NanoFabNet

international Hub for sustainable industrial-scale Nanofabrication

Concepts & Disciplines of Sustainability in Nanotechnology & Nanofabrication

NanoFabNet Report

NanoFabNet

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1. Executive Summary

This report is devoted to a review of the concepts and disciplines of Sustainability in Nanotechnology and Nanofabrication. It presents and gives a thorough description of the content and of the constituting concepts of the three identified pillars of the NanoFabNet own concept of Sustainability in Nanotechnology and Nanofabrication, to be developed further across the NanoFabNet project: Environment, Health & Safety issues in Nanotechnology and Nanofabrication; Life Cycle Sustainability issues in Nanotechnology and Nanofabrication; Ethics and Governance issues in Nanotechnology and Nanofabrication.

Based on a literature review combined with Project Partners knowledge, this report realizes a mapping of the key notions to be considered when dealing with sustainability in Nanotechnology and Nanofabrication. It can both inform any stakeholder in Nanotechnology and Nanofabrication on the relevant aspects of sustainability to be considered in his activities, and contribute to the identification of the aspects of technology sustainability to be further incorporated into the own NanoFabNet Concept of 'Sustainable Nanofabrication'.

The chosen method in this report is a list-based delineation of the different disciplines and sub-disciplines involved, with a presentation of their constituting terms and concepts. This report doesn't pretend to be a glossary, but it provides for each term or notion a descriptive paragraph focused on the relevance of the term for the stake of sustainability in Nanotechnology and Nanofabrication.

An introduction reminds the global challenges of technological sustainability. Then a special chapter is devoted to each of the three identified pillars. A last chapter describes some integrated tools and strategies able to support sustainability-informed decision-making processes in Nanotechnology and Nanofabrication.

2. Introduction

2.1 The challenges of technological sustainability

Sustainability is a key-issue in an "age of sustainable development" (Sachs, 2015) in which important environmental and social problems must be given some solutions. Sustainability also concerns the process of technology, if it is taken to be one of the causes of the environmental and social problems at stake. Sustainable development has been high on the agenda of many public and private actors since the time when the notion popped up in official reports. In Our Common Future, the report of the Bruntland Commission, sustainable development was defined as "development that meets the needs of the present without compromising the ability of future generations to meet their own needs". Hence the familiar vision of sustainable development as some kind of conciliation of several stakes and goals relating to the three different spheres of economy, ecology and society. This initial vagueness of the term "sustainable development" has not been helped by its opening up to some other new challenges and by its overuse in all kinds of contexts and speeches. The concept was shown to be exposed to the risk of being an oxymoron if economic growth is accompanied by a depletion of natural resources and a deterioration of the environmental services (Spaiser et al., 2017). Similarly concerning the new Sustainable Development Goals (SDGs), the International Council of Science showed that "the framework as a whole might not be internally consistent - and as a result not be sustainable" (ICSU & ISSC, 2015, p.9). The situation of sustainable development is thus paradoxical: on the one hand, it appears as a consensual program and ideology that functions worldwide as a compass for all countries and actors; on the other hand, it is sometimes viewed as an obsolete framework on the ground that, after several decades, it has failed to foster significant human changes (WWF, 2020).

Some lessons must be drawn from the success and failures of the sustainable development model, if the notion in a similar perspective is to be applied to the "sustainable technology". Mulder et al. (2011) bring a very interesting contribution to that point, and we propose to follow their reasoning. They remark that technologies have played an important role in creating the environmental and social problems, and that they will also play an important role in solving them (Idem, p.1). Achieving advances in specific sectors of human development such as food, energy or medicine is indeed critically important. And of course, technological changes can be perceived as easier to accomplish than lifestyle changes that might be required to solve the problems that we face (Idem, p.2). But technology and

society always co-evolve (Idem, p.4). The social and environmental impacts of new technologies depend not only on inherent characteristics of them, but also on the way they are perceived and used in the social context, and on the way they affect or even transform it (Idem, p.2). In order to not aggravate other problems while trying to fix a technological one, it remains thus important to keep a clear vision of all aspects of sustainable development when addressing specific technological problems (Idem, p.4). For example, an increased resource efficiency in the providing of a same technological functionality might create a stimulus for consumption, the well-known 'rebound effect', that makes the problem worse (Idem, p.5). Identically, prescribing technologies with less harmful side effects might lead to a transfer of production or illegal use, thereby aggravating problems (Idem, p.6). These kinds of paradoxes must be faced, assumed and overcome both by the designer and by the society at large. Certainly, history has also shown that a new technology is sometimes able to reconcile opposing demands (Idem, p.6)[1]. But it would be naïve to think that there is a technological fix for every problem. Assessing the sustainability of a new technology is thus a complex task, for which the global perspective of sustainable development gives in fact very little focus for action (Idem, p.3). It is not sufficient to flag a design as sustainable by referring to simple categories such as "pollution free", "creating local employment", "being renewable", etc. (Idem, p.3). Mulder et al. (2011) propose thus to take as a first step the "awareness of the multitude of sustainable development challenges that play a role in production, use, recycling and end-of-life disposal of designs" (Idem, p.5). And the list they propose for the a posteriori global sustainability assessment of the historical technologies they study can certainly be a source of inspiration for the sustainability assessment of emerging technologies (Idem, p.6): (1) What articulations of sustainable development informed the design process? (2) What sustainability effects were caused by this technology? (3) Who or what was affected, where and when? (4) Could the designer have foreseen these consequences? (5) How did the designer judge and anticipate them? (6) How was societal interaction dealt with during the design process?

2.2 The NanoFabNet concept of Sustainability in Nanotechnology and Nanofabrication

A particular concern to the different elements summarized above will be kept throughout the NanoFabNet Project. It will remain the case even if the NanoFabNet concept of Sustainability in Nanotechnology and Nanofabrication, to be promoted further in the NanoFabNet hub, rests also on strong and well-identified pillars. The three pillars identified by the NanoFabNet Project for its concept of Sustainability are these ones: a) Environment, Health & Safety issues in Nanotechnology and Nanofabrication; b) Life Cycle Sustainability issues in Nanotechnology and Nanofabrication; c) Ethics and Governance issues in Nanotechnology and Nanofabrication. The following report is devoted to a presentation of these three pillars, and to an up-to-date list-based delineation of their different constituting concepts and disciplines. Three specific chapters (chapters 3, 4 and 5) are dedicated below to these three pillars. A transversal chapter (chapter 6) will complete the picture, describing some integrated tools and strategies able to support sustainability-informed decision-making processes in Nanotechnology and Nanofabrication.

3. Environment, Health & Safety issues in Nanotechnology and Nanofabrication

Ensuring the safe development and application of nanotechnologies has been included in the broad line of activities of the Horizon 2020 proposal. The new technology applications not only should be safe themselves but should also offer substantial improvements to human health and environment protection while still remaining competitive (Savolainen et al., 2013). Due to the rapidly increasing production and use of Engineered NanoMaterials (ENMs) and utilization of nanotechnologies, it is self-evident that safety aspects must be fully understood and addressed. Nanotechnology is a dynamic discipline: ENMs are in constant evolution and we are assisting to a rapid shift from first (passive nanostructures), second (products containing active nanostructures), third (of integrated nano-systems) to fourth generation of nano-devices (heterogenous molecular nano-systems that allow the

[1] Mulder et al. (2011) give as an example the Dutch Oosterschelde storm surge barrier, in which they see the materialisation of the successful reconciliation of safety demands for the local population, and the protection of a valuable ecosystem (*Idem*, p.6).

manufacture of molecular devices 'by design'). Thus, it is turning clear that also ENMs safety assessment should not be based anymore on static paradigms but it is time to change the approach.

Nanosafety is a complex discipline asking for the cooperation of multiple sectors such as material science, biology, and toxicology and risk assessment. Scientists and regulatory bodies are currently facing a big challenge since the available tools for risk assessment are often laborious or inadequate when applied to ENMs. Despite these lacks and after several debates they decided to keep the standard structure for risk assessment of chemicals as starting point to build on a new, adapted (where needed) procedure, specific for ENMs.

The different phases suggested by the NanoSafety Cluster as pillars that need to be carefully characterised are (Savolainen et al., 2013):

1) nanomaterial identification and classification;
2) nanomaterial exposure and transformation;
3) hazard mechanisms related to effects on human health and the environment (potential toxicity);
4) tools for the predictive risk assessment and management including databases and ontologies.

The concept of a "predictive" risk assessment and management is introduced here to remind again about the need of dynamic disciplines compared to the static structures of the standard approaches.

The ultimate goal of the scientists addressing the safety of ENM in their research is to assure the safety of nanotechnologies from the handling of the nanomaterials, the manufacture of products incorporating these materials, to their safe use by the final user and their disposal i.e. safety throughout their entire life cycle.

Another important point to emphasize is the need of international collaboration in the context of OECD, ISO and CEN to provide harmonized and standardized protocols and tools for each phase of the safety assessment. Public acceptance towards nano-enabled products could increase if manufacturers can demonstrate their safety, if regulatory bodies can guide such manufacturers providing clear and harmonised regulations, and if consumers perceive the product as "safe" taking into account that when we are talking about "safety" we are implicitly referring to a compromise between risks and benefits of related products.

In this chapter the main concepts related to environment, health and safety issues in nanotechnology and nanofabrication are both listed and defined (or described/explained). One tries in particular to delineate the corresponding regulatory context and boundaries, and to highlight the main current criticisms, conscious nevertheless that we are far from being exhaustive.

Of course, some terminology is common to the one used in the standard approach of safety assessment of chemicals, but here we want to focus on the adaptation to ENMs evaluation.

The chapter is organised in four main sections reminding to the four pillars already identified by the NanoSafety Cluster:

1) **Nanomaterial identification and classification**
2) **Exposure characterization and ENM transformation (environmental fate)**
3) **Hazard characterization: human and environmental health**
4) **Predictive risk assessment, management and governance**

As emphasised in the joint report JRC-EASAC (Aebi et al., 2011), a regulatory framework for the safety assessment of nanomaterials should follow the same principles and sector-specific requirements as for other products: risk is a function of hazard and exposure. Direct exposure depends on the intended application; indirect exposure arises from involvement in manufacturing processes and from the environment more generally.

3.1 Nanomaterial identification and classification

Concept	*Definition/Description/Explanation*
Nanomaterial Characterization	It requires the description of different aspects of the nano-objects. The level of details and the particular parameter that need to be investigated depend also on the specific purposes of the characterization. OECD has developed detailed descriptions of these physical chemical property endpoints and as well as OECD and non-OECD test methods (OECD, 2009b).

Concept	Definition/Description/Explanation
	Generally speaking we talk about: 1) The properties of the primary nano-objects of the material (nanoparticles, -fibres, -sheets) themselves; 2) The interactions between the nano-objects within a given environment or formulation; 3) The interactions of the material with components thereof (OECD, 2012a). The physicochemical properties and material characterization that may be required for testing (in hazard assessment) are described in more detail in OECD (2008).
Nanomaterial Identification	Attribution of a specific identity to the nanomaterial by using "identifiers". Identifiers have to be considered on a case-by-case basis. Properties to be considered as identifiers could include chemical composition, crystallinity, surface coatings, morphology, size (range), etc. (OECD, 2009b). Alternatively, the nanomaterial may be considered and treated as UVCB substance (Substance of Unknown or Variable composition, Complex reactions products or Biological materials) (OECD, 2012a).
Nanomaterial Classification	A first distinction between *synthetic* and *biological identity* of nanomaterials has been suggested. A more detailed classification could be based on the following criteria (Savolainen et al., 2013): *1. Classification by dimensionality / shape / morphology:* shape-based classification related to define nanomaterials, and already synopsized in the ISO terminology. *2. Classification by composition / chemistry:* this approach groups nanomaterials based on their chemical properties. *3. Classification by complexity / functionality:* the nanomaterials that are in routine use in products currently are likely to be displaced by nanomaterials designed to have multiple functionalities, so called "2nd-4th generation" nanomaterials. *4. Classification by biointerface:* this proposal relates to the hypothesis that nanomaterials acquire a biological identity upon contact with bio-fluids and living entities. Systems biology approaches could help to identify the key impacts and nanoparticles interaction networks.

3.2 Exposure characterization and ENM transformation (environmental fate)

Concept	Definition/Description/Explanation
Occupational exposure	The European Agency for Safety and Health at Work established a Risk Observatory that includes also nanomaterials and addresses exposure to these materials during manufacturing and use that may occur through inhalation, dermal contact and ingestion (OECD, 2009d). OECD was called to work on identification and compilation of guidance information • for exposure measurement and exposure mitigation for manufactured nanomaterials in occupational settings, including manufacture and use of products in industrial, institutional and commercial settings; and • to analyze existing guidance information for their adequacy in addressing manufactured nanomaterials, identify issues that are unique to manufactured nanomaterials, and prepare recommendations for next steps to be undertaken by the WPMN (OECD, 2009c). OECD (2015a) shows a tiered approach that is systematic, consistent, practical, and flexible and that addresses the need for a methodology for conducting field-based workplace exposure measurement and assessment of airborne NOAA released in the workplace. This is specifically dedicated to NOAA, that

Concept	*Definition/Description/Explanation*
	refers to solid, insoluble, engineered nano-objects (<100nm) and their agglomerates and aggregates (including structures ≥100nm).
Exposure monitoring	It is referred to the tracking of manufactured nanomaterials (MNs) movement and concentration in the environment allowing for the definition of Predicted Environmental Concentrations (PECs) and for the development and confirmation of *in silico* models. The challenging aspect is the development of technologies for sample collection, monitoring, detection and measurement of NMs in complex matrices (e.g. air, water, soil and sediments) sensitive enough to detect very small particles at very small concentrations (OECD, 2016e).
Environmental Fate	The environmental fate of nanomaterials is affected by the physical-chemical composition of the environmental compartments, and the chemical and physical-chemical composition of the nanomaterial. In modelling and assessing the fate of nanomaterials, it is common to use a bottom-up approach in which the basic processes/mechanisms are integrated in an overall fate model that is typically applicable to a specified class of chemicals (OECD, 2016a). Biotic or abiotic processes could be responsible for transformations of nanoparticles or their coatings resulting in potential changes of the particles' properties and consequently of the environmental fate. Nanomaterials may also act as carriers for other substances, and the potential for this should be addressed in the assessments (OECD, 2012a).
Bioaccumulation/ Bioconcentration	For simple organic chemicals, there is an established relationship between octanol/water partition coefficient (K_{OW}) and bioaccumulation or bioconcentration factor (BCF). However, there is not a wide body of evidence that this relationship will hold true for many nanomaterials. Consequently, it is not yet recommended that risk assessors make attempts to predict bioaccumulation on the basis of chemical modelling programs. However, empirical BCF tests on the nanomaterial are recommended (understanding the influence the environmental form will have, as well as any corona effect). Empirical studies should be further supported by addressing the relevance of uptake by an organism in terms of whether the nanomaterials may cross cell membranes, whether they will embed in tissues and release ions, whether they are excreted, etc. In the absence of this information, reasonable worst case assumptions based on the size and chemistry will provide insight into potential for bioaccumulation (OECD, 2012a).
Biomagnification	Information on persistence and bio-accumulation will inform on the potential for transfer from aquatic species to mammalian wildlife (and further to humans). However, predictive models in turn do not currently exist to describe how to quantify the transfer between species. Empirical trophic transfer experiments may be necessary to measure food chain exposure. There is no confidence that approaches employed for chemicals are applicable to nanomaterials (OECD, 2012a).
Persistence	While in conventional chemical assessment it generally refers to the enduring state of a molecular structure, in the case of nanomaterials, persistence is often used to refer to the size and shape of the particles (physical persistence) as well as the more conventional use of the word. However, it should be made clear in the use of these terms whether the nanomaterials are still present in another form (e.g., agglomerated) (OECD, 2012a). NM transformation can influence distribution within an organism or in the environment. Assessing transformations will need to be considered in terms of assessing the fate of the "core" material, as well as any functionalisation or surface coating, as alternations of either will affect properties and consequently their distribution pattern. In addition, fate of the material may not necessarily be viewed only in terms of degradation; aggregation/agglomeration will impact how materials distribute and whether dis-aggregation is likely upon settling in a tissue or compartment (OECD, 2012a).

Concept	*Definition/Description/Explanation*
Predicted Environmental Concentrations (PECs):	Although the concept is common to standard approach to Safety Assessment of chemicals, few criticisms are still persisting. Metrics of PECs remains a challenge and ERAs should include a justification for why a particular metric was used. Sufficient and appropriate information on exposure metrics/descriptors during ecotoxicity tests will need to be obtained to allow comparison with environmental exposure concentration information on the same basis or vice versa. There is the need to identify the forms of the nanomaterial present in the receiving environment (e.g., free primary particles, agglomerates/aggregates, ions etc.) (OECD, 2012a).
Ingestion and Dermal exposure	Literally exposure of internal tissues to nanomaterials through absorption by the oral and dermal routes. At the state-of-art technology it is currently low or undetectable. Nevertheless, a mechanistic understanding is required for quantitative assessment (but also qualitative statements). At present, such understanding of the molecular and cellular barriers as well as passages is limited (OECD, 2012a).
Inhalation	It represents the principal route of potential human exposure to nanomaterials in view of their presence in air. Because of their size, ENMs could escape the classical mechanism of clearance through phagocytosis by alveolar macrophages and then being available for potential translocation into the respiratory epithelium. For improved quantitative hazard assessment, methods and (mathematical) tools similar to PBPK / TK20 models for “conventional” chemicals to describe not only isolated steps but the pathway(s) as a whole may be required (OECD, 2012a). The OECD has published recommendations on adaptation of current inhalation toxicity test guidelines for nanomaterials hazard assessment (OECD, 2012b). Details of major EU projects having dealt with nanosafety can be found in the different NanoSafety Cluster Compendiums (see in particular Riediker, 2013 and Lynch, 2017) and further guidance e.g. in testing and exposure assessment in the ECHA web page (OECD, 2015b).
Nanoparticle Translocation	Inhalation remains a likely route of accidental exposure to nanomaterials (e.g. in an occupational or environmental setting). Passage of nanoparticles into the blood (“translocation”) and their delivery to secondary organs could be a compelling explanation for potential systemic effects induced by NP inhalation. There is now a consistent body of evidence from animal studies which demonstrate nanoparticles can cross the alveolar barrier and settle in extrapulmonary organs. Only few studies on humans are available yet but a significant one shows how Au NPs were detected in urine after inhalation (Raftis et al., 2019).
Background and Cumulative Exposure	Nanoparticles of natural origin and those generated unintentionally by human activity involve all individuals to be routinely exposed to nanoparticles throughout life. The increasing use of manufactured nanoparticles adds to this exposure. Hence, the assessment of risks from cumulative and aggregate exposure to nanomaterials requires consideration. In addition, “background noise” may present a challenge to exposure measurements (OECD, 2012a).

3.4 Hazard characterization: human and environmental health

Concept	*Definition/Description/Explanation*
Hazard identification	The hazard of a substance is its potential to cause harm (OECD, 2012a). Hazard identification involves gathering and evaluating toxicity data on the types of health injury or disease that may be produced by a substance and the conditions of exposure under which injury or disease is produced. Health and environmental hazards have been demonstrated for a variety of manufactured nanomaterials (OECD, 2015b). However, it should be noted that not all nanomaterials induce toxic effects. As there is not yet a generally applicable paradigm for nanomaterial hazard identification, a case-by-case approach for the risk assessment of nanomaterials is still warranted (European Commission, 2012).
Hazard assessment	Estimation of the toxic effects exerted by MNs on the environment and/or human health by using a tiered testing strategy. It is mandatory for C&L request of any substance, including manufactured nanomaterials. The evaluation is done using testing systems: *in vivo*, *in vitro*, *ex vivo*, *in silico*. *in vivo* models*:* they are represented by living organisms exposed to the substance *In vitro* models*:* allow "increasing system complexity" meaning that substances can first be tested in the "simpler" more high-throughput *in vitro* systems and then in a more complex *in vitro* system that more closely mimics the *in vivo* situation (OECD, 2012a). *Ex vivo* models: are performed with excess of tissues or organs collected from organisms (humans or animals). They are useful to evaluate MN penetration, uptake, and distribution, as well as toxicokinetics and translocation. They may help for prioritisation and ranking of MN toxicity (Kim et al., 2014; Wohlleben et al., 2011). *In silico* models: computational techniques used for the analysis of effects data, playing a crucial role in MN studies. The integration of the size-related properties (making NMs different from any other chemicals) would help to develop standard predictive models with defined parameters that can accurately and efficiently predict human and ecological toxicity of MN with minimal biological experimentation (OECD, 2016e).
Integrated Approaches to Testing and Assessment (IATA)	Combination of multiple methods (*in vitro/ex vivo*) in a tiered strategy for prediction of potential relevant biological outcomes coming from exposure to chemicals. There are a number of different nano-specific alternative testing strategies under development. IATA can be used to identify and prioritise MN safety research needs, to assess the safety of a chemical using alternative testing methods, and identify situations where *in vivo* testing is not needed. The framework has the following structure: 1) evaluation and organisation of existing data (using tools such as Adverse Outcome Pathways [AOPs]); 2) measurement of p-chem properties; 3) evaluation of the life cycle and biokinetics of the MN; 4) selection of appropriate context-specific toxicity tests (e.g. p-chem properties, use, release, potential exposure scenarios); and 5) application of a weight of evidence (WoE) analysis ('evidence based approach'), that considers and evaluates (based on the type and quality of data), all the results from the previous steps to reach a conclusion about the MN in question. There are available IATAs *for* skin irritation and corrosion (OECD, 2014c), human health risks of MN in food (Cockburn et al., 2012), medical applications (Dusinska et al., 2013), ecological assessments (Oomen et al., 2014; OECD, 2016e).
Dose-metrics	For NMs the actual metric that best describes the observed effects in test organisms or environmental fate and distribution may not be mass-based

Concept	*Definition/Description/Explanation*
	(usually expressed as mg/kg body weight or mg/L or mg/m^3). There are indications that the number of nanoparticles, the surface area, or another metric can be, in some cases, a better metric to relate dose to the observed fate, behaviour, and effects of a specific nanomaterial (Aitken et al., 2011; Hankin et al., 2011; OECD, 2012a). The most appropriate dose metrics should be evaluated on a case-by-case basis or for defined groups of nanomaterials. Altering the metrics for hazard would require also using consistent units for exposure and risk estimation. This includes classification and labelling, where most hazards of a substance are related to mass concentration. Consideration must be given to the choice(s) of metric(s) for definition of the limit value, to exposure measurement methods and detection limits, and to reliable methods for conversion if required (OECD, 2009a; OECD, 2012a).
(Eco)Toxicity (ENMs)	Property of a material conferred by a constituent or a substructure that is responsible for the harmful effects of that material on the environment and/or human health (e.g. an impurity, an aspect ratio, a surface charge etc.) (OECD, 2012a).
Toxicokinetics	Quantitative biokinetics information may be highly relevant for hazard and rational risk assessment of nanomaterials, but more specific guidance on testing and interpretation / use is needed to put concepts into practice. Focus should be put on agglomeration and dissolution properties as well as selection of specific target tissues/organs of accumulation (fat, testis) (OECD, 2013). From the small fractions accumulated in secondary organs after short-term exposure no adverse health effects are likely. However, NM may trigger mediators in the primary organ released to blood; these mediators may well initiate adverse health effects elsewhere. During chronic exposure NM concentrations in secondary organs may accumulate high enough to trigger adverse health effects; unfortunately very few long-term exposure studies have been carried out to date (OECD, 2013; OECD, 2016b).
Lowest / No Observed Effects Concentration (LOAEC/NOAEC)	Definition shared with the standard approach to RA on chemicals. When working with MNs, the implications of interacting factors such as dispersion media and protocol and their unknown relevance are that a considerable measure of uncertainty is introduced to the calculation of a Lowest or No Observed Effects Concentration (LOAEC/NOAEC) when using some of the current standard tests employed for chemicals (OECD, 2012a).
Generic Occupational Exposure Limits (OELs)	Currently, there are no specific regulatory OELs established for manufactured nanoparticles. Nevertheless, Interim or draft OELs have been developed for certain nanomaterials, including “benchmark exposure levels” based on analogy with OELs for other particles or fibres (BSI, 2007), and separate OELs for titanium dioxide based on particle size (NIOSH, 2005; Dankovic et al., 2007). In addition, OELs have been proposed by some producers of multi-walled CNTs and an interim OEL for multi-walled CNTs has been issued (NIOSH, 2010). One approach proposed is to develop OELs based on categories of nanomaterials with similar properties and modes of action (Hansen et al., 2007; BSI, 2007; Schulte et al., 2010; OECD, 2012a).
Safety-by-design	This concept aims to promote the development and the use of safer nano-enabled product or service based on recommendations and on the results of previous alternative testing. Producers can start incorporating decision making feedback into material design, and should take a life-cycle perspective, incorporating current knowledge of how MNs behave in various matrices (OECD, 2016e).
Harmonization	Regulatory approaches for chemicals and manufactured nanomaterials differ within OECD countries. However, all are based on the basic risk assessment paradigm (hazard identification, hazard characterisation including dose-response assessment, exposure assessment, and risk characterisation) and the use of similar technical or scientific information to assess risks. With regard to

Concept	*Definition/Description/Explanation*
	defining, classifying and communicating hazard information, international cooperation has resulted in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), which provides common and consistent criteria replacing various different standards (UN, 2009) (OECD, 2012a). Harmonisation of standardised operation procedures (SOPs), including reference materials and appropriate controls, media and conditions, and technologies/equipment, as well as harmonisation of information reporting will result in faster, more consistent, and more reliable data generation. Wherever global harmonization is still not possible because of variability amongst MNs, production of SOPs for particular groups or categories of MNs is recommended (OECD, 2016e).
Validation	Official acceptance of new methods/approaches for testing of substances. In the context of MNs the reference documents are: 1) The Guidance Document on the Validation and International Acceptance of New or Updated Test Methods for Hazard Assessment (OECD, 2005) which provides detailed information on the conduction and validation of test methods for hazard assessment. The document provides detailed information on study design, different approaches to validation, important supporting documentation for new test submissions and general criteria for regulatory acceptance; 2) "Solna Principles", showing the fundamental approaches and considerations also relevant for the physico-chemical testing of nanomaterials; 3) Guiding principles for measurements and reporting for nanomaterials: physical chemical parameters (not necessarily for regulatory purposes but also for academic research) (OECD, 2019a).
Standardization	Literally, it refers to consistency between approaches, protocols, testing organisms, testing models, data interpretation (OECD, 2016c). Standardization related to the safety of ENM promotes the spread of good practices and the rationalization of the communication between the authorities and the industry, and other stakeholders. Standards in the field of nanotechnologies are considered as very important because they can facilitate the introduction of new products by bridging the gap between research and marketable products, and also because they will contribute to the public acceptance of these innovations. Different initiatives have been promoted by the European Standardization Bodies CEN / CENELEC for the elaboration of standardization activities to take into account the specific properties of nanotechnology and nanomaterials, and few proposals have been integrated in the joint report JRC-EASAC (Aebi et al., 2011).
Benchmarking	It means determining how MNs are similar to, or differ, from conventional chemicals. Some MNs have similar toxicity profiles to their bulk or ionic counterparts, and therefore may not require additional testing. Benchmarking NMs against conventional chemicals could expedite testing and help prioritisation. To achieve this, diagnostics must be developed to determine when MNs behave more like conventional chemicals (e.g. those that dissolve completely into metal ions) and when their nanoscale properties create novel behaviour. Work performed on fine or particulate matter may be applicable for MNs. Models used for other chemicals, such as pesticides, may be applicable to MNs (OECD, 2016e).
Grouping	Grouping may include formation of a "chemical category" or identification of (a) "chemical analogue(s)" (OECD, 2014a). The strategy may also be a quick method to prioritise MNs for further assessment, but the real efficacy of it has to be demonstrated (OECD, 2016e). The terms "category approach" and "analogue approach" are used to describe techniques for grouping of chemicals. Actual grouping should be defined on a case-by-case basis, using a practical approach based on what is known about/available for specific MNs. Current methods are based on heat and self-organising maps to group MNs by bioactivity, use of p-chem data to inform structure-property relationships

Concept	*Definition/Description/Explanation*
	(SPRs), structure-activity relationships (SARs), quantitative structure-activity relationships (QSARs) or Principal Component Analysis (PCA) (OECD, 2016d).
Equivalence	The equivalence of new and known nanomaterials is assessed on the basis of physical-chemical property criteria (OECD, 2016a).
QSARs	QSAR, computational approaches to advance our ability to categorize and group materials for decision making. These tools will allow prediction of toxicity and provide Weight-of-Evidence to validate other empirical data being generated (OECD, 2012a).
Read-across	The term "read-across" is reserved for a technique of filling data gaps in different approaches used for grouping of chemicals (OECD, 2016d). As an alternative to testing, toxicological properties of one substance may sometimes be inferred from those of a very similar substance or a group of related substances (see also OECD, 2007) For these reasons is possible to distinguish among four different approaches: • One-to-one (one analogue used to make an estimation for a single chemical); • Many-to-one (two or more analogues used to make an estimation for a single chemical); • One-to-many (one analogue used to make estimations for two or more chemicals); or • Many-to-many (two or more analogues used to make estimations for two or more chemicals). Read-across principle needs to be demonstrated for using with nanomaterials. Until such time this approach should be used with caution and accompanied with scientific rationale to justify its use (OECD, 2012a).
Multiple Path Particle Dosimetry Model (MPPD)	Model for particle deposition prediction after short-term exposure. Its use for the prediction of lung burden following repeated exposure to nanomaterials, should be done with great care due to issues with respect to clearance, solubility and possibly regional deposition of small heavy material (OECD, 2016b).
Effective concentration or dose	The effective concentration or dose resulting in an adverse biological response derived for a manufactured nanoparticle. From in laboratory studies the EC of NMs is likely to be influenced by the abiotic (and biotic) composition of the exposure pathway, variations which may influence nanoparticle structure, form and behaviour (OECD, 2012a). Notably, the effective dose of a nanomaterial may be smaller on a mass basis than the effective dose of larger particles of the same material if the mode of action relates to the total particles number or surface area (Handy et al., 2008).
High Throughput Screening (HTS)	This approach allows for the evaluation/investigation of a large number of unique MN formulations in a relatively rapid manner. HTS involve screening materials in batches, typically at rates of hundreds or thousands of readings per day and may take advantage of automated equipment, such as robotic liquid handling and/or computerised image capture (OECD, 2016e).
Prioritization	Strategy applied to perform an orderly and optimised risk assessment and/or risk management of chemicals/nanomaterials. Prioritisation schemes are driven by legislation (which varies country by country) and depend on the availability of physical-chemical properties of the NMs, data quality, and use of GLP for data production/collection. A detailed description of Prioritization process for chemicals and in particular for material at the nanoscale is reported in OECD (2019c).

3.5 Predictive risk assessment, management and governance

Concept	*Definition/Description/Explanation*
Weight of Evidence (WoE)	Weight of Evidence: (1) A process of making inferences from multiple pieces of evidence, adapted from the legal metaphor of the scales of justice. (2) The relative degree of support for a conclusion provided by evidence. The result of weighing the body of evidence (USEPA, 2016). Weight of Evidence: A process of weighted integration of lines of evidence to determine the relative support for hypotheses or answers to a question (SCHEER, 2018). Weight of Evidence refers to a positive expert opinion that considers available evidence from different independent sources and scientific viewpoints on a particular issue, coming to a considered view of the available, oftentimes conflicting data. It is preferred when every source does not provide sufficient information individually (OECD, 2014b), (OECD, 2019b).
Risk Characterization (ENMs)	Risk is the likelihood that harm will occur, taking into account wider considerations of exposure and uncertainty. Risk Characterization, in the context of Safety Assessment of ENMs, refers to the combination of qualitative and quantitative approaches to understand and describe the risk that a nanomaterial poses to human health or the environment. The various lines of evidence explored during the assessment are considered in a weight-of-evidence approach to evaluate the potential for harmful effects of a nanomaterial (OECD, 2012a).
Risk Assessment (general concept)	Requires information on both the potential hazard, the release of the substance into the environment and the likelihood and/or degree of resulting short- and long-term exposure (OECD, 2012a). *Structure* (Royal Society of Chemistry, 2013): a) Identification of the property or situation that could lead to harm (problem formulation); b) Identification of consequences if the hazard would occur (hazard identification); c) Estimation of the magnitude of the consequences, which can include consideration of the spatial and temporal scale and the time to onset of the consequences (release assessment); d) Estimation of the probability of the consequences, which considers the presence of the hazard, the probability of receptors being exposed to the hazard and the probability of harm resulting from exposure to the hazard (exposure assessment); e) Evaluating the significance of a risk, which is the product of the likelihood of the hazard being realized and of the severity of the consequences (risk characterization) (OECD, 2015b).
Environmental Risk Assessment	In environmental RA integration of hazard, release and exposure data can be carried out in three steps (Fairman et al., 1998): a) Effects Assessment by identification of the hazard based on the physico-chemical properties, ecotoxicity and intended use, and estimation of a Predicted No Effect Concentration (PNEC), from ecotoxicity data and the application of assessment factors; b) Exposure Assessment by calculation of a Predicted Environmental Concentration (PEC) derived using monitoring data, realistic worst cases scenarios and predictive modelling techniques taking into consideration

Concept	*Definition/Description/Explanation*
	control and mitigation measures, release, degradation, and transport and fate mechanisms; c) Risk Characterization by calculation of the PEC/PNEC ratio, which if larger than 1 indicates that the substance presents a risk to the environment (OECD, 2015b).
Human Risk Assessment	Human RA can be characterized through the integration of an exposure level with a no-effect level. Under the European REACH Regulation (European Commission, 2007) the exposure level is compared with the appropriate Derived No Effect Level (DNEL) obtained from toxicity data and the application of assessment factors. In this case the risk associated to a certain exposure scenario can be considered to be adequately controlled if exposure level does not exceed the appropriate DNEL (ECHA, 2011). If the DNEL cannot be calculated, a semi-quantitative or qualitative risk assessment can be performed: e.g. for non-threshold endpoints the Derived Minimal Effect Level (DMEL) may be useful (ECHA, 2011). In the US the exposure level is compared with the appropriate Reference Dose or Concentration (RfD, RfC) obtained from toxicity data and the application of assessment factors. In case the substance shows a non-threshold mode of action, the exposure level is integrated with the Slope Factor (SF), which indicates the increased risk from a lifetime exposure to a certain substance (USEPA, 2005; OECD, 2015b).
Nano-Specific Risk Assessment/ Methods	RA methodologies for the evaluation of conventional chemicals are widely used and are generally applicable to nanomaterials; nevertheless, specific aspects related to nanomaterials still require further development. This will remain so until there is sufficient scientific information available to characterize the harmful effects of nanomaterials on humans and the environment (SCENIHR, 2009). *Aim:* providing assistance on the essential issues which should be taken into account when dealing with nanomaterials, and offering support on the information required for performing risk assessment and risk management decisions. Some of these risk assessment methodologies were developed for specific manufactured nanomaterials because nanomaterial's risk is influenced by the relationship between toxicity and physical properties rather than chemical properties alone (OECD, 2015b). Some available Methodologies are: Precautionary Matrix for Synthetic Nanomaterials[2] Nano Risk Framework[3] Risk Assessment of manufactured nanomaterials[4] NanoCommission Assessment Tool[5] Precautionary Strategies for Managing Nanomaterials[6]

[2] See https://www.bag.admin.ch/bag/en/home/gesund-leben/umwelt-und gesundheit/chemikalien/nanotechnologie.html

[3] See www.nanoriskframework.com

[4] See https://en.aist-riss.jp/research/assessment/

[5] See www.bmu.de/en/service/publications/downloads/details/artikel/responsible-use-of-nanotechnologies-1

[6] See Precautionary Strategies for Managing Nanomaterials – Summary for Policy Makers. 2011. German advisory Council on the Environment (SRU).
http://www.umweltrat.de/SharedDocs/Downloads/EN/02_Special_Reports/2011_09_Precautionary_Strategies_for_managing_Nanomaterials_KFE.pdf?__blob=publicationFile

Concept	Definition/Description/Explanation
	SafeNano Scientific Services[7]
Risk Management	It's the result of the integration between RA and socio-political needs (Linkov et al., 2011). Combination of measures (Reduction, Mitigation, Refinement) that should be undertaken to ensure the substance can continue to be used safely in commerce, but under specific restrictions (OECD, 2012a). *OECD Recommendation of the Council on the Safety Testing and Assessment of Manufactured Nanomaterials*: The Recommendation states that nanomaterials be regulated using the existing regulatory chemical framework, but regulations might need to be adapted to account for nanomaterials' unique properties. The regulatory frame defines the (un)acceptable risk level and takes into consideration the following factors: identification, physical-chemical properties, fate in the environment, human health effects, environmental effects, exposure pathways to humans and the environment, as well as others (OECD/LEGAL/0400; OECD, 2016a).
OSIRIS	Optimized Strategies for Risk Assessment of Industrial Chemicals. It is the web-tool for ITS (Integrated Testing Strategies) developed during the homonymous project. It allows following the developed decision trees online. It is supported by the local QSAR and database system. It belongs to the tools developed with the aim to significantly increase the use of non-testing information for regulatory decision-making[8].
Monitoring and review	Refers to evaluation, review and continuous improvement of the risk governance process (Isigonis et al., 2019).
Risk Governance for ENMs	Evolving concept based on few pillars born from previous European initiatives in the same context (Nano Risk Framework[9], ISO 31000:2018 Risk Management framework for new technologies (ISO 31000), Risk Governance Framework of IRGC for NMs[10] (Renn et al., 2011), the iNTeg-Risk project Emerging Risk Management Framework (ERMF) NanoTEST (Ovanovic et al., 2013), MARINA[11], SUN[12], NANoREG[13], NANoREG2[14], caLIBRAte[15] and NanoMILE[16]). Some of the main elements are 'risk pre-assessment', 'risk concern/safety assessment', 'risk evaluation', 'risk management and decision making', complemented by continuous supporting processes such as 'risk communication' and 'monitoring', as identified by Isigonis et al. (2020).
SoS (System of Systems)	Online hub project for risk governance of nanotechnologies (Isigonis et al., 2019).

[7] See www.safenano.org

[8] See www.ufz.de/osiris/

[9] See www.nanoriskframework.com

[10] See https://doi.org/10.5075/EPFL-IRGC-233739

[11] MARINA FP7 Project [Online], https://cordis.europa.eu/project/id/263215 (accessed: May 2020)

[12] SUN FP7 Project [Online], http://www.sun-fp7.eu/ (accessed: May 2020)

[13] NANoREG FP7 Project [Online], http://www.nanoreg.eu/ (accessed: May 2020)

[14] NANoREG2 H2020 Project [Online], http://www.nanoreg2.eu/ (accessed: May 2020)

[15] caLIBRAte H2020 Project [Online], http://www.nanocalibrate.eu (accessed: May 2020)

[16] NanoMILE FP7 Project [Online], http://www.nanomile.eu-vri.eu (accessed: May 2020)

Concept	Definition/Description/Explanation
Mental modelling theory	The International Risk Governance Council (IRGC) references the mental models approach implicitly in a white paper on nanotechnology risk assessment (IRGC, 2006) and in its overall risk governance framework (IRGC, 2005; Malsch et al., 2015).

4. Life Cycle Sustainability issues in Nanotechnology and Nanofabrication

Apart from ensuring that new technologies such as nanotechnologies are "safe", investors, policymakers, funding agencies or consumers are pushing towards sustainable innovation and solutions. Although the meaning of sustainability can be fuzzy and can differ among different actors, it usually implies a certain long-term balance between human civilization and the biosphere capacity. In order to understand the damages due to environmental pollution and energy and material scarcity, life-cycle-oriented approaches were developed in the 1960s in collaboration between universities and industry. From a material and energy accounting along the life cycle of product systems, the translation into potential environmental impacts, such as climate change or eutrophication, was further investigated, which has been officially consolidated into the Life Cycle Assessment (LCA) methodology in 1990 (SETAC, 1991). With the identification of the three pillars of sustainable development, i.e. environment, economic and social (also considered in the concept of the "Triple bottom line" (Elkington, 1997)), LCA methodology was complemented in the 2000s by Life Cycle Costing (LCC) and Social Life Cycle Assessment (SLCA) to form the Life Cycle Sustainability Assessment (LCSA) of product systems (Kloepffer, 2008).

LCA practitioners started to study the environmental impacts of nano-enabled products in the beginning of the 2000s while the field is growing fast in the last years (particularly since 2014), recording more 150 LCA publications related to ENMs. While LCA methodology is flexible enough to be applied to any type of product or process, the assessment of ENMs or nano-enabled products raises specific challenges due to the lack of representative inventory data (low maturity, confidentiality issues) and of (eco)toxicity impact factors. LCC and SLCA methodologies are less mature than LCA (e.g. no methodological standards defined by ISO) and were rarely applied to ENMs.

The key aspects of lifecycle-based methodologies and approaches, their application to ENMs highlighting specific challenges, are detailed below.

4.1 Life Cycle Sustainability Assessment methodologies

The table below list common assessment methodologies based on life cycle perspective to evaluate one (e.g. carbon footprint) or several dimensions of sustainability (e.g. several environmental indicators in LCA or several sustainability pillars in LCSA).

Concept	Definition/Description/Explanation
Life Cycle Sustainability Assessment (LCSA)	Evaluation of all environmental, social and economic negative impacts and benefits in decision-making processes towards more sustainable products throughout their life cycle (UNEP-SETAC Life Cycle Initiative[17]).
Life Cycle Assessment (LCA)	Compilation and evaluation of the inputs, outputs and the potential environmental impacts of a product system throughout its life cycle. LCA was applied in more than hundred studies to assess the environmental impacts of nano-materials or nano-enabled products. Besides LCA can be applied to any type of product, the evaluation of ENMs raises some challenges related to the low maturity of related technologies (lack of representative data and uncertainty regarding upscaling effects or market deployment) and to the difficulty to model the (eco-)toxicity impacts of nanoparticles (lack of release

[17] See https://www.lifecycleinitiative.org/

Concept	Definition/Description/Explanation
	data, need to adapt fate and exposure modelling, reliability of testing procedures, etc.) (Cucurachi and Blanco Roch, 2019; Salieri et al., 2018; ISO 14044).
Environmental Life Cycle Costing (LCC)	Assessment of all costs associated with the life cycle of a product that are directly covered by one or more of the actors in the product life cycle with complementary inclusion of externalities that are anticipated to be internalised in the decision-relevant future. LCC has been rarely applied to ENMs. Economic performances of ENMs mostly focus on production costs, or market price, without considering a lifecycle perspective (Hunkeler et al., 2008).
Social Life Cycle Assessment (SLCA)	Assessment of the social and sociological aspects of products, their actual and potential positive as well as negative impacts along the life cycle. SLCA is an emerging field, which has been rarely applied to ENMs (UNEP-SETAC Life Cycle Initiative).
Environmentally extended input–output analysis (EEIO)	Linking environmental impacts to economic demand using economic input–output tables originally developed for macroeconomic systems analysis and planning by combining them with tables that describe how much direct environmental impacts each economic sector causes per economic output during a year of production. EEIO has been rarely applied to ENMs but can be useful to understand effects at sectorial level, in complementarity of LCA evaluation (e.g. as in Lloyd et al., 2005) (Hauschild et al., 2017).
Carbon footprint	Measure of the direct and indirect greenhouse gas (GHG) emissions associated with all activities in the product's life cycle. Products are both goods and services. Such a carbon footprint can be calculated by performing (according to international standards) an LCA that concentrates on GHG emissions that have an effect on climate change. Carbon footprint is the most widely used LCA indicator, also for ENMs assessment, while it is recommended to consider other effects to avoid any impact transfer (e.g. toxicity, resources scarcity) (UNEP-SETAC Life Cycle Initiative).
Water footprint assessment	Compilation and evaluation of the inputs, outputs and the potential environmental impacts related to water used or affected by a product, process or organization. Water footprint has been rarely applied to ENMs, but it is a growing field, especially since 2014 when it was formalized by ISO standards (ISO 14046).

4.2 Life Cycle Assessment methodology

Since LCA is the most common methodology applied to assess the sustainability of ENMs (even if it covers only environmental impacts), the different methodological steps of LCA, as defined by ISO 14040/44 (2006) are detailed below, highlighting the specific challenges for ENMs evaluation in each of them.

Concept	Definition/Description/Explanation
Goal and scope definition	This first step describes the objectives of the study (intended application, target audience) and sets the modelling framework. It includes the definition of the functional unit (used to compare equivalent systems), system boundaries (from the extraction of raw materials, to the product manufacturing, use and end-of-life), the chosen environmental indicators or other modelling assumptions. For the application of LCA to ENMs, the definition of functional unit is quite crucial to perform a comparative assessment with conventional products.

Concept	*Definition/Description/Explanation*
	Indeed, ENMs can add functions to a product (such as extension of life duration or self-cleaning), which should be considered. However, uncertainties remain regarding these performances due to the lack of feedback from product testing in real conditions.
Life cycle inventory	LCI reflects the input and output flows of the studied system. Foreground data are specific to the evaluated process and are usually collected from the producer or stakeholders (primary data). They can include direct exchanges with the environment (called elementary flows, e.g. emission of carbon dioxide into the air, of phosphate into the river, or extraction of hard coal), but also the use of transformed products (called technosphere flows, e.g. consumption of electricity). To reflect the upstream and downstream processes of these flows, background data are used, usually from LCI database, such as ecoinvent[18]. The main challenges regarding the LCI modelling of ENMs are the lack of representative data for the different life cycle stages of the product (low maturity, confidentiality issues) and the uncertain estimation of nanoparticles emissions along the lifecycle.
Life cycle impact assessment	LCIA aims at translating the LCI results (all environmental exchanges quantified for the studied system) into environmental impacts. To do so, elementary flows are classified into impact categories and characterized according to their effects. This is done *via* characterization factors (CFs) expressed according to the unit of reference for the environmental indicator. The multiplication of the LCI amount of an environmental flow (e.g. 10 kg of methane) and its CF (e.g. 30.5 kg CO_2-eq./kg methane) gives the LCIA result for this substance (305 kg CO_2-eq.), which is summed with the LCIA results of other contributing substances to obtain the LCIA score of the category. Environmental indicators include climate change, acidification, eutrophication, ecotoxicity, human toxicity, land use, mineral or fossil resource depletion or water scarcity. They can be grouped into endpoint indicators representing the final damage targets, i.e. human health (effects are translated into DALYs, i.e. Disability-Adjusted Life Years), ecosystem quality and resources depletion. Normalization (e.g. per person-equivalent) or weighting (according to cultural perspective) are additional optional steps of LCIA. For the application to ENMs, various works have been published to develop new CFs for the emissions of nanoparticles, based on the knowledge developed in risk assessment field (e.g. use of SimpleBox4Nano fate model, integration of MPPD model, application of EC50 values). This research work is still under development and no consensual CFs are available yet.
Results interpretation	The obtained LCA results can be analysed to identify the hotspot substances (gravity analysis) and processes (contribution analysis). The scenarios are compared, and sensitivity and uncertainty analyses can be performed to understand the influence of uncertain parameters/assumption on the results. The quality of the results should be checked, including data quality, completeness, and validation. Since LCA studies of ENMs include several uncertainties (e.g. regarding functional unit definition, inventory data, nanoparticles release and characterization), the use of sensitivity and uncertainty analyses is crucial to test the validity of the results and to refine modelling parameters.

[18] See https://www.ecoinvent.org/

4.3 Sustainability approaches related to life cycle thinking

Besides quantitative assessment methodologies described above, management/design approaches can be applied to support decision makers, also relying on life cycle perspective (which can be further supported by quantitative life cycle sustainability assessment).

Concept	*Definition/Description/Explanation*
Life Cycle Management	Business management approach that can be used by all types of business (and other organizations) in order to improve their sustainability performance. A method that can be used equally by both large and small firms, its purpose is to ensure more sustainable value chain management (UNEP-SETAC Life Cycle Initiative).
Eco-design	Integration of environmental aspects into product design with the aim of improving the environmental performance of the product throughout its whole life cycle (European Commission, 2009).
Circular economy	Model of production and consumption, which involves sharing, leasing, reusing, repairing, refurbishing and recycling existing materials and products as long as possible. In this way, the life cycle of products is extended (European Parliament[19]).
Cradle-to-cradle® design	Set of design principles which was developed in the 1990s by Prof. Dr. Michael Braungart, William McDonough and EPEA Hamburg. Cradle to Cradle® describes the safe and potentially infinite circulation of materials and nutrients in cycles. All constituents are chemically harmless and recyclable (EPEA[20]).

5. Ethics and Governance issues in Nanotechnology and Nanofabrication

Due to the generic and enabling nature of nanotechnology and nanofabrication, the diversity of their applications and of their possible impacts, they are *de facto* involved in a array of societal and ethical issues including as diverse concerns as privacy, autonomy, social divide, environmental justice, human enhancement, etc. The revolutionary promises and the problematic social expectations associated to them since the early stages of their development[21] have also importantly shaped the public debate on nanotechnologies, and even aroused a strong social opposition to them in some countries. Nanotechnology and nanofabrication are more generally concerned by complex governance and regulation issues due to the difficulty to promote both their economic development and the safety and sustainability of it.

In terms of ethical and societal impacts of nanotechnologies, important reference documents have been published all over the years (particularly in the 2000's) by diverse institutions worldwide[22]. A specialist journal is also devoted since 2007 to nano-ethics and to ethics of emerging technologies (*NanoEthics,* published by Springer[23]). Among the many questions related to the ethical governance of nanotechnology addressed both by scholars and by different kinds of stakeholders (including civil society), some recurrent are: Does the development of nanotechnology raise really *new* ethical issues? Even if the problems are new, do they really require the consideration of *new* ethical principles? Is nanotechnology a morally neutral instrument, or does it convey an intrinsic (and possibly problematic) morality? Who should be responsible for identifying and resolving ethical issues related to nanotechnology (scientists, ethicists, industrialists, consumers, experts, lay people, society in general, etc.)? Which ethical methods are to be used (in particular are anticipatory ethics or ongoing ethics the most adapted to the current innovation landscape)?[24].

[19] See https://www.europarl.europa.eu/news/en/headlines/economy/20151201STO05603/circular-economy-definition-importance-and-benefits

[20] See https://epea.com/en/about-us/cradle-to-cradle

[21] See for example the famous transhumanism-inspired report from Roco and Bainbridge (2003).

[22] Among others: The Royal Society & The Royal Academy of Engineering (2004); Commission de l'éthique de la science et de la technologie - Quebec (2006); EGE (2007); UNESCO (2007); CCNE (2007).

[23] See https://www.springer.com/journal/11569

[24] On these topics, see for example Doridot (2013).

More generally, governance of nanotechnology has evolved along the years from a simple risk governance (concerned with minimizing the risks of harmful effects) to a more inclusive innovation governance aiming at influencing technological choices. Modern societies are engaged in the quest of a kind of governance able to direct innovations towards socially agreed objectives, benefits and priorities (in terms of growth, employment, cohesion, protection, social justice, environmental sustainability, etc.); to be flexible, adaptable and dynamic; to anticipate future developments and to define the balance between risks and benefits; to ensure safety and sustainability; to organize a collective approach of the ethical stakes; to build trust, acceptance and support amongst all stakeholders, including the public (Murphy et al., 2016). Such a purpose is of course ambitious, and often hampered by the more traditional expression of private interests and conflicts of interest in the definition of the innovation strategies and the sharing of their added values. This goal is currently addressed in Europe through the Framework of Responsible Research and Innovation (RRI) (as presented below in this report), where the focus is in particular on an upstream engagement of a diversity of stakeholders. The future will show if RRI is able as such to overcome the inherent difficulties of modern technologies governance. For sure, more than ever, every stakeholder is nanotechnology and nanofabrication must be aware of the necessity to be able to discuss his ideas, practices and discoveries, to take time for public information, to think in terms of global benefit, to anticipate and to try to be clear about the blind spots of his innovations and the possible problems they can raise.

This chapter is organized in three main sections. The first section provides some general references and concepts useful for the understanding of ethics and governance issues in Nanotechnology and Nanofabrication. The second section describes some concepts and tools more specifically related to the governance issues in Nanotechnology and Nanofabrication. The third one describes some concepts and tools more specifically related to the ethical issues in Nanotechnology and Nanofabrication.

5.1 General references and concepts useful for the understanding of ethics and governance issues in Nanotechnology and Nanofabrication

Responsible Research & Innovation (RRI)

Responsible Research and Innovation (RRI) is the generic term used by the European Union's Framework Programmes to describe the kind of scientific research and technological development process they want to promote[25]. RRI is in particular a main focus of the Horizon 2020 European Commission's program. RRI has been described as a “transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the acceptability, sustainability and societal desirability of the innovation process and its marketable products, in order to allow a proper embedding of scientific and technological advances in society” (Von Schomberg, 2013). Additionally, RRI “refers to ways of proceeding in Research and Innovation that allow those who initiate and are involved in the process of research and innovation at an early stage to obtain relevant knowledge on the consequences of the outcomes of their actions and on the range of options open to them, to effectively evaluate both outcomes and options in terms of moral values […], and to use these considerations as functional requirements for the design and development of new researches, products and services” (Porcari & Mantovani, 2015, pp.7-8). RRI is thus including as broad principles anticipation, reflection, deliberation, responsiveness, precaution, vigilance, collective co-responsibility (Shelley-Egan et al., 2018, p.5). Von Schomberg & Hankins (2019) constitutes an important up-to-date resource and provides global perspectives on the development of RRI.

The societal and governance challenges around research and development in nanotechnology have played an important role in the emergence of the RRI concept. Today the RRI activities concerning nanotechnology can be described at different levels including the macro-level of national policies, the meso-levels of the shaping of funding programmes and of the soft regulation of industrial practices, and the micro-level of the direct integration of RRI into R&D practices of individual organizations (Shelley-Egan et al., 2018, pp.9-16).

Human Rights

Human rights are norms that aspire to protect all people everywhere from severe political, legal, and social abuses. Examples of human rights are the right to freedom of religion, the right to a fair trial

[25] See for example European Commission (2015).

when charged with a crime, the right not to be tortured, or the right to education[26]. The respect of the fundamental human rights (such as stated in the International Bill of Human Rights[27]) is part of most of the texts and declarations related to the responsible development of nanotechnologies (including the European Code of Conduct for Responsible Nanosciences and Nanotechnologies Research, which highlights the respect of the "fundamental rights" of individuals and society).

Sustainable Development Goals (SDGs)

The Sustainable Development Goals (SDGs) are a collection of seventeen global development goals set in 2015 by the United Nations General Assembly and intended to be achieved by the year 2030[28]. They include "No Poverty", "No Hunger", "Good Health", "Quality Education", "Gender Equality", "Climate Action", etc. Each of them has a list of targets which are measured with approved indicators. They succeeded in 2016 to the eight Millennium Development Goals (MDGs) that had been established following the Millennium Summit of the United Nations in 2000. Nanotechnology is frequently associated to the SDGs as a key technology able to contribute significantly to achieving these goals (with applications including improving energy production and storage, increasing agricultural productivity, improving diagnosis and treatment of diseases, etc.). As an example, the 2008 European Commission Code of Conduct for Responsible Nanosciences and Nanotechnologies Research was explicitly referring to the Millennium Development Goals. Nevertheless, some social and economic factors (such as intellectual properties issues, lack of skilled labor in developing countries, etc.) are also frequently highlighted as able to interfere with such a contribution to these goals (Guston, 2010b, p.782).

Precautionary Principle

The Precautionary Principle consists in adopting caution, pausing and review in the development of innovations and new technologies with potential for harm if extensive scientific knowledge and conclusive evidence on the matter are lacking or are not yet available (Read and O'Riordan, 2017). After having emerged in the 1970s and having been adopted by the Rio Declaration in 1992, the Precautionary Principle became also part of the European Commission recommendations around the 2000s (see for example European Commission, 2000). Despite being sometimes complex to be applied and subject to diverse criticisms, the Precautionary Principle is currently part of an increasing number of international treaties, declarations and juridical frameworks worldwide. Due to the state of the art in risks studies and toxicological research, the development of nanoparticles, nanomaterials and nanosystems is a typical case where the Precautionary Principle should be applied. Nevertheless, such a statement doesn't determine in itself the precautionary measures that should be taken (which could range from a hard moratorium - sometimes pleaded for by some civil society actors - to the progressing bridging of the gaps of knowledge) (Guston, 2010b, pp.624-626). "Precaution" is one of the fundamental principles promoted in the European Code of Conduct for Responsible Nanosciences and Nanotechnologies Research (European Commission, 2008).

Civil society and public engagement

In the general context of deficit of public trust concerning science and technology, and following a succession of well-known technological controversies, public engagement concerning nanotechnology has been seen widely from the beginning as a key enabler of the responsible development of it (Guston, 2010b, p.635). Public engagement is in particular today an important pillar of the European Responsible Research and Innovation (RRI) framework.

An upstream public engagement has been over the years tried out in a number of countries and in different ways, including in particular research-initiated dialogues, industry-initiated dialogues, CSO-initiated dialogues, debates and dialogue forums initiated by national governments (and by the European Commission in Europe), European projects initiatives, etc. As suggested by Porcari & Mantovani (2015, p.21), public engagement initiatives can be grouped in three categories: 'upstream' public engagement (policy level), 'midstream' engagement (R&D practices), 'downstream' strategies (communication, outreach, education and training). "Broadly speaking, the U.S. experience has been

[26] Stanford Encyclopedia of Philosophy (https://plato.stanford.edu/index.html)

[27] See for example: https://www.escr-net.org/resources/international-bill-human-rights

[28] See: https://www.un.org/sustainabledevelopment/sustainable-development-goals/

particularly focused on downstream strategies (in particular education on nanotech for young people). In Europe, the focus has been more on upstream and midstream engagement" (*Idem*). Laurent (2017) gives a thorough review of the democratic experiments devoted to the development of nanotechnology in Europe and the United States.

In Europe, different generations of deliberative processes on Nanotechnology have been deployed since 2004, involving different kinds of stakeholders, pursuing different purposes, and meeting different kinds of results (European Commission, 2010). Scholars have pointed how diverse social and political contexts can shape the societal engagement processes, and how diverse are the impacts of these events on the decision-making processes (Krabbenborg and Henk, 2015). In France, the National Public Debate on Nanotechnology (2009-2010) encountered a radical critique of technological development (see for example Doridot, 2016).

"Inclusiveness" is one of the fundamental principles promoted in the European Code of Conduct for Responsible Nanosciences and Nanotechnologies Research. OECD (2012c) provides some guidelines for consideration when planning and evaluating public engagement activities in nanotechnology. It deserves to be reminded that stakeholder engagement does not necessarily deliver consensus, even if expected. Scholars call today for a complete reinvention of public engagement practices in more experimental, reflexive, anticipatory, and responsible ways (Chilvers & Kearnes, 2020).

Codes of Conduct

A code of conduct is a set of agreed and established norms of behavior, rules and responsibilities, common values, ethical standards or proper practices applicable to an individual, a group or an organization[29]. A code of conduct is most of the time not legally binding.

As an important reference document, the 2008 European Commission Code of Conduct for Responsible Nanosciences and Nanotechnologies Research (European Commission, 2018) provides a significant list of basic principles related to nanosciences and nanotechnologies: Meaning; Sustainability; Precaution; Inclusiveness; Excellence; Innovation; Accountability (responsibility).

There exist also some industry-initiated codes of conduct devoted to nanomaterials[30].

5.2 Concepts and tools related to Governance issues in Nanotechnology and Nanofabrication

Governance, Anticipatory Governance, Participatory Governance

The concept of Governance is a contemporary result of attempts to understand how the state and non-governmental actors (such as civil servants, representatives of scientific communities, business, industry, civil society, etc.) interact in politics. In the worldwide context of deflation of the traditional attributions and powers of the states, and of blurring of traditional demarcations between state, society, and markets, governance denotes the process of defining collective goals and making political priorities by a large number of different players (Guston, 2010a, pp.291-296).

As an enabling technology, nanotechnology crosses many areas, disciplines and responsibilities. Nanotechnology governance is multilevel and incorporates many actors: supranational arenas (like EU or OECD), national governments, nanotechnology companies, research institutes, funding councils, financial institutions, etc. (Idem, p.294). Nanotechnology governance is facing different and sometimes competing issues: enabling technology to foster innovation and economic growth, and guaranteeing the responsible development of nanotechnologies (in terms of EHS, sustainability, social and ethical issues, etc.) Important nanotechnology governance questions concern funding, knowledge transfer, regulation (in particular soft regulation), but also transparency, responsibility, and trust. Early public engagement, participatory and deliberative democracy are important features of nanotechnology governance.

[29] Adapted from SATORI (2017a) and from Rodrigues and Broadhead (2018).

[30] As an example, see the BASF Code of conduct for nanomaterials: https://www.basf.com/global/en/who-we-are/sustainability/we-produce-safely-and-efficiently/resources-and-ecosystems/nanotechnology/safety/code-of-conduct.html.

Anticipatory governance of nanotechnology aims at introducing more adaptive, flexible and forward-looking modalities in nanotechnology governance (such as soft law approaches in terms of regulation, including codes of conduct, voluntary reporting schemes, etc.).

Participatory governance focuses on involving more deeply the citizens in the processes of governance.

The need for new forms of governance adapted to the complexity of nanotechnology is often recognized (Idem, p.296).

EHS and ELSI/ELSA approaches

Environment (E), health (H) and safety (S) (together EHS) is the discipline that studies and implements practical aspects of environmental protection and safety at work. EHS management approaches have been first introduced by the chemical industry in the 1980's as a reaction to several catastrophic accidents. Today EHS guidelines cover categories specific to each industry as well as those that are general to most industry sectors. Regulatory requirements play an important role in EHS discipline[31].

The acronyms ELSI (in the United States) and ELSA (in Europe) refer to research activities that anticipate and address ethical, legal and social implications (ELSI) or aspects (ELSA) of emerging sciences. The term appeared in the 1980's, in particular in the context of the development of the Human Genome Project, and various ELSI or ELSA programs have been developed worldwide since. The ELSI or ELSA approach has been endorsed by academics studying the societal impact of science and technology, but has also been criticized for its reductionism[32].

In terms of nanotechnology and nanofabrication, EHS issues include the potential risks to human health and the environment from the manufacture and use of nanoparticles and nanomaterials, the lack of knowledge about what these potential risks might be and how to deal with them, the lack of data which makes it difficult for manufacturers, suppliers and users to have effective risk management processes and to comply with their regulatory duties, and the need of all stakeholders (regulators, companies, etc.) to start to address these potential risks (Murphy et al., 2016, p.38). In terms of nanotechnology and nanofabrication, ELSI and ELSA issues include risk management and regulatory issues, public perception and public engagement, commercialization and governance issues, and other application specific issues such as ethical ones (Idem, pp.38-39).

Technology Assessment, Constructive Technology Assessment, Participatory Technology Assessment

Quoting the words of Armin Grunwald, Technology Assessment (TA) is a "widely used designation of systematic approaches and methods to scientifically investigate the conditions for and the consequences of technology, and to denote their societal evaluation. This name covers activities such as forecasting technology impacts and side effects, assessment and communication of risk, promotion of innovation, social shaping of technology, improving the legitimacy of decisions on technology, mediating in technological conflicts, and observing sustainability" (Guston, 2010b, p.751). TA as such arose in the 1960s and 1970s, and gathered progressively an international community, a part of which working as experts in institutions explicitly devoted to TA (in particular in the Health field). Traditional TA has been often criticized for coming too late, and for failing in matching the dynamics of Science and Technology, and in shaping their development in society (Guston, 2010a, p.18).

Constructive Technology Assessment (CTA) was developed in the Netherlands in the 1980s. It aims at influencing the design and implementation of technological innovations mostly by facilitating dialogue and interactions among various actors (and, for example, by involving users of technology in the development and innovation process). It has been applied to a broad variety of technologies, including nanotechnology.

Participatory Technology Assessment (pTA) focuses on the methodical involvement of various kinds of social actors as assessors and discussants (including civil society organizations, representatives of the state systems, individual stakeholders and citizens (lay persons), scientists, technical experts, etc.).

The development of TA and of its diverse schools have also corresponded to a direct engagement of social science researchers in the enterprise of innovation itself (Guston, 2010a, p.18).

[31] Adapted from diverse sources, including Wikipedia, The Free Encyclopedia, Article "EHS".

[32] Adapted from diverse sources, including Wikipedia, The Free Encyclopedia, Article "ELSI/ELSA".

5.3 Concepts and tools related to Ethical issues in Nanotechnology and Nanofabrication

Ethics/Morality/Deontology

Ethics is the branch of philosophy concerned with the evaluation of human conduct. It can also refer to the moral principles that govern a person's behavior or the conducting of an activity. One usually distinguishes between descriptive ethics, normative ethics, applied ethics, meta-ethics, etc.

Morality is a more or less implicit system of beliefs and values concerning how people should behave, accepted by a particular person or group. Morality usually comes with social sanctions, but not legal ones.

Deontology is the study of ethical concepts dealing with permissibility and impermissibility (duties, rights, obligations, etc.). It can also refer to an explicit code of obligations and prohibitions valid for a profession (physicians, lawyers, journalists, etc.).

Ethical traditional theories (Virtue ethics, Consequentialism, Utilitarianism, Deontological ethics, Kantian deontologism, Care ethics)

(Some of the descriptions below are adapted from Perry Glossary[33] and from Stanford Encyclopedia of Philosophy[34]).

Virtue ethics is an approach to ethical theory frequently traced to Aristotle. It is centered on the daily practice of the virtues, and the achievement of the person in choosing a good life which leads to personal happiness ('Eudaimonia' or highest good, supposed to be the ultimate goal in life and the only end in itself). Virtue is defined as a happy medium between two extremes. According to the philosophical and theological tradition, the four cardinal virtues are prudence (phronesis), justice, courage, and temperance.

Consequentialism is the theory according to which human conduct is right or wrong because of its tendency to produce favorable or unfavorable consequences. Deontological ethics rejects consequentialism, and holds that the rightness of action depends at least in part on things other than the goodness of relevant consequences. Utilitarianism is the consequentialist theory usually connected to the doctrines of Bentham and Mill, which took the goodness of consequences to be measured by their effect on the happiness or welfare of sentient creatures. At the opposite, according to Kantian deontologism, the principle under which an act is done determines whether it is right or wrong. For Kant the only moral action is the one dictated by the "categorical imperative", of which one version is: "Act only according to that maxim whereby you can at the same time will that it become a universal law".

The Ethics of Care is a more contemporary theory criticizing the application in ethics of generalized standards, and emphasizing rather questions like "how to respond?", with an insistence on interpersonal relationship, care and benevolence as important concerns.

Traditional ethical theories distinctions can have direct applications related to the development of nanotechnology, for example in governance matters. As an example, a strict utilitarian-based risk analysis can lead to support nanoproducts due to their benefit for society, even if they are not labeled as containing nanomaterials, and if there are no requirements for their premarket testing or for any review of them. But a dose of deontological thought added to such a situation can lead to consider also the ethical principle of Autonomy (without labeling, a consumer cannot choose to accept or reject nanomaterials) (Guston, 2010a, p.219).

Ethical preferences and choices must then be considered and questioned in diverse situations opened by the development of nanotechnology and nanofabrication.

Ethical Values and Principles

Ethical values and principles are basically the norms of ethical evaluation. They can be proscriptive and prescriptive beliefs which affect ethical behavior of a person or a group and are the basis of their

[33] Perry Glossary of philosophical terms, Oxford University Press (Online). See: https://global.oup.com/us/companion.websites/9780199812998/studentresources/pdf/perry_glossary.pdf.

[34] See: https://plato.stanford.edu/index.html

intentional activities[35]. One distinguishes sometimes between *values* as internal and subjective to a person and *principles* as more objective and shared by a group, but this distinction is not universally accepted. Ethical principles are sometimes organized in a system or in a code of conduct.

It's impossible to give an exhaustive list of ethical values and principles, and it's impossible to give a definitive definition of them. Even if the ethical principles are sometimes thought precisely as transcending the contextual differences, values and principles can in practice vary across different contexts, cultures and issues. Some often promoted or quoted ethical values and principles in the field of development of technology are or have been: Privacy; Dignity; Autonomy; Responsibility; Accountability; Integrity; Excellence; Solidarity; Efficiency; Freedom; Justice (in particular Distributive Justice); Equality; Fairness; Safety; Security; Sustainability; Transparency; Precaution; Inclusiveness; Benevolence, Non-maleficence, Non-discrimination; Informed consent; Right to know; Data protection; etc. Autonomy, justice, beneficence and non-maleficence are known as being the principles of bioethics (non-maleficence being the principle of 'above all, do no harm' as stated in the Hippocratic Oath) (Beauchamp and Childress, 2019). Informed consent is an important principle in medicine and in research involving human persons (as the conduct of clinical trials on medicinal products for human use).

The list of ethical principles provided by the CEN reference document on Ethics assessment for research and innovation (SATORI, 2017a) is in some ways relevant for dealing with nanotechnology and nanofabrication. The document distinguishes between general ethical principles relevant for all fields of research and innovation (Research integrity; Social responsibility; Protection of and respect for human research participants; Protection of and respect for animals used in research; Protection and management of data; Dissemination of research results; Protection of researchers and the research environment; Avoidance of and openness about potential conflicts of interest) and additional field-specific ethical principles particularly relevant for the different fields of research and innovation (concerning the engineering sciences and technological innovations field, the principles mentioned are these ones: Avoidance of public health and safety risks; Social responsibility; Avoidance of risks to the environment; Protection of animals; Protection of researchers and the research environment; Dual use of engineering research and technology; Avoidance of misuse of research and materials and results) (SATORI, 2017a, p.20).

Ethical issues in Nanotechnology and Nanofabrication

It is commonly agreed that the different sectors of application or the different disciplines of nanotechnology and nanofabrication can give raise to a diversity of ethical issues. From a thematic point of view, R. Sandler proposed to distinguish between social context issues, contested moral issues, technoculture issues, form of life issues and transformational issues (Guston, 2010b, pp.477-480). In terms of applications, more or less thorough reviews of the issues can be found in the literature (see for example ANSES (2014, pp.102-106) and Porcari & Mantovani (2015, pp.15-19)). It's usual to distinguish the issues associated to the use of nanotechnologies and nanomaterials in consumer products and for industrial use (issues of transparency and responsibility in particular); those associated to the energy and environmental applications of nanotechnologies and nanomaterials (assessment of real sustainability, societal challenges, etc.); those associated to the ICT applications enabled by nanotechnology in particular for safety and security (personal data protection, privacy, confidentiality, traceability; discriminations, digital divide, dual use, novel applications exploring man-machine interactions, etc.); the numerous ones associated to nanomedicine (informed consent, increased personal responsibility related to novel diagnostic tools, intellectual property rights and patenting policy, emerging issues such as autonomous and making decisions nanorobots in the human body, special ethical issues related to non therapeutic human enhancement, etc.); those associated to the military applications of nanotechnology and nanomaterials (loss of control, dual use such as surveillance of civilian populations, breaking of the world nuclear deterrence, care for animals, etc.).

Social divide in general refers to the gaps and inequalities created in a society by the development and use of a new technology. *Digital divide* in general refers to the uneven distribution in the access to, the use of, or the impact of Information and Communication Technologies (ICT) between distinct social or geographic groups[36]. *Dual use* in general refers to a research or innovation developed for benefit but

[35] Adapted from diverse sources, including Wikipedia, The Free Encyclopedia, Article "Value (ethics)".

[36] Adapted from diverse sources, including Wikipedia, The Free Encyclopedia, Article "Digital divide".

misapplied to do harm (typically for a military, terrorist, criminal or malicious purpose)[37]. Due to the broadness and genericity of nanotechnology industry, dual use is relevant in many areas of it (electronics, structural materials, energy storage and conversion, biochemical sensors, robots, small satellites and launchers, body implants, etc.), in particular in those cases where nano-devices can be produced in small and cheap installations (Guston, 2010a, p.172).

Ethical Impact Assessment (EIA)

As summarized in SATORI (2017a, p.7), Ethical Impact Assessment (EIA) is a "process of judging the ethical impacts of research and innovation activities, outcomes and technologies, that incorporates both the means for a contextual identification and evaluation of these ethical impacts, and the development of a set of guidelines or recommendations for remedial actions aimed at mitigating ethical risks and enhancing ethical benefits, typically in consultation with stakeholders". EIA is also "the overall process of ethical impact anticipation, determination and evaluation", and "a means of actioning social responsibility in research and innovation" (*Idem*). Diverse methods of EIA related to emerging technologies have been developed for many years. These methods "differ from one another in terms of their objective and focus, the kind of data they analyze, the stakeholders that participate in the process, and the innovation they bring to the fore" (Reijers et al., 2016, p.58). Thorough reviews of them can be found in Reijers et al. (2016, pp.58-65) and in Rodrigues & Broadhead (2018, pp.15-18). The CEN Reference document SATORI (2017b) provides researchers and organizations with guidance on ethical impact assessment, and delivers a comprehensive (and fully "nano-relevant") approach for ethically assessing the actual and potential mid- and long-term impacts of research and innovation on society.

Foresight Analysis

Foresight is an "action-oriented, multidisciplinary and participatory strategic intelligence exercise focused on alternative futures" (SATORI, 2017b, p.9). "Foresight methods aim to produce knowledge interactively between multiple stakeholders with specific interests and differing perspectives towards the topic under exploration, to facilitate interaction between the relevant stakeholders, and to catalyze the desired developments and strategies" (Idem). "A foresight analysis involves approaches to help "look forward" into the (near, medium or longer-term) future of science, technology, the economy and society. The ultimate objective is to identify areas of strategic research and the emerging technologies likely to be particularly salient (and/or beneficial and/or harmful; depending on the reason for the analysis) in any one aspect of society (social, health, economic areas etc…)" (Rodrigues & Broadhead, 2018, p.9).

Different foresight methods have been developed for many years and can be used in order to anticipate ethical impacts of emerging technologies (some of them being already integrated in the methods for ethical impact assessment). An thorough review of them (including "Trends", "Weak signals", "Wildcards", "Horizon and technology scanning", "Vision building", "Scenarios", "Delphi", "Road mapping", "Futures Wheel") can be found in Reijers et al. (2016, pp.65-79).

Value Sensitive Design

Value-sensitive design (VSD) is a concept that promotes the upstream consideration of human preferences in terms of principles, values and moral standards in the development of technology. Assuming the non moral neutrality of technology, VSD aims at providing technologists, designers, business leaders and others involved in developing new technologies with strategies for identifying and incorporating human values into the design and development processes. The values to be taken in consideration are those of both direct and indirect stakeholders. An example of Value Sensitive Design is Privacy by Design.

As summarized by R. Sandler, "value-sensitive design involves identifying value judgments in engineering design processes, cultivating space within the engineering process for reflective discourse on those judgments, and developing the capacity for productive reflective discourse". Sandler (2012) provides an interesting framework for the application of VSD to nanotechnology.

[37] Adapted from SATORI (2017a).

6. Integrated Tools for Decision-Making Support in Nanotechnology and Nanofabrication

Some of the sustainability approaches and indicators detailed above can be combined and integrated to support decision makers for the development and deployment of nanotechnologies.

Concept	*Definition/Description/Explanation*
Multi-Criteria Decision Analysis (MCDA)	MCDA represents a top-down decision making approach. It refers to a collection of methods used to impart structure to decision processes that invoke incommensurate or irreducible objectives, multiple and divergent stakeholders, and (in many cases) incomplete information (Linkov et al., 2011). MCDA refers to a group of methods used to improve understanding of a complicated or uncertain decision-making process. Generally, the MCDA process consists of four steps: (1) structuring the problem by identifying criteria through stakeholders elicitation and assessment of the different criteria that are relevant to the given decision; (2) eliciting the parameters of the model, such as alternatives, decision criteria, relative weights, and preference thresholds, and evaluating the performance of each alternative on each criterion; (3) applying a decision algorithm that ranks each alternative from most to least preferred; (4) interpreting results of the model and reiterating the process from step 1 or 2 by re-evaluating the model. An advantage of the methodology is the ability to link performance information to decision criteria allowing for visualisation of the trade-offs involved in the decision-making process (Linkov et al., 2011).
Triple Bottom Line (TBL)	It is a form of accountability that envisions the environment, society, and economy as three pillars of sustainability (Elkington et al., 1997).
Value of Information (VoI) analysis	Method to prioritize further research. To aid this decision-making task, Linkov et al. (2011) proposed an iterative top–down decision framework in which technical data to assess the risk is combined with decision criteria and value judgments expressed by stakeholders through a stochastic multi-criteria decision model, and then used value of information (VoI) analysis to prioritize further research that will reduce the most uncertainty. Thus, uncertainty does not disrupt the decision-making process; instead, uncertainty is harnessed to improve the quality of decisions as new data become available (Linkov et al., 2014).
Causal diagram assessment	Smita et al. (2012) developed and applied the “causal diagram assessment” method for nanoparticles, to handle the complex interactions of MNs with environmental processes. It is a non-quantitative methodology that uses available scientific information to describe the interactions, but it also requires extensive knowledge to be applied and interpreted (Isigonis et al., 2019).
SUNDS	SUNDS (for Sustainable Nanotechnologies Project Decision Support System) is a cloud-based decision support system (DSS) to assess the sustainability of nanoproducts including technical performances, environmental and human health risks, life cycle environmental, economic and social impacts, aggregated into MCDA tool (Malsch et al., 2018).
LICARA nanoscan	Screening tool included in SUNDS, specially dedicated to support SMEs for assessing benefits and risks associated with new of existing nanoproducts (Van Harmelen et al., 2016).
Ashby material selection strategy	Enhance Ashby material selection strategy with risk data, prices and cumulative energy demand. This method was applied by Falinski et al. (2018) to support the selection and design of nanomaterials.
Analytical hierarchy process	Weights of criteria based on a scale from 1 to 9, judged by experts. This weighting scheme was used in combination with LCA and process integration techniques to support the development of chitosan-based TiO2 nanotubes (Ong et al., 2020).

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