of properties is the structure. For MNM, the shape and the way the different structural components are distributed is really important. For example, a functionalized carbon nanotube can show completely different properties than an un-functionalized one. Therefore, for each MNM it is relevant to consider more about the overall structure, and the location of the different structural components. The samples with such as composite structure may be classified as follows: Simple, core-Shell, Multi-layers, Functionalized, and mixtures. The value “Mixture” represents the possibility of the co-existence in the same substance of different forms of MNM. It is important to keep in mind that “the acceptable impurities” might be also being part of the structure and often an atomic substitution of the impurities. In NANoREG and specifically Deliverable 2.4, provide methods for enabling identification and quantitative analysis of both inorganic and organic surface coatings of manufactured nanomaterials. Readers are advised to review the D2.4 document for information of the SOPs.

After the structure is defined, for each structural component the chemical composition is defined. Materials fall under a different category of chemical identities such as metals and alloys, metal oxides, carbon-based, organic, biological, mixtures of other unknown identities. In this aspect, particular attention was given to metal oxides and carbon-based materials. A generic sub-classification scheme was proven based on the structural complexity and composition and successfully applied to silica-based nanomaterials. In short, bare silica nanoparticles are grouped to 1st generation, silica with organic or inorganic as their secondary components are in the 2nd Generation and finally, silica comprising of both organic and inorganic as their counterparts as 3rd Generation. The classification system is not restricted to silica nanoparticles, but can be applied to broad range of sizes and materials of any composition. In the scheme, it is also proposed a nomenclature for all the three-generation materials.

We also proposed a conceptual categorization of carbon-based materials, in particular to carbon nanomaterials. The scheme considers three parameters such as descriptive, topology and chemical information of CNTs. The scheme seems to cover a range of CNTs and is now validated by selecting core-nanomaterials of NANoREG.

2) Shape/Porosity

Another important part of the categorisation is shape/porosity, which is describing both the structural and textural properties of various nanomaterials (Figure 4). The particles shape, which reflects the number of dimensions of the nano scale substance, has to be analysed and be integrated into the material classification. The shape of nanomaterials can vary a lot. The proposed list is limited to the most common possibilities, such as sphere, elongated, rod, tubular, mixture or other/unknown. However, other shapes can be included here as needed. In NANoREG and Deliverable D2.10, developed SOPs for the quantitative

size and shape analysis of manufactured nanomaterials using TEM and were validated by inter- and intra-laboratory comparison. Readers are advised to review the document for more information on the analysis of the SOPs.

Finally, surface area as an inbuilt property of nanomaterials and hence porosity considered as another important aspect to consider for the classification. Indeed, EU definition has considered volume specific surface area (VSSA, greater than $60 \text{ m}^2/\text{cm}^3$) as a complementary definition to distinguish nano vs. non-nanomaterial. Likewise, in NANoREG and Deliverable D2.11, the applicability of the volume specific surface area (VSSA) as a reliable, simple tool to identify nanomaterials is validated and was compared with the results obtained by electron microscopy as reference.

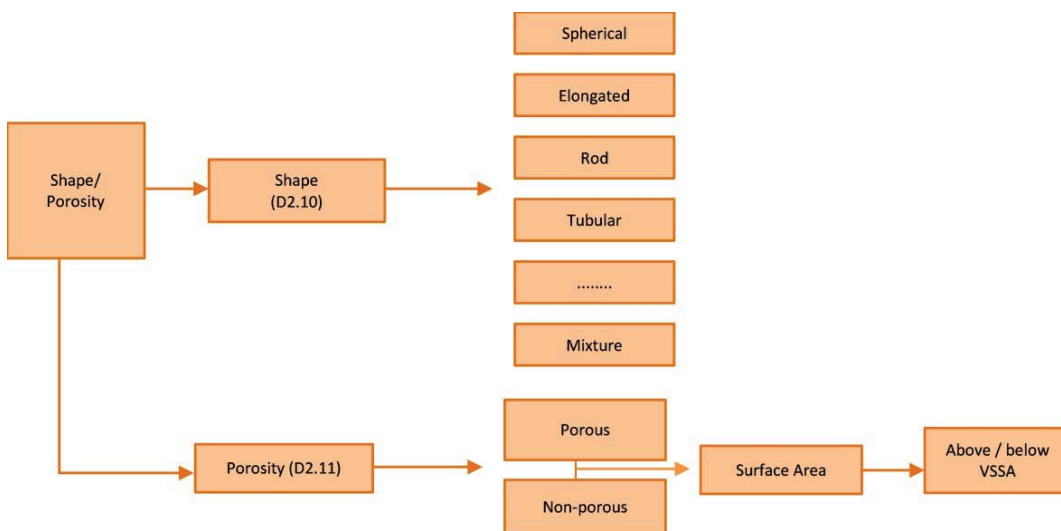


Figure 4: Second group of characteristics for MNM categorisation.

3) Specific phys-chem properties

In addition to the structural and chemical properties, nanomaterials possess other specific properties, which make them distinct from their bulk form. The properties such as stability, reactivity, and surface charge are the important characteristics of MNMs. The scope of these properties in the categorization scheme is to include in the MNM name that can support the underlining of important phys-chem differences in different nano-forms. Figure 5 shows three specific properties of MNMs under different environments or testing conditions.

Stability of the substance is an important parameter. To know how the MNM behave in standard media will give useful information about a MNM, or on the form of a substance. In this case, both chemical and physical stability were considered. Among the MNM properties, solubility is always considered as prominent, because an entirely soluble MN is not a nanomaterial anymore. Solubility is a function of the dispersion media, and it may proceed with different kinetics and for the entire or only for a part of the MNM. For example, a nanoparticle with a soluble coating is different than the same nanoparticle with an insoluble coating. However, in the classification scheme we limit the minimum requirements to a “standard” media such as DI water. We are aware of the properties of nanomaterials and their changes associated with the testing media. To limit the classification scheme relevant for physicochemical properties of nanomaterials, other testing media is not needed.

As per the physical stability, particles might aggregate or agglomerate depending on the environment. Here we are not sure of the level of the aggregation/agglomeration and how it reflects the Phys-chem properties of the substances. The user is advised to follow the ISO and REACH definitions and carefully understand

their impact. In any case, we advise readers to check the physical stability in "standard" media such as DI water.

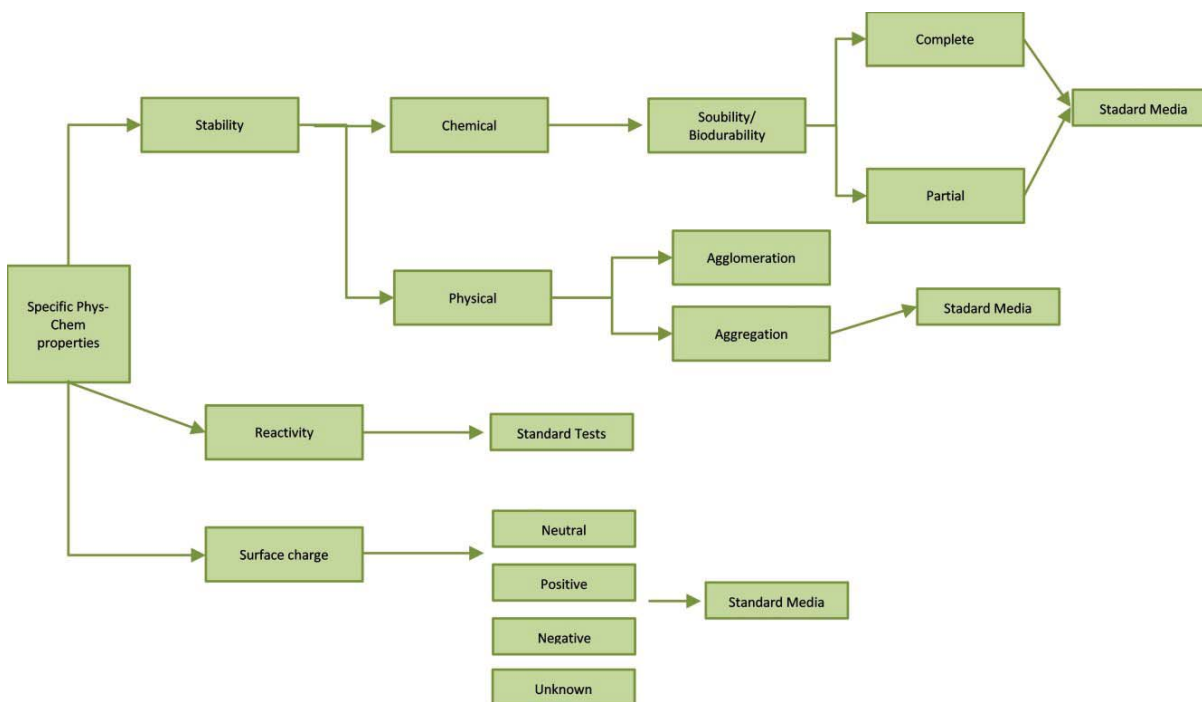


Figure 5: Highly relevant specific phys-chem parameters considered for categorisation of MNMs.

Reactivity can be either due to redox activity, photo- or chemical interaction and are coupled processes in natural systems and involve the transfer of electrons to and from chemical moieties. A number of MNMs may be composed of or contain constituents that undergo reduction, oxidation, or both in aquatic and terrestrial environments. Therefore, it's of another important end-point of nanomaterials for their classification.

Surface charge influences the fate and transport of nanoparticles. Any surface charge on nanoparticles causes electrostatic repulsion between particles of similar charge, which can counter the tendency to agglomerate. Therefore, it's essential to know the surface characteristics of the substances under "standard" media in order to determine their effect on stability and reactivity.

Overall, the proposed categorization scheme considers relevant phys-chem properties of nanomaterials by subgrouping them into 1) Structure/Chemical composition, 2) Size/Shape/Porosity, and 3) Specific phys-chem properties. Considering each subgroup is equally important, the materials are further categorised by considering several Phys-chem properties. This classification system has been validated (ANNEX III) by selecting a range of simple to complex nanomaterials from list of NANoREG core materials. This tool can be used as a guidance document for categorization of various nanomaterials, irrespective of their physical, structural and chemical complexity.

2.4.3.1 NM nomenclature:

EU has indicated that the lack of a nomenclature system continues to pose challenges in regulating nanomaterials. Without an appropriate nomenclature system for nanomaterials, many countries are unable to differentiate nanomaterials from each other and from bulk/molecular forms. Under ISO TC/229, a joint ISO-International Union on Pure and Applied Chemistry (IUPAC) has been initiated to develop a chemical-

based nomenclature system, and the US Environment Protection Agency is working with its Chemical Abstract Service (CAS) to develop a nomenclature system for carbon nanotubes.

Apart from traditional IUPAC and CAS chemical nomenclature systems, other proposals particularly address various forms of carbon, including fullerenes and Nano-diamonds. Inagaki and co-workers [17] have proposed a system of nomenclature for carbon-based nanomaterials based on factor controlling the preparation and production process. Suarez-Martinez and co-workers [18] proposed a system that focuses on morphological and geometrical transformation rather than process and properties. In any case, there is yet any nomenclature defined neither in the literature nor in the public domains.

In a recent draft by ISO (ISO/TR 14785_2014), the following general considerations are listed to assess the degree to which existing chemical nomenclature systems are adequate to provide a common system of naming nano-objects.

- The system should be able to describe and distinguish among nano-objects to a reasonable degree;
- The system should have a minimum set of descriptors that result in names from which a knowledgeable person can understand the nano-object's chemical and structural composition;
- The naming rules should be sufficiently simple and clear to evaluate studies and work on the same nano-object;
- The system should be robust to encompass advances in nanotechnologies;
- For a nomenclature system to be robust, techniques to measure the pertinent parameters should be available.

Keeping this in mind, we herein proposed a robust system for naming which provides a minimum set of descriptors that enables one to understand a substances' chemical and structural composition. Our chemical nomenclature system is NOT generic and considers each chemical component such as metals, metal oxides, carbon, organics...etc as an individual case. In this part of the work package, we particularly focused on metal oxides and carbon nanotubes, to define their naming and compatibility with the classification scheme.

Nomenclature of Metal Oxides (MOs):

We propose a general nomenclature for metal oxides (Figure 6) based on the composition and structural complexity induced by mixing, doping or surface treatment with other components (elements, compounds and materials). The compositional grouping of the metal oxides is determined by the type of components (organic or inorganic) or combinations thereof while the complexity is determined by the extent (i.e., amount) and location of the components. The surface treating components can be substituted either as a core (C) or external (E) or a mixture of both to the metal oxide matrix.

The nomenclature used is constructed to report how complex the metal oxide substance is and the agents used for changing the function: organic or inorganic or both and location of those. The notations also give preliminary information required for characterization needs. In order to derive the notation, one has to understand the manufacturing process, and reactants used and by-products in making of such substances. Therefore, our notation for metal oxides gives direct and sufficient information on the nature of the reported substance as it takes both the materials and their physical location into account. This type of information is assumed to be highly critical for identification of materials that should be subject to additional analysis.

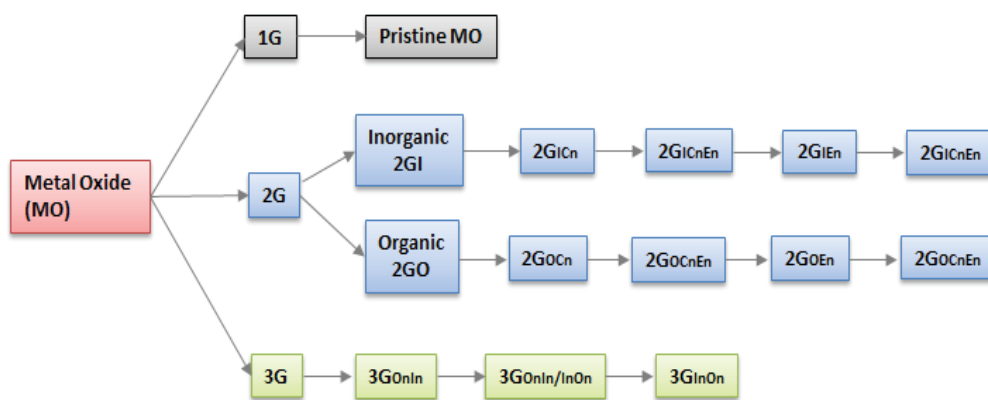


Figure 6: A simplified nomenclature procedure for Metal Oxides (MOs)

1st Generation (1G): Pristine form of metal oxides (MOs). As discussed in earlier section, the purity of Metal Oxide is of concern to discriminate between multi to a mono-constituent. Considering “acceptable impurities” levels in a range of metal oxides depend on the composition and manufacturing process. But, to define the pristine form of metal oxides, we designed the nomenclature as MO-1G_n (% of acceptable impurities), where “n” is the % purity of metal oxides.

Simple Nomenclature	Fully described Nomenclature	Description
SiO ₂ (Amorphous) – 1G _n	SiO ₂ (Amorphous) – 1G ₉₉ (1% Al ₂ O ₃)	Above 99% pure amorphous Silica with 1% of acceptable impurities Al ₂ O ₃
Fe ₃ O ₄ (Maghemite) – 1G _n	Fe ₃ O ₄ (Maghemite) – 1G ₉₈ (1% Al ₂ O ₃ and 1% -CH ₃)	Above 98% pure Iron Oxide with 2% of acceptable impurities.
ZnO ₂ – 1G _n	ZnO ₂ – 1G ₉₉ (1% Silane)	99% pure Zinc Oxide with 1% a silane compound
TiO ₂ (Rutile) – 1G _n	TiO ₂ (Rutile) – 1G ₉₈	

2nd Generation (2G): The composition of metal oxides comprising of one or more organic or one or more inorganic components as their secondary phase. Here the descriptors are quantity of the components and their location. Depending on the complexity of the components, the 2Gs are further divided into Organic (2GO) and Inorganic (2GI). Complexity is the location of the components either external (E) or as a core (C) of metal oxide or combination of both. With respect to the combination and location of Organic (O) or Inorganic (I) components, the 2GO and 2GI groups are further described as follows.


- 1) MO- 2G_{OEn}; where the external (E) surface of metal oxide consists of organic compounds,
- 2) MO- 2G_{OCn}; where the organic phase is present as a core (C) to the metal oxide, and
- 3) MO- 2G_{OCnEn}; where the metal oxide consists of an organic component as a core and an additional organic component at the external surface of metal oxide. The notation 2GOCnEn also covers doping of metal oxides at atomic level. The term “n” corresponds to the weight% of different organic compounds with the metal oxides.




Likewise:

- 1) MO- 2G_{IEn}; where the external (E) surface of metal oxide consists of inorganic compounds,
- 2) MO- 2G_{ICn}; where the inorganic phase is present as a core (C) to the metal oxide, and

3) $MO-2G_{ICnEn}$; where the metal oxide consists of an inorganic component as a core and an additional inorganic component at the external surface of metal oxide. The notation $2G_{ICnEn}$ also covers doping of metal oxides at atomic level. The chemical nomenclature for the organic or inorganic components is defined as per the IUPAC notation.

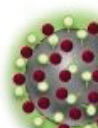
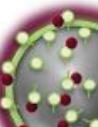

Examples:

Simple Nomenclature	Fully described Nomenclature	Simplified Image	Description
SiO ₂ (Amorphous) – 2GIC _n	SiO ₂ (Amorphous) – 2GI _(CdS) C ₅		Second generation silica shell on a core of 5 wt% CdS (core-shell type)
SiO ₂ (Amorphous) – 2GIE _n	SiO ₂ (Amorphous) – 2GI _(Fe₂O₃) E ₅		Second generation silica with 5 wt% of Fe ₂ O ₃ coated on silica.
SiO ₂ (Amorphous) – 2GIE _n	SiO ₂ (Amorphous) – 2GI _(CdS) E?		Second generation silica shell on a core of (unknown wt%) CdS.
SiO ₂ (Amorphous/ Maghemite) – 2GIC _n E _n	SiO ₂ (Amorphous) – 2GI _(Fe₂O₃) C ₁₀ E ₂₀		Second generation silica with inorganic 10 wt% and 20 wt % Fe ₂ O ₃ on both at the core and external to the silica matrix.
SiO ₂ (Amorphous/ Maghemite) – 2GIE _n	SiO ₂ (Amorphous/ Maghemite) – 2GI _(Fe₂O₃) E ₅₀		Second generation silica with 50 wt% of Fe ₂ O ₃ coated on silica. Here silica prepared first and coated with iron oxide in a later stage.
Fe ₂ O ₃ (Maghemite) – 2GIE _n	Fe ₂ O ₃ (Maghemite) – 2GI _(SiO₂) E ₅₀		Second generation Iron oxide with 50 wt% of silica coated on iron oxide. Here As per the process, iron oxide prepared first and coated with silica in a later stage.
SiO ₂ (Amorphous) – 2GOE _n	SiO ₂ (Amorphous) – 2GO _(APES) E ₁₀		Second generation silica functionalized with 10 wt% of organics, APES.

SiO ₂ (Amorphous)- -2GO _n E _n	SiO ₂ (Amorphous)- 2GO _{(APES/FITC)-E10/5}		Second generation silica functionalized with organics such as 10 wt% APES and 5 wt% FITC dye.
SiO ₂ (Amorphous)- -2GOC _n E _n	SiO ₂ (Amorphous)- 2GO _{(APES/FITC)-C10/5-E10/5}		Second generation silica functionalized with organics such as 10 wt% APES and 5 wt% FITC dye on both internal and external to silica matrix.
TiO ₂ (Rutile/ Maghemite)- -2GIC _n E _n	TiO ₂ (Rutile/ Maghemite)- -2GI _{(Fe2O3)-C7E7}		Second generation-Fe ₂ O ₃ -doped-TiO ₂ . It is unknown the location of TiO ₂ in the iron oxide matrix.

3rd Generation (3G): The composition of metal oxides comprising both organics and inorganics as their counterparts.

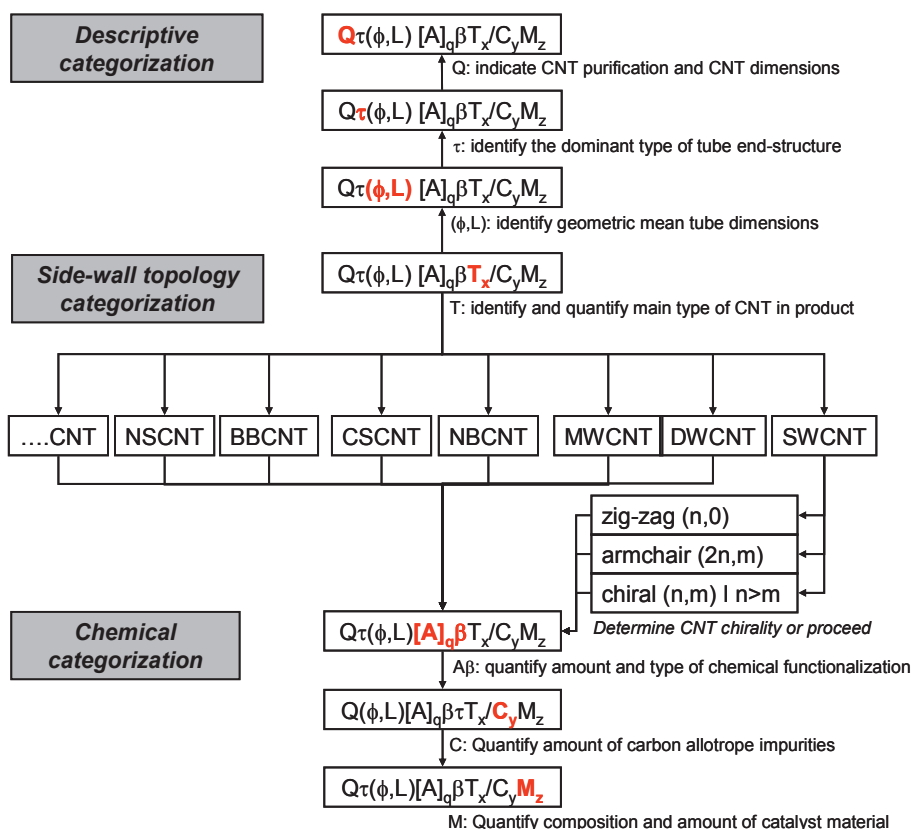
The 3rd generation is a derivative of the 2nd generation where the multifunctional characteristics of metal oxides achieved by combination of both one or more organic and one or more inorganic functionalities, respectively. Depending on the function and application of the metal oxides, different combinations of multi-constituent substances have been developed. Based on an extensive literature search and variety of metal oxides developed so far, it was possible to divide 3rd generation metal oxides into three major class; 1) Organic/Inorganic (MO- 3GOnIn), 2) Inorganic/Organic (MO- 3GInOn) and 3) Organic/Inorganic - Organic/Inorganic (MO- 3GOnIn-InOn), where n indicates the weight % of organic and inorganic compounds in the multi-constituent or UVCB substances.

Simple Nomenclature	Fully described Nomenclature		Description
SiO ₂ (Amorphous/ Maghemite) - 3GOnIn	SiO ₂ (Amorphous/ Maghemite) - 3GO _{10/5} (10%APES, 5% Fe ₂ O ₃)		Third generation External surface of silica is functionalized with 10 wt% APES and further coated with 5 wt% Fe ₂ O ₃ .
SiO ₂ (Amorphous/ Maghemite) - 3GOnIn/O _n In	SiO ₂ (Amorphous/ Maghemite) - 3GO _{10/5} /O _{10/5}		Third generation, a mixture of silica containing 10 wt% of functional groups, APES and coated with 5 wt% Fe ₂ O ₃ .
SiO ₂ (Amorphous/ Maghemite) - 3GI _n O _n	SiO ₂ (Amorphous/ Maghemite) - 3GI ₅ O ₁₀		

Nomenclature of Carbon nanotubes (CNTs):

For categorization of CNT nanomaterials, it is important to note that most CNT nanomaterials do not consist of one phase. They do not have a fixed molecular size such as the spherical fullerenes and they may contain both carbonaceous and catalyst impurities of different kinds. Current CNT grouping simply use the CNT structure and their functionalization, where functionalized types by some are considered “metanotubes”, i.e. the pristine CNT is a substrate, structural skeleton or host for a new compound.

The proposed nomenclature system is based on the general sidewall topology, a mineral-like structural and impurity chemical formula, and a descriptive indicator of post-production treatment and carbon tube characteristics (below). The system has also been proposed in a recent document for the Danish EPA [19].



The CNT nanomaterial can then be described using the following formula:

$Q\tau(\Phi;L)[A]_q\beta T_x/C_yM_z$, where

- A: functionalization/coating of compound [A] in q weight fraction
- β : type of functionalization divided into adsorbed (\bullet), endohedral ($@$) atoms, molecules and compounds, and functionalizations with a covalent bond (written in continuation)
- T: type of CNT (SW, DW, MW, ...) in x weight fraction of the sample and chirality for SWCNT.
- /: Associated y and z weight fractions of carbonaceous (C) and specific catalyst (M) impurities, respectively.
- Q: Labeling of post-production treatment as an indicator of the quality of the CNT nanomaterial product: Industrial grade (I), Milled/Grinded (M), Purified in acid (P), Annealed/Oxidized (A), Size-fractionated/filtered (S) etc.
- $(\Phi;L)$ geometric mean CNT diameter (Φ) and length (L).
- τ : type of tube ends denoted o , c , m for open-ended tubes, close-ended tubes, and close-ended by catalyst material, respectively.

Consequently, $[A_q]^\beta T_x / C_y Z_z$ describes the CNT sidewall topology and chemical composition and $Q\tau(\Phi;L)$ is a physical quality descriptor. Hence, using the reporting strategy :



Describes a purified open-ended single-walled COOH-functionalized SWCNT with a mean tube diameter of 1.2 nm and a length of 1 μ m, with impurities of 1 wt% of other carbon materials as well as 3 wt% Fe and 1 wt% Co catalyst material. If the SWCNT also had been size-fractionated, the descriptive categorization would have been PSo(1.2nm;1 μ m).

Overall, the proposed nomenclature system is intended to give immediate and structured description of the complex CNT materials. The nomenclature is developed based on material characteristics and chemistry, which is of interest from technological point of view, but also from their toxicological properties.

2.4.3.2 Evaluation and conclusions

Review:

Overall, there is currently no globally accepted and fully ideal definition of nanomaterials. Though a size-based definition is prevalent, the different definitions proposed are not in full agreement among the international organizations and institutions. The challenge remains for the policy makers to introduce a meaningful and practical unique definition of a nanomaterial for regulatory use, which is clear, concise and, in particular, understandable by the end-users.

Different parameters have been proposed for classification and categorization of nanomaterials including size, the location of the nanostructure and structural complexity of the substance. The technical system proposed by ISO highlights the importance of size and dimensions of the nano-object, while other systems proposed for risk assessment for example considers the location of the nanostructure in the material (air, liquid, solid). However, it is evident that size alone is insufficient for chemicals classification of nanomaterials; other parameters must be taken into account, such as general composition, the number and abundance of compounds, and the surface chemistry.

Validation of existing MNM categorization paradigms:

A tiered classification and categorization approach is useful to reduce the amount of testing and data to collect for reporting, and to filter the different MNM in a simpler way. The ISO approach, i.e. to start the categorization by using size/shape alone, and then including all other phys-chem at a later stage, is not useful for a hazard-based categorization approach, because size/shape can divide MNM into categories that are not really linked to a specific concern (e.g. same size with different coating can result in different groups). On the other hand, it would make sense in regards to HARNs.

In general, however, categorization has to be multidimensional, i.e. involving different properties. Also, the scope of the grouping should be clearly identified: is it naming only (i.e. REACH substance identification), or groups linking physicochemical properties to hazard? In grouping, the most important issue is "how similar is similar", i.e. to decide when a MNM is similar enough to another MNM to be able to put both MNM in the same group, which can be achieved by identifying appropriate benchmarks.

New proposal:

The phys-chem based categorization scheme proposed herein is based on the existing chemical registration scheme in REACH while introducing relevant physicochemical properties of nanomaterials by subgrouping them into 1) Structure/Chemical composition, 2) Shape/Porosity, and 3) Specific Physicochemical properties. Considering each subgroup is equally important, the materials are further classified by considering several physicochemical properties. This classification system has been demonstrated by the use of selected NANoREG core MNM with simple to complex physicochemical characteristics. This tool can be used as a guidance document for classifying various nanomaterials, irrespective of their physical, structural and chemical complexity. The proposed classification scheme seems to work on the nanomaterials tested, and after further testing it could be proposed to support MNM classification for regulatory use. Finally, the nomenclature proposed for metal oxides and carbon nanotubes were demonstrated with the data available on the NANoREG MNM. The applicability of the proposed scheme needs further testing considering a wider variety of real industrial MNM with different levels of physicochemical complexity.

3 Deviations from the work plan

This report is developed as part of NANoREG, Deliverable 2.5 (T2.2c). The goal of this document is to propose a suitable nomenclature and categorization paradigm for nano-objects on the basis of physical and chemical properties.

The actual task 2.2 was set on the description and categorization of MNMs such as fullerene, carbon nanotubes, graphene, surface-modified “old” MNM, including organoclays, cosmetics and pharmaceutical derivatives.

Due to the exit of partner AIDICO and inability to attract other partners to task 2.2c as well as considerations on the current regulatory needs, the task was modified to take a more generic approach for naming and categorization and exemplify the systems using different MNMs in the chemical categories included among the NANoREG core MNM. Consequently, our categorization scheme can be adopted to any “nanomaterial like” material and is not limited to carbon-based nanomaterials. We also demonstrate the applicability to metal oxides.

The phys-chem categorisation, and hence the need of characterisation of each property, proposed in this deliverable is intended to be supported by different characterization methods considered in the other WP2 tasks, which will all be merged and summarized in D2.12.

As per the DoW, the deliverable was due on M18 but this date was not found feasible due to priorities on other tasks at project start-up. Consequently it was agreed with the NANoREG project office to postpone D2.5 to M34.

4 References / Selected sources of information

See references at the end of the report.

5 Annexes

Annex I

Annex II

Annex III

5.1 ANNEX I

Review of the existing nomenclature and procedures for substance ID and reporting

Executive Summary

The European Commission has been active for issuing policies that regulate substances at nanoscale and issued different advisory reports. However, there are some uncertainties and unclear guidelines for issues such as the definition of nanomaterial, nanoscale size limits, natural vs. man-made nanomaterials, classification and categorization of nanomaterials, information requirements for substance identification and reporting of nanomaterials, naming a substance with nanoscale properties, to name a few. Herein, we report a concise summary of developments made in the last few years on the issues mentioned as above. The report is developed based on a review of existing scientific publications, and guidelines published by various international organizations.

In the order of priority, Section 2 reviews the existing definitions of nanomaterials. It is clear that the definition of nanomaterial has been a topic of debate by different organizations. Although a size based definition is prevalent, proposed definitions are not fully coherent between the international organizations. Therefore, one challenge remains to introduce a meaningful definition of nanomaterial, which is clear, concise and in particular acceptable and practical to the by nanotechnology industries.

Section 3 reviews the parameters proposed for classification and categorization of nanomaterials including size, composition, location of the nanostructure, product matrix and structural complexity. It is clear that all of these properties depend on manufacturing process and “size and composition” being dominant properties of the categorization. Section 4 describes the substances at nanoscale. It is argued that substances at nanoscale must be considered as special substances and evaluated following a case-by-case approach. A common scheme for substance identification may not work for all nanomaterials. Size could be a primary identifier that distinguishes nanomaterial from a bulk material, but clear, and concise additional identifiers must also be reported that indicates the specificity of the nanomaterial. For specific areas and applications, modifications of any overarching definition may be needed due to specific requirements regarding risk assessment for regulatory purposes.

Section 5 reviews the status of the information requirements set by different organizations. It has been identified that particle size, shape, and surface area seem to be the dominant parameters to consider when reporting substances at nanoscale, as recommended by all the organizations. However, there are uncertainties related to the reporting a bunch of physicochemical parameters and different organizations have different guidelines and reporting requirements. Another important legislation that needs a review is the labelling of consumer products containing nanomaterials. It is necessary, or at least highly beneficial, to develop a harmonized system for identification, reporting and labelling of substances at nanoscale, to avoid different terms in different branches all covered by the same overall regulation.

5.1.1.1 A long-lasting definition of “Nanomaterial”

Materials exist in different forms and sizes depending on the source and manufacturing process. Nature has a large number of nano-sized materials with properties that are distinct and relatively comparable to man-made nanomaterials. Man-made nanomaterials are defined as either *manufactured* nanomaterials or *engineered* nanomaterials or *synthetic* nanomaterials or *modified* nanomaterials. Either bottom-up or top-down process has been developed for their synthesis. Monodisperse particles with spherical shape are simple to define under the term “nanomaterial” under the EU definition. However, in reality the particles do not exist in free form and in many cases the particles are not in uniform shape, particularly when the material productions are scaled up. Particles do agglomerate and aggregate and have different size ranges depending on the use and the testing or use environment. Therefore, there is a challenge to the research

community, risk assessor and policy makers to introduce a meaningful operational definition for the term nanomaterial. The defined term should be as clear and simple as possible and should be understandable by end-users. Considering the term “nanomaterial”, no universal definition exists so-far, and several international organizations, committees and institutions have proposed their own definition. Just to give an example, Table 1 presents an overview of existing or in-use working definitions of a “nanomaterial”.

According to Table 1, different organisations have set the “NanoScale” range, as minimum 0.2 nm to a limit of approximately 100 nm. The terminology (highlighted as italics in Table 1) for setting the size-limits is not clearly defined: “approximately 100 nm” or “of the order of 100 nm” does not support a clear definition of a nanomaterial. In some definition, the upper limit of 100 nm does not take into account all types of materials with nanoproperties. Likewise, the lower limit of the nanoscale in most cases is set at 1 nm, but some particles such as fullerenes, single-walled CNT, and graphene may have dimensions below 1 nm in size. Though these materials are considered to be nanomaterials, the typical nanoscale size-definitions do not seem to be valid for those. The specific carbon-based compounds are, however, specifically included in the definition proposed by the EC. For future needs it would be better to have a clear size-limit for the nanoscale. In a similar context, ISO and many other organizations have used the terms such as “external,” “internal” or “surface structure” for defining the nanomaterial [22].

Not only have a size-related definition of a nanomaterial, but also qualifiers based on physicochemical properties been proposed. The European Commission based on SCENIHR considerations [20] and Wolfgang et al. [23] have considered the volume specific surface area (VSSA) greater than $60 \text{ m}^2/\text{cm}^3$ as a complementary parameter to help identification of a nanostructured vs. non-nanostructured powder material.

Likewise, several other important clarifications are needed in several of the definitions including consideration of agglomerates and aggregates, particle size distribution thresholds, and novel properties. Other important differences included the borderline nanoscale properties versus macroscopic properties, number size distributions versus weight distributions, and natural versus man-made materials. It is obvious that defining nanomaterial in a single sentence may not be possible and indeed size alone does not define the properties associated with nanoparticles vs. bulk properties. Without a clear definition of a nanomaterial, issues such as classification and categorization, their identification, the possible affects in-terms of their toxicity or the reporting aspects of nanomaterials, becomes more difficult to resolve. Therefore, an urgent need of revision and harmonization of the existing definitions are recommended considering the entire size-range of MNM and key nanoscale properties.

Overall, it is clear that there is no ideal definition for nanomaterials which clearly distinguish materials from μm -scale to nm-scale materials. Although a size-based definition is prevalent in the existing definitions, the definitions previously proposed are not fully in agreement between the international organizations. One challenge remains with the policy makers to introduce a meaningful definition of a nanomaterial, which is clear, concise and in particular understandable by end-users. In a JRC report [24], “Towards a review of the EC recommendation for a definition of the term nanomaterial-Part 3”, the JRC presented the information on scientific-technical issues considered when reviewing the current EC nanomaterial definition. The outcome of this task was used in the EC meeting in December 2014 for further review of the definition “nanomaterial”.

Continued from previous page

Organization / Country	Proposed Nanomaterial Definition	Reference
EU SSCP	Material with one or more external dimensions, or an internal structure, in the nanoscale, which could exhibit novel characteristics compared to the same material without nanoscale features.	http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_123.pdf
EU (Cosmetic Products)	An insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, in the <i>nanoscale from 1 to 100 nm</i> .	Regulation EC/1223/2009 on Cosmetic Products)
EU (Novel Foods)	“Engineered nanomaterial means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale.	http://data.consilium.europa.eu/doc/document/PE-38-2015-INIT/en/pdf
European Medicines Agency (EMA)	From the atomic level at <i>around 0.2 nm up to around 100 nm</i> .	EMA (2006) Reflection Paper on Nanotechnology-Based Medicinal Products for Human Use. EMA /CHMP /79769/2006, p. 3 (2006);
American Chemical Council (ACC)	An Engineered Nanomaterial is any intentionally produced material that has a size in 1, 2, or 3 dimensions of typically <i>below 100 nanometers</i> .	
Food and Drug Administration (FDA)	FDA has not established regulatory definitions of “nanotechnology,” “nanomaterial,” “nanoscale,” or other related terms. These terms are commonly used in relation to the engineering (i.e., deliberate manipulation, manufacture or selection) of materials that have at least one dimension in the size range of <i>approximately 1 to 100 nm</i> .	http://www.fda.gov/regulatoryinformation/guidances/ucm257698.htm
Health Canada	a. It is at or within the nanoscale in at least one spatial dimension, or; b. It is smaller or larger than the nanoscale in all spatial dimensions and exhibits one or more nanoscale phenomena. (The term “nanoscale” means <i>1 to 100 nanometers</i>)	http://www.hc-sc.gc.ca/srsl/consult/_2010/nanomater/draft-ebauche-eng.php

Continued from previous page

Organization / Country	Proposed Nanomaterial Definition	Reference
UK Royal Society & Royal Academy of Engineering	The nanometer scale ranges from the atomic level at <i>around 0.2 nm up to around 100 nm</i> . (2004)	www.nanotec.org.uk/finalReport.htm
DEFRA	"Nano-scale materials are defined as having two or more <i>dimensions up to 200nm</i> " (DEFRA 2008)*	http://webarchive.nationalarchives.gov.uk/20130123162956/
BSI	Material having one or more external dimensions in the nanoscale or which is nanostructured (Nanoscale size range from <i>approximately 1 nm to 100 nm</i>) (BSI: PAS 136: 2007)	http://www.defra.gov.uk/environment/quality/nanotech/documents/vrs-nanoscale.pdf
Australia (NICNAS)	Industrial nanomaterials are those industrial materials intentionally produced, manufactured or engineered to have specific properties or specific composition, and one or more dimensions typically <i>between 1 nm and 100 nm</i> . The size range considers only primary particle sizes and does not take into account agglomeration of particles.	http://www.nicnas.gov.au/Publications/Chemical_Gazette/pdf/2010oct_whole.pdf#page=14
China	A nanomaterial is a material which has a structure in the three-dimensional space in at least one dimension in the nanometer scale (<i>from 1 nm to 100 nm range of geometric dimensions</i>), or constituted by the nano-structure unit and a material with special properties.	GB/T 19619-2004: (Terminology for nano materials) (AQSIQ) (Effective on 1 April 2005).
Danish Ministry of the Environment (Denmark)	Nanomaterials can be defined as materials which are <i>less than 100 nanometres</i> in length along the shortest side or have structures which have such small dimensions but are build into larger materials (i.e. nanostructured surfaces).	http://eng.mst.dk/topics/chemicals/nanomaterials/
US Environment and Protection Agency	Engineered nanoscale material is any particle, substance, or material that has been engineered to have one or more dimensions in the nanoscale. The nanoscale size is generally, but exclusively, <i>below 100nm and above 1 nm</i> .	http://www.epa.gov/oppt/nano/hmstp-conceptpaper.pdf
Japan	"Nanomaterial" refers to, among solid materials manufactured using elements, etc. as a raw material, a nano-object with at least one of the three dimensions of <i>approximately 1nm – 100nm</i> and a nano-structured material composed of nano objects (including matter composed of aggregated/agglomerated nano-objects).	Notice on Precautionary Measures for Prevention of Exposure etc. to Nanomaterials (31 March 2009)

Continued from previous page

Organization / Country	Proposed Nanomaterial Definition	Reference
South Korea	<p>“Nanomaterials” means nano-objects and nano-structured materials (including materials having an internal nano-sized structure or materials with condensed nanoparticles), in a solid form, that are <i>smaller than 100 nm</i> in any dimensions.</p>	<p>Guidance on Safety Management of Nano-based Products (Korean Agency for Technology and Science Public Notice No.2011-0108 of 12 May 2011</p>
The Council of Labor Affairs, Taiwan	<p>nanomaterial is one which is intentionally manufactured or designed and meets any of the following conditions: A) Material with one or more external dimensions or an internal or surface structure <i>on the scale from 1-100 nm</i>; B) It is smaller or larger than the nanoscale above in all spatial dimensions and exhibits one or more nanoscale phenomena/property (for example, increased intensity and chemical reactivity).</p>	<p>http://nanotechnology.americanchemistry.com/Nanotechnology/PanelActivities/NanotechnologyDefinitions/Nanotechnology-Panel-Presents-at-Society-of-Toxicology.pdf</p>
Wolfgang et al.	<p>A nanoparticulate material, if it has a volume specific surface area (VSSA) equal to or greater than, $60\text{m}^2/\text{cm}^3$ volume of the material.</p>	<p>[23]</p>

5.1.1.2 Classification and Categorization of Nanomaterials

Many different types of nanomaterials exist (e.g., compositions) with great variations in characteristics (e.g., size and surface area) and properties (e.g., photocatalytic reactivity). Development of nanomaterials towards commercial applications is in high pace and a high number of nanomaterials and their nanocomposites are already used in the consumer products. Unfortunately, there is no systematic approach in grouping or classifying various manufactured nanomaterials by their composition, properties, application, or risk assessment. Many combinations of nanomaterials can be created with unlimited set of known or unknown properties. Examples are the incorporation or doping of organic functionalities with specific binding sites on an inorganic substrate with superior optical, electronic, magnetic or thermal properties. This is due to change in nano-scale properties over a magnitude higher than their bulk properties. Making a validated method for classifying nanomaterials is very tricky and needs careful choice of wording and a systematic procedure.

ISO has proposed a “nano-tree,” as a globally harmonized methodology for classifying various nanomaterials. The document (ISO/TR 11360:2010) is published as Nanotechnologies – Methodology for the classification and categorization of nanomaterials [15]. The classification system utilizes 1) special dimension, and 2) quantum confinement as the basis for classifying wide range of nanomaterials including nano-objects, nanostructures and nanocomposites. Especially the dimension is defined as any external dimension of the material in the nanoscale between 1 nm and 100 nm while the quantum confinement uses the size of a solid material as compared to the wavelength of the particles that interact with the system. The dimension approach is used as the preferred method for the classification system rather than the quantum confinement. This is because of the high technical information requirement such as the electron wave function, which is not readily accessible to the majority of industrialists and the scientific community.

As per the technical report ISO/TR 11360:2010, the “nano-tree” consists of four parts that describe a nanomaterial including Dimension, Internal/external structure and type of nanomaterials, Chemical Nature/identity and Properties/behavior. A simplified sketch of the nano-tree based on dimension (D) approach is shown in Figure 2. Accordingly, 1D, 2D and 3Ds describe if any one, two or three of the external dimension of the material is less than 100 nm, respectively. Each dimension is subdivided by their composition and structure into single-, multi-component or nanostructured material containing a discrete nanoscale feature. More complex nano-objects and nanostructures are further subdivided based on their chemical identity/nature, highlighting the effect of chemical nature or bonding on the overall properties of nanomaterials. One of the key characteristics when downsizing a material is the change in their “functional” properties in terms of their physical, chemical, mechanical, biological properties. The fourth part of the “nano-tree” includes those properties to aid the classification system. The aforementioned properties are subsequently further broken down based on characteristics of each nanomaterial.

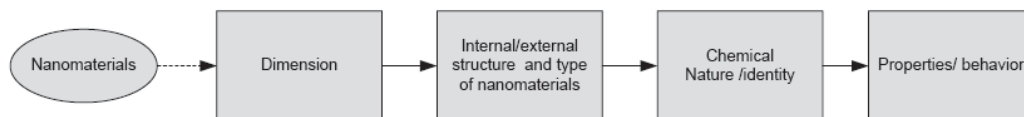


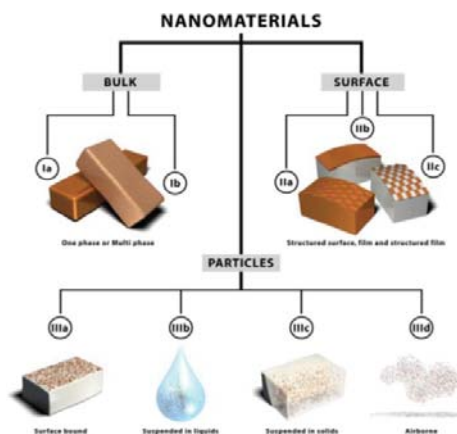
Figure 2: A simplified sketch of the “nano-tree” based on dimension approach for classification and categorization of nanomaterials proposed by ISO.

The ISO methodology serves an effective way to classify various nanomaterials by their 3D *nanodimension* and associated properties. The report considers size as the base for the classification, but the extent of components (e.g., surface treating agents) in a multicomponent nano-object or nanostructures or

nanocomposites is not defined. In addition, morphology at nanoscale is an important parameter that was not considered, for example, spherical spheres vs. faceted spheroids. The facets size can be below 100 nm, and the surface properties differ obviously by the surface energy at the intersection though the overall diameter of the particle is larger than 100 nm. Nanomaterials may have different shapes under different manufacturing conditions but still possess the same composition. According to ISO, silica, as an example, occurs as colloidal nanoparticles, monodispersed nanoparticles, rod-shaped nanoparticles or faceted nanoparticles, will fall into different classes in their categorisation system. Consideration of chemical identity/nature as a parameter for classifying nanomaterials might be difficult for complex nanocomposites as they can contain more than three different types of nano-objects and exhibit multiple characteristics in different environments. Under the method, properties/behaviour column does not give any information about the properties that distinguishes nanomaterials vs. bulk materials. In addition, the categorization method does not link the properties for evaluation of toxicity of nanomaterials. Categorization of nanomaterials with the hazard identification may render great benefit for manufacturers to end users.

Hansen et al. [25] proposed a different categorization system for risk assessment based on the *location of the nanoscale material or structure* in the system/material. They suggested a hazard identification scheme that combines the categorization framework with the inherent physical and chemical properties, relevant for each particular category of nanomaterials. The three main categories in the classification system and their subcategories shown schematically in the Scheme 1. The main category-I contain nanostructures in the bulk of the material while, in category-II nanostructures present on the surface of the material. Category-III contains nanoparticles that are nanosized in at-least two dimensions.

Tervonen et al. [26] proposed a decision support system for classifying nanomaterials into different risk categories. The classification system was based on a set of *performance metrics* that measure both the toxicity and physic-chemical characteristics of the original materials, as well as the expected environmental impacts through the product life cycle. Stochastic multi-criteria acceptability analysis (SMAA-TRI), a formal decision analysis method, was used as the foundation for this task. They demonstrated the application of the framework by classifying five nanomaterials such as C60 (fullerene), multi-walled carbon nanotube (MWCNT), CdSe, silver nanoparticles, and aluminum nanoparticles. Particle size was used as the main quantitative criterion. The results show some uncertainty for the nanoparticles in terms of the risk posed by these particles.



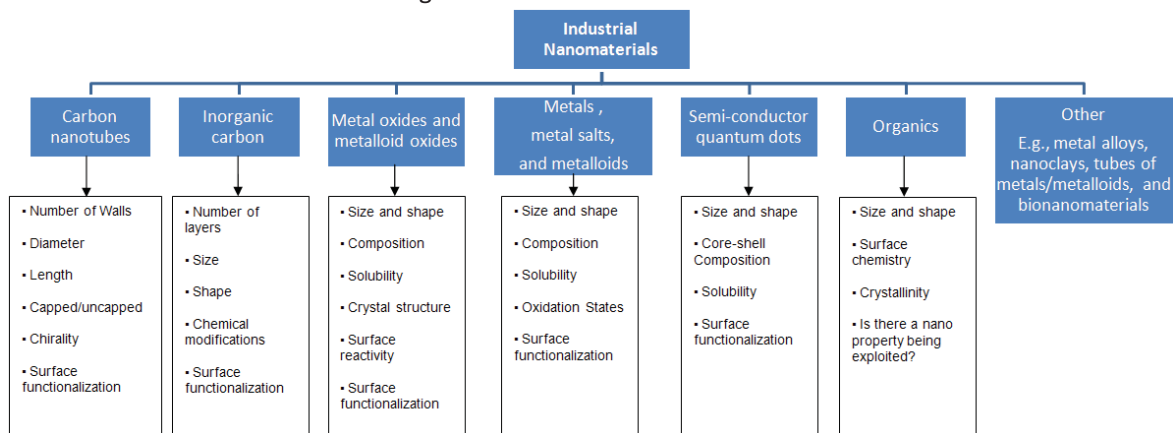
Scheme 1: Categorization scheme for nanomaterials using the the location of the nanostructure in the material, proposed by Hansen et al. [25].

Hallock and colleagues[27] suggested a classification system to aid waste treatment and disposal of nanomaterials. Accordingly, nanomaterials are grouped by *product matrix* as pure nanomaterials, items contaminated with nanomaterials, liquid suspensions, and solid matrices. The US National Institute of

Occupation Safety and Handling (NIOSH) suggested grouping of nanomaterials by physical state to improve safe handling and reduce worker exposure as [28]:

- (a) bound of fixed nanostructures (polymer matrix);
- (b) liquid suspension, liquid dispersion;
- (c) dry dispersible nanomaterials and agglomerates; and
- (d) Nano aerosols and gas phase synthesis (on substrate).

Stone et al.[6] suggested decision trees that could be used for the classification of nanomaterials, for strategies to assess their toxicity, and /or strategies to inform safe handling of nanomaterials. The classification schemes for nanomaterials are based on *size and similarities in chemical composition* from an environmental perspective. Scheme A uses dimensions and shape as a starting point, while Scheme B uses composition as a starting point. Neither scheme is complete, but instead provides an indication of the types of formats and content a scheme might include; clear definitions for each term would be required. The advantage of such an approach is that it provides clear guidelines, for non-experts, industry and regulators as well as scientists with respect to how to handle a new nanomaterial for characterization, hazard and exposure assessment purposes. However, the difficult part of making it as a practical approach is the lack of knowledge regarding which physicochemical characteristics are most key and what decisions should be derived on the basis of such knowledge.

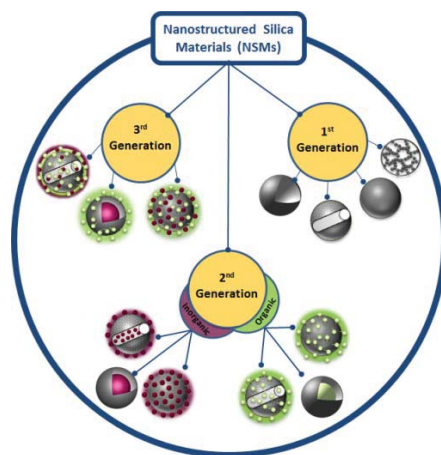


Scheme 2: Proposed classification scheme of RCC based on similarities in chemical composition.

Similarly, the nanotechnology initiatives program by the Regulatory Cooperation Council (RCC) of Canada and USA proposed a classification scheme (Scheme 2) based on *similarities in chemical composition*. Nanomaterials are considered as new substances, and regulated in Canada and the US under the Canadian Environmental Protection Act (CEPA) and Toxic Substances Control Act (TSCA), respectively. The classification scheme represents the *intrinsic* physicochemical parameters which are similar between two nanomaterials for them to be considered for read-across or analogue information. Depending on the composition of nanomaterials, various physicochemical parameters are considered for example, carbon nanotubes are grouped by the number of walls, dimensions, chirality and surface functionalization while metal oxides and metalloid oxides consider size and shape, composition, solubility, oxidation states and surface face functionalization. A large number of nanomaterials fall in the classification Scheme, but some important nanomaterials cannot fit in the scheme, for example, graphite and graphene.

In our recent work on nanostructured silica materials (NSMs)[29], we reviewed various forms of NSMs and for the first time, recommend a classification system (Scheme 3) by their composition and structural complexity. Though, size being the dominant property of the classification, structural complexity of NSMs is indeed considered as an important parameter. The structural complexity derived by the location and the

extent of surface treating agents including organic or/and inorganic compounds. Bare silica nanoparticles are grouped to 1st generation NSMs (1G-NSMs), nanocomposites of silica with organic or inorganic as their secondary phase are in the 2nd Generation NSMs (2G-NSMs) and finally, nanocomposites of silica comprising both organic and inorganic as their counterparts as 3rd Generation NSMs (3G-NSMs). The proposed classification enables to identify various NSMs by their complexity and helps to define the requirements for risk and hazard assessment.

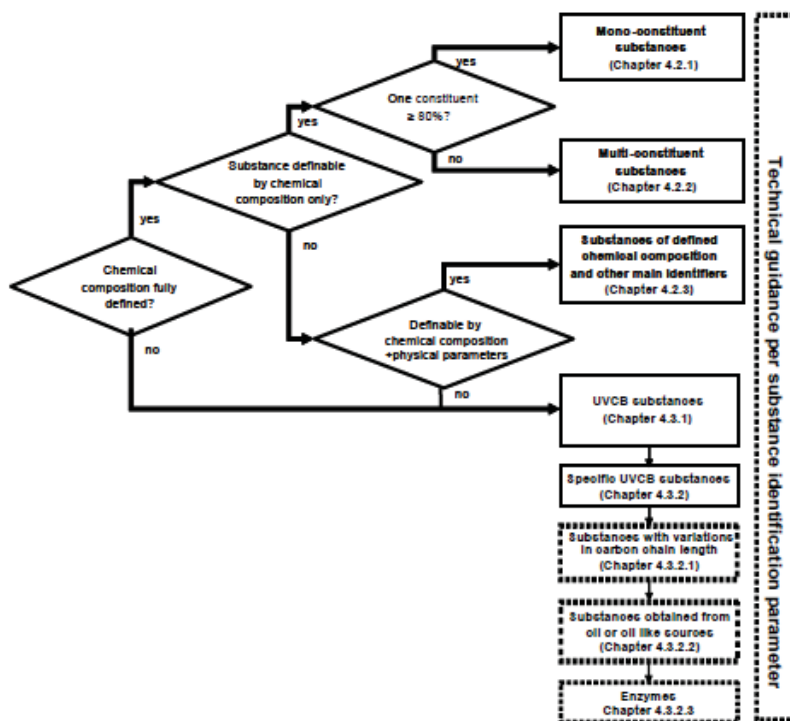


Scheme 3: Illustration of the proposed classification paradigm for nanostructured silica materials (NSMs) with sub-groups illustrating non-porous and porous types and presence of surface-treating agents as organic and/or inorganic as their counterparts.

Overall, different parameters have been proposed for classification and categorization of nanomaterials including *size*, *location of the nanostructure*, *chemical composition*, *structural complexity* and *product matrix* of substances. The recommendations proposed by ISO highlight the importance of size of the nano-object, while others proposed the location of nanostructure and composition of the substances. It is clear that all of these properties depend on manufacturing process and “size and composition” being dominant properties of the categorization. However, not all nanomaterials can be classified based on size and composition alone; other potential parameters must be taken into account, for example, surface chemistry or surface properties at nanoscale....etc.

5.1.1.3 Substance identification: Substances at Nanoscale

In 2006, the European Commission launched a system for the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) and established the European Chemical Agency (ECHA) to implement it. Later, a new legislation system for Classification, Labelling and Packaging (CLP) of chemical substances and mixtures is introduced based on the United Nations Globally Harmonized System (UN GHS). Under the REACH legislation, regulations of nanomaterials are covered by EU legislation (covered by the definition of “substance”) even-though there is no explicit reference to nanomaterials and guidance documents applicable to nanomaterials (Scheme 4). Under REACH and CLP (ECHA 2007, 2012, and 2014) guidance [9,30], a substance is usually identified by its chemical composition, the chemical identity and the content of each constituent in the substance. Well-defined substances can be mono- or multi-constituent depending on the concentration range of constituent.



Scheme 4: Specific guidance for the substance identification of various types of substances. (Reprinted from the guidance document REACH and CLP, 2014).

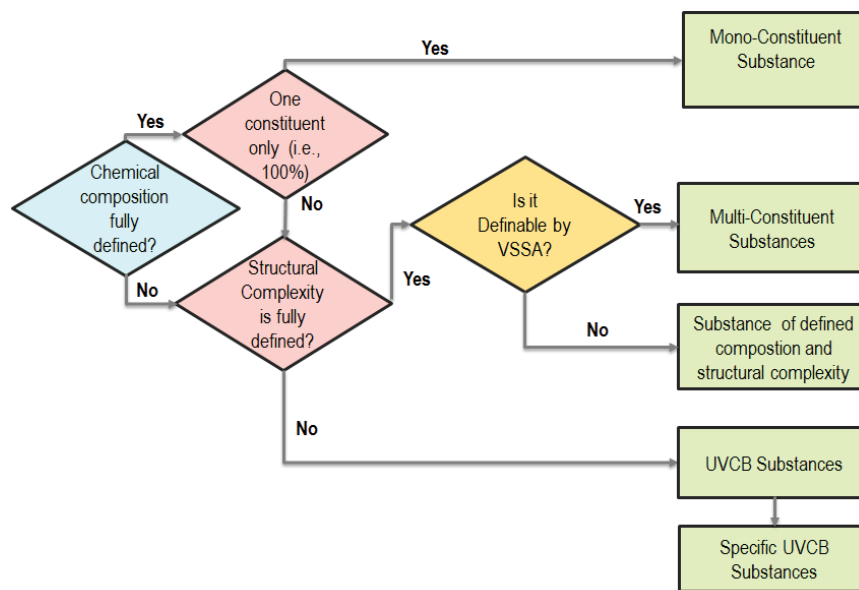
A substance that has at least 80% of a constituent by weight is considered as mono-constituent substance, while one or more constituents present at greater than 10% and less than 80% is considered to be a multi-constituent substance. A mono-constituent substance is named after the main constituent while the multi-constituent substance is named as a reaction mass of the main constituent of a substance (i.e., not the starting materials needed to produce the substance). On the other hand, substances of Unknown or Variable Composition, Complex reaction products or Biological materials, are grouped under UVCB substances. UVCB substances are defined by their manufacturing process or reactants used for predicting their final composition. It's argued that for regular substances, the constituent wt% determines whether it is the main constituent or an impurity. Nevertheless, 80/20 wt% argument is not a good measure for well-defined substances, in particular to identify nanomaterials and their nanocomposites. For example, surface hydrophobization of silica nanoparticles at as low as 1.5 % by weight of methyl groups, is enough to get distinct dispersion properties compared to bare silica [31]. On the other hand, silica-coated magnetic nanoparticles were also prepared at a thickness of 5 nm on a 7 nm iron oxide nanoparticle for reducing their aggregation [32]. The wt% will not give any information on the surface coverage of nanoparticles as it does not take surface properties, such as surface area, into account. Therefore, special provisions for substance identification are needed for substances at nanoscale.

In 2010, the EU commission initiated several REACH implementation projects on Nanomaterials (RIP-oNs) [11,12] to evaluate the applicability and validation of the existing REACH guidance to nanomaterials, and if needed develop specific advice on how the guidance could be updated considering substances contains nano-objects. In the proposal RIP-oN 1, substance identification of nanomaterials was evaluated towards

the existing guidance documents and highlighted few important identifiers for substances contain nano-objects. Various identifiers have been proposed such as size and surface treatments as the main identifiers, and other potential identifiers such as surface area and aspect ratio. There was a strong disagreement between the experts in relation to whether these parameters should be identifiers or characteristics to describe the nano-form of a substance. Consensus could not be reached on these issues among the experts and further policy advice on the issues before developing a specific guidance was suggested. The report summarized identification and naming of carbon nanotubes as an example. CNTs can be identified by their diameter and tube length. Composition is a good parameter to identify CNTs, but it is not sufficient to allow the distinction from graphite and diamond. Accordingly, CNTs are identified by their dimension and atomic structure and considered as “well-defined substance plus additional identifiers or as UVCB substances.

We have recently identified volume specific surface area (VSSA) as an additional identifier and proposed a scheme (Scheme 5) for identification and reporting of Nanostructured Silica Materials (NSMs) [29]. We argued that VSSA must be reported to define their origin and properties by association of organic and inorganic compounds. The surface treatment induces change not only in specific surface area but also in the specific density of the nanocomposite. Variation in the specific density highly depends on the concentration, molecular density of the surface treating agent and manufacturing method. Particularly, silica-based nanomaterials have shown to have high surface areas and low-bulk densities, and any variation in their composition may lead to significant change in their properties. As a matter of fact, silica-based aerogels are the best known for their low density and high specific surface area. However, surface treatment of aerogels has shown to reduce the surface area and increased the density. Under this approach, bare silica nanoparticles are justified as mono-constituted substances; substances of known constituents are considered to be a multi-constituent substance and substances of unknown or complex composition as UVCB substances. In the scheme, structural complexity of a nanocomposite is used as a cross check to define VSSA an additional identifier. Accordingly 1G, 2G and 3G NSMs can be identified by their composition, structural complexity and VSSA.

Therefore, it is clear that substances containing nano-objects should be considered as special substances and evaluated considering a case-by-case approach. A common scheme for substance identification may not work for all nanomaterials. Size could be a primary identifier that distinguishes nanomaterial from a bulk material, but a clear, and a concise additional identifier may also be used to indicate the specificity of the nanomaterial.



Scheme 5: Possible routes for identifying various silica based nanomaterials.

5.1.1.4 Information requirements for reporting of Nanomaterials

Several organizations have realized the importance of nanomaterials and put a mandatory or voluntary reporting requirement of manufacturing or imported substances at the nanoscale. Table 2 reports the overview of reporting status of various organizations. The EU commission has proposed mandatory reporting of substances at the nanoscale, depending on the tonnage and hazard class. Since 1 June 2008, substances at the nanoscale (non-phase-in substances), and which are manufactured or imported in quantities of 1 ton/year or more need to be registered before manufacturing or importing. According to REACH, reporting schemes and deadlines as follows,

- 31st December 2008 - end of **Pre-registration**
- 1st December 2010 - end of **Registration** (> 1,000 tonnes/year)
- 1st December 2013 - end of **Registration** (> 100 tonnes/year)
- 1st December 2018 - end of **Registration** (> 1 tonnes/year)

Recently (April 2014) [33], a number of NGOs published a paper commenting on the current EU legislation on nanomaterials. They proposed that nanomaterials need to undergo a thorough risk assessment, including an assessment of the potential risks deriving from their novel properties. The NGOs also comment on the quantity thresholds and suggested that all nanomaterials on the market produced in amounts of over 10 kg/year must be registered with ECHA on the basis of a full registration dossier specific to the nanoform.

Under EU legislation, substances at the nanoscale are considered as “new-substances” and must be reported with the required physical-chemical properties and associated hazard data. Standard information requirements for substances manufactured or imported in quantities of 1 ton or more covers in Annex VII (REACH). It includes reporting of several properties such as composition (incl. purity), melting/freezing point, boiling point, relative density, vapour pressure, surface tension, water solubility, partition coefficient n-octanol /water, flash point, flammability, explosive properties, self-ignition temperature, oxidizing properties, granulometry, adsorption /desorption, solubility in organic solvent and degradation production,

dissociation constant and viscosity. An updated guidance for reporting of substances at nanoscale included with two new sections describing SHAPE (R.7.1.19) and SURFACE AREA (R.7.1.20) [34,35]. These additional requirements were set based on the advice report RIP-oN2 [12], and the guidance document was updated in-view of nanomaterials. RIP-oN 2 also advises to report few additional physicochemical properties such as Surface energy, Surface chemistry, Surface charge, Redox potential, Cell-free ROS/RNS production capacity, State of dispersion and State of agglomeration. However, these were not included in the recent version of the REACH guidance documents. It is important to note that, REACH regulation exempts for products or substances imported or manufactured at above 1 ton per annum also for a limited period under the scheme of product and process orientated research and development (PPORD), to facilitate innovation and exclude less burden for SMEs. However, at this stage it is unclear if the rule applies for the substances at nanoscale. On the other hand, critical information requirements for higher tonnage levels such as TOXICOLOGICAL INFORMATION and ECOTOXICOLOGICAL INFORMATION vary in addition to the physical-chemical properties of the substance and special provisions have been set at those levels (Annex VIII, IX and X).

Table 2: Summary of approaches based on voluntary reporting or on mandatory reporting of nanomaterials by various organizations around the world.

Mandatory reporting of Nanomaterials By Region/Country	Remarks	Voluntary reporting Countries	Remarks
Canada (2009)	Canada sought to set a mandatory reporting scheme for manufacturers or importers of more than a kilogram of a nanomaterial. The scheme is still not come to fruition. (August 24, 2013 issued registration requirements for Carbon nanotubes)	Australia (2006)	ADHA a voluntary reporting scheme for nanomaterials manufactured or imported between 2005 and 2006
European Union (2007-2008)	In the EU A mandatory reporting came into force in 2007, depending on tonnage and hazard class, the REACH regulation covers all substances manufactured in or imported into the EU in tonnages of 1 tonne per year or more.	Germany (2005-2006)	BAuA and VCI set a corporate survey to collect information on a voluntary basis
France (2013)	France launched its mandatory Declaration of Nanomaterials, the French Environment agency published results of the first round of reporting in November 2013	UK (2006)	DEFRA stated a voluntary reporting scheme of engineered nanomaterials
Denmark (2014)	The Danish Environmental Protection Agency launched a nano-product reporting scheme with many exemptions in 2014; the deadline for the first round of registration was 30 August 2015	Ireland (2006)	started a voluntary survey
Norway (2013)	Norway is seeking to set a register of nanoscale materials under its Pollution Control Authority (SFT). From 2013, the Norwegian Product Register requires information for chemicals containing ‘a substance in nano form’.	USA (2008)	EPA launched 2 year-long voluntary reporting scheme for nanoscale materials.
Sweden and Italy	Sweden and Italy are considering setting up mandatory reporting schemes.		

In the aspect of tonnage reporting requirement, The Canadian Department of the Environment (CDE) has taken the initiative for a mandatory reporting of few nanomaterials in a quantity greater than 10 kg in one calendar year [36]. It is interesting to find that CDE has set case-by-case information requirements for various nanomaterials; examples include multiwall carbon nanotubes, aluminate, magnesium and vanadate, and potassium titanate. Under this provision, multiwall carbon nanotubes have special dimensions set for their reporting as:

“Substance” means short tangled multi-walled carbon nanotubes having the following characteristics:

- a. At least 90% of the substance composed of elemental carbon;
- b. The nanotubes measure from 0.09 to 10 micrometres in length, with a 1.1 micrometre average; and
- c. The diameter of the nanotubes measures from 5 to 25 nanometres, with a 12 nanometre average.

OECD released a guidance document in July 2013, which deals with the information requirements on active substances and biocidal products [37]. However, the guidance on nanomaterials is still pending, and OECD is reviewing all existing methodologies in order to identify and implement the necessary changes needed for their application to nanomaterials. In a OECD expert meeting (July 2014) on the physical-chemical properties of manufactured nanomaterials and test guidelines [38], the experts focused the discussion on selected endpoints including 1) State of Dispersion, Aggregation and Agglomeration of Nanomaterials, 2) Size (and Size Distribution) of Nanoparticles, 3) Surface Area and Porosity, and 4) Surface Reactivity. Therefore, it is assumed that the OECD guidance document may consider these properties to be included in the reporting documents for substances at nanoscale.

The Danish EPA (Environmental Protection Agency) has summarized information from existing projects/reports/references and proposed a stepwise information requirement scheme for nanomaterials [39]. They proposed tonnage driven information requirements including low tonnage level (below 10 Kg/year) and key regulatory testing requirements such as the use of exposure-driven testing, use of “scaling” for toxic potency consideration, sample preparation and dosimetry and choice of metric(s) for reporting hazard (and exposure) data. In addition, they recommend new information requirements compared to information normally required for chemicals such as primary particle size distribution, Agglomeration/aggregation, Specific surface area and morphology/shape/aspect ratio.

United Kingdom has drafted a supplementary guide for voluntary reporting scheme [40]. The report includes information on the key physical characteristics of the nanomaterials such as the size, shape, structure, solubility, and surface area, along with details of the measurement technique used. The scheme aims for developing reasonable and responsible approaches for managing the risks from nanomaterials and hence does not consider tonnage level as a base for registering criteria.

Many peer-reviewed articles were also published to address the issues related to legislation of nanomaterials. Hansen et al. proposed a Scheme for categorization of nanomaterials and proposed 9 properties being the important for estimating the toxicity of nanomaterials such as: 1) Chemical composition, 2) Size, 3) Shape, 4) Crystal structure, 5) Surface area, 6) Surface chemistry, 7) Surface charge, 8) Solubility, and 9) Adhesion. A total of 428 studies were reviewed based on the above categorization method and recommended that the location of the nanoscale structure in the system as well as the nine relevant physical and chemical properties must be reported in the data sheets. Recently, Petit et al. proposed the minimum physicochemical parameters required to describe nanomaterials adequately for regulatory purposes including size, shape, surface charge, surface modification, crystalline form, and oxidation state. They argued that nanoforms with the same core chemistry but distinctive differences in the physicochemical characteristics should be treated as separate entities for regulatory purposes. In addition, use of multiple methods to describe a given physicochemical parameter is strongly recommended.

Overall, it is clear that particle size, shape and surface area seem to be the dominant parameters to consider when reporting substances at nanoscale, as recommended by all the organizations. However, different organizations have different guidelines and reporting requirements. It may lead to registration problems between the countries and may show considerable impact in the international mobility of the nanotechnology industries. Another important legislation needs review is the labelling of consumer products containing nanomaterials. A generic labelling or a claim displayed on a product containing nanomaterials may mislead to the consumer. In a recent report by JRC[13] “Considerations on information needs for nanomaterials in consumer products,” two different ways of transparency and traceability of nanomaterials were considered, namely by nanolabelling of products containing nanomaterials and by collecting information in the product register of inventory. The nanolabelling

regulations indeed create problems in the requirements of nanolabelling and could create cross-border trade issues. Therefore, it is necessary to develop a harmonized system for reporting and labelling of substances at nanoscale.

5.2 ANNEX II

M20 Evaluate the suitability of existing MNM categorization paradigms (case studies)

5.2.1.1 Introduction

The goal of this document is to categorize a range of nano-objects on the basis of physical and chemical properties, by applying two existing categorization schemes. The selected nano-objects (case studies) are characterized by a variety of physical chemical properties, to cover a reasonable range of phys-chem parameter values. The exercise will lead to the identification of issues in the application of the two schemes, as a first step toward the formulation of a NANoREG proposal.

Categorization and grouping are two terms that are used synonyms. According to OECD, 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” [42]. Therefore, a category is a set (group) of elements with some characteristics in common. The degree of similarity has to be decided according to criteria that are usually scientific in nature, but in the end interpreted by policy. In this document, categorization and grouping are to be considered the same term.

It is important to highlight that the categorization is based only on physical-chemical properties, and the properties link to hazard, risk, or safety is not taken into consideration. The regulatory term of reference is the identification and naming procedure of REACH. Therefore, the goal is to identify phys-chem properties that are suitable for the MNM Identification and Naming.

Methods

5.2.1.2 MNM case studies

MNM case studies need to have a good physical-chemical characterization, carried out according to standardized or at least homogenised procedures. Such data are still not easily found, but several of the data collected as start on the NANoREG core MNM are of high quality and made following well-described procedures. Therefore, case studies were selected among the core MNM included in the NANoREG project. The case studies cover different chemical composition, shape, and size. The list of MNM is reported in Table 1, along with some characteristics. The detailed phys-chem characterization is reported in the material data sheets produced by D2.2 and are available from the NANoREG project web-site.

Table 1. MNM case studies, with basic characteristics.

MNM Code	Name	Chemical composition	Size (nm)	Shape
JRCNM02000a	Amorphous Silica (SAS)	- SiO ₂ - Inorganic impurities - No functional groups detected	around 18 nm	Nanoparticles 0.39 sphericity 1.567±0.353 aspect ratio
JRCNM04000a	MWNT	- C - inorganic impurities - organic coating	D 13.6 nm L 850 nm	Highly bended MWCNT

Continued on next page

MNM Code	Name	Chemical composition	Size (nm)	Shape
JRCNM04001a	MWCNT	- C - inorganic impurities - no organic coating	D 64 nm L 4 µm	Highly bended MWCNT, with branched CNTs
NCF	Nanocellulose Fine	- cellulose - no coating	D 2-15 nm L 2-20 µm	Aspect ratio 100-1000. Presence of fibre bundles and thicker fibres
NFC	Nanocellulose medium-coarse	- cellulose - no coating	D 3 nm L 2 -50 µm	Aspect ratio 100-5000. Presence of fibre bundles and thicker fibres
JRCNM03002a	Ag	- Ag - no coating	D 200 nm L 3 µm	Fibre
JRCNM03000K	Ag	- Ag - no coating	D 16.7 nm	Nanoparticle
JRCNM01001a	TiO ₂	- TiO ₂ - inorganic coating - organic coating	D 6 nm Aspect ratio 1.5	Nanoparticle, spherical-ellipsoidal. Solubility of impurities observed.
JRCNM0100a	TiO ₂	- TiO ₂ - inorganic coating - no organic coating	D 110 nm Aspect ratio 1.39	Nanoparticle, spherical-ellipsoidal. Solubility of impurities observed.
JRCNM01100a	ZnO	- ZnO - inorganic coating - no organic coating	D 147 nm Aspect ratio 1-2	Two populations observed
JRCNM01101a	ZnO	- ZnO - inorganic coating - organic coating	D 141 nm Aspect ratio 1-8,5	Two populations observed
-	Fullerenes	-		-

Categorization methods

These MNM will be categorized following two schemes. The first one is the ISO Nano Tree, as reported in the Technical Report ISO/TR 11360, published in 2010. The other approach is the categorization scheme recently drafted by the RCC of USA and Canada. The two methods were selected because they rely on different physicochemical parameters. For example, ISO starts with the size and shape as main parameters, while RCC is based on chemical composition.

ISO Nano Tree

The ISO scheme, called Nano Tree, is a proposal to categorize and classify nanomaterials taking into account both the main physicochemical properties (i.e. size), and the internal/external structures, chemical composition, and mechanical, biological, physical, and other properties. The classification identifies relevant categories and shows the relationships among concepts. The primary utility is in identifying those concepts that help in properly categorizing nanotechnology. According to the document, the proposed

methodology is based on current science understanding of nanotechnology (in 2010), and it “does not claim to provide full coverage of the whole range of nanomaterials” (ISO/TR 11360, 2010).

The ISO approach is based on size, since it is the main feature characterizing nanomaterials. ISO considered initially two ways to measure size, i.e. spatial dimension, and quantum confinement. Spatial dimension is based on at least one dimension being below 100 nm. On the other hand, the quantum confinement is based on the effect of size on the confinement of free carrier when the size of a solid material becomes comparable to the wavelength of the particles that interact with such a system. Quantum confinement is difficult to quantify (knowledge of electron wave function behaviour, differences between different MNM, difficulty to apply the method to complex MNM such as layers, composites). Therefore, the spatial dimension, which is in principle more easily measurable, was chosen as size metric. This choice is however limiting the knowledge linked to quantum confinement which has a link to various specific MNM properties.

The Nano Tree is composed by 4 classification steps. The scheme includes:

- C1: Dimension
- C2: Internal/external structure and type of nanomaterials
- C3: Chemical nature/identity
- C4: Properties/behaviour

C1: dimension is explicated as 1, 2, or 3 dimensions below the 100 nm size limit.

C2: here, each MNM is divided into single component, multi component, and nanostructured. A multi-component MNM is defined as an object “composed of areas or regions with identifiable, local, chemical and structural fluctuations” . An example can be a TiO₂ crystal with two parts with two crystal phases (anatase and rutile). To different structures are associated different MNM types (e.g. 2D nanorods, 3D nanoparticles).

C3: the third column is dedicated to the chemical composition, which is divided into metallic, ceramic, synthetic or natural polymers, semi-metallic, carbon-based and organic. The composite (multicomponent) MNM from C2 can contain more than one of C3 values. In addition, different MNM dispersed in know matrix can be classified as nanocomposites.

C4: the fourth column is the identification of the MNM properties (physical, mechanical, chemical, biological and combined properties - magneto-optic, electro-optic, piezoelectric, pyroelectric, thermoelectric and electromagnetic behaviour of nanomaterials). A more in depth analysis of the C4 column is necessary to evaluate the applicability of the Nano Tree to the scope of the Milestone.

Physical properties: physical properties include different sub-categories: magnetic, electric, thermal, optical, acoustic. Magnetic properties are very specific. Electric properties are focused on dielectric and conductivity/superconductivity. For example, there is the Energy band gap, or the Fermi level. The thermal properties include e.g. heat of polymerisation, of melting, of fusion, of reaction, of evaporation, and so on. Optical properties include e.g. refraction index, absorptivity, and reflectivity. Finally, the acoustic properties include parameters such as acoustic loss, speed of sound, etc. There are several phys-chem parameters usually measured for MNM that are not easily classifiable according to C4 categories.

Mechanical properties: mechanical properties include elastic and plastic properties, viscoelastic, rheology, creep, fatigue, and abrasion parameters. Mechanical properties are more linked to “engineer” type applications.

Chemical properties: these properties include catalytic reactivity, chemical resistivity/solubility, absorptiveness, and lyophobicity/lyophilicity. This category can include all chemical properties of MNM, but the appropriate properties need to be defined, as for example solubility or degradation.

Finally, the Biological properties include all parameters concerning the interaction of MN with the biota, from bioduration, bioaccumulation, antibacterial, toxicity. These parameters are not relevant for the phys-chem categorization, thus they are not considered in the case study application.

RCC approach

The goal of the Regulatory Cooperation Council (RCC) Nanotechnology Initiative is to increase the alignment of regulatory approaches for nanomaterials in USA and Canada. Among the different work-elements (WE), WE2 is dedicated to priority settings, i.e. which nanomaterials are of concern (they behave differently from the bulk) or of no-concern (similar behaviour of bulk material). In order to identify concern/no-concern MNM, the WE2 developed a categorization approach, which for now is limited to physical-chemical properties. The inclusion of biological properties is foreseen in the future.

MNM are defined as: (1) a size range of 1-100 nm; while the US also uses additional criteria to identify nanomaterials: (2) a minimum of 10% of the particles need to be between 1-100 nm and/or (3) particles which exhibit properties unique to their nano size. The classification system is based on chemical composition similarities, and it aims to identify MNM of concern, and to support the selection of read-across/analogue information to estimate MNM properties within the groups. The scheme is also supporting the identification of characterization properties necessary for different classes of MNM for regulatory purposes.

WE2 discussed several options for MNM classification (e.g. exposure, final product, toxicological mode of action), but for the RCC system the chemical composition approach was selected, since it is suitable to be applied to current chemicals regulations.

The RCC approach is applicable to MNM with a simple chemical composition. What is called hybrid MNM in the WE2 document, i.e. a carbon based MNM with a metal functionalization, is not included in the system, and it is still evaluated in a case-by-case approach without read-across/analogue information.

The scheme is starting from industrial nanomaterials, therefore excluding natural NM. For each chemical category, a list of specific physical-chemical properties is identified; the scope is to give an indication of the parameters that needs to be similar to be able to apply the read across/analogue approaches, such as for example, to estimate the MNM behaviour in natural waters. However, the physical-chemical “similarity” between two MNM in the same class is not clearly defined, and a process to identify benchmarks or criteria to establish the similarity is under way.

The chemical groups and the specific properties identified so far are:

Classes	Properties
Carbon nanotubes	Number of walls, Diameter, Length, Capped/uncapped, Chirality, Surface functionalization
Inorganic carbon	Number of layers, Size, Shape, Chemical modifications, Surface functionalization
Metal oxides and metalloid oxides	Size and shape, Composition, Solubility, Crystal structure, Surface reactivity, Surface functionalization

Continued on next page

Classes	Properties
Metals, metal salts, and metalloids	Size and shape, Composition, Solubility, Oxidation states, Surface functionalization
Semi-conductor quantum dots	Size and shape, Core-shell composition, Solubility, Surface functionalization
Organics	Size and shape, Surface chemistry, Crystallinity, Is there a nano property being exploited?
Others: metal alloys, nanoclay, tubes of metals/metalloids, bionanomaterials	

In this scheme, solubility is the degradation/dissolution of the particle over time as result of surface interaction with solvent media, while size refers to primary particle size.

Also, the information included in the categorization scheme is not applicable to infer toxicological properties.

5.2.1.3 Case studies

ISO Nano Tree application

The Nano Tree scheme was applied to the MNM case studies to evaluate its applicability and potential limitations, taking into account the framework of reference. The results of the Nano Tree application are reported in Table 2. The application is limited to the Columns from 1 to 3. The C4 is not reported in Table 2 because it includes a set of properties that are already normally included in Material Data Sheets. The C4 content is described in the discussion of Nano Tree application.

Table 2. Classification of MNM according to ISO/TR 11360. Comments refer to possible interpretation.

MNM Code	Name	C1	C2/C2S	C3
NM-200 / JRCNM02000a	Amorphous Silica (SAS)	3D	Single component Nano Object*, Nanoparticles	Semi-Metallic
NM-400 / JRCNM04000a	MWNT	2D	Single component Nano Object, Nanotubes (HARN)	Carbon based
NM-401 / JRCNM04001a	MWCNT	2D	Single component Nano Object, Nanotubes	Carbon based
NCF	Nanocellulose Fine	2D	Single component Nano Object, Fibres	Organic
NFC	Nanocellulose medium- coarse	2D	Single component Nano Object, Fibres	Organic
JRCNM03002a	Ag	2D	Single component Nano Object, Fibres	Metallic

Continued from previous next page

MNM Code	Name	C1	C2/C2S	C3
NM300K	Ag	3D	Single component Nano Object, Nanoparticle ¹	Metallic
JRCNM01001a	TiO ₂	3D	Multi component Nano Object, Nanoparticle	Metallic, Organic
JRCNM01000a	TiO ₂	3D	Single component Nano Object, Nanoparticle	Metallic
JRCNM01100a	ZnO	3D 2D	Single component Nano Object, Nanoparticle Single component Nano Object, Nanorod [†] Nanoparticle	Metallic
JRCNM01101a	ZnO	3D 2D	Multi component Nano Object, (Core-Shell) Nanoparticle [°] Multi component Nano Object, Nanorod (max a.r. 8.5)	Metallic, Organic Metallic, Organic

* Can the presence of different shapes within the sample be regarded as a multicomponent substance?;+ the ISO definition is “one dimension significantly larger: is length sufficiently larger than diameter in this case? AR is 1.4; ° the ZnO has a coating, therefore it can be considered also as a core-shell structure, where the 3D already give the idea of a nanoparticle (generic term, really); # according to ISO, maybe, this is a multi-component Nano Object, since from core to coating there is a chemical local fluctuation. However, what about impurities?

Discussion

The Nano Tree application was performed following the C1-C4 order, and on the basis of information available in the NANoREG Material Data Sheets (MDS). Some of the MDS are still incomplete, but the data available were sufficient to achieve the goal of the activity.

In detail, the application started with the C1, defining the number of dimension with a size < 100 nm. The MDS reported size measurement using different methods, and its allowed to identify with some certainty of the 1D, 2D, 3D class. For example, JRCNM02000a (NM-200) having an average size of around 50±55 nm, can be classified as 3D nanomaterial, while JRCNM04000a (NM-400), a carbon nanotube with a diameter around 18 nm and a length around 850 nm, is a 2D MNM. However, in case of a sample of MNM with two populations, with clear difference in size, it is difficult to identify a single class. A tentative to solve the issue was done for JRCNM01101a (NM-111), namely ZnO, where both 3D and 2D classes were identified, especially on the basis of aspect ratio, which for population 2 was 2 to 8.5. With a size within 10 and 450 nm, the population 2 could be classified as a 2D MNM. Another possibility is to quantify the percentage of each population, and define a % threshold for which a population is relevant or not in the sample (i.e. if it is a population or “impurities”).

¹ The majority of particles have a round shape, while some triangular and trapezoidal shapes were identified.

The second column (C2 and C2S) are dedicated to the structure of a nano-object. Considering our case, an uncoated MNM is to be considered as single component MNM (see JRCNM02000a and JRCNM04000a), while NM111 is a multi-component nano-object, since it is coated with triethoxycapryl silane, an organic coating. The C2S column is dedicated to the identification of the type of nano-object. JRCNM02000a is a nanoparticle. JRCNM04000a is a nanotube. JRCNM04000a classification as HARN can be useful here, even if not reported in the Nano Tree. The HARN concept is different from the fibre paradigm, since a bended nanotube has a high aspect ratio, but it can be shorter than 5 µm, and thus not being a fibre of concern according to WHO definition or not showing the typical fibre effects, thus being not comparable to asbestos (Donaldson et al., 2010²). This point is also relevant for the shape parameter, which is not clearly described in the C2S column. It can be probably added as a C2SS column, but up to now there is no specification. 3D JRCNM01101a can be classified either as nanoparticle or core-shell because of the coating. A definition of core-shell is not reported in the ISO technical report, and coated particle is not available as a choice. The 2D JRCNM01101a can be classified as nanorod, but also here the coating is not mentioned and not available as a choice. It is shown in the “multi-component nano-object” that the structure of the nano-object is not simple, but the reference to chemical composition is not specified in C2. According to ISO Nano-Tree a multi-component nano-object can also have a physical difference.

The third column is referring to the chemical composition, and in this column the chemical composition of all the different components of the nano-objects is included. The available classes, as provided, are not covering the usual chemical compositions. For example, metal oxides are missing, while there are ceramics. It is possible that from the formulation of the Nano Tree to current times, the definition of chemical classes of MNM has evolved. Anyway, JRCNM02000a was classified as semi-metallic, JRCNM04000a as carbon-based, and JRCNM01101a as metallic for the core (metal oxides is missing as a choice) and organic for the coating.

Column 4 (C4) is for the inclusion of nano-objects properties. The list of possible choices, even if not exhaustive, is long, and it covers several classes of properties, also linked to the specific uses (e.g. magnetic properties, elastic properties). However, as it is proposed in the Nano Tree, the properties are seen more as descriptors, rather than as grouping parameters.

In addition, the commonly measured phys-chem properties (e.g. zeta potential) are not explicitly included in the list, and sometimes it is difficult to decide where to put the measured property. For example, the crystallite structure is not in the Nano Tree at the moment. The crystal structure is important for some MNM, because different crystal structures lead to different phys-chem properties. In our view, the Nano Tree can accommodate the crystal structure in the Chemical properties group (C4), since the crystal structure is depending on the chemical composition. The zeta potential can be included in Electric properties in C4. It is an important property defining the interaction of MNM with the surrounding environment. Zeta potential is not strictly an inherent property, but it can be used to predict the behaviour of the MNM on the basis of zeta potential and thus valuable in a categorization scheme. Finally, dustiness is an essential property of MNM in powder form, and it is related in particular to occupational safety and to safety in general. It is measurable, and an inherent property of the MNM. Therefore, it should be part of the categorization. Dustiness can be included in the Mechanical properties (C4).

In general, during the application of the Nano Tree, it emerged that the ISO scheme is structured to identify categories of MNM on the basis of size, shape, and chemical composition, in this order. The properties included in C4, which are not ranked according to priority and relevance, are more like phys-chem descriptors than grouping parameters. It is not clear how and when two MNM, even in the same class (e.g. 3D, Metals), are considered similar. Similarity can be defined as two MNM having the same (or close) value for a given set of (in this case) phys-chem parameters. Similarity between two MNM can allow read-across,

² Donaldson et al. Particle and Fibre Toxicology 2010 7:5

i.e. the inference of similar behaviour, but the Nano Tree does not report any indications of what similarity means, and it is not giving criteria to measure the similarity of MNM.

RCC approach application

The results of the application of the RCC approach to the selected MNM are reported in Table 3. In this table are included also the phys-chem values as found in the MDS. If the data was missing (not measured or pending), the sign “ - ” was used.

Table 3. Classification of case study MNM according to RCC approach.

MNM Code	Name	Chemical class	Properties
JRCNM02000a (NM-200)	Amorphous Silica (SAS)	Metal oxides	<p><u>Size and shape</u>: mean diameter 50±55 nm, round or slightly elongated nanoparticles</p> <p><u>Composition</u>: Si=44.77 % wt, O=53.02 %; impurities: > 0.1:Na,S; > 0.01%: Al, Ca; > 0.05-0.001%: Fe, K; 0.001-0.005%: Mg, Zr (Na₂SO₄, AlO(OH), Cristobalite)</p> <p><u>Solubility</u>: Partially soluble</p> <p><u>Crystal structure</u>: Synthetic amorphous silica</p> <p><u>Surface reactivity</u>: (surface area) 189.16 m²/g</p> <p><u>Surface functionalization</u>: None</p>
JRCNM04000a (NM-400)	MWNT	Carbon nanotubes	<p><u>Number of walls</u>: 3? (thickness of one wall is 5.1±1 nm)</p> <p><u>Diameter</u>: 16.2±3.5 nm</p> <p><u>Length</u>: 846±446 nm (geodesic length)</p> <p><u>Capped/uncapped</u>: capped</p> <p><u>Chirality</u>: -</p> <p><u>Surface functionalization</u>: None</p>
JRCNM04001a (NM-401)	MWCNT	Carbon nanotubes	<p><u>Number of walls</u>: -</p> <p><u>Diameter</u>: 67±24 nm</p> <p><u>Length</u>: 4048 ± 2371 nm (geodesic length)</p> <p><u>Capped/uncapped</u>: uncapped</p> <p><u>Chirality</u>: -</p> <p><u>Surface functionalization</u>: None</p>
NCF	Nanocellulose Fine	Organics	<p><u>Size and shape</u>: diameter around 2-15 nm, with thicker fibres and bundles. Average length 50 μm. Long fibres.</p> <p><u>Surface chemistry</u>: no coating</p> <p><u>Crystallinity</u>: -</p> <p><u>Degradability</u>: -</p> <p><u>Solubility</u>: Not soluble</p> <p><u>Zeta potential</u>: -15 mV</p>
NFC	Nanocellulose medium-coarse	Organics	<p><u>Size and shape</u>: diameter around 2 nm, with thicker fibres and bundles (3-10 nm). Average length 20 μm. Long fibres</p> <p><u>Surface chemistry</u>: no coating</p> <p><u>Crystallinity</u>: -</p> <p><u>Degradability</u>: -</p>

			<p><u>Solubility</u>: Not soluble</p> <p><u>Zeta potential</u>: -32 mV</p>
JRCNM03002 (NM-302)	Ag	Metal	<p><u>Size and shape</u>: diameter 200 nm, length 3000 nm. Metallic fibre.</p> <p><u>Composition</u>: Ag</p> <p><u>Solubility</u>: -</p> <p><u>Oxidation states</u>: Ag⁰, Ag⁺</p> <p><u>Surface functionalization</u>: no inorganic, organic pending</p>
JRCNM03000k (NM-300K)	Ag	Metal	<p><u>Size and shape</u>: average diameter 17.24±3.17 nm. Shape predominantly round, while others are triangular or trapezium-like.</p> <p><u>Composition</u>: metallic silver 100%</p> <p><u>Solubility</u>: The release of silver into the elution matrix (acrylic matrix with different media: deionised water, nitric acid 0.5% and physiological buffer) was observed up to 13 days without removing and exchanging the elution media</p> <p><u>Oxidation states</u>: Ag⁰, Ag⁺</p> <p><u>Surface functionalization</u>: None</p>
JRCNM01001a (NM-101)	TiO ₂	Metal oxides	<p><u>Size and shape</u>: 5-6 nm average diameter. Shape is spherical, with some elongated particles. The suggested 3D structure is spherical or ellipsoidal</p> <p><u>Composition</u>: Ti 58.79%, O 40.35%; impurities: >0.1%: Na, Al; >0.01%: P, S, Zr; 0.001-0.005%: Ca, K</p> <p><u>Solubility</u>: impurities such as Al, Si and Fe were detected appearing to be unstable and at least partly dissolved.</p> <p><u>Crystal structure</u>: anatase</p> <p><u>Surface reactivity</u>: (surface area) 316 m²/g</p> <p><u>Surface functionalization</u>: Organic coating 8% (mass loss): silane, hexadecanoic acid methyl ester, hexadecanoic acid, octadecanoic acid</p>
JRCNM01000a (NM-100)	TiO ₂	Metal oxides	<p><u>Size and shape</u>: average size 110±57 nm. The 3D structure suggests they are spherical or ellipsoidal.</p> <p><u>Composition</u>: Ti 58.57%, O 40.08%; impurities: >0.1% K, >0.01%: P; 0.005-0.01%: Zr; 0.001-0.005%: Ca, Na</p> <p><u>Solubility</u>: Impurities such as Al, Si and Fe dissolve in the first 24 h experiment</p> <p><u>Crystal structure</u>: anatase</p> <p><u>Surface reactivity</u>: 9 m²/g</p> <p><u>Surface functionalization</u>: None</p>
JRCNM01100a (NM-110)	ZnO	Metal oxides	<p><u>Size and shape</u>: two populations detected (P.1 20-250 nm, P.2 50-350 nm). Shape P.1 hexagonal, spherical particles, P.2 cubic, tetragonal and orthorhombic, elongated particles</p> <p><u>Composition</u>: Zn= 89.80 % wt</p> <p><u>Solubility</u>: 2.5-4 ppm in DI water after 6-21 days</p> <p><u>Crystal structure</u>: Hexagonal zincite structure</p>

			<u>Surface reactivity:</u> (surface area) 12.4±0.6 m ² /g <u>Surface functionalization:</u> None
JRCNM01101a (NM-111)	ZnO	Metal oxides	<u>Size and shape:</u> two populations detected (P.1 20-200 nm, P.2 10-450 nm). Shape polyhedral and with variable morphology. P.1 spherical particles, P.2 elongated particles <u>Composition:</u> Zn= 87.39 % wt <u>Solubility:</u> - <u>Crystal structure:</u> Hexagonal zincite structure <u>Surface reactivity:</u> (surface area) 15.1±0.6 m ² /g <u>Surface functionalization:</u> organic 1% (weight loss) triethoxycapryl silane

Discussion

The application of the RCC approach highlighted that a comparison of MNM similarity within each chemical group can be done only on the basis of the physicochemical properties. Contrary to the Nano Tree, the RCC approach is limiting the number of properties to measure for each chemical composition class. In some cases, some parameters are generic, such as surface reactivity, and it can be measured by using different methods, as well as proxy parameters. In our case, specific surface area can be a proxy, but more direct measurements can be also useful.

To identify similar MNM in the chemical classes, the RCC approach suggests that there has to be a significant similarity between the measured properties values. It is also true that similarity can be relative to a specific MNM behaviour, and thus referred to a limited set of the measured parameters. It can be toxicity, wastewater treatment effectiveness, persistence, bioaccumulation in organisms, and so on. However, for this exercise we selected different MNM to cover different aspects of the categorization approaches, therefore it is expected to have MNM that are not similar. For example, JRCNM01100a and JRCNM01101a, both metal oxides, show close values for almost all measured parameters (e.g. size distribution, core chemical composition, specific surface area). However, JRCNM01101a is coated, while JRCNM01100a is uncoated. Since surface determines most of the MNM relations with biotic and abiotic environment, it is not immediately possible to group these two MNM. The same for JRCNM04000a and JRCNM04001a, where one MN is capped and shorter, and the other is uncapped and longer. However, the impression is that the RCC approach is more rational and suitable to define MNM categories on the basis of physical-chemical properties.

5.2.1.4 Conclusions

In general, the categorization based on the two existing schemes highlights some aspects that can be considered for a NANoREG specific categorization.

1. A tiered approach is useful to reduce the amount of testing and data to collect at each stage, and to filter the different MNM in a simpler way;
2. To start with size/shape alone is not useful, because it divides MNM into categories that are not really linked to a specific concern. The same is valid for the chemical only grouping, which could lead to horizontal subgrouping encompassing different MNM originally in different groups. It is also true that the chemical composition is a parameter that determines the phys-chem properties that are relevant to measure the level of concern;
3. Grouping has to be multidimensional, i.e. involving different properties. Also, the scope of the grouping should be clearly identified. Phys-chem based grouping is only one dimension of the

overall scheme. What is the final result should be clearly understood, as well as how the final result can be used for an overall risk-based grouping.

4. The phys-chem categorization based only on the “usual” properties (i.e. size, shape, chemical composition, solubility) is leading toward a grouping that is not really useful for a risk assessment, because it is a pure descriptive grouping. The goal is to link the basic categorization parameters (low endpoints) to measurable higher level measurements (mid endpoints) such as surface reactivity or persistence, that are in the end linked to biological effects and interaction of MNM with surrounding environment;
5. In grouping, the biggest issue is “how similar is similar” , i.e. decide when a MNM is similar enough to another MNM to be able to put both MNM in the same group. One way is to define benchmarks (thresholds) that define the limits of being part or not of a group (e.g. solubility, reactivity). Benchmarks have to be defined on the basis of science, but since science is progressing, changes in benchmarks are possible. On the other hand, for normal chemicals grouping is based on algorithms, and the similarity is defined by the user, and within the results (chemicals with similar structure), the best choice is made by the user. A similar approach can be applied to MNM;
6. It is suggested that important parameters are: size distribution, shape (to identify HARN), solubility (but solubility rate, not per se), surface reactivity (which is determined by several other phys-chem parameters, including coating). Chemical composition is relevant for the identification of CRM properties.

5.2.1.5 Supporting info

Comparison: Material Data Sheet vs. ISO scheme

For each parameter measured in the Material Data Sheet, a description of its use within the ISO scheme will be done, and if the specific parameter is not included in the ISO scheme, hypotheses about its use or place will be offered (see text in *Italic*).

1. Shape: shape is measured primarily via TEM. Shape (including primary particles, and not aggregates/agglomerates), in coordination with size, is essential to identify the type of nanomaterial (e.g. for C2S: nanoparticle, nano-rod, nanotube). In some cases, there can be different populations, with different aspect ratio or shape (e.g. spherical, triangular). It is not clear within the ISO document how to deal with these cases. In addition, the carbon nanotubes, while having a very high aspect ratio (> 3), sometimes the length is below $5 \mu\text{m}$ (requisite to be a fibre of concern according to WHO), and they appear to be tangled and not straight. Therefore, high Aspect Ratio Nanomaterials (HARN) are not necessarily fibres according to the WHO definition. However, HARNs are not included in the ISO scheme at the moment. Aspect ratio is reported in point 3.
 - a. *In principle, the application of shape in Nano Tree should lead to one classification per material, but if there are two populations, one 2D and the other 3D, it could be possible to define two different set within the same sample.*
 - b. *The HARN type of nanomaterial should be included in the list of 2D nanomaterials*
2. Core size distribution: it is defined as the size distribution of the primary particles, while sometimes also size distribution of aggregates/agglomerates is given. It is measured with TEM and XRD. This parameter enters the Nano Tree only in the definition of 1D, 2D, and 3D indication in C1. There are no other places where size enters the Nano Tree as a number.

- a. *It is not clear if in the Phys-chem categorization the actual size is relevant. There is the issue of quantum confinement effect that occurs below a certain size, but it is different for each material, and difficult to quantify. A paper [41] reported the benchmark being around 20-30 nm for selected metal oxides. It can be proposed to add a separate value in C2S for 3D MNM (low aspect ratio) with all dimensions below 20 nm.*
3. Aspect ratio: the aspect ratio is used to identify the type of MNM (C2S) in 2D nanomaterial. In particular, the WHO fibre paradigm is defined for materials with an aspect ratio > 3, a length > 5 µm, and a diameter < 3 µm. Therefore, by combining size and aspect ratio it is possible to define the MNM being a WHO fibre of concern or not. However, the HARN paradigm needs to be considered (see point 1a and b).
4. Surface morphology/topology:
5. Specific surface area: the specific surface area (SSA) is used as a proxy in the category Chemical properties (CS4), as proxy for catalytic reactivity and absorptiveness.
 - a. *Specific surface area is an important parameter and it is not linked to chemical properties, but to size and structure of the MNM. Therefore, it should be used to categorize MNM from a phys-chem point of view in the first steps, not only as a proxy of other properties.*
6. Crystallite structure: it is not in the Nano Tree at the moment.
 - a. *The crystallite structure is important for some MNM, because different crystal structures lead to different phys-chem properties. Therefore it should be included in the properties part, or as a proxy for other properties. The Nano Tree can accommodate the crystal structure in the Chemical properties group (C4), since the crystal structure is depending on the chemical composition.*
7. Core material (elemental composition): the chemical composition (including coating and impurities) as such is not explicitly included in the Nano Tree. Chemical composition is used to identify the structure of the MNM in the C2. If there is a local chemical discontinuity, the structure is “multi component”. There is the Chemical category in C4, concerning the properties, but it is used to define the properties linked to the chemical nature of the particle, rather than the composition. However, it is reasonable to assume that the Nano Tree can accommodate the chemical composition in Chemical properties in C4.
8. Overall material composition (including degree of purity, known impurities or additives): see point 7.
9. Impurities: see point 7
10. Coating: see point 7.
 - a. *Coating is essential to categorize the MNM, since the relationship of the MNM with the surrounding environment is through the surface. Coating is determining several properties of nanomaterials, besides their toxicity. Coating should be explicitly reported. For example organic or inorganic coating. Functional groups (point 11) are also relevant.*
11. Functional groups present on the coating: see point 7 and 10.
12. Zeta potential: zeta potential is not explicitly included in the Nano Tree.
 - a. *Zeta potential can be included in Electric properties in C4. It is an important property defining the interaction of MNM with the surrounding environment. Zeta potential is not strictly an inherent property, but it can be used to predict the behaviour of the MNM on the basis of zeta potential and thus valuable in a categorization scheme.*

13. Hydrodynamic radius: the hydrodynamic radius is a measurement of the size of the MNM at given conditions in a given medium. It is not included in the Nano Tree as such, and it is also difficult to include (it should go into column C1).
 - a. *The hydrodynamic radius is a measurement that depends on the chemical nature of the MNM, but more by the dispersion medium characteristics. It is easily measured, and it gives an idea of the tendency of MNM to agglomerate. It is not an inherent property. However, this parameter can be used to predict the behaviour of a MNM in a matrix.*
14. Dustiness: it is not included in Nano Tree. Dustiness is an essential property of MNM in powder form, and it is related in particular to occupational safety and to safety in general. It is measurable, but a property with values that changes with test methods. It could be part of the categorization.
 - a. *Dustiness can be included in the Mechanical properties (C4), even if it is not clear if what Nano Tree means as Mechanical property. Examples provided by ISO include parameters such as elastic properties, abrasion, and fatigue. Dustiness can be a useful phys-chem categorization parameter, but the applied methods must be defined (e.g., currently CEN methods in development) and there can be the need to define a threshold for qualitative scaling of the values.*
15. Dissolution and hydrochemical reactivity: these parameters have to do with reactivity of the MNM. They are not explicitly included in the Nano Tree. They are clearly linked to Chemical category.
 - a. *Reactivity is an inherent property of the MNM, and it can be used in a phys-chem categorization.*
16. Short- and long-term solubility and degradation: these parameters are in some way included in the Nano Tree (chemical resistivity/solubility), specifically in the Chemical properties group (C4). However, the example given by ISO is about resistance to chemical abrasion. Solubility can be included in the Chemical group.
 - a. *Solubility is a key parameter for several metallic MNM, and it is the key to evaluate the safety of MNM in different legislations (e.g. food, cosmetics). If the MNM is soluble, then it is no more a nanoform, but a "normal" chemical. The phys-chem characterization should include this parameter.*
17. Magnetic moment: it is included in the Physical properties of the Nano Tree. It is never measured up to now. It is an engineer and medical type of property. It could be used to identify magnetic and diamagnetic MNM.

5.3 ANNEX III

Examples

In this part, an example is given to illustrate how the classification could be used. The NMs are selected from the NANoREG database and the material data sheets have been used to derive the values of each of the characteristics. Both simple and complex type of nanomaterials are selected and processed through the classification scheme. Users are advised to follow the scheme with the available data for reach out to a useful category of any substance.

CNTs

- NM400/JRCNM04000a
- NM401/JRCNM04001a

Silica

- NM200 /JRCNM02000a

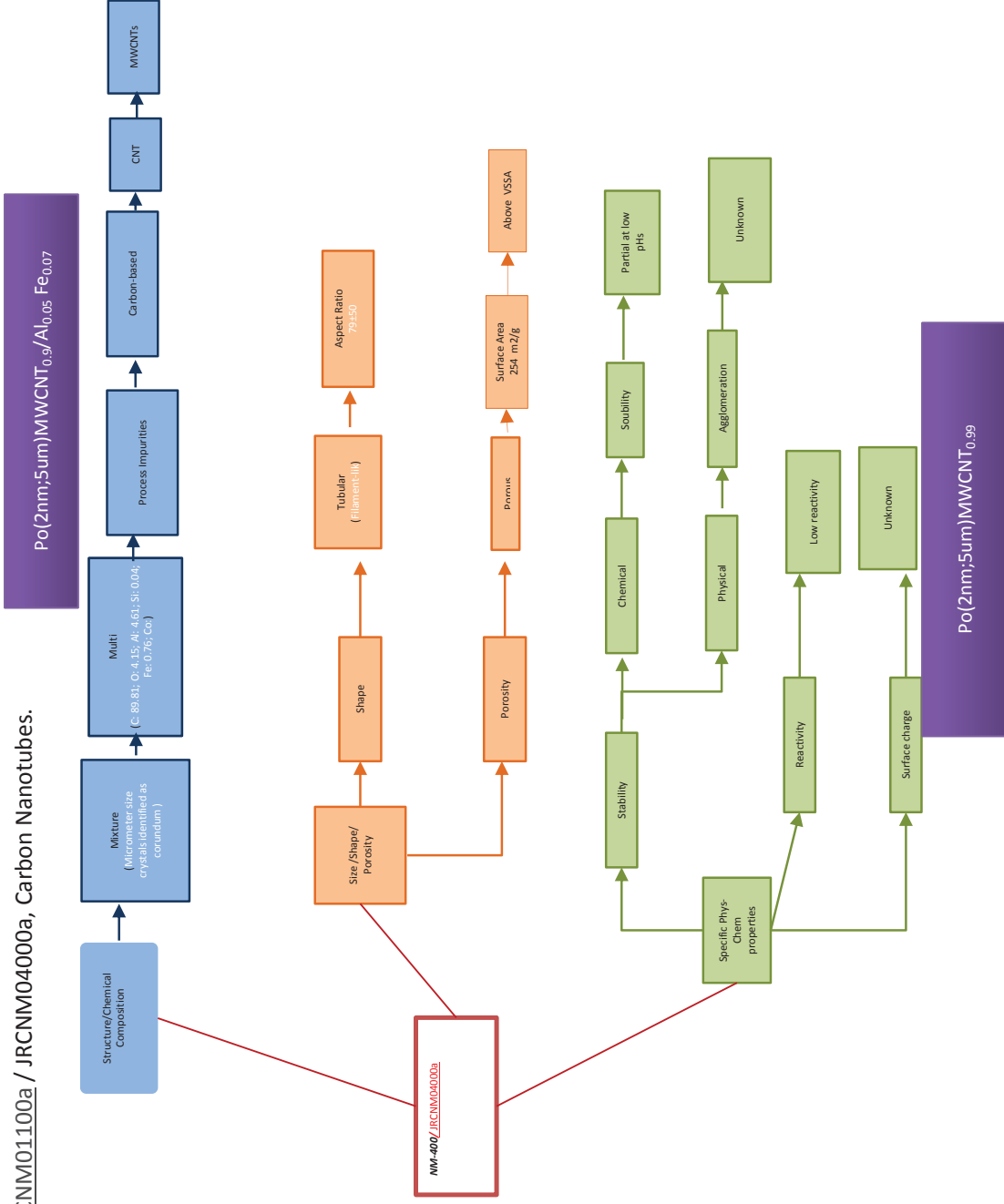
TiO₂

- NM101/JRCNM01001a

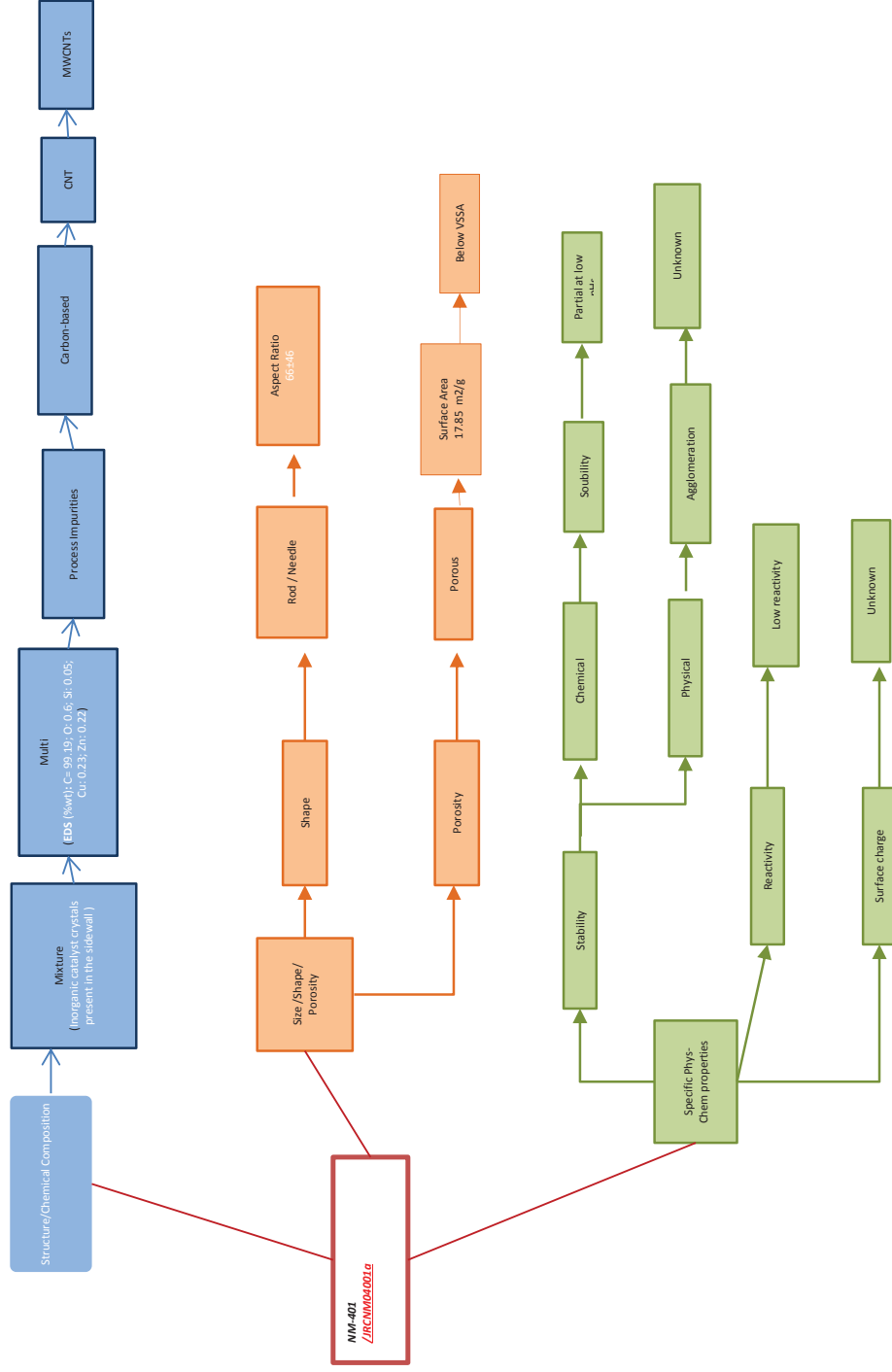
ZnO

- NM 111/JRCNM01101a

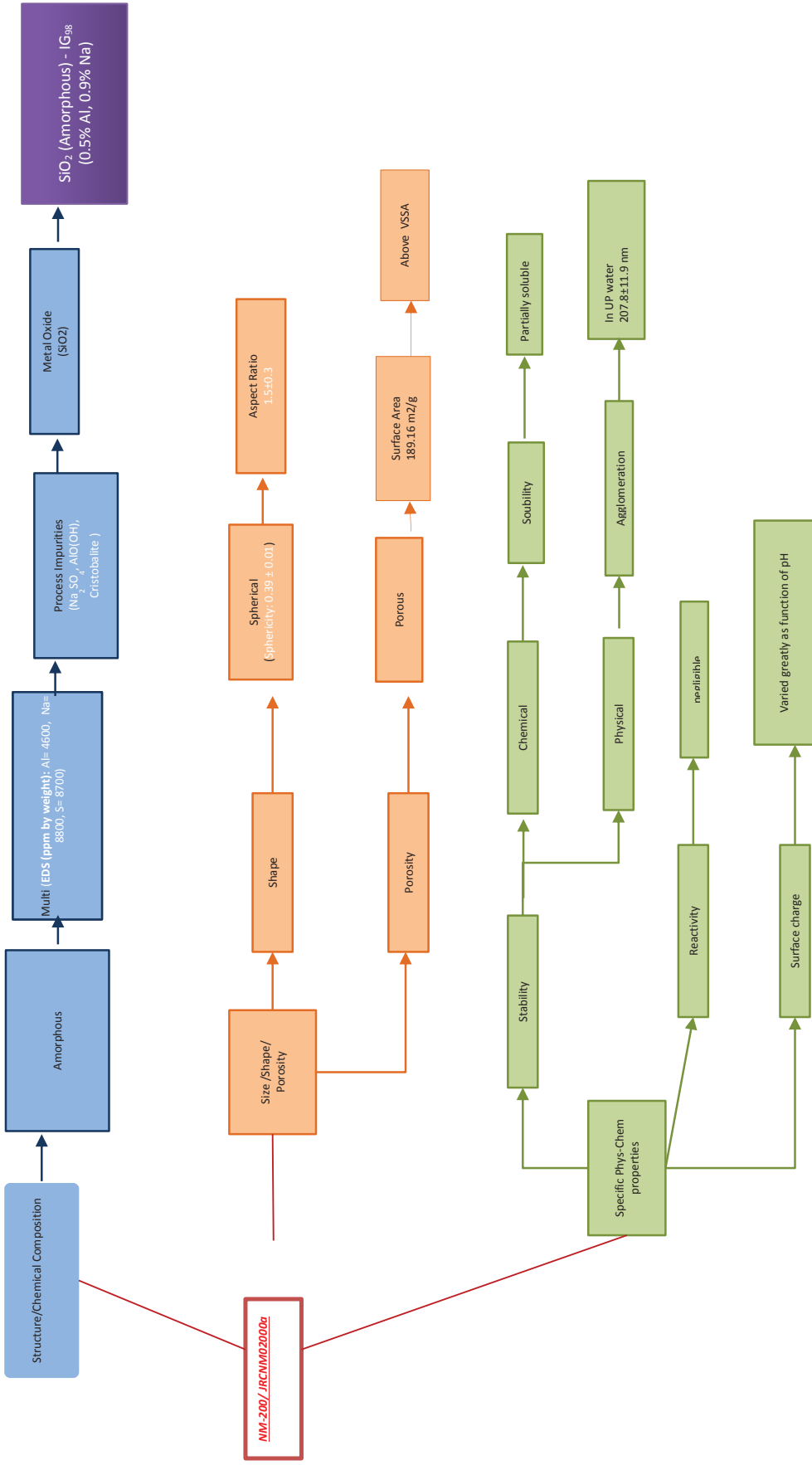
- JRCNM01100a / JRCNM04000a, Carbon Nanotubes.



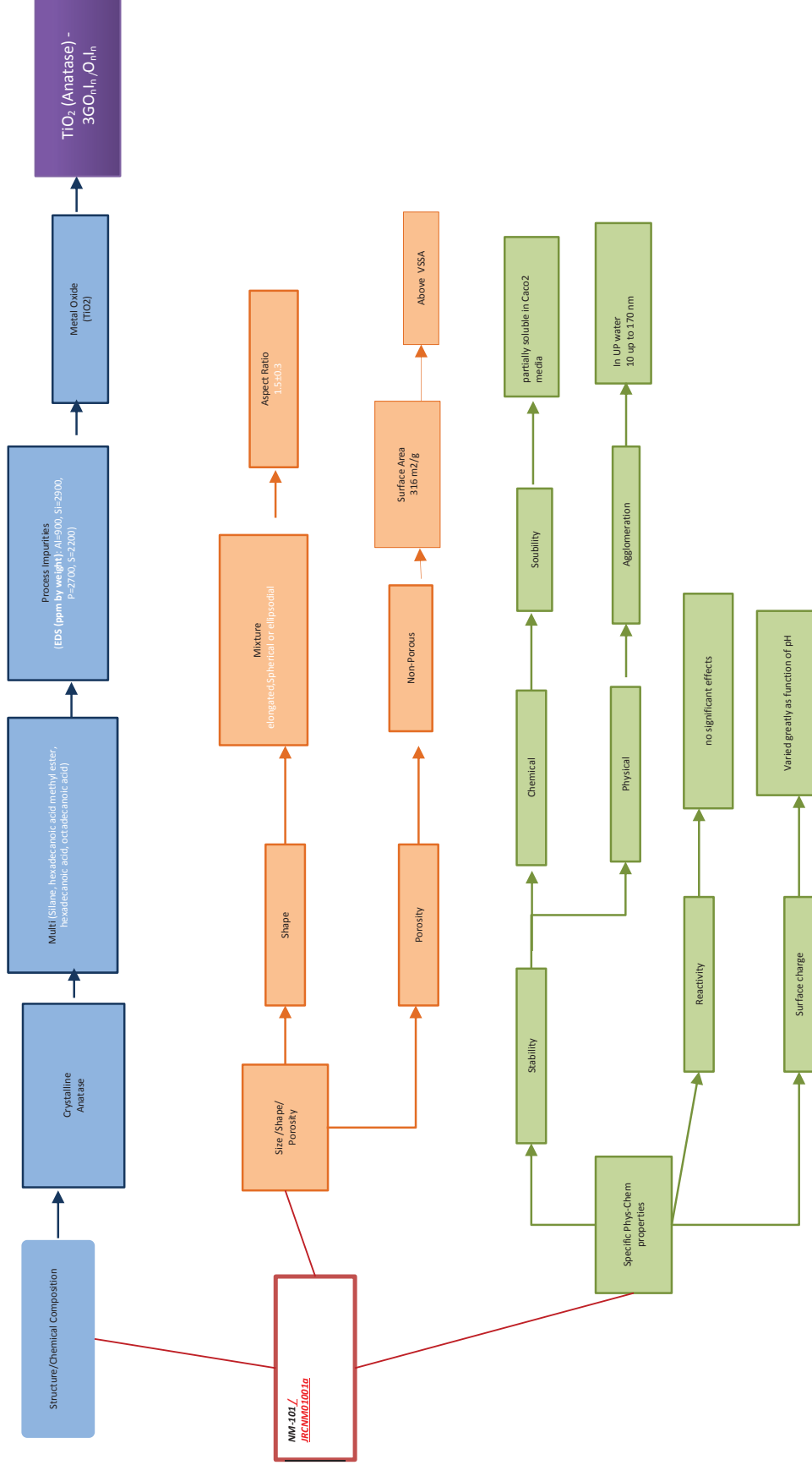
- NM 401/JRCNM04001a, Carbon Nanotube



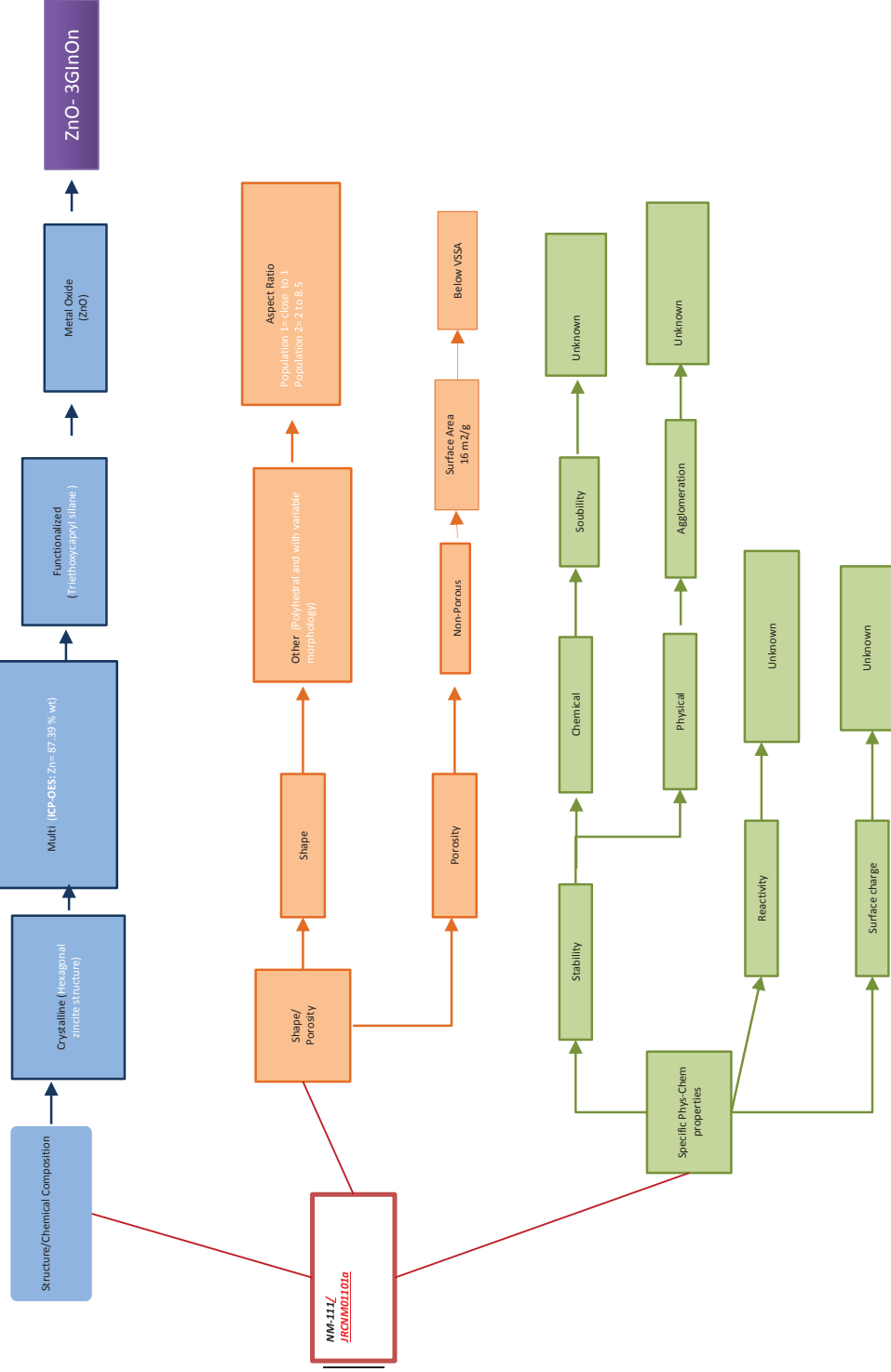
- NM 200/JRCNM02000a, Synthetic Amorphous silica



- NM-101/JRCNM01001a, Titanium Dioxide



- NM-111/JRCNM01101a, Zinc Oxide



Reference List

- [1] Nanomaterials Producers Directory 2014-2015. 1-108. 2014. Future Markets Inc.
- [2] T. J. Brunner, P. Wick, P. Manser, P. Spohn, R. N. Grass, L. K. Limbach, A. Bruinink, and W. J. Stark, In vitro cytotoxicity of oxide nanoparticles: Comparison to asbestos, silica, and the effect of particle solubility, *Environmental Science & Technology*, 40 (2006) 4374-4381.
- [3] Consumer Products Inventory <http://www.nanotechproject.org/cpi/>. 2014.
- [4] EU-funded research projects and project results, http://cordis.europa.eu/projects/home_en.html. 2014.
- [5] E. Gaffet, Nanomaterials: A review of the definitions, applications, health effects. How to implement secure development, *C. R. Phys*, 12 (2011) 648-658.
- [6] S. Vicki, N. Bernd, B. Anders, v. d. B. Nico, v. d. K. Frank, D. Maria, H. Richard, H. Steven, H. Martin, J. Erik, and F. F. Teresa, Nanomaterials for environmental studies: Classification, reference material issues, and strategies for physico-chemical characterisation, *Sci. Total Environ.*, 408 (2010) 1745-1754.
- [7] Nanomaterials in REACH. <http://echa.europa.eu/regulations/nanomaterials>
- [8] Guidance on information requirements and chemical safety assessment. 4-30-2012.
- [9] Guidance for identification and naming of substances under REACH and CLP. <http://echa.europa.eu/guidance-documents/guidance-on-reach> . 2-7-2014.
- [10] European Commission, Commission Recommendation of 18 October 2011 on the definition of nanomaterial, *Official Journal of the European Union*. 2011/696/EU: 38-40, 2011
- [11] REACH Implementation Project Substance Identification of Nanomaterials (RIP-oN 1). <http://echa.europa.eu/guidance-documents/guidance-on-reach> AA N°070307/2009/D1/534733. 2011.
- [12] Specific Advice on Fulfilling Information Requirements for Nanomaterials under REACH (RIP-oN 2). RNC/RIP-oN2/FPR/1/FINAL. 7-1-2011.
- [13] K.Aschberger, H.Rausche, H.Crutzen, K.Rasmussen, F.M.Christensen, B.S.Kluttgen, and H.Stamm. Considerations on information needs for nanomaterials in consumer products. EUR 26560 EN. 2014.
- [14] <http://www.nanodefine.eu>.
- [15] Nanotechnologies - Methodology for the classification and categorization of nanomaterials. 7-12-2010.
- [16] K. Donaldson, F. A. Murphy, R. Duffin, and C. A. Poland, Asbestos, carbon nanotubes and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma, *Part. Fibre. Toxicol.*, 7 (2010).
- [17] M. Inagaki and L. R. Radovic, *Nanocarbons, Carbon*, 40 (2002) 2279-2282.

- [18] I. Suarez-Martinez, N. Grobert, and C. P. Ewels, Nomenclature of sp(2) carbon nanoforms, *Carbon*, 50 (2012) 741-747.
- [19] Jensen, K. A., Bøgelund, J, Jackson, P, Jacobsen, N. B, Clausen, P. A, Saber, A. T., Wallin, H, and Vogel, U. B. Carbon Nanotubes. 1805, 1-150. 2015. The Danish Environmental Protection Agency.
- [20] SCENIHR: Scientific basis for the definition of the term "Nanomaterial" SCENIHR opinion for public consultation approved by written procedure on 6 July 2010. http://ec.europa.eu/health/ph_risk/risk_en.htm . 6-6-2010.
- [21] Specific Advice on Exposure Assessment and Hazard/Risk Characterisation for Nanomaterials under REACH (RIP-oN 3). RNC/RIP-oN3/FPR/1/FINAL. 7-1-2011.
- [22] Nanotechnologies- Vocabulary -- Part 1: Core terms. 2010. ISO. ISO/TS 80004-1.
- [23] W. G. Kreyling, M. Semmler-Behnke, and Q. Chaudhry, A complementary definition of nanomaterial, *Nano Today*, 5 (2010) 165-168.
- [24] Towards a review of the EC recommendation for a definition of the term nanomaterial. EUR 26567 EN . 2014.
- [25] S. F. Hansen, B. H. Larsen, S. I. Olsen, and A. Baun, Categorization framework to aid hazard identification of nanomaterials, *Nanotoxicology*, 1 (2007) 243-U369.
- [26] P. Wang, S. M. Zakeeruddin, P. Comte, I. Exnar, and M. Gratzel, Gelation of ionic liquid-based electrolytes with silica nanoparticles for quasi-solid-state dye-sensitized solar cells, *J. Am. Chem. Soc.*, 125 (2003) 1166-1167.
- [27] Marilyn F. Hallock., G. Pam, D. Lou, and K. Dan, Potential risks of nanomaterials and how to safely handle materials of uncertain toxicity, *J. Chem. Health. Saf*, 16 (2009) 16-23.
- [28] General Safe Practices for Working with Engineered Nanomaterials in Research Laboratories. 2012. NIOSH.
- [29] R. Atluri and K. A. Jensen, Classification and Reporting of Nanostructured Silica Materials, *Chem. Rev.*, Manuscript (2016).
- [30] Guidance for identification and naming of substances under REACH. http://guidance.echa.europa.eu/docs/guidance_document/substance_id_en.pdf 1.3. 7-1-2007. ECHA.
- [31] V. M. Gun'ko, M. S. Vedamuthu, G. L. Henderson, and J. P. Blitz, Mechanism and kinetics of hexamethyldisilazane reaction with a fumed silica surface, *J. Colloid Interface Sci.*, 228 (2000) 157-170.
- [32] J. Lee, Y. Lee, J. K. Youn, H. Bin Na, T. Yu, H. Kim, S. M. Lee, Y. M. Koo, J. H. Kwak, H. G. Park, H. N. Chang, M. Hwang, J. G. Park, J. Kim, and T. Hyeon, Simple synthesis of functionalized superparamagnetic magnetite/silica core/shell nanoparticles and their application as magnetically separable high-performance biocatalysts, *Small*, 4 (2008) 143-152.
- [33] Recommendations for the safer development of nanotechnology for the EU's REACH regulation implementation. 2014.
- [34] Appendix R7-1 Recommendations for nanomaterials applicable to Chapter R7a Endpoint specific guidance. ECHA-12-G-03-EN . 2012.

- [35] Appendix R7-1 Recommendations for nanomaterials applicable to Chapter R7b Endpoint specific guidance. ECHA-12-G-04-EN. 2014.
- [36] The Canadian Department of the Environment: Mandatory reporting of nanomaterials. 2014.
- [37] Guidance on information requirements on active substances and biocidal products. 1.0. 2013. Finland, European Chemicals Agency.
- [38] Addendum to the report of the OECD expert meeting on the physical chemical properties of manufactured nanomaterials and test guidelines: Presentations given at the workshop. 6-4-2014.
- [39] Christensen Frans and Larsen, Poul B. Information Requirements for nanomaterials - IRNANO. <http://eng.mst.dk/about-the-danish-epa/news/report-information-requirements-for-nanomaterials/>. 2013.
- [40] Nanomaterials: Hazards and risks to health and the environment, A supplementary guide for the UK Voluntary Reporting Scheme. 2008.
- [41] M. Auffan, J. Rose, J. Y. Bottero, G. V. Lowry, J. P. Jolivet, and M. R. Wiesner, Towards a definition of inorganic nanoparticles from an environmental, health and safety perspective, Nat. Nanotechnol., 4 (2009) 634-641.
- [42] OECD terms: <http://www.oecd.org/chemicalsafety/risk-assessment/groupingofchemicalschemicalcategoriesandread-across.htm>).