A common European approach to the regulatory testing of nanomaterials

NANoREG

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Proposal to monitor innovations in new nanomaterials and their applications

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1 Description of task

The D6.1 is part of the Task 6.1, linking risk analysis into innovation, and it developed by 3 partners (i.e. RIVM, ER, GenOk). According to amended DoA, the Task is focused on two actions, covering the issues '*being prepared*' and '*turning risks into business opportunities*' [innovation for risk research]. The products of this task are:

A. a proposal to monitor innovations applying new MNMs and their applications (horizon scanning) and how to gain insight at the impact of these innovations on risk analysis in a regulatory context.

B. a first structural screening on possibilities to address the research bottlenecks raised by EHS researchers, but also raised by the Value Chain Case Studies initiated by the regulation authorities and industry (Task 1).

The deliverable D6.1 is the result of action A, and it is the finalization of the activity started with MS22. In detail, action A requires the following steps:

• Identify techniques of horizon scanning relevant for innovation towards the application of existing and the next generations of MNMs with regard to their expected domains of application;

• Identify relevant domains for applying these techniques and generate examples of horizon scanning. The DoA suggest that collaborations with new or running initiatives on horizon scanning should be exploited, but during the duration of the project, no potential collaboration was identified;

• EHS problem formulation is the initial, qualitative phase of risk assessment that defines who might be at risk, what they may be at risk from (identifying potential impacts), and which specific areas (e.g., health via specific exposure routes) should be assessed in the subsequent phase of quantitative risk assessment. This problem formulation will be an important first step in this task;

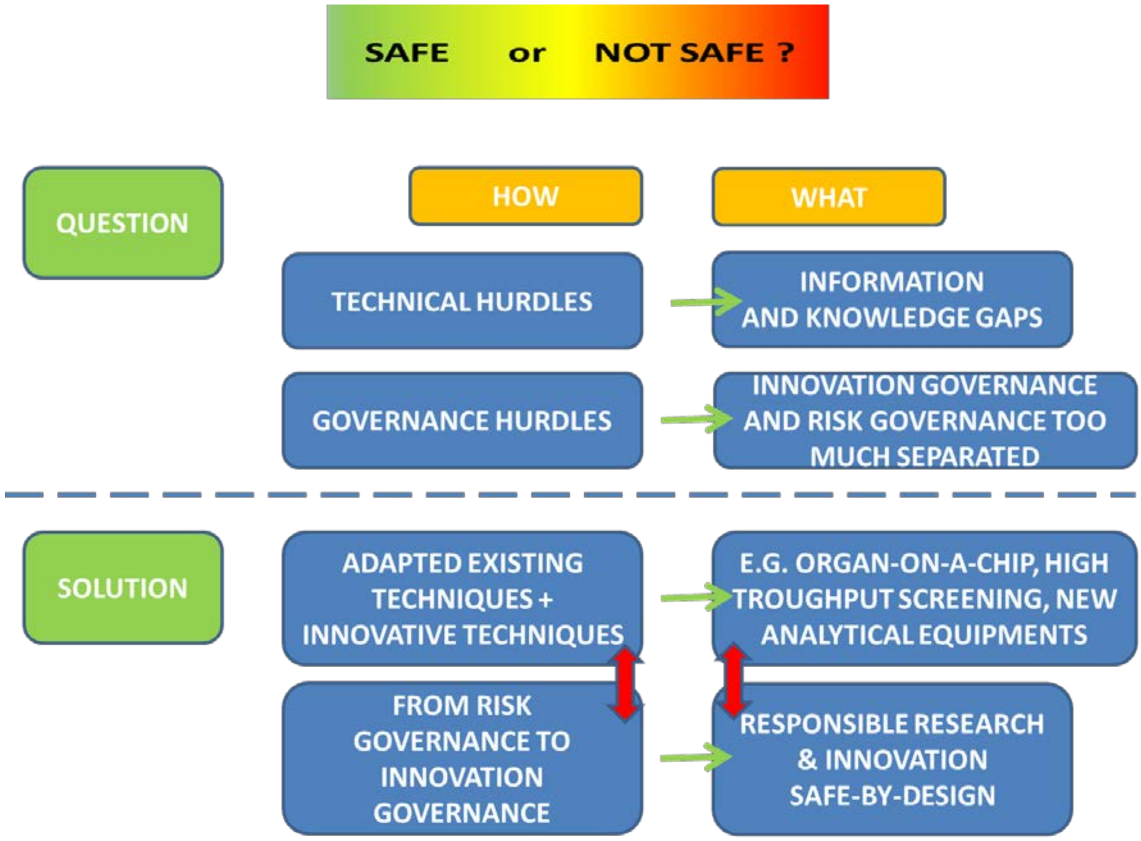
• Discuss potential impact on risk analysis for these foreseen innovations;

• Develop a methodology to identify and minimize human and environmental health risk uncertainties by combining structural horizon scanning actions with effective risk problem formulation at various stages of the innovation process;

Action B was developed in D6.2, already accepted by MC. The steps included in this action per DoA are:

• Define the most pivotal omissions in available techniques to address questions regarding risk analysis, both based on literature (e.g. RiPon reports) and other already ongoing initiatives, as well as on the knowledge gained within Value Chain Case Studies (Task 1.6 in WP1);
• Exploration of potential tools to address these omissions;
• In parallel, the wide spectrum of competences represented in this task would also provide an insight on the future development of the different fields of research which are integrated within the risk analysis. Another objective of this task will be then to evaluate how such techniques may impact, also from a commercial point of view, turning identified risks into business opportunities with respect to cost saving and shorter time to market.
This, in details, can be achieved by:
• A different approach is the evaluation of the potential benefits from sensing platforms developed within lab-on-a-chip devices for different purposes (biomarker detection from cancer research, detection of metals into contaminated soils, etc.) for their application into hazard assessment and environmental exposure;
• Learning from the experience in other fields of study on the use of innovative methods not yet applied in risk analysis, and liaising with industries producing the next generation of equipment, to understand if these methods can provide relevant information to engineered nanomaterials risk assessment;
• Critically evaluating the possibility to translate these methods into a regulatory perspective and as valuable instruments for the NANoREG tool box.

For details about how these points were addressed, please refer to the deliverable D6.2. The following picture shows the overall conceptual approach of the activity carried out in D6.2 and Action B.



The evaluation of nanotechnology innovation safety is blocked by two main hurdles: technical issues and governance issues. Technical issues are linked to capability to generate and collect robust safety data for application in a regulatory context. This field, while still under development, shows some progress in terms of physicochemical characterization, as well as exposure and hazard testing. The development of new techniques, improvement of existing methods, validation and standardization activities, testing strategies including in silico methods, and standardization of databases, all contribute to the achievement of a solid base for regulatory safety assessment. Examples proposed in D6.2 are organ-on-chip, high throughput and high content screening, and new analytical techniques.

The governance hurdles are much more complex to tackle, involving a structured dialogue between science, decision makers, industry, and society. Up to now, what the nanosafety community is doing is risk governance rather than innovation governance and there is still a significant gap among the two. Governance, as defined from its etymology, is closer to the process of steering a ship addressing all the known and unknown factors, whether they can be changed or not by the pilot, to reach the foreseen destination. Governance includes four parts: Information, Communication, Feedback, and Progress assessment towards the goals. The goal for the next few years is to build a risk governance, by developing Information collection and assessment (e.g. database, methods), Communication of the information among stakeholders (e.g. trusted environments), Collecting feedback from the present, the past and the future (e.g. safe-by-design), and finally developing ways to monitor Progress toward the established goals.

The road from risk to innovation governance entails a broadening of scope, from “simple” safe products, to defining a destination for EU society and policies to achieve the desired future. Approaches such as Responsible Research and Innovation, placed in a structured context, may allow the definition and implementation of such a policy orientation of the EU.

2 Description of work & main achievements

2.1 Summary

D6.1 content is focused on proposing a methodology to monitor innovation and evaluate the potential adverse impacts of nanomaterials and their likely applications in a time horizon included in the next 5 to 10 years, thought the combination of Horizon Scanning (HS) and Screening Risk Assessment (SRA).

The first part of the deliverable introduces the background information, providing the context in which the proposed methodology is developed. Background includes a description of the governance of innovation, in general and for nanotechnology, in connection with adaptive governance. Responsible Research and Innovation (RRI) approach is the way that the EU has chosen to implement the innovation governance, and thus some space is devoted to the discussion of the link between the concepts of RRI and foresight approach and Horizon Scanning as one of the foresight tools to be applied in the D6.1 goal context. Since NANoREG is a regulatory-oriented project, the link between innovation governance, foresight, and HS is explored in some detail. In this part, also the current approach toward nanosafety and screening risk assessment as a tool are reported, justifying the use of a screening risk assessment approach for nanotechnology foresight on the basis of scientific criteria. The last section of the background deals with the description of contribution of D6.1 to NANoREG regulatory questions and to WP6 in general.

The second part of the deliverable is focused on the description of the proposed foresight approach (NANoREG foresight system) for the innovation monitoring and assessment. The proposed system includes a Horizon Scanning phase, which aims at identifying Target Applications to be assessed in the Screening Risk Assessment phase. The Target Applications are selected following a process, which should involve stakeholders from the beginning, in order to properly address the stakeholder (e.g. regulators, decision makers) requirements. This step is discussed in what is called "general concern", which is the main input of the approach. In the "general concern" step, it is decided if the concern is for a nanomaterial, if it is for an industrial sector, or for a specific application. For each one of this entry, a procedure is established to achieve a list of target applications, which are described in terms of technical, safety, and regulatory knowledge to be used as input for the SRA. The SRA is carried out in steps, from the definition of the nanomaterial life cycle in relation to the specific application, to the preliminary risk assessment and finally to the final report, discussing the identified risk hypotheses.

The picture below shows the overall framework, with the different phases, input, outputs, and the role of different stakeholders and experts.

The NANoREG foresight system (from now on: system) aims at making a qualitative screening risk assessment (SRA) of practical applications, or group of applications based on use profile (e.g. certain pesticides are used more or less in the same way), for a specific nanomaterial. The SRA is performed on the whole life cycle of the nanomaterial, for all potential targets (workers, environment, consumers, indirect through environment), on the basis of available data and information, also on similar products or same products not nano enabled. The assessment of entire industrial sectors or value chains is out of the scope of the system. It cannot allow, if not indirectly, to plan a research strategy at national level. Also, the system does not include socio-economic assessment, which is considered part of the regulators and decision makers role, which is exerted implicitly at the beginning of the procedure in the dialogue with stakeholders, and explicitly after the results of this proposal are delivered. Finally, it does not include a regulatory Risk Assessment. The NANoREG foresight system is mainly thought for regulators; therefore, regulators requirements are foremost in the development of the proposal. However, industry can benefit from the use of the system to assess the potential uses of the application and the related risks, and focus the development of a specific use, or think about risk mitigation measures. Also financial institution can identify prospective applications to fund on the basis for the SRA result. The expected results of the system are the assessment of negative impacts of relevant (for the specific stakeholder) innovations, the comparison of the available data for SRA and the data gaps in terms of safety assessment, and the regulatory implications in terms of current regulation and needed regulation/guidelines.

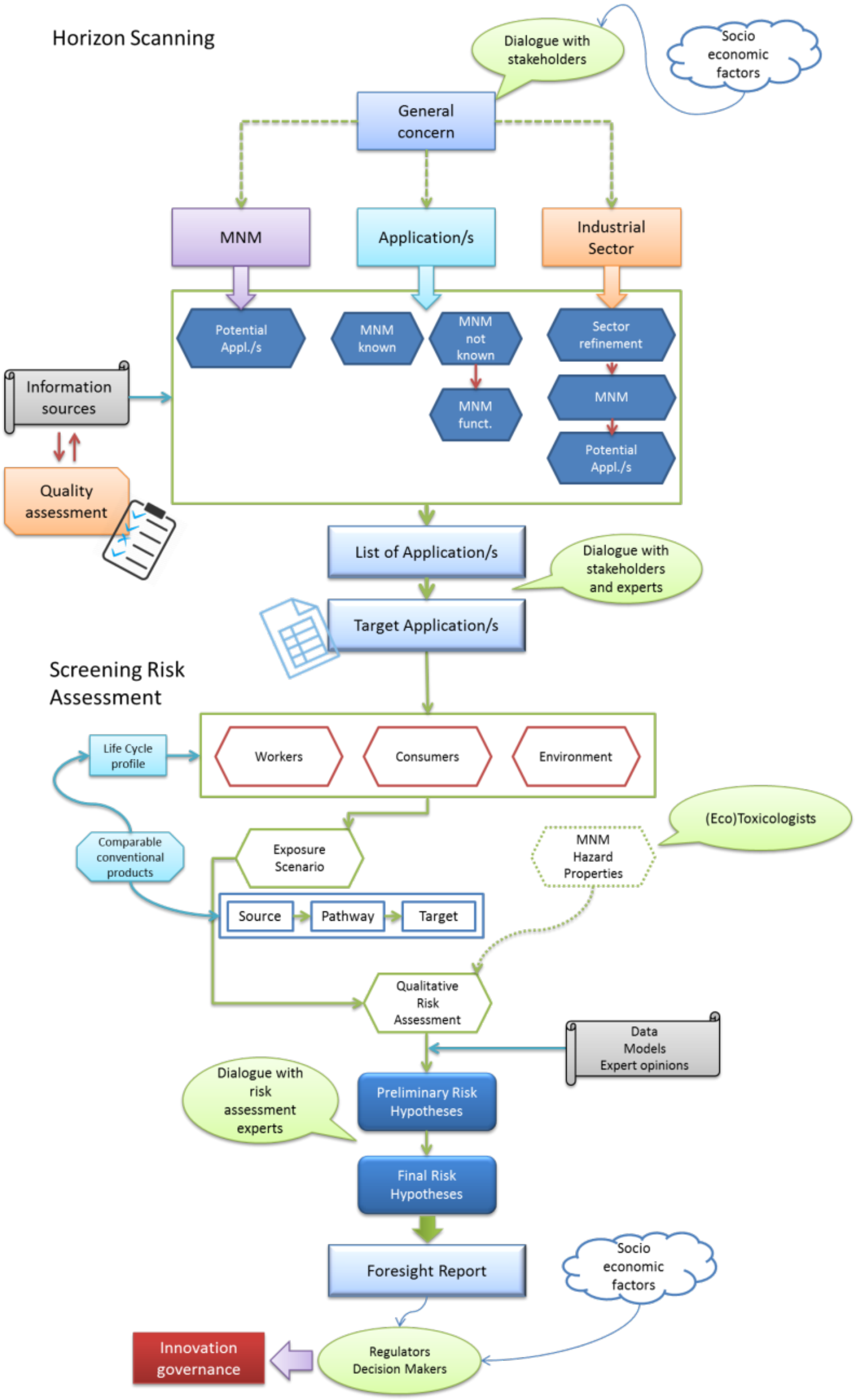
The application of the system has to be supported by tools and by expert judgement. Since the system is going to be applied on materials and applications for which nearly no data are available, tools that can be used are for example exposure estimation models, grouping approaches, read across schemes. Expert opinions are needed in different phases of the procedure, to collect and interpret information and conclusions.

The NANoREG foresight system for innovation monitoring is illustrated with a practical example in the third section of the deliverable. The case study is a specific application of graphene to water filtration membranes, selected because it is at low TRL stage with a time to market around 5 years, it has a high beneficial potential for the society and the environment, and there is in general a huge investment of resources on graphene. At the same time, the water filtration membrane can cause direct and indirect exposure to graphene for workers, consumers and environment.

The result of the exercise shows that a foresight exercise requires the input of experts in different fields, from production processes to toxicity assessment, to regulators, to allow for inference from the scarcely available data along the life cycle of the nanomaterial. The NANoREG foresight system proposal can allow identifying hot spots and critical aspects of the risk hypotheses linking sources, exposure pathways, targets, and expected effects. On this basis it is possible to identify in a general way the data needs to address the main obstacles for a proactive evaluation of the potential adverse impacts of a nanomaterial innovative application.

The proposed system is linked to the Safe by Design approach, because it can be useful in the starting phases of the innovation process, where ideas are tested. The system may support Safe by Design by providing a picture of most promising applications in terms of safety, described following a risk assessment approach.

A proposed acronym for the NANoREG foresight system is ForeNANo.



2.2 Background

The background of the proposed method for monitoring the innovation includes an analysis of the different parts of the methodology itself.

The first topic is the link between Horizon Scanning (HS) and the Adaptive Governance concept. Since the goal of the task is to promote a proactive approach toward nanosafety, complementing the work done in the Task 6.2 with the Safe-by-Design approach development, in order to keep the same approach followed in D6.2 and in D6.4 and 6.5, the link between Responsible Research and Innovation (RRI), Adaptive Governance, and HS as a tool to implement these two concepts is discussed. Following this discussion, a short introduction to the Horizon Scanning concept, approaches, and applications to nanotechnology, and links between HS and regulators in terms of regulatory requirements is reported.

The second topic is the approach to risk assessment of nanomaterials. This topic is the subject of several recent research projects, and consequent publications, describing in essence the lack of robust data to perform a full risk assessment as foreseen e.g. by REACH, but also the need to start assessing the risk posed by nanomaterials to health and the environment, by using semi-qualitative approaches. The scope of this paragraph is to present these approaches, and to describe the general framework that can be used to perform the Screening Risk Assessment in the NANoREG foresight system. The framework will be kept general to allow the analysis for different regulatory contexts, besides REACH. HS outcomes can be included in different sectors of nanomaterials application, and while REACH is the main chemicals horizontal legislation, other vertical legislations provide specifics for defined consumer products safety assessment. For example, while exposure is mostly relevant for food safety as highlighted by the EFSA risk assessment guideline (EFSA, 2011), it is just an element in REACH where hazard is mandatory and necessary also to comply with the Classification, Labelling and Packaging Regulation.

Finally, the link to NANoREG questions of D6.1, as well as the link of D6.1 to Safe-by-Design are discussed, to frame the deliverable into the overall project as well as in the WP6 activity.

2.2.1 Looking for future nanotechnology applications: tools for innovation governance

2.2.2 Governance of Innovation

Governance of innovation is a concept that can be defined as a system that allows the development, steering and control of research, development, and application, of a technology. Integrated into the governance is the compliance to regulations requirements, but also the adoption of voluntary approaches and standards, such as certification schemes and industry responsibility initiatives (Read et al., 2016). Talking about safety, one of the key purposes of governance is to act as a safeguard in society and to provide opportunity for the improvement in health and well-being, and to ensure human rights and the environment are protected.

Innovation governance has several problems to overcome, observed along the years in different cases such as Genetically Modified Organisms. These problems are applicable to governance of nanotechnology in terms of items to consider and errors to avoid. A recent report by the European Commission (European Commission, 2013) discussed some issues in the governance of innovation, showing some cases of contested as well as successful innovations. The report is framed in the context of the Grand Challenges, societal and ethical, to be addressed in and through the research and innovation. Some examples are food safety, climate change, ageing population. Examples of innovations that failed to produce a benefit due to societal contrast include: i) GMO; ii) Stem Cell Research; iii) Biotechnology; iv) Carbon Capture and Storage technology. All these technologies have in common the fact that:

1. Their technical and economic feasibility has been demonstrated;
2. There is an apparent sound ethical reason to adopt or implement them;
3. Large investments have been undertaken;
4. They have been contested and frustrated on the basis of security, social or ethical concerns.

Despite the huge investment, contested innovation fails when ethical and societal factors are not taken into account at the beginning of their development. The existence of an apparent sound ethical reason is not enough, it has to be proved and supported. The risks, concerns and uncertainties of new technologies oftentimes are considered only at a late stage, often just before market introduction and their implications are not made to bear upon the design and development of new research, products and services.

The innovation system often fails to anticipate future societal needs, especially when it comes to problems in the distant future of future generations. Similarly, the research system as a whole fails to sufficiently consider such ethical and societal aspects.

There are different actors affected by failure to innovate: 1) research funders, public and private, which do not get the full benefit from their investments due to lack of consideration for societal needs; 2) the institutions carrying out the innovation, which are not fully competitive on the global scale because they are producing research that is not fully in line with societal needs; 3) European citizens that are not fully involved in the R&I process due to lack of funding, processes for inclusion, and public awareness; 4) regulators and legislators, that need to translate the societal needs into law, and the law into actual responsible actions and policies.

The key feature of all these issues is that it is more profitable for everybody to include ethical and societal considerations in the research and innovation process early on. One of the emerging pathways to achieve this result in the governance of new technologies is the cooperation between different actors. As discussed more extensively later on, the engagement of the stakeholders in the governance of nanotechnology is seen as a central effort to achieve a sustainable and beneficial development of nanotech innovation. To support this dialogue, increase of public awareness and availability of timely information about the potential impacts of innovations is essential. Most often, the contested reaction by the public is the result of incomplete or skewed information provided by interested parties. In the next paragraph some of these issues will be discussed more in detail, since they provide the framework for the application of the proposed foresight methodology within the Safe by Design and Safe Innovation. Foresight can be a potent tool to inform in advance all involved stakeholders, and to support the effective dialogue between different actors. In this meaning, the proposed methodology is framed by the responsible and inclusive innovation concept.

2.2.2.1 Cooperation in Governance Innovation

As seen earlier, the need for cooperation between different organizations and individuals at different levels of responsibility, from the international organization to the single consumer is seen as a key feature for the proper governance of new technology. This complex network includes politicians, regulators, industry/ business, nongovernmental organizations (NGOs), media, and the public, all with each own motivation and values. This broad range of actors makes the development of a effective governance a challenge, which is made even more difficult by the differences in rules and regulations between countries. An example is the relationship between the EU and USA. Even if a dialogue is underway to commonly define a governance for nanotechnology allowing safe products to reach the market (for example also within the NANoREG framework), the regulatory approach between the two sides of the Atlantic ocean is the opposite. In EU there is often a pre-authorization by regulators, based on safety concerns and a dossier assessment, which supports the companies in their responsibility to market safe products. Even if there is no positive list, as it is the case for medical devices, there is the control of a certification body (Notified Body) that acts as intermediary to assess and certify the safety of the product. Therefore, it may be concluded that given the obvious responsibility of the companies to put safe product on the market, there is a preliminary public control. In the USA the responsibility to put safe products on the market falls mostly on the producers, which can put on the market products relying only on a notification, without the need of a pre-authorization from Authorities. There is a recent change in this policy, promoted by national agencies such as FDA and EPA, requiring a notification of a complete dossier before marketing a product, especially if it makes use of nanomaterials, but the position and regulatory culture is not completely in favour of this approach.

In addition to regulatory differences among countries, the innovation scope and political reasons are often complicated, plural, and dynamic. Behind a simple goal such as greener energy, there are a lot of different motivations (Owen et al., 2013). Besides this "purpose" problem, the uncertainty concerning the interactions and unintended impacts of innovation is high, linked to what is called by Thompson (Thompson, 1980) "the problem of many hands" which is reflecting the irresponsibility as an emerging property of innovation systems, where many actors interacts at different levels. The interactions and implications can become evident later on, only when the use scenario is evident, presenting then a complete different set of societal and safety issues.

Te Kulve (Te Kulve, 2014), in the context of the anticipatory market introduction of nanotechnology-based drug delivery systems, highlighted few issues related to the problem of many hands, and the different motivations and perspectives of the actors involved in the innovation. Te Kulve identified two categories of actors, the enactors and the comparative selectors. On one hand, the enactors are identifying themselves with the new technology, considering it the best and only solution to the problem at hand, with a bias toward the positive effect of the technology. On the other hand, the comparative selectors view the new technology only as one of the many possible solutions, thus selecting the choices taking into account also risks and costs. Balancing these dynamics is one of the goals of the governance of innovation.

To address the dynamics of actors interactions, different governance systems have emerged along time, based on a range of principles going from the solely enforcement of regulations and hard law to only soft tools and voluntary-based approaches, passing through a mixture of the two.

Landeweerd and his co-authors (Landeweerd et al., 2015) published a paper about the different governance styles developed and adopted in Europe in the last 30 years. They identified three different approaches of governance:

1. Technocratic style
2. Applied ethics style
3. Public participation style

The technocratic style is characterized by the participation of only scientists and legislators to the decision process. The decision is delegated from citizen to parliament, which establishes the regulatory framework, which in turn delegates the decision on risk to the scientific and technical community. In this scheme the society opinions are never considered: the moral and ethical considerations that could come from the citizens are considered as biased and irrational, while science is considered neutral and well informed. This top-down approach is still used in some instances in EU law, as for example in the medical sector. This approach caused some problems, as it happened in the past for the GMOs. The science defined the risk as acceptable, but the reaction of the public opinion to the un-naturalness of the “created” plants, and to the patenting issues, made the diffusion of the new technology practically impossible. Another problem of this approach is that the societal needs are considered only at the end of the innovation process, and thus there is the need to consider wider societal implications earlier on the process.

The applied ethics style was a development of the technocratic style, by adding an ethical dimension to the scientific and regulatory sides of innovation. Ethical committees were formed to advice about moral issues, but also mediating between the public and the decision makers in terms of transparency, democracy and trust of the debate. This approach is often summarized as Ethical, legal and social aspects (ELSA), and a report detailing its application on nanotechnology was published in 2008 by the European Commission (EC, 2008). The activities described in the report, both at national and European levels, included actions devoted to support dialogue on benefits and risks of nanotechnology involving great parts of the public and basing on informed judgement. ELSA of nanotechnology comprise a broad range of topics, such as privacy issues, acceptance, human health, access, liability, regulation and control. The approaches used in the ELSA framework included diffusion to a wide public, multipliers and specific target groups, as well as discussion fora between nanotechnology stakeholders, policy makers and the public. The drawbacks of this approach are linked to the potential of ethics-expertise to decide where research has to go, and what is better for the society as a whole. It is seen that this kind of decisions are political in nature, and that regulators use ethical experts to justify a decision that is already made (e.g. to reach a consensus), rather than to reach a decision among real possibilities.

The last style is the public participation approach, which emerged from the loss of trust in the government and science alone to represent and consider the societal impacts and public perception. This approach is a development of the ethical style, by putting into a formal system the dialogue with the public through a plethora of mechanisms, such as surveys, focus groups, public hearings, and citizen juries. This approach is seen as being able to address the threat of public adversity toward a new technology, a function that the technocratic style alone cannot perform. Criticisms of this style are: i) lack of efficacy and quality benchmarks; ii) democratic legitimacy of the public representation (a single NGO is not representing the whole society); iii) the framing of the public participation is often already established by other actors.

Focusing on the last point, framing a technology means describing it, defining how it is perceived and discussed. A technology can be “old” as a fundamental breakthrough, or as a simple improvement of an existing technology, and these different views of the same object are serving different agendas. The existence of different framings and the narrowness of the framing are the main factor causing societal conflicts (Read et al., 2016). An example put forward by these authors concerns GMO, which is seen at the same time by different groups as an extension of plant breeding, and an un-natural way of tinkering with nature.

Governance of nanotechnology is evaluated by Read et al. (2016) by taking into account three aspects, i.e. 1) purpose of nanotech governance, 2) specific challenges, and 3) existing approaches.

The nanotechnology governance purpose is to shift the focus from risk management to innovation management, steering the technological choices toward societal benefits in general, including societal needs and perspectives. To do so, it is necessary to build trust between stakeholders through engagement. However, the dialogue may not necessarily lead to consensus. Another purpose is to favour the development of nanotechnology, transferring the benefits to the society, assuring at the same time sustainability and safety. In general, it is necessary to build a solid network of relationships among actors involved in the governance, with a high degree of cooperation, coordination, and communication. Overall, the nanotechnology governance asks for a “responsible development” enabling research while balancing negative consequences. Responsible development is complemented by an anticipatory approach, trying to identify risks and benefits early on in the innovation process.

Nanotechnology governance faces challenges, such as the time lag between nano-products marketing and regulatory development, as well as the diversity of nanomaterials coming to the market calling for new and flexible governing approaches. In addition, the uncertainties about nanomaterials EHS are not supporting a timely risk assessment, and even if stakeholder involvement may contribute to reduce the later emergence of risks, risk management actions may be necessary anyway should a risk occur. The difference of regulatory frameworks in different countries is also a challenge for effective governance. While international harmonization initiatives are ongoing, still a lot of work is necessary, especially concerning trade of goods and regulatory barriers. Another issue is the need to adopt and improve tools and programmes aimed at growing the public scientific awareness of nanotechnology, and to increase the public trust in industry. Finally, there is the need to increase the exchange of information about stakeholders, finding a way to communicate the uncertainties.

Read et al. (2016) concluded the paper by providing suggestions for clarifying the vision for optimal governance, testing the robustness of the identified optimal governance vision, and to implement the vision. These three steps are sequential. Some elements of this strategy are:

- mapping the future concerning what is the goals of stakeholders and what is the level of consensus needed;
- identifying the requirements of an adaptive governance approach;
- demonstrating the efficacy of hazard and risk pathways knowledge;
- identifying the actions and approaches needed to implement the vision;
- exploring generic scenarios for new technologies to test elements of the governance vision in more detail;
- identifying the action needed to achieve the vision, to be described in a roadmap supporting the identification of political, social and economic costs to achieve the desired result;
- developing initiatives to streamline the engagement of stakeholders in governance;
- developing good practice guidance for all stakeholders and actors.

Some of these actions are taken into account in this deliverable as elements supporting the development of the proposed foresight system. In particular: supporting the identification of requirements for the identification of early impact assessment of nanotechnology applications, demonstrating the efficacy of risk pathway in an adaptive governance approach, and the exploration of generic scenarios for new technologies to test elements of the approach in more detail.

2.2.2.2 Responsible Research and Innovation

One of the approaches that is mentioned by many authors in relation to the implementation of an adaptive governance of innovation in Europe is the Responsible Research and Innovation (RRI). RRI is the overall approach in EU to address the issue of innovation governance. RRI is discussed in details in D6.2, therefore it is not the scope of this deliverable to discuss in detail the link between RRI and nanotechnology. In this context, RRI is discussed in relation to the application of Horizon Scanning in Technology Assessment, and its role for the implementation of RRI as an adaptive governance approach.

DG-Research published in 2013 a report titled “Options for Strengthening Responsible Research and Innovation” (EC, 2013). The need to write such a report was born from the existence of a number of initiatives that have been undertaken by EU Member States and the European Commission to achieve better alignment of research an and innovation with societal needs.

In that report, Responsible Research and Innovation (RRI) is defined as:

“the comprehensive approach of proceeding in research and innovation in ways that allow all stakeholders that are involved in the processes of research and innovation at an early stage (A) to obtain relevant knowledge on the consequences of the outcomes of their actions and on the range of options open to them and (B) to effectively evaluate both outcomes and options in terms of societal needs and moral values and (C) to use these considerations (under A and B) as functional requirements for design and development of new research, products and services".

One of the six actions points that are included in the RRI framework according to DG-RTD (EC, 2012) is Governance, which is the umbrella under which all aspects of RRI are covered, and that is expressed as *the responsibility of policy makers to prevent harmful and unethical developments in research and innovation*.

The other 5 actions are:

- Engagement: all actors, such as industry, researchers, policy makers, and civil society, need to be engaged in the innovation process, to address ethical and societal needs, and to support mutual learning. This kind of dialogue is necessary for safe innovation and early-on identification of risks and uncertainties;
- Gender equality: women need to be included in the innovation process, especially in the research phase, and not only as consumers;
- Science education: a sustainable research and innovation process needs a knowledge-based society, where there is a higher number of researchers, but also the wider public need to have the basic knowledge to responsibly use the technological innovation, and to formulate their needs in relation to the potential technological uses. This is a process, not a one-time initiative, thus entailing a change in the education system;
- Open access: in relation to education and engagement, it is important to give free access to data and information generated within publicly funded projects;
- Ethics: the last action is related to the common European values, and the research and innovation must respect the highest ethical standards. This will increase the chances of innovation acceptability by society as a whole.

The need for RRI arise from the experience of socially contested innovations, which while having technical and economic feasibility, an apparent sound ethical reason for their implementation, and a large committed investment, are nevertheless critically viewed by society, because ethical concerns and societal needs were not integrated in the innovation development. Among the contested innovations stands nanotechnology.

According to a research strategy by BAuA (2006), risks, uncertainties, and in general safety concerns of new technologies are addressed at a late stage, often just before market introduction, as required by authorization procedures in existing legislation (e.g. REACH). The lack of safety concerns from the early stages of the technology development can result in moratorium and loss of investments, as well as loss of potential benefits transfer to society and economy. RRI was developed to address these potential adverse outcomes.

von Schomberg (2013) described the vision behind the RRI approach. Von Schomberg highlighted two dimensions of RRI relevant for the topic discussed in this deliverable: the product dimension, linked to normative anchor points, and the procedure dimension.

Normative anchor point that is reflected in the product dimension is the mandatory compliance to the safety protection levels set by the EU. Besides the current risk assessment approach required by the EU for marketing approval, this compliance has to be seen in a more proactive and broader perspective, for example already at the proposed research stage, thus starting a dialogue with other stakeholders and controlling/financing bodies at earlier stages; ii) being sustainable; and iii) being socially desirable, e.g. contributing to the quality of life, to the gender equality, etc.

The process dimension relates to the development of a more responsive, adaptive, and integrated management of the innovation process. The process should be based on a multidisciplinary approach, involving stakeholders and leading to an inclusive innovation process: technical innovators take into account societal needs, while societal actors provide constructive inputs defining societally-desirable products.

This vision, translated in the RRI approach, can be implemented by using different tools. One of them is the **technology assessment and foresight**. Technology Assessment and Technology Foresight can reduce the cost of trial and error and take advantage of a societal learning process involving stakeholders and technical innovators. It creates a possibility for anticipatory governance, leading to products that are more societally robust. Horizon Scanning, as a part of the Technology Assessment, is a tool that can identify relevant (in terms of RRI) innovations and provide indications for the Foresight and anticipatory governance.

Concerning Horizon Scanning application to nanotechnology, in the context of Adaptive Governance and RRI, Schaper-Rinkel published in 2013 a review of how future-oriented technology assessment was applied in USA and in Germany (Schaper-Rinkel, 2013). In this paper, Technology Assessment is seen as governance tool, defining governance scope as anticipating and realizing future opportunities and identifying and reacting to potential risks, covering government and non-state actors, and is characterized by continuing interactions among network members. The different development of the adaptive governance between the two countries is an example about how the cultural and societal factors are relevant in determining the different ways the assessment of future impacts of novel technologies, and thus the RRI principles, are implemented in different contexts.

The USA approach to nanotechnology perspective was double-faced. On one hand, nanotechnology future was seen as molecular manufacturing (Drexler, 1987). In some ways it was a visionary approach to nanotechnology revolution. The second approach toward nanotechnology future is included in the work of the US National Nanotechnology Initiative (NNI). The first report addressing the nanotechnology vision for the future was a report called “Vision for Nanotechnology Research and Development in the Next Decade”, written with the contribution of government, agencies, industry and researchers. The focus of this effort was on the technological development, rather than on toxicology and social impacts. The view was that society has to adapt to technology to make its applications successful. For its part, the government's role is to improve and accelerate the uptake of technology through funding, education and awareness-raising.

Since 2004, after NNI establishment, the involvement of the public into the nanotechnology development, and the consideration of risks, ethical, and societal aspects, where introduced as part of the vision. The new vision report of 2010 was written engaging a wider expert base (i.e. from industry, NGOs, physical and biological sciences, engineering, medicine, social sciences, economics, and philosophy). In comparison with the first vision, the new report emphasized governance and concepts to involve and mobilize an increasing variety of stakeholders. The report stressed two main concepts: the concept of “anticipatory governance of nanotechnology”, meaning having participatory FTA be taken up into on-going sociotechnical processes to shape their eventual outcomes at all levels including to the point of the lab; and the concept of “real time technology assessment”, related to the integration of natural science and engineering investigations with social science and policy research from the outset. The two visions are summarized as Nano 1, i.e. dominated by a science-centric ecosystem, and Nano 2, i.e. participatory user-centric ecosystem. Nano 2 approach is addressed along the whole innovation chain, including R&D, innovation, infrastructures including education, and risk governance.

In Germany, nanotechnology as policy issues started to be discussed in early 1990 by the government. Early stages, focused on technological development, started in 1980s, with the work of the German Engineer Association, which produced the so called technology analyses, focused mainly on economic impacts. The goal of further studies carried out in earlier 1990s, was to “identify new and promising fields for research funding, to deliver a sound and broad information basis for funding decisions in these research fields and to prepare these issues for funding activities”. The goal of these activities was mainly to increase the competitiveness of specific industrial sectors with nanotechnology research. Other agencies, more concerned with the safety of nanotechnology applications, entered the field later on, when the funding strategies where already established. According to the author, “Germany lacks an organizational structure that brings together the expertise of the broad variety of ministries, agencies, stakeholders, and research to pool the distributed “strategic knowledge” gained from different activities such as technology intelligence, parliamentary technology assessment, technology monitoring and dialogue processes”.

The main conclusion of the review by Schaper-Rinkel (2013) was that “*looking ahead to the next decades, an inter-organizational governance framework is crucial to uptake the knowledge as well as the requirements derived from various stakeholders*”.

The development of a Foresight approach, integrated in the regulatory system, that can support decision making about safety of nanomaterials applications by integrating also the vision, requirements and goals of regulators, together with other initiatives, represents a step forward to this achievement.

2.2.3 Foresight

In order to frame and understand the scope of the NANoREG Foresight System and of the Horizon Scanning, a short introduction to the foresight concept is shown in the next paragraph. Importance is given to the overall concept of foresight, the scope of foresight, and the relationship of foresight with decision making and regulators.

2.2.3.1 Foresight concept

Foresight is defined as "The ability to take a forward view and use the insights gained in organisationally useful ways" (R.A. Slaughter, 1999). Foresight can also be defined as "early awareness and alert (EAA)" activity. Foresight goal is not to identify the future outcomes, but to identify a set of possible futures, the implications linked to the different scenarios, and then to support decision makers to act in order to achieve the preferred scenarios, or to avoid the unwanted outcomes. The information from the future is analysed on the basis of patterns learned from the past, to inform the present about the best strategic curse of action.

Foresight is a process, more than a collection of tools, and it aims to build in an organization the capacity to think strategically about the future, in a continuous way. Foresight is also different than strategic planning. Strategic planning (i.e. conventional planning) is based on the improvement of the current paradigm, rather than challenging it. It is a pragmatic approach in the sense that: it is linear (there is only one future from the today starting point) and therefore are not prepared to deal with the unexpected, it does not look into long term future (i.e. 15-20 years), it makes preferably use of quantitative data over qualitative information, and it rely only on experts, without including other stakeholders needs and views.

Foresight, in contrast, is based on three concepts:

- Seeing: to understand the relevant change (environmental scanning)
- Thinking: to identify potential impacts, devise alternative scenarios, and deciding on actions (strategic thinking)
- Doing: Implementing actions (strategic planning)

The foresight process can also be described as in the Figure 1, as reported by Voros J. (2003):

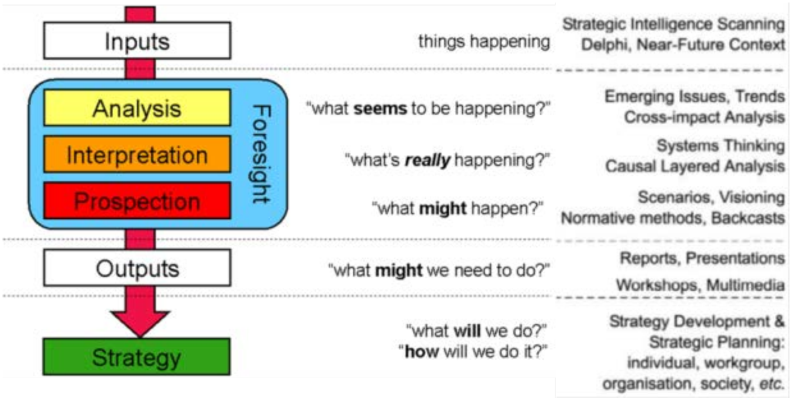


Figure 1. Foresight process described as questions, and examples of methods to carry out the different phases

The four phases are Inputs, Foresight work, Outputs, and Strategy.

1. Input is the gathering of the information, which is usually done via Environmental Scanning or Delphi methods.
2. The Foresight work consists of three steps: analysis is a first evaluation of emerging issues and trends, which are then fed to the interpretation step which system dynamics and drivers, to conclude with the prospection, which creates and examined the different future development, by using different methods. Prospection is the step where various views of alternative futures are examined or created. It is where scenario planning, "visioning" and so-called "normative" ("preferred" futures) methods are located in the broader foresight process.
3. Outputs of the Foresight approach are both tangible (reports, presentations) and intangible (change of perception and thinking generated by the process).
4. Finally, the Strategy is the phase where decision makers take the results of the foresight approach and use them to plan actions to achieve their goal, which can be a better innovation, or company reorganization, new guidelines needed, etc.

Since the goal of the foresight process is to identify/generate futures, it is important to identify which kind of futures are we talking about. Voros (2003) distinguished between 4 types of futures:

- Possible future: all futures that are imaginable and that may happen, even if far-fetched or only allowed by law of physics (what might happen);
- Plausible future: is the future that can happen on the basis of our current knowledge (what could happen);
- Probable future: it represents what's likely to happen, on the basis of the actual trend (what is likely to happen);
- Preferable future: it is about what we want to happen, and it is more normative in nature (what do we want to happen).

In relation to NANoREG and D6.1, the goal is to look at Probable futures, with a hint of Plausible futures. Therefore, in the NANoREG foresight system it is expected to look for both current knowledge and trends. This approach is of course based on the available information, which can come from different sources, as detailed in paragraph 2.2.4.2, and the degree of quantitative or qualitative assessment can be variable.

In the EFONET FP7 project, a report concerning the foresight relationship with decision makers was published in 2008 by IZT (Wehnert and Jörß, 2008). The scope of the report was to describe the foresight process application to energy sector decision makers, but in doing so, they also discussed issues that are valid for other decision makers, such as in nanotechnology. One of the first expectations of decision makers is that foresight will answer the question “how will the future looks like?”, but in reality foresight is exploring different futures, usually through scenario thinking, identifying probable futures, and sometimes likely and desirable futures. The second point is that there is no robust solution to all possible scenarios, but it is better to define options that allow the organization to react quickly to changes. Finally, it is very important to communicate to the stakeholders the limitations of information, especially if it is modelled.

The role of foresight, and in particular the output form that is expected, is another issue that depends upon the definition. Foresight can be either explorative or normative. In the first case, which is unusually applied by private companies, the goal is not to define how to achieve a desired goal, but to test strategies against different scenarios based on different socio-economic conditions. On the contrary, the normative foresight is based on the assumption that the strategy and the final goal is to change the socio-economic conditions through policy actions. Therefore, while the first type (explorative) does not require recommendations, the normative type often requires recommendations to be formulated. In case foresight is applied in regulatory context, a mix of exploratory and normative application is performed. For example, in NANoREG the question is known (e.g. how to support a sustainable development of nanotechnology? How to support regulators to use more effectively existing data and tools?).

The last point is the ownership of the foresight results, intended as the perceived importance and usefulness of the scenarios analysis. The issue is how to effectively communicate the results and in case the recommendations to the relevant group in order to have the largest possible impact. To involve decision makers in the foresight process, it is necessary to: i) engage high-level decision makers in the whole process, form the beginning (agenda definition) to the research questions and the output assessment; ii) involve decision makers in the scenario assessment, especially the baseline assumptions. The selection of the relevant stakeholders to engage however is complicated by the diversity of institutions with different goals.

2.2.3.2 Foresight tools

There are several tools that can be used to address the different stages, No single tool can be applied to all steps. Different authors tried to organize and describe in a systematic way the tools currently used. For example, Popper (2011), developed the Future Diamond, as shown in Figure 2.

Figure 2. Foresight Diamond organizing the foresight tools in four categories (creative, expert based, evidence based, interactive), and in three types (qualitative, quantitative, semi quantitative).

The different tools to perform Foresight are grouped in four categories, and in three types. The four categories are:

1. Creativity-based methods are based on imaginative thinking, both from single skilled individuals to group discussion. Tools are Science Fiction, Role play, Scenario development. Creativity is essential in foresight to discuss and identify non-linear future options and to devise innovative strategies;
2. Expert-based methods make use of highly specialized individuals, with knowledge in a particular area or subject. These methods are frequently used to provide advice and make recommendations. Methods used in this category are expert panels, MCDA, and Roadmapping. Experts can be very useful, providing a complete view of a topic and identifying missing pieces of information, or to give the right context and value to the information. However, relying only to expert advice is limiting since a lot of possible futures (especially the not so obvious from the business as usual point of view) could be missed.
3. Interaction-based methods concerns the engagement of stakeholders in the foresight process. This activity is essential to understand the needs of the recipient of the results, and thus to provide a useful recommendation. Also, early engagement can support the creation of the “future thinking” that is one of the main results of the foresight approach. However, it is often difficult to engage the right stakeholders, and to encourage the participation.
4. Evidence-based methods are tools that rely on information and data and their analysis. Evidence based approaches are useful to understand the state of the art of the development of the investigated topic, but also to infer the trends and patterns. These methods can also be used as a way to initiate creative thinking, and support interaction and stakeholder engagement. Horizon scanning is an evidence-base tool.

2.2.3.3 Foresight in relation to policy making

Foresight is usually applied in policy making, to support the decision makers in different ways. Foresight programs in EU, covering different fields, are often organized to analyse public policy issues, and give recommendations (see chapter …). However, as already reported earlier, the application of normative foresight has its own issues and characteristics, which are dictating the structure and goal of the foresight process and tools selection. One way to address this issue is to identify the functions of Foresight for policy making, and try to understand how foresight can meet the decision-makers expectations in one or more functions.

The FORLEARN project (http://forlearn.jrc.ec.europa.eu/guide/1_why-foresight/objectives.htm) produced a set of documents and knowledge about foresight methodologies and tools, in particular regarding the relationship with policy making. Da Costa et al. (2008) published a paper on this topic. The identified functions are:

- Informing policy: it means to provide decision makers with knowledge about changes, trends, risks and opportunities, costs and benefits, in a specific policy topic. This is considered one of the main function of foresight, which results in reports including priority lists, scenarios, critical technologies, recommendations for action plans;
- Facilitating policy implementation: this function is related to the change of the attitude of engaged actors toward the change of policy linked to the foresight process. The engagement of stakeholders in the policy making process can provide an agreed vision toward required policy changes, involving also actors usually outside the decision process. This network and increased understanding of the future promote the smoothness of new policy implementation;
- Embedding participation in policy making: this function is linked to the previous one, and it concerns the involvement of civil society in the decision making process, increasing the transparency and credibility of the policy actions;
- Supporting policy definition: this function is related to the conversion of information to policy actions, which is often not so simple because of the barrier in communication between the foresight experts and the political world. An added function can be performed by involving relevant policy makers early on in the process and options discussion, and by including some specific tools;
- Reconfiguring the policy system: Foresight exercise may highlight the inadequacy of current policies, both because of short-term/long-term perspectives and compartmentalized/multidisciplinary approaches. It can happen that the policy system is modified to better address the policy issues;
- Symbolic function: as a signal of the serious and rational-based decision making by the policy-makers. It is maybe a less important function for the practitioners, but for policy makers it is an important point that needs to be addressed in the dialogue.

More recently, the main focus of foresight shifted from informing to supporting policy implementation, therefore shifting the scope from producing reports to the effects of the participation to the exercise as a way to shape policy. This development is introducing challenges to address foresight functions, because producing actual policy recommendations and action plans involves different levels in the decision-making process, with actors participating to shape policy. Therefore, in designing a policy-oriented foresight method, policy action support is an essential part that needs to be addressed, or via a specific phase, or via regulators involvement in the process.

Some guidelines were proposed by da Costa et al. (2008): i) analyse the policy context, taking into account the initiatives already ongoing and adapting the foresight process to the decision making process; ii) shape the exercise within the boundaries, which means to identify the constrains and limits, i.e. what cannot be changed, to focus on the margins of manoeuvre, i.e. what can be changed; iii) involvement of policy makers in the design, meaning that decision makers need to be aware of the limits and possibilities of the foresight approach, and support the building phase of the system; iv) participation of policy makers to the process: this is a debated issue, since while policy makers involvement can increase the results impact (ownership of the result), on the other hand policy can constrain the creative identification of alternatives; v) adding a policy definition phase; vi) reservoir approach: presenting the foresight results as a source of options, that can be taken up in time, when considered appropriate; vii) addressing choices and values: the foresight system needs to identify and clarify the set of values and normative objectives it is addressing.

In relation to D6.1, the focus is on two functions of foresight, namely informing policy and supporting policy definition. The last one includes the involvement of stakeholders in the foresight process, and this topic will be addressed in the proposed method.

2.2.4 Horizon Scanning

Horizon Scanning is the tool selected in the proposed NANoREG foresight system to evaluate the current and future applications of nanomaterials, including next generation nanomaterials. Horizon scanning, also known as environmental scanning is a tool that is considered exploratory, but that can support the creation of scenarios and options, that are than evaluated for their impact. In this chapter, Horizon Scanning (HS) definition, functioning, methods, and applications, are briefly discussed.

2.2.4.1 Horizon Scanning definition and tools

Miles and Saritas (2012) reported the definition of Horizon Scanning as:

. . . the systematic examination of potential threats, opportunities and likely future developments including but not restricted to those at the margins of current thinking and planning. Horizon scanning may explore novel and unexpected issues as well as persistent issues or trends

According to the definition, Horizon Scanning is a structured process that identifies emerging phenomena and examines the information to select the topics of concern and its related issues (benefits and impacts, with associated uncertainty). The goal is to define likely future scenarios, including unexpected outcomes and possibilities (beyond the simple search and into breakthroughs), as well as to evaluate the development of trends and patterns, considering what can accelerate, decelerate, or change them.

Horizon scanning is a subset of the Environmental Scanning. Environmental Scanning can be defined as “The systematic identification, monitoring and examination of issues of relevance to the topic of concern”, therefore regarding all topics, not only new developments or emerging issues.

Horizon Scanning is organized in 4 steps, also depicted in Figure 3 (Miles and Saritas, 2012):

1. Application of one or more scanning processes to identify relevant issues from some source(s) of data. The quality of the HS will depend upon the efficiency of the scanning process, the adequacy of its tailoring to the needs of the intended users, and the appropriateness of the data sources;
2. Appraisal of the large number of issues that are initially identified, so as to select those that are most liable to be of substantial significance to our topic of concern;
3. Analysis of these issues and explication of their relevance (or rather, of what is known and unknown about their relevance);
4. Feeding of these results to end-users or into other futures processes that can make use of them (for risk analysis, scenario building, etc.).

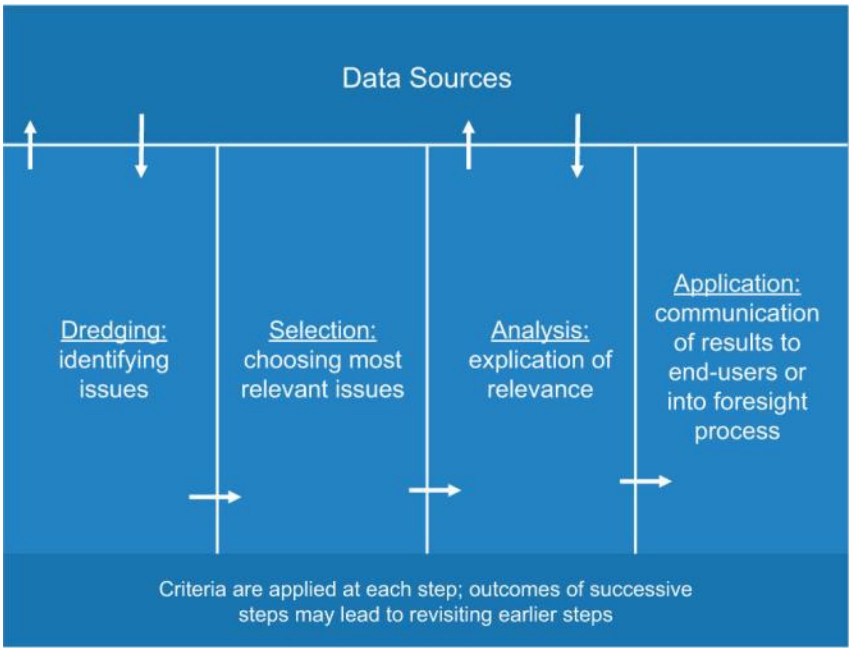


Figure 3. Phases of the horizon scanning process

In detail, the kind of information that we are looking for is:

- Weak signals: 'warnings (external or internal), events and developments that are still too incomplete to permit an accurate estimation of their impact and/or to determine their complete responses';
- Wild cards: Wild cards are events with a surprising character, a low probability and a high impact;
- Emerging issues: 'stories about what the future, or possible futures, may or will (depending on the narrative) look like and that connect these possible futures to current issues for political debate (the discourse)'. They are expressed as scenarios, or mini scenarios, describing what could happen in the future in relation to the possible development of a technology.

In the next paragraph, few examples of Horizon Scanning applications are reported in a schematic way.

2.2.4.2 Horizon Scanning applications

A literature review of Horizon Scanning applications was carried out to evaluate the field of application, methods applied, the goal of each program, the outcomes, and the information sources. In general, Horizon scanning is applied to different sectors, including public health, environmental preservation, safety, business, technology innovation, and security.

The goals of these applications are different, going from the prioritization of dangers to the environment, to the identification of benefit potentials of a new medical practice or pharmaceutical to better plan public health investments, to the identification of national security issues.

The sources of information used can be grouped in two categories, web-based and expert-based.

Web-based sources are: i) search engines; ii) blogs; iii) newsletters; iv) discussion groups; v) active actions; vi) snowball sampling; vii) peer reviewed journals; viii) RSS feeds.

Concerning expert-based sources, examples are: i) Delphi approaches; ii) Expert panels; iii) Meetings and conventions; iv) R&D institutions and companies.

A focus about how HS is used for nanotechnology is reported in the next paragraph. The work reported here is the combination of the work done in D6.1 NANoREG and in ProSafe, D2.2, where in D2.2 of ProSafe an update of the review was carried out. Both are reported here for convenience of the reader.

2.2.4.2.1 Horizon Scanning applications for nanotechnology

Horizon Scanning, and Foresight, is already applied to nanotechnology, with different scopes and goals. Within D6.1, a first literature review was carried out to identify why Foresight and HS are used in the regulatory context, and if some ideas about approaches and trends could be identified. Foresight on nanotechnology started at the beginning of the century. For example, the Asia-Pacific Economic Cooperation (APEC), with the Industrial Science and Technology Working Group, published in 2002 a report titled “Nanotechnology: The Technology for the 21st Century” (Tegart, 2002). The goal of the foresight activity in this report was to define alternative scenarios for nanotechnology development till 2015. The study identified ten issues for nanotechnology development: i) definition of nanotechnology, ii) opportunities, iii) scientific and technological inputs, iv) education and training, v) R&D funding, vi) regional collaboration and networks, vii) commercialisation, viii) metrology, ix) implication for small economies, x) societal implications. The scenarios developed on the basis of these issues were all focused to the benefits of nanotechnology, and safety was a secondary concern, and the policy definition aimed at increasing the acceptability of nanotechnology.

The European Foresight Monitoring Network published a report by Birgitte Rasmussen and Per Dannemand Andersen (2004), developed by Risø National Laboratory and organized by The Danish Ministry of Science, Technology and Innovation. The goal of the work was to deliver the National action plan for Danish nano-science and nano-technology, including research, innovation, and education policy. Important building blocks in the Danish Nano-foresight process were hypotheses and statements about future research, industrial possibilities and consequences both beneficial and adverse of nano-science and nano-technology. A basic concept in the process was the formulation of statements about the scientific and commercial potentials of nanotechnology within a time horizon of 20 years, and then to allow a critical scientific discussion on them.

The last example of foresight reference is “Foresight for the semiconductor industry in Taiwan”, published in 2006 by Yuan et al. The scope of the study was to explore the possible future business environment, industrial structure, technological transformation, and market for the semiconductor industry in Taiwan. The results were technological and economical in nature, and no safety issues were addressed.

An updated analysis was performed in the context of the ProSafe project, D2.2, aiming at identifying specific trends and development of potential future applications of nanomaterials. Due to limited resources, the work was limited to a review of already published Foresight exercises and HS. For reader convenience those findings are included here, since those findings are useful for this deliverable, and because ProSafe deliverable is not published yet.

Alencar and colleagues examined in 2007 the patents related to nanotechnology from 1994 to 2005, evaluating the patenting patterns in USA, Japan, and Germany, along three development life cycle stages: raw MNM, nano-intermediates, and nano products. Although patenting analysis is limited due to discrepancies between patents and product (not all patents are finally developed into products), patenting can provide a good overview of the technology development.

On the basis of 46 terms nominated by experts, the search gave around 20,000 single hits, with the main categories represented by semiconductors and non-metallic components (more than 2,000 hits), and medical and cosmetic applications, nanostructures, catalysis (1,500 – 2,000 hits).

In particular in Germany, specific patents on coating, plastic, textiles, ceramics, ink, and glass were issued by large industrial groups (e.g. Bayer, Degussa, BASF), while large research groups (e.g. Max Planck, Fraunhofer) were more focused on catalyst, sensors, cosmetics. The patent analysis is a good tool to identify trends and potential future developments. It is necessary to update the research terms to include new generation MNM, and to update the search to 2015.

Patenting analysis can also give indications about the time scale to be considered in the foresight assessment. In 2007, Daim et al. performed an assessment of the time lag between research funding, patenting, and research publishing, using Nanoscope as case study and analysing data with a set of mathematical models. Conferences presentations right after the funding were granted, journal articles 2-3 years after funding, and patenting 5-6 years after initial funding. These results and the same method (if applied to other cases) can be helpful to identify timescales of nanotech innovation along innovation chain, and to identify when a MNM can reach the market.

De Miranda Santo M et al., in 2006, reported the work done by the Brazilian Center for Management and Strategic Studies to inform the federal government R&D strategy for nanotechnology development. In particular, result of text mining concerning nanotech publications was shown. The main results were illustrated as tables, with frequency of keywords found in papers from 1994 to 2004. A table shows keywords in key countries (i.e. USA, Japan, Germany, France, UK, Switzerland, Spain, Sweden, and Canada) and in competitor countries (i.e. China, South Korea, India, Taiwan, Israel, Australia, Singapore, Mexico, South Africa, and Malaysia), with respect to Brazil, which includes terms such as nanocrystals, quantum dots, carbon nanotubes, fullerenes, and nanowires. However, these terms are not useful to identify thematic areas. More interesting is the analysis of the general worldwide view of nanotech publications. The terms in this table include sectors and techniques, such as nanolithography, nano-electronics, nanofabrication (between 500-700 occurrences), and with much less counts (less than 50) terms like nanomedicine, nanodrugs, nanophotonics, nanofilters, and nanocatalyst. These results, as old as they can be, can give an indication of growing research fields, and an update of the results by using the same (or similar) keywords can be carried out.

In 2014, Bowles et al. assessed the potential use of nanodevices to manage the supply chain. In the paper, particular attention was posed on nanosensors for: i) supply chain management system (e.g. tracking logistic) performed trough customized nanomaterials; ii) innovative packaging and labelling to detect leaks and microbiological conditions; iii) detection of environmental conditions along the supply chain (i.e. temperature, humidity, gas and hazardous substances); iv) food chain safety (e.g. detection of type and source of spoilage DNA chips to detect pathogens); v) tracking (e.g. mobile and distributed self-powered sensors). However, according to the authors, potential health and environmental problems, privacy issues, and occupational downturns, require policymakers to develop new laws to manage nanotechnology's potential risks.

On the same line, Robinson et al. published in 2013 the results of the application of the Forecasting Innovation Pathways approach to nanobiosensors. The procedure, including four stages ((1) Understand, (2) Profile and Link, (3) Project and Assess and (4) Report), produced several useful outputs, concerning four application domains: healthcare, environmental monitoring, agri-foods, homeland security and defence. The first output is about the main R&D areas, which includes mainly chemistry, biomedical science, and military science. Also, main applications of nanobiosensors were identified on the basis of MNM structure and functions, in fields such as toxicity identification, disease diagnosis, microorganism identification, and explosive sensing. With the support of experts and researchers, two main innovation pathways were identified:

Pathway 1. Enhancing biorecognition/bioconjugation using nanostructured materials in biosensors. In general, this path uses nanomaterials passively, that is it focuses on surface properties, such as surface to volume ratio, surface affinity, and selectivity to biomolecules and cells.

Pathway 2. Enhancing signal transduction or creating new transduction mechanisms using nanomaterials in biosensors. In general, this pathway seeks to utilize nanomaterials in a more active way, taking advantage of unique properties of materials with nanoscale dimensions, such as quantum effects, piezoelectric effect, etc.

- Pathway 2.1: cell-based sensing
- Pathway 2.2: sensing macromolecules, such as proteins and DNA
- Pathway 2.3: sensing small chemical molecules such as Fe, O_2, etc.

The construction sector is a subject of different reviews found in open literature. For example, van Broekhuizen et al. published in 2011 a paper about the use of nanomaterials in construction sector, also analysing some occupational safety aspects in 4 hypothetical situations. A survey carried out in 2009, which was revised and updated by consulting a panel of experts and companies, identified a set of representative applications in the construction sector. In 2009, the main MNM were TiO_2, ZnO, aluminium oxide, Ag, and SiO_2. The main uses were coatings (68% of the market), while concrete and insulation type products covered only the 7 and 12% of the market, respectively. TiO_2 and ZnO are mainly used in coatings. SiO_2 is mainly used in cement and insulation; however, SiO_2 cement covers only the 5% of the whole concrete market.

Another paper by Khitab and Arshad, published in 2014, reviews uses of MNM in construction sector, on the basis of information collected recently. The findings reported in the paper shows that SiO_2 is used in cements to obtain ultra-high performance products; TiO_2 is used in paints and in self-cleaning concrete; CNT is used in scratch-resistant paints, while only studies are at the moment available for their use in concrete; carbon nanofibers are proposed to be used in self-de-icing surfaces, but still no actual applications are reported.

Arora et al. (2014) published a paper concerning the nanotechnology application in building construction sector. A table summarized the expected development, as seen from 2006. The main developments are in the Table 1.

Table 1. Nanotechnology uses in construction sector, as foreseen in 2006. Arora et al. (2014).

Applications	Nano enabled property	Enhanced functionality	Timescale
Steel coating	Nano-polymer bonds to material surface, eliminates oxidation	Steel coated with nano-polymer has higher resistance to corrosion	2007-2016
Glass coating	Titanium dioxide film affixed to surface of glass	Decomposes organic materials upon contact which self-cleans glass surface	2007-2012
Ceramics	Carbon nano-tubes or other nano-tube based materials are grown through bottom up approach to form nano-structured ceramics	Improved resistance to stress; increased strength and flexibility; reduced deterioration; less volume and weight; surfaces can conduct electricity	2012-2026
Concrete	Carbon nano-tubes are mixed into the concrete replacing steel rebar	Improved strengths and reduced thickness; less volume and weight vs. strength	2012-2026
Insulation	Nano-pores of air or nitrogen are created within gels or polymers	Efficiency increased due to high surface-to-volume ratio; reduced toxics and non-renewables	2007-2016

The analysis carried out by the authors about the innovation preparedness and intention to use MNM in building construction among building companies (i.e. a sample of 19 stakeholders was interviewed), showed that even if there are already beneficial nanotechnology solutions (measured by assessing the number of patents), the awareness is moderate, and there is a low level of assessment and use, due to risk-averse nature of the building construction sector.

The analysis identified a set of technologies, including specific MNM, such as: carbon nanotubes, nano-silver, Cryogel™, nanopolymers, organic LED in paint, lanthanum hexaboride, bio-active agents in concrete, alumina foam (insulation), Pyrogel®. All these technologies can be seen as relevant examples to further investigate to identify potential promising MNM.

Finally, in 2015, Hincapié et al. published a study of the use of MNM in constructions in Switzerland, with considerations about their flow in construction and demolition waste. A survey of business representatives of Swiss companies found, as previous reviews, that MNM are mainly used in paints and cement. Also, the most frequently used MNM were found to be TiO_2, SiO_2, ZnO, and Ag. The qualitative study about the flow of the nanomaterials showed that 14t/y of TiO_2, 12 t/y SiO_2, 5 t/y ZnO, and 0.2 t/y Ag are used in paints. The main potential of release into environment and technical compartments was estimated during recycling phase.

Hussein et al. published in 2015 a comprehensive review of nanotechnology used in renewable energy applications. The paper is organized in tables, reporting applications at both experimental and theoretical stage for solar energy, hydrogen energy, wind energy, and geothermal energy. Mentioned technologies include:

i) nanowire arrays,

ii) nanofluids,

iii) TiO_2 nanowires coated with Au or Ag ENP,

iv) graphite, carbon black, silver, and Al_2O_3 MNM in nanofluids,

v) MgO MNM for solar heating systems,

vi) Al particles and Al nanofluid in diesel fuel,

vii) TiO_2/SnO_2 particles in fuel cells,

viii) Ag/TiO_2 nanocomposite films,

ix) CNT, and cobalt oxide/graphene nanocomposite in fuel cells,

x) KF/CaO nanocatalyst in biofuel production,

xi) nano-magnetic solid-base catalyst,

xii) nano-colloidal boron nitride additive as component of wear protective coating

Among different Horizon Scanning systems in use in Europe, there are two examples that are worthy of a deeper analysis and presentation. The first program is EuroScan (The International Information Network on New and Emerging Health Technologies). EuroScan is a network of national agencies and institutions, performing foresight activities on public health matter, including important emerging new drugs, devices, procedures, programmes, and settings. While it is not focused on nanotechnology, since nanomedicine is an important application of nanomaterials, EuroScan can become a resource to inform the EC and consumers about potential positive and negative impacts of nano applications. Each agency participating to EuroScan has its own approach to the foresight activity, but a baseline approach and toolkit was identified and proposed as guideline to the network.

The other program make reference to the FP7 project SESTI (Scanning for emerging science and technology issues). The project aimed at gaining more insight in how weak signal scanning can facilitate policy to better anticipate on emerging future issues. In this project, the actual scanning for weak signals in a specific domain was combined with the gaining of experience to translate them to the policy community. The approach developed in SESTI can provide important aspects and reflections to address the linkage between the NANoREG foresight approach and the decision-making process.

Amanatidou et al. (2012) highlighted how horizon scanning has the role to alert policy-makers to anticipate better and earlier emerging issues that will probably need their attention. To fulfil this application, the authors wrote that a comprehensive method is needed to scan and assess early warning signals that may indicate potential emerging issues from of a variety of media and sources. However, SESTI project findings highlighted that the way Horizon Scanning assessment is taken up by policy makers is a function of the selection and communication of the most important issues at the right time, and in a way that is effective for the policy agenda (see Regulatory Preparedness as a discussion point). At the same time, it seems that the HS results are considered less valuable than other foreseeing approaches, like macroeconomic modelling.

In the end, if proactive actions in nanosafety are considered necessary by the European Commission and European actors in general, it is necessary to increase the availability and quality of the collected information and its analysis, which requires a constant investment into talents and resources. A Nanotechnology EuroScan-type initiative might be a good solution to achieve the intended results.

2.2.5 Risk Assessment as a tool for potential impact assessment

In order to evaluate the potential impacts of forthcoming innovations, it is necessary to have a tool that can take the available information, use it as best as possible, if necessary indicate what kind of data are needed to complete the assessment, and finally to provide a description of all potential impacts associated to a specific nano-related application or a MNM. In the current regulatory framework, this role is assumed by the Risk Assessment, which is used in all EU regulatory frameworks to assess the chemicals and product safety.

The paradigm for Risk Assessment (RA) of chemicals, composed by hazard assessment, exposure assessment, and risk characterization, is considered applicable to MMN, but specific aspects related to nanomaterials need further developments (SCENIHR, 2009, Stone et al., 2013). The European Commission published in 2008 a regulatory review of nanomaterials, identifying all the regulations that were relevant for nanomaterials safety and identifying the status of nanomaterial safety assessment (EC, 2008). The document concluded that while risk assessment is applicable, "*Knowledge on essential questions such as characterisation of nanomaterials, their hazards, exposure, risk assessment and risk management should be improved*."

This position is at the basis of the efforts going on in all NanoSafety Cluster and nanosafety projects in general in the last 10 years, aiming at understanding the specific nano-aspects, applicability and adaptation of existing tools and methods, and development of new tools to perform the risk assessment of nanomaterials, with a focus on the regulators requirements.

Risk Assessment (RA) is based on sound scientific principles supporting the scientific analysis of potential negative impacts of nanomaterials applications along the whole life cycle. Despite the considerable volume of research and regulatory activity in the nanoEHS area, the RA exercises carried out so far have identified serious gaps in our basic understanding of key nano-bio interactions, mechanisms of biological uptake, fate, distribution and bioaccumulation. All these gaps are serious barriers for the performance of quantitative risk assessment asked by regulators and decision makers, and the ongoing work in recent research projects is only starting to give answers in this direction.

In 2010, Grieger et al. published a paper about the definition of risk research priorities for nanomaterials. The authors made the case for the development of more rapidly deployable decision making tools as necessary to address the nanomaterial safety, in a context of anticipatory governance of innovation. The problem is that the whole approach and data amount and quality that could allow a full risk assessment (e.g. quantitative risk assessment according to REACH) is not available yet, not even after 6 years from that analysis was published. The scientific community, with regulator and industry is working toward that point also developing new approaches and trying to reduce the need for experimental data (e.g. by developing grouping approaches and exposure models), but the effort is not sufficient to provide decision makers with useful information right now.

The work in terms of developing adaptable risk assessment approaches is ongoing in different projects, from GuideNano, to MARINA, NANoREG, SUN. Hristozov et al. (2016) published a paper comparing frameworks and tools available right now for nanomaterial safety assessment. The review identified 12 several frameworks overall. In this context, a framework is defined as a conceptual paradigm of how RA should be understood and performed. The result of the review highlighted that:

1. The frameworks are all based on the RA paradigm for chemicals and recommend a number of adaptations to address the complexity associated with MMNs (e.g. life cycle thinking);
2. Most of the frameworks allow for considering exposure aspects at the initial stage of the RA to inform (eco)toxicological investigations, thus allowing waiving due to demonstrated lack of exposure;
3. The data requirements are similar to the ones set in REACH and emphasize the need for comprehensive characterization of physicochemical properties;

The authors concluded that none of the reviewed frameworks was applicable to support the decision making about nanomaterials safety, and they recommended the development of a comprehensive framework for RA of MNs that addresses:

1. nano-specific requirements;
2. life-cycle thinking;
3. pre-assessment;
4. exposure-driven approach;
5. iterative and adaptive structure;
6. transparency of objectives and communication with all stakeholders;
7. allowing grouping and read across;

All this work is eventually leading to the development of a decision making system based on risk assessment that will be used to evaluate safety of nanomaterials and nano-products in a regulatory context.

2.2.5.1 Risk Assessment as a tool for impact assessment in foresight analysis

The work to develop frameworks and tools that can be applied to perform a full risk assessment for nanomaterials is perfectly sound in the context of marketed nanomaterials, when the availability of a full safety dossier prepared under the proper regulatory context is expected, and the only limit is the availability of standardize and robust testing approaches.

However, in the context of the assessment of nanotechnology innovation that is going to be marketed in five years, it is reasonable to sustain that the amount of available information will be scarce, qualitative, and limited to certain aspects of the nanomaterial and nano-product life cycle. In a sense, to apply risk assessment to a foresight analysis is like assessing the potential impacts of nanomaterials as it was 10 years ago. The only difference is that there is more knowledge about the environmental behaviour, toxicity, and bio-interaction of nanomaterials. However, it is difficult to use this information if no reliable models are available. Grouping, read across, exposure estimation models, are lacking or not validated at this point, therefore there is no possibility to perform a full risk assessment in the foresight proposal.

In order to assess the safety of up-coming, potential, nanomaterials in relation to their applications it is necessary to rely on more qualitative approaches.

From a regulatory point of view, REACH allows a qualitative risk characterization (RC) in certain conditions, especially when no quantitative data are available. Qualitative RC is defined as “the likelihood that effects are avoided when implementing the exposure scenario”. Qualitative RC aims at reducing or avoiding contact with the substance; therefore, the implementation of RMMs is highly important in this context, and the strictness of the required measures is linked to the hazard classification according to the CLP Regulation. According to the ECHA guidance, the human health endpoints for which a qualitative risk characterisation may be necessary are irritation/corrosion, sensitisation, acute toxicity, carcinogenicity and mutagenicity. For the environment, a qualitative RC is recommended when a PNEC cannot be calculated, but also in another case: i.e. when the calculated short-term PNECs show no risks, but a long-term effect is suspected or possible according to inherent properties of the substance, such as Kow and Kd partitioning coefficients.

The qualitative RC for human health is carried out by the following steps. In order:

1. Identify substance hazard category;
2. Identify exposure routes;
3. Build exposure scenarios;
4. Estimate exposure;
5. Estimate risk;
6. Iterate.

This framework is similar in structure to the RA framework that is described by Van Leeuwen and Vermeire (2007), which is composed by 4 steps: problem formulation, exposure assessment, hazard assessment, and risk characterization.

In turn, this framework is essentially the same as the one proposed by the US-EPA for the ecological risk assessment, as shown in the Figure 4, as defined in the EPA's Guidelines for Ecological Risk Assessment (US-EPA, 1998).

The problem formulation provides the foundation for the ecological risk assessment. It is an iterative process for generating hypotheses concerning why ecological effects occurred from human activities. The problem formulation articulates the purpose and objectives of the risk assessment and defines the problem and regulatory action. The quality of the assessment depends on rigorous development of the following products of problem formulation:

1. Assessment endpoints that reflect management goals and the ecosystem they represent
2. Conceptual model(s) that represents predicted key relationships between stressor(s) and assessment endpoint(s)
3. Plan for analysing the risk

Planning is a very important initial step, where the interaction with the decision maker/s is achieved, resulting in the following products:

(1) clearly established and articulated management goals

(2) characterization of decisions to be made within the context of the management goals, and

(3) agreement on the scope, complexity, and focus of the risk assessment, including the expected output and the technical support available to complete it.

In the second phase of the risk assessment process (i.e. analysis phase), the risk assessors evaluate exposure to stressors (exposure characterization) and the relationship between stressor levels and ecological effects (ecological effects characterization). The risk assessor performs the following tasks:

1. Selects the data that will be used and determines the strengths and weaknesses of the data
2. Analyses the sources of stressors, distribution in the environment, and potential or actual exposure to the stressors
3. Examines stressor-response relationships and the relationship between measures of effect and assessment endpoints
4. During these analyses, the scientists evaluate the uncertainties in the exposure and effects characterizations. The products of the analysis phase are two profiles:
5. Exposure profile based on environmental fate and transport data
6. Ecological effects or stressor-response profile

The risk assessors and risk managers continue to interact throughout this phase.

The risk characterization is the final phase in which exposure and ecological effects characterizations are integrated into an overall conclusion (risk estimation). In this phase, the risk assessor compares the levels of exposure (estimated environmental concentrations) expected in the field to those levels that produce toxic effects in laboratory tests.

The integrated risk characterization includes the assumptions, uncertainties, and strengths and limitations of the analyses. It makes a judgment about the nature of and existence of risks.

Risk assessors and risk managers continue their dialogue throughout this phase. After this phase is completed, risk assessors formally communicate and discuss their results with risk managers. In addition to the risk assessment report, risk managers consider other information, such as social, economic, political, and legal issues, in their decisions.

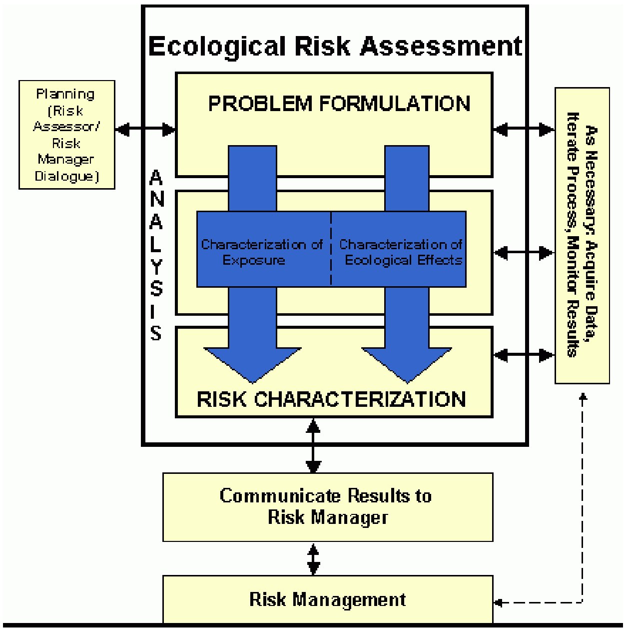


Figure 4. Ecological Risk Assessment Framework (US-EPA, 1998).

2.2.5.1.1 Relevance of US-EPA framework for the foresight approach aim

The US-EPA framework is considered relevant for the estimation of the potential innovation EHS impacts in a foresight context.

The framework can be applied to predict the likelihood of future adverse effects (prospective) or evaluate the likelihood that effects are caused by past exposure to stressors (retrospective). To make a parallel, what we are doing in the foresight proposal is a prospective risk assessment toward workers, consumers and the environment, with very little data, and where the input is the nanomaterial linked to its application/s.

The framework is built to address anthropogenic stressors (i.e. the chemical, organism, or physical phenomenon potentially causing adverse effects), and it is defined in a risk management context, where the risk management represents stakeholders in general, including regulators. The role of risk managers is to define the acceptability of adverse effects, which usually takes into account social and economic aspects.

In addition, the US-EPA framework is adaptable because it is built to allow the descriptions of the likelihood of adverse effects ranging from qualitative judgments to quantitative probabilities. When quantitation of risks is not always possible, it is better to convey conclusions (and associated uncertainties) qualitatively than to ignore them because they are not easily understood or estimated.

This approach is in line with the needs of the proposed NANoREG foresight approach. Of course, it needs adaptation to include nano-specific elements, such as life cycle thinking, but the flexible structure and generic indications that the framework provides are advantages that allow the easy transfer of the RA concept to the foresight approach.

Among the four phases, the most important is the Problem Formulation, because it lays down the foundation of the whole risk assessment. Problem formulation is a process for generating and evaluating preliminary hypotheses about why effects may occur, from human activities. It starts from the planning phase, where the overall goal of the work is defined with the more general needs and strategies of decision makers, but it goes more in depth defining the details of the problem. The final result of the Problem Formulation is the Conceptual Model.

The Conceptual Model is the representation of the relationships between the stressor and the likely target organized in risk hypotheses which are the summary of the link between stressor/s, the exposure pathway/s, and the target/s. Usually risk hypotheses are organized in diagrams. Risk hypotheses are also a basis to plan the collection of necessary data in the analysis plan, that are used to test the hypothesis, and estimate the risk associated to the specific adverse effect.

Putting everything into the innovation perspective, the problem formulation could allow defining risk hypotheses on the basis of potential MNM applications, identifying the exposure pathways and the target. This description would be based on literature data and expert judgment, but it also will guide the collection of additional information to qualify and estimate the likelihood of the occurrence of the hypothesized adverse effects, in a regulatory and management context.

Therefore, the concepts and the structure of the US-EPA framework will be used as the basis to formulate the risk assessment part of the foresight approach.

2.2.6 Link to NANoREG regulatory questions

The D6.1 can answer two of the regulatory questions addressed by NANoREG. In particular, it is addressing Q14, and Q15, namely risk assessment and risk management. D1.9 includes text about the potential answers that the D6.1 can provide to Q14 and Q15. Only a general reflection is reported here.

In general, since D6.1 will provide data about prospective risk assessment, it is possible only to give generic indications about likely risk scenarios based on literature data and expert knowledge, and the preliminary analysis of the regulatory context suitability to address the safety issues inherent in the identified risk scenarios. Also, the need of Risk Management Measures, being them of technical, managerial, or political nature, can be assessed and reported.

In general, D6.1 results are more supporting regulators, due to the scope of the proposed foresight system. However, the results can be useful also for producers, to identify the less risky application among their possible choices, or to avoid the further development at all due to high concerns. Also, financial institutions can benefit from the foresight system, because it gives indications about the riskiness of specific sectors (through the example of model and representative application/s).

2.2.7 Link to Safe-by-Design and Innovation chain (D6.3, D6.4)

One of the bottlenecks in the governance of new technologies is timely anticipation of regulators to secure that regulations cover all safety aspects of such a new technology. It is obvious that for MNMs and MNM containing products this has not been the case.

To our opinion regulators were not enough and not timely aware of the innovative aspects of MNMs in order to realize that regulations and guidance were not adequate to regulate MNMs properly. Conceptually, approaches like Horizon Scannings and Foresight Studies could help to avoid such situations or at least could help to diminish the magnitude of the problem.

In more practical terms, the link relies in the scope of the Safe by Design, which is in simple terms, to allow the integration of the potentials for health and environmental risks as early as possible in the innovation chain, for all the actors interacting in the value chain, including regulators.

The NANoREG foresight system for innovation monitoring as designed in D6.1 can be applied a little before the early stage of the stage-gate approach, i.e. at the idea phase. Idea, in this case, means that there are some studies at lab scale that indicates that a given nanomaterial has certain properties useful in a given application (e.g. conductivity for consumer electronics), or there is the plan to test the specific nanomaterial more extensively on the basis of one single experiment to be applied in a set of applications. Therefore, the idea should be very innovative, at the Research stage with a low TRL, and with a medium term to market. In this case, if an industry, regulator or a decision maker have some concerns about the potential impacts of such application/s, and if the application/s is/are new and very few if even no safety data are available, the NANoREG foresight system for innovation monitoring approach can be applied to identify issues that need to be addressed early on. Also, the approach can support the comparative assessment of different R&D choices for a promising MNM on the basis of expected impacts.

In summary, the NANoREG foresight system for innovation monitoring approach is ending when the Safe by Design is starting, but there is a certain degree of overlapping, since the information collected during the application of the D6.1 approach can be a starting point for the “idea” assessment in terms of safety.

2.3 Innovation monitoring and assessment proposal

The NANoREG foresight system aims at providing an early estimation of potential negative impacts caused by nanomaterials and nanoproducts that can potentially be employed in different sectors and placed on the market in the future. The methodological basis of the System is the combination of two well-known approaches: 1) Horizon scanning; 2) Screening Risk Assessment (SRA).

Horizon scanning, as described in chapter 2.2.4, is widely used by national organizations, as well as by private institutions, to evaluate the future development of the market, as well as positive and negative impacts of specific technologies. For example, the national health organizations have the role to study the development of possible new health treatments (e.g. pharmaceuticals, medical devices), specifically so as to provide legislators the means to plan research and adoption strategies. There are several horizon scanning approaches currently in use. Some of these studies/methods are also already being applied to nanotechnology (chapter 2.2.4.2.1). The SRA is also a well-established approach, as reported in chapter 2.2.5.

Therefore, the system is based on sound methodologies, already used for other sectors and chemicals that can be applied to nanotechnology as well.

The goal of this chapter is to describe the NANoREG foresight system, including its scope, aims, users, and needed input for the system to provide good results, the expected outputs, the potential users, the way it can be used by different stakeholders. The first part is the description of the conceptual framework, which will support the development of the practical approach (second part).

Disclaimer: the proposal of the NANoREG foresight system presented in this document is deemed to be improved, with the support of other organizations, and other nano-safety research projects. The interactions between regulators, science, and industry are not easy to identify and manage. In NANOREG[2], an exercise to build a Trusted Environment where industry and regulators can share information, as well as the implementation of the Safe-by-design approach as developed in NANoREG, can provide additional input and information to improve this proposal.

2.3.1 Scope of the proposal

The scope of the NANoREG foresight system is to assess the potential impacts of nanotech innovation on Environment, Health, and Safety. The system aims at making a qualitative screening risk assessment (SRA) of practical applications, or group of applications based on use profile (e.g. certain pesticides are used more or less in the same way), for a specific nanomaterial. The SRA is performed on the whole life cycle of the nanomaterial, for all potential targets (workers, environment, consumers, indirect through environment), on the basis of available data and information, also on similar products or same products not nano enabled.

The assessment of entire industrial sectors or value chains is out of the scope of the system. It cannot allow, if not indirectly, to plan a research strategy at national level. Also, the system does not include socio-economic assessment, which is considered part of the regulators and decision makers role after the results of this proposal are delivered. Finally, it does not include a regulatory Risk Assessment.

The NANoREG foresight system is mainly thought for regulators; therefore, regulators requirements are foremost in the development of the proposal. However, industry can benefit from the use of the system to assess the potential uses of the application and the related risks, and focus the development of a specific use, or think about risk mitigation measures. Also financial institution can identify prospective applications to fund on the basis for the SRA result.

The expected results of the sytem are the assessment of negative impacts of relevant (for the specific stakeholder) innovations, the comparison of the available data for SRA and the data gaps in terms of safety assessment, and the regulatory implications in terms of current regulation and needed regulation/guidelines.

The application of the NANoREG foresight system has to be supported by tools. If possible, no new tools will be developed, but existing tools will be suggested at different stages of the proposal. Since the proposal is going to be applied on materials and applications for which nearly no data are available, tools that can be used in the application of the system are for example exposure estimation models, grouping approaches, read across schemes. The novelty of the system is the combination of Horizon Scanning and SRA in a regulatory setting for specific applications.

2.3.2 Proposal description

The NANoREG foresight system conceptual framework is depicted in Figure 5. The main goal of the conceptual framework is:

- to describe phases, functions, users, outputs, and targets of the foresight system;
- to provide a framework to guide the identification of the stakeholders needs;
- to frame the process to build a simple, lean and efficient approach that can be used to collect information (both on the web and through expert opinions) that can serve as input of the foresight system, and produce outputs targeted to different needs;
- to identify steps of the foresight system (defined in this document as decision points) where the stakeholders input is needed;
- to support the definition of a foresight system that is flexible and potentially useful for the whole innovation chain, by linking it to the stage-gate innovation approach, in order to provide useful information also for the Safe by Design approach and methods;

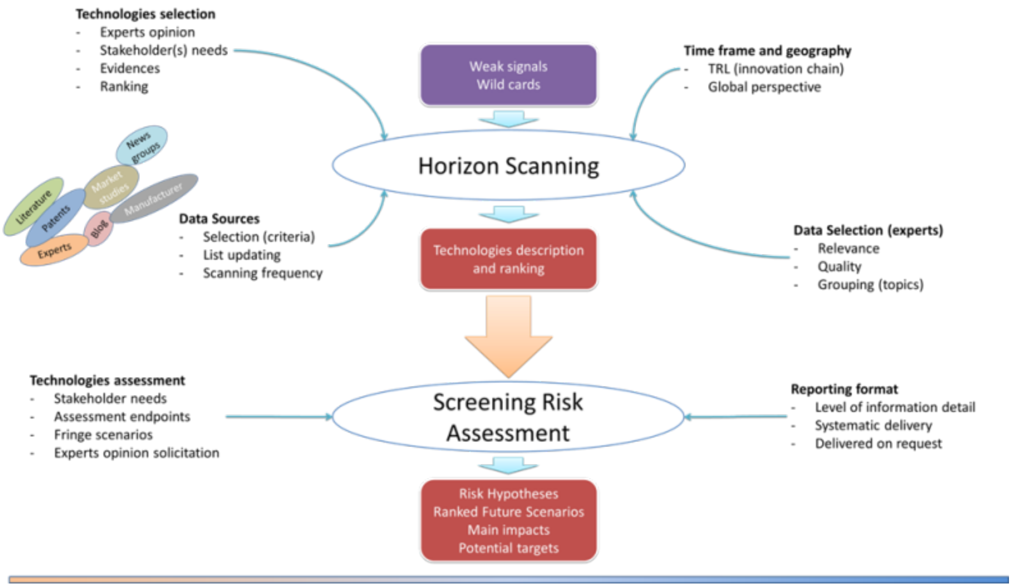


Figure 5. Conceptual framework of the foresight system

2.3.2.1 Description of the Framework Phases

The NANoREG foresight system includes two main phases.

The first phase is the Horizon Scanning (HS). The goal of this phase is to generate a list of applications, or group of applications, which are based on a specific nanomaterial and pertaining to a given industrial sector, which can be perceived as a potential threat to the safety of humans and the environment. To identify these applications, there is the need of data input, e.g. result of foresight studies on nanotechnology, weak signals (as defined in chapter 2.2.4.1). Data input can come from different sources.

The second phase is the Screening Risk Assessment (SRA). This is the core of the system, where the identified applications are evaluated to estimate the potential risks for different relevant targets. The SRA proposed in this system is following the Ecological Risk Assessment framework of US-EPA (US-EPA, 1998). The particular nature of this approach, as described in chapter 2.2.5, makes it appropriate to integrate the socio-economic importance in the scientific risk assessment from the start of the procedure, pending the availability of applicable tools. The scope of the SRA is to develop and to evaluate risk hypotheses, giving as a result a set of qualitative evaluations of the potential of the application/s to be harmful, and giving some regulatory implications for safety assessment and management.

2.3.2.2 Potential Users of the System

The proposed NANoREG foresight system is mainly thought for regulators, which are both users and main target of the system. However, industry can benefit from the use of the system to assess the potential uses of the application and the related risk in association with the innovation stage they are in, and focus the development of a specific use, or think about risk mitigation measures. Also financial institution can identify prospective applications to fund on the basis for the SRA result.

Why should a stakeholder be interested in using this system? There are different points of entry to this question, related to the awareness level of the nanotechnology applications of the user. A stakeholder may know about the word "nanotechnology", and wanting to know more about the potential threats for human health. Another stakeholder may know a nanomaterial that appears to be interesting for several sectors of industry, and promising to provide benefits for the community, but not much about adverse effects are known. Finally, it is possible that a specific potential application catches the attention of a regulator, which wants to know more about the risks potentially posed by the specific technology before it goes to R&D.

However, it is important to highlight that to use the system there is the need to have a minimum knowledge of the problem that it is wanted to be tackled. A generic question like "please identify relevant nanotechnology applications in the next 15 years" cannot be addressed by the system as it is. The amount of information that is available on all sectors is at the same time too huge and fairly qualitative to allow such an analysis. Therefore, a preliminary discussion between parts is essential to grow awareness at the point where a focus of the concern is possible. It is possible to identify criteria to "measure" the level of concern and select the applications. This kind of criteria, at screening level, has to come from the stakeholders, rather than from scientists.

To conclude, best users of the system are regulators that have some ideas about what kind of nanomaterial or application they are concerned about.

2.3.3 Horizon Scanning

Horizon Scanning (HS) is the input of the NANoREG foresight system. HS identifies the applications to be assessed. However, taking into account the SRA approach as described in the next chapter, the HS needs some socio-economic input as well, besides the data necessary to describe the application/s. In order for the system to give useful output, the input about nanotechnology interest has to be focused, and relevant for the user/stakeholder. The system is not built to scan all the possible uses of nanotechnology, but it requires the definition of some search boundaries.

A detailed description of the different steps included in the Horizon Scanning phase is shown in Figure 6. A discussion of the different steps included in the workflow are reported below, indicating the nature of the step, the rationale behind the action to be taken, and the tools that can be used to perform the action.

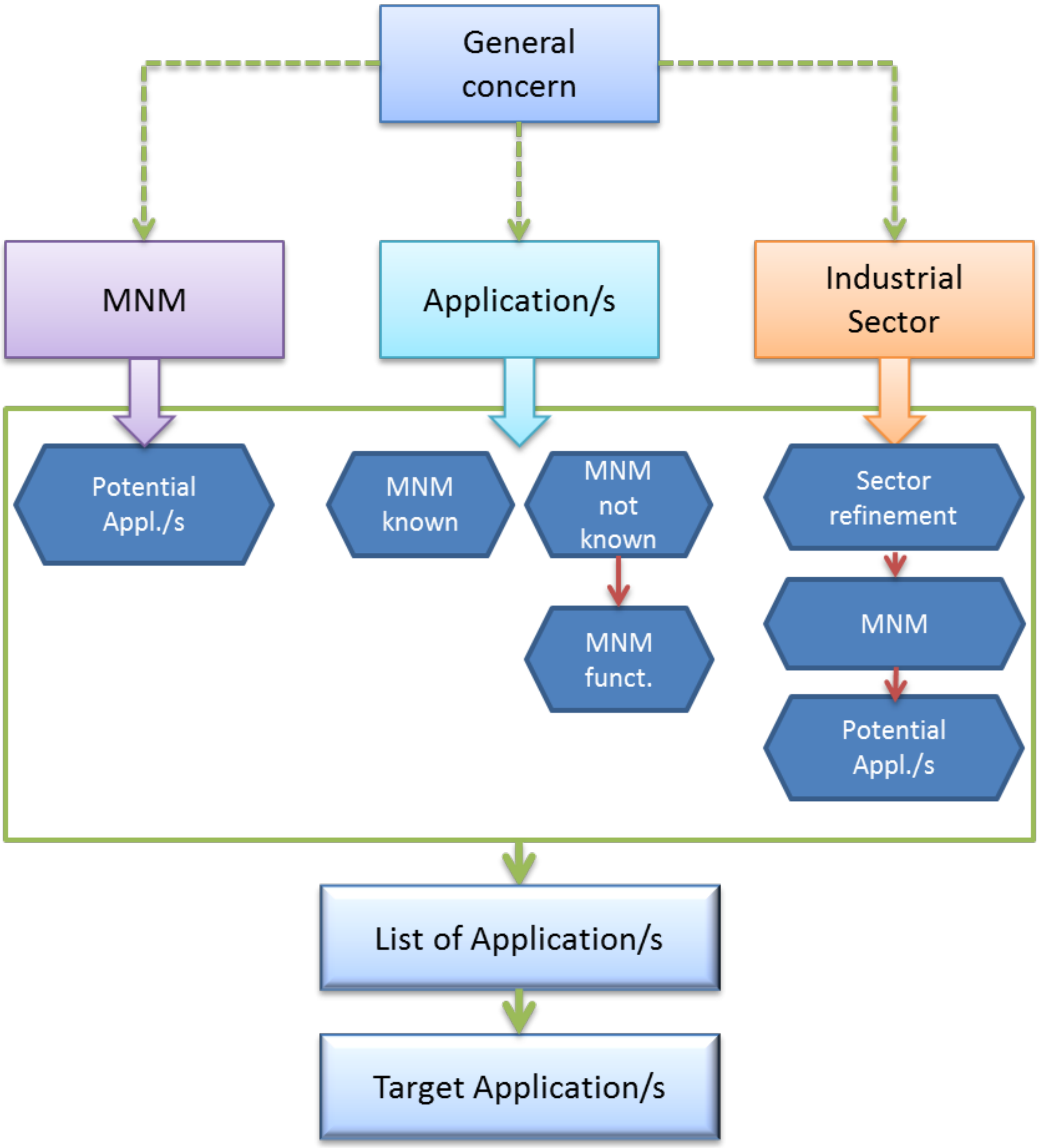


Figure 6. Detailed description of the workflow of the Horizon Scanning phase of the NANoREG Foresight System. Appl/s.: Application/s; MNM: Manufactured Nano Material/s; funct.: functionality

A. General Concern: the first input point is the most general situation, where a regulator is generally concerned about nanotechnology, and he/she wants to know if there are going to be issues or problems for public health, environment, and/or workers. As already highlighted in the previous paragraph (Users, § 2.3.2.2), this kind of scenario is not a workable input for the system as it is designed. To perform a Screening Risk Assessment, there is the need to have a clear scenario, including an application (i.e. MNM and use profile), an exposure profile, potential targets, and expected negative impacts on the targets. Therefore, a generic concern has to be focused, and this can become a really difficult task. Regulators does not have time, usually, to afford a lengthy introduction to nanotechnology applications, and due to the horizontal nature of nanotechnology (KET can be applied in all industrial sectors) it is difficult to effectively cover everything in a short time. Therefore, at this level the selection of the HS focus has to be based on policy issues, and policy criteria, to identify broad sectors. A criterion can be the public perception of nanomaterial for the specific sector. Nanomaterials in food as ingredients are seen as problematic by the public, while nanomaterials in sport equipment or in technological goods (e.g. mobile phones) do not raise concerns by the public. The main issue seems to be immediate exposure to the MNM. On the contrary, specific nanomaterial waste management may not be a public concern right now. Other policy criteria can include worries that regulators may want to address in advance, such as strategic relevance for the national and European economy and scientific competitiveness, huge benefits foreseen for the users and the public in general, and improvement of the national and European budget (reduction of expenses). However, to address these high level criteria, there is the need of an exchange of views with the stakeholder to focus the work, with the inclusion of scientific advisors in the dialogue. It is also true that in Europe there are programs to evaluate the strategic development of nanotechnology (e.g. NANOFUTURES platform) which already are entertaining a dialogue with different stakeholders, and which can be a valid starting point to give indications to regulators, and to identify the main lines of work. The result of this stage can be seen as a mandate including the terms of reference (i.e. why to do the HS, if possible for what application/sector, and what is expected as a result), given by the requesting party.

At the second level there is the actual input point of the Horizon Scanning. There are three possible inputs, that will trigger different procedures to reach the final stage, and each input point can be the result of the focus from the general concern, or an independent input.

a. MNM

The request of the NANoREG foresight system application can be triggered by the identification of a specific nanomaterial, or a group of nanomaterials. For example, graphene is raising a lot of expectations in different industrial fields, but the number of actual applications on the market or near the market are still scarce (http://www.physics.manchester.ac.uk/our-research/research-impact/graphene/; accessed 06/07/2016), and thus it is not possible to collect data about regulatory risk assessment. In this case, the workflow will be based on the identification of all possible and reasonable applications of the MNM, for all sectors. Once the list is drawn, it is necessary to identify the most interesting applications.

Some work on this line was published by Piccinno et al. (2016). In this paper, a Multi-Perspective Application Selection approach, based on the economic, technical, and environmental assessment of different possible applications, was proposed to support companies to identify the best solution to invest in cellulose nanofiber composites. The approach is composed by three main steps:

1. Identification and Segmentation of Application Fields
2. Technical and Economic Viability Score
3. Environmental Advantage and MPAS Score

The part of the methodology that was considered in the NANoREG foresight system is the first, i.e. the Identification and Segmentation of Application Fields. Starting from a MNM, it is possible to identify all its possible uses on the basis of its functionality. For example, in Piccinno et al. (2016), taking the cellulose nanofiber used in polymers as case study, the functions were identified on the basis of literature and known uses of reinforced polymers. Therefore, it is assumed that the final product can be used as the conventional one.

The main functions, identified taking into account the main material properties (i.e. strength, lightweight, biocompatibility), were: Ballistic protection, Fuel Efficiency, Carrying/Structural function, Design, and Human Body Interaction. For each one of these functions, industrial sectors (e.g. body armour, construction, consumer goods, packaging) were identified, and the final category of application (e.g. private airplanes, luxury cars, containers, wind turbines, implants) was selected.

A similar approach can be taken to address the MNM entry point of the Foresight System. A main issue is the identification and selection of information sources. However, a discussion about the data sources in general is reported later on.

b. Application/s

A stakeholder can be interested in a specific application, or set of applications, linked to a specific MNM. It is the reverse of MNM entry point. In this case it is clear the industrial sector and sometimes the type of product (e.g. reflective paint for energy friendly constructions). In some cases, there is also a clear indication of the MNM included in the application. However, the application should not to be already on the EU market. This case is much more focused with respect to the previous one, and it is possible that already a sufficient amount of data is available to properly describe the application. This case resembles the kind of assessment requested by Health Institutions to evaluate the applicability of a new technique or diagnostic tool, to be adopted by the public health services, balancing efficacy, benefits for patients, benefits for the public health services, and safety for the users. The NANoREG foresight system is focused only on safety, but for a short term assessment (i.e. products coming on the market within 1-2 years, or that can be imported in EU market from another country with lower safety and market authorization requirements compared to EU) this case applies.

In some cases, it is possible that only a generic use of nanomaterials in the application is known, but the specific MNM is not known. There can be different MNM with the same functionality, and maybe the stakeholder is really interested in the specific widespread application, with the question: “what if a nanomaterial is used instead of the conventional chemical to obtain the same functionality? Is there going to be a safety problem for human health, environment, or workers?” This can be the case of structural material, e.g. in mobility, where a lighter nano-enabled material can be used instead of the conventional material. The lightweight function can be produced by using different MNM. In this case, the workflow will identify MNM potentially linked to the identified application, and evaluate the different combinations application-MNM as different entities to be assessed by the SRA. As a default, the use profile is the same for the same application, nano implemented or not, therefore the only change would be the specific MNM and its intrinsic properties, which could lead to different environmental fate and hazard profile.

c. Industrial Sector

The third entry point is the most generic one. In this case, only one industrial sector is identified as of-concern, as for example the agrifood sector. The industrial sector can be as generic as “transportation”, or more detailed as for example “pesticides”, or “nutraceuticals”. The more focused is the sector, the more effective the HS can be. For generic indications (like agrifood), and if possible with the support of the stakeholders, the generic industrial sector can be broken down into specific sub-sectors to simplify the analysis. To do so, the NACE codes (http://ec.europa.eu/eurostat/ramon/nomenclatures/index.cfm?TargetUrl=LST_NOM_DTL&StrNom=NACE_REV2) can be used as guidance, as well as open literature and business information sources.

Following the identification and structuring of the identified industrial sector, the workflow will proceed by identifying applications where nanomaterials can be used, on the basis of appropriate sources of information.

List of Applications: all three input points, going through the workflow, will result in a list of applications. Since there is no selection or ranking of applications in the previous steps, the list may include a long list of potentially relevant applications. For each application there is a basic description, including the following points:

- Industry sector (name and NACE code)
- Sub-sector (name and NACE code)
- Generic application name
- Commercial application name (if available, patent)
- Similar conventional products already on the market
- Production method
- Production scale (lab, prototype, industrial)
- Foreseen use
    - Professional
    - Consumer
    - Industrial
- MNM (name and physical-chemical properties)
- MNM function
- Source of information (e.g. Website, News, University press release, Paper Reference, Patent)
- Source quality
- Information type and quality (level of confidence in the information)
- Regulatory Context
    - Existing or missing
    - European/National/Both
    - Nano-specific or not

In order to be able to provide a robust and meaningful SRA estimation, it could be necessary to apply a filtering procedure to the List of Applications. Also, the type and number of applications to assess are linked to available resources, and the skills of the assessment team.

The filtering procedure is a ranking (or grouping) of applications on the basis of relevance for the stakeholder interest and for the ultimate NANoREG foresight system goal, which is to provide an assessment of the safety concern of nanomaterials and related applications potentially reaching the EU market. The criteria to rank the applications at this stage are socio-economic in nature, and may require the interaction with stakeholders and experts.

A report by Thomas Langer (2006), published under the European Network of Health Technology Assessment, and describing the Horizon Scanning Systems about health, argued that often the so called "prioritization process" of applications is done by consensus, being thus more prone to subjectivity. More explicit systems based on clear criteria scored and weighted were discarded for their complexity with respect to the expected results. According to the author, "up to now the specific conditions of priority setting in HSS, particularly the limited availability of data and corresponding resources, complicate the establishment of an explicit and transparent selection process".

In order to keep some transparency into the selection of the applications and to have a homogeneous evaluation, it is anyway necessary to identify a list of criteria to be considered.

Douw and Vondeling (2006) made a review of the selection criteria of Health Applications. Most of the criteria were related to benefits of the application. For example, some criteria used by Horizon Scanning Systems identified by the two authors are:

- Costs at population level (91% of the systems)
- Health benefit at population level (82% of the systems)
- Organizational consequences (73% of the systems)
- Rate of Diffusion (64% of the systems)
- Ethical, Legal, or Social issues (64 % of the systems)
- Number of Patients (55% of the systems)
- Innovativeness of the technology (36% of the systems)
- Cost-effectiveness (27% of the systems)
- Severity of Illness (18% of the systems)
- National policy relevance (18% of the systems)

These criteria were used as guidance in meetings, held by experts working for the Agency in charge of the HS, or by experts contacted by the same Agency. The problem with this system was that most of the time, the list of criteria is not systematically addressed, but more "an on the-back-of-our-mind exercise" is used. Sometimes the impact of one expert opinion will dictate the prioritization results. However, accountability and transparency of decisions taken is essential for the use of HS results by regulators. There cannot be robust data without an assessment of uncertainty and traceability of the decision making, especially in highly uncertain evaluations like a horizon scanning. So, why a certain application has been selected and another was not, has to be clear.

Therefore, for the NANoREG foresight system, a list of criteria to be systematically addressed by the person/s in charge of the filtering process has to be defined. It is important to highlight that at this stage the safety issues are not taken into account, since they are evaluated during the SRA phase. Taking into account a review carried out by the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services (AHRQ, 2013), a list of proposed criteria, which could be adapted to the specific application and in case modified, is listed as follows:

- Estimated level of use (is it going to be widespread?)
- Type of use (what is the target? Is there the possibility of misuse of the application?)
- Sensitive population (is there a sensitive population?)
- Included in EU and/or national economic strategies (is there an economic relevance?)
- Public perception (how is the application seen by the public?)
- Potential benefits (how important are the expected benefits? For which target?)

For each application, even a short answer for all the criteria must be provided, if possible with an indication of the source of the information, if existing: it can be for example a market report, an EU report, an expert opinion, or a peer reviewed scientific paper.

Target application/s: the final result of the HS phase is the identification of target applications, considered relevant for the request posed by the stakeholder/s, and that can be evaluated through the SRA to estimate a qualitative risk assessment for workers health, consumer health, and environmental impacts.

2.3.3.1 Information sources: identification and assessment

To perform the Horizon Scanning it is necessary to collect information on new technologies, MNM, and potential applications. There are several potential sources of information that can be tapped to collect weak signals and potential interesting applications, such as web sites, specialised scientific journals, other HS reports, news and RSS feeds from news services, patents databases, and expert groups. Different sources have different importance for the HS as a whole, and for the different steps of the HS. Different authors proposed metrics to be applied to different aspects of the information source assessment.

A way to measure the importance of different sources of information is to assess them against the HS steps. In particular, within the SESTI project, the importance for different kind of sources in different steps of data collection, processing, and analysis, was evaluated (Amanatidou et al., 2012). SESTI FP7 project (Scanning for Emerging Science and Technology Issues) aimed at contributing to the development of an effective trans-national system for early identification of weak signals and emerging issues. Weak signals are defined as 'warnings (external or internal), events and developments that are still too incomplete to permit an accurate estimation of their impact and/or to determine their complete responses' and have the following characteristics (Amanatidou et al., 2012):

- Articulate credible observations about current or imminent changes (either sudden, gradual, or between these poles).
- Are felt to be potential indications of new emerging issues that may have received insufficient attention.
- Can be meaningfully shared, elaborated and assessed by the participants.

SESTI approach included three different phases:

1. Phase 1: identification of weak signals;
2. Phase 2: processing of weak signals;
3. Phase 3: analysis and interpretation of emerging issues with relevance for policy-making.

The following Table 2, taken from Amanatidou et al. (2012) shows the importance of different information sources for the three phases.

The information concerning MNM, Application/s, and industrial sectors, are weak signals, in the category of technical and scientific developments. Therefore, the assessment in Table 2.3.2.1 is valid also for the Foresight System, and can support the identification of the best information sources to be used.

According to this analysis, the most useful information source is the expert group in all three phases. While discussion with experts is for certain useful and provides focused assessment of potential developments in a specific field, to maintain an expert group and to manage the regular meetings needed to carry out a HS, is posing the need of an organization dedicated to the task. Therefore, while it is true that experts are needed during the phase 3, but also in phase 2, it is difficult and time consuming to consult experts for the collection of weak signals. Other more automatic systems, like internet resources (newsletters, twitter, interest groups) and text mining can be more useful and especially less time consuming. The following weak signal processing, including filtering the collected data, can be done also by using experts and evaluation criteria, and experts can give indications for missing weak signals. Similar to expert reviews, surveys, while providing useful information in second and third phases, need a lot of time to define the right questions, and to find the right panel of experts to answer the survey. Also, the answer rate is normally low, requiring a large number of invited experts to have a sufficient number of responses.

Table 2. Relevance of information sources of the three different phases of the SESTI project approach (Amanatidou et al., 2012).

Table 2. Comparison of tools used in scanning process (rate of appropriateness and usefulness: low, medium, high)

	Phase 1: Identification of weak signals	Phase 2: Processing of weak signals	Phase 3: Analysis and interpretation
Focused expert review	High	High	High
Wiki	Low	Low	Low
Twitter	High	Low	Low
Surveys	Low	High	High
Conferences	Low	Medium	High
Text-mining	Low	Medium	Medium

One important issue is the assessment of the quality of the sources. Looking for weak signals is a time consuming task, and it has to be addressed with the highest efficiency. Smith et al. (2010) evaluated the criteria used to assess and select information sources by the National Horizon Scanning Centre (NHSC) in England. The NHSC is working on the assessment of potential health technologies, and the scope of the work was to update the list of criteria on the basis of a literature review.

Smith et al. (2010), through a refinement process involving the processing of experts opinions through Analytic Hierarchy Process (AHP), a Multi Criteria Decision Analysis approach, derived a set of criteria with a scoring system, and the relative importance of the single criteria (criteria weight).

The result is shown in Table 2 and 3, both taken from Smith et al. (2010). In the NANoREG foresight system, it is proposed to use the criteria developed by Smyth et al. (2010) to evaluate the information sources. Of course it is not possible to evaluate their use in this report, due to lack of dedicated resources and time. However, while applying the system to the case studies, the criteria listed here will be considered in the evaluation of the data quality and will influence the uncertainty of the outcome (sources with lower quality will lead to poorer assessments).

Table 3. Selection criteria for information sources and scoring system for HS usefulness (Smith et al., 2010).

Table 2. Evaluation Criteria, Scores, and Recording System

	Usefulness to horizon scanning				
Factors and description	Very low 0 points	Low 10 points	Moderate 20 points	High 30 points	Score
Accessibility of information: level of effort required	Limited access	Resource intensive: manual scanning of literature	Medium effort: Internet sites, keyword search	Minimal effort: automatic email alerts, links to articles	
Contact point for the source: contact details for further information	No	–	–	Yes	
Cost: level of annual subscription or registration cost	>£1,000	£500–1,000	<£500	Free access	
Coverage: approximate percentage of relevant information in source	<10%	10–50%	50–70%	>70%	
Efficiency of search: estimated time to identify one potentially significant health technology or other relevant information	>1 hour	30–60 minutes	10–30 minutes	<10 minutes	
Frequency of scanning: how often the source information is updated	Yearly or less	Quarterly	Monthly	Daily, twice weekly, weekly, bi-weekly	
Memory: news archive	None	<3 months	3–6 months	>6 months	
Quality of information: should be reliable, accurate, objective	No quality	Questionable quality, elements of bias	Accurate, reliable	Accurate, objective, reliable, author cited	
				Total score:	

Table 4. Weights of the selection criteria for information sources (Smith et al., 2010).

Table 3. Criteria Ranked According to AHP Priority

Horizon analyst 1	AHP priority	Horizon analyst 2	AHP priority	Horizon analyst 3	AHP priority	Horizon analyst 4	AHP priority
Coverage	0.34	Coverage	0.35	Coverage	0.29	Efficiency	0.31
Quality	0.26	Quality	0.27	Quality	0.28	Coverage	0.23
Efficiency	0.16	Efficiency	0.15	Efficiency	0.17	Quality	0.14
Access	0.09	Access	0.08	Access	0.10	Frequency	0.11
Frequency	0.07	Frequency	0.07	Frequency	0.07	Access	0.09
Cost	0.04	Cost	0.03	Cost	0.05	Memory	0.06
Memory	0.03	Memory	0.03	Contact	0.03	Contact	0.04
Contact	0.02	Contact	0.02	Memory	0.02	Cost	0.01

AHP, Analytic Hierarchy Process.

2.3.4 Screening Risk Assessment

The second phase of the NANoREG foresight system is the Screening Risk Assessment (SRA), where the potential impacts of prospective applications are estimated. Since the quantity and quality of information available for the target applications is limited, the SRA is qualitative or semi-quantitative when models are used to estimate impacts. SRA is based on the development of scenarios in the form of risk hypotheses, as in the Problem Formulation phase of Ecological Risk Assessment (US-EPA, 1998; chapter 2.2.6). The detailed workflow of the SRA phase is shown in Figure 7.

2.3.4.1 Life Cycle profile

The input of the SRA is the Target Application/s as defined in the HS phase. For each application, following the Life Cycle thinking, all steps of the MNM and Application/s, from the production to the end of life, are addressed. This step is similar to the second step of the Nano Risk Framework (Environmental Defense – DuPont, 2007[1]), where nanomaterial's properties, inherent hazards, and associated exposures profiles are defined for each life cycle step. The considered Life Cycle (LC) steps are material sourcing, production and use, and end-of-life disposal or recycling. The Framework also provides templates of base sets of data to be collected to assess risks of nanomaterials and nano-products.

A similar approach is followed in the NANoREG foresight system. To build a life cycle profile of an innovative and potential application is not as building the life cycle profile of an existing product. However, the majority of innovative products are not different than existing products in their use profile. The final function of the product is the same (e.g. a paint), but the inclusion of MNM in the product is done to improve the functionality or add new functions, changing the risk of the product. In some cases, it can be that a nanotechnology/nanomaterial can lead to a completely new product, never placed on the market, with a function that may not be yet available. In this case, it is much more difficult to develop the life cycle profile, since there are no points of reference.

Life Cycle description is a common step in recently proposed risk assessment approaches for nanomaterials, therefore there is no need to go into details. For the scope of D6.1, only few indications are given, taking into account that little information on most of the LC is available for innovative MNM and their applications.

The four life cycle steps to be considered are:

- Production (of MNM and of the product)
- Use
- Recycling/Disposal

For each stage, a description of the MNM properties, application and/or product, and processes and activities to which MNM and application/products are subjected to, is reported, with an indication of the available data. Also, potential targets are identified (e.g. environment). A list of information that could be useful in the subsequent steps of the SRA is reported below.

The result of this step is a Life Cycle profile of the Target Application/s, including some basic data useful to build the risk hypotheses.

[1] Environmental Defense and DuPont, 2007. Nano Risk Framework (http://qsinano.com/wp-content/uploads/2014/05/nano_risk_framework_dupont.pdf)

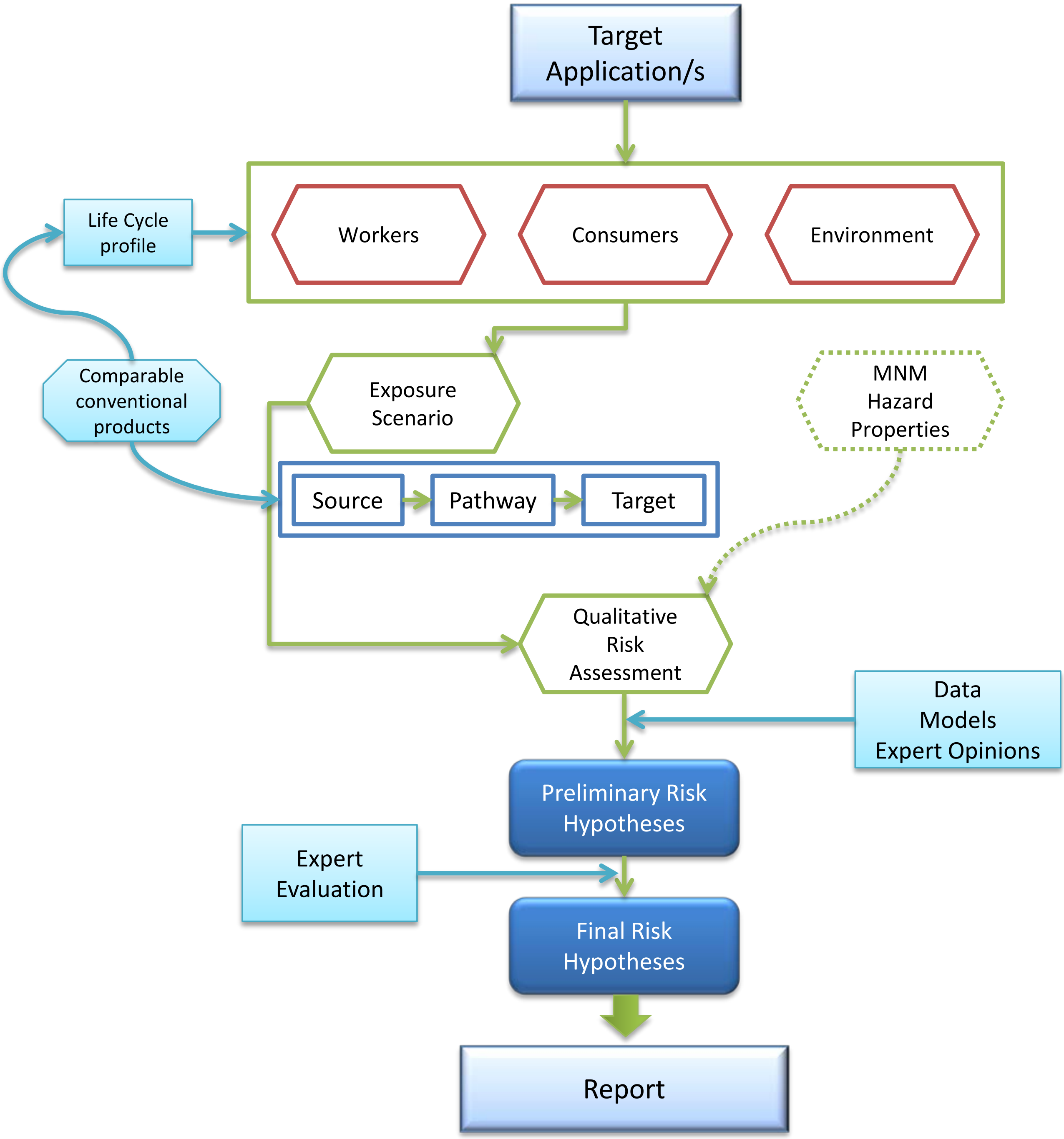


Figure 7. Screening Risk Assessment workflow, with main inputs (light blue boxes) and outputs (dark blue boxes).

2.3.4.1.1 Production

Production phase is important for the assessment of impacts on workers and the environment. Given the nature of the applications assessed in the NANoREG foresight system, it is often not possible to rely on detailed information about the production processes. An exception can be the case when the target application is a MNM-based version of the conventional application, for which production processes are well known, and where only the implications of MNM inclusion in the process have to be assessed. For example, MNM handling and processing, cleaning, and product packaging. In all other cases, the assessment has to rely on reasonable assumptions, justified by the existence of similar or applicable procedures. In this phase, also potential for Risk Management Measures implementation has to be considered.

Concerning the hazard side, given the nature of the NANoREG foresight system, it is not possible to perform testing on innovative MNM to measure hazard endpoints. Therefore, it is necessary to use the available information, also on bulk form if possible.

MNM production

Information	Why
Production scale	Different production scales are an indication of the possibility to collect data and indicate the potential target, including number of involved workers, and applicable protection devices and risk management measures. It is also an indication of the position of the innovation along the Innovation Chain.
Production process	It supports the assessment of potential for release (e.g. open/closed step, high/low energy process).
MNM properties	MNM phys-chem properties and MNM form are useful to evaluate exposure (e.g. dustiness, powder or liquid form), and at the same time to potentially evaluate hazardous properties.
Wastes	How are wastes handled? Can the MNM end up in the environment?

Application/product production

Information	Why
Production scale	Different production scales are an indication of the possibility to collect data and indicate the potential target, including number of involved workers, and applicable protection devices and risk management measures. It is also an indication of the position of the innovation along the Innovation Chain.
Production process	Production process may not be available. However, if there is a pilot plant or if the focus of the analysis is a MNM-based version of a common application/product, where the MNM is just another component, it is possible to gather information about this point. It supports the assessment of potential for release (e.g. open/closed step, high/low energy process).
Amount	Amount included in the application/product is a measure of the potential amount dispersed in the working and external environment. It is not easy to have this data, but for more advanced applications, it can be available.
MNM properties	MNM phys-chem properties and MNM form are useful to evaluate exposure potential (e.g. powder or liquid form, fixed in matrix), and at the same time to potentially evaluate hazardous properties.

2.3.4.1.2 Use

Use phase is relevant for professional users, consumers, and for the environment. In this part of the Life Cycle, what’s relevant to known for the system scope is the use profile of the application, leading to the assessment of the exposure potential to the MNM. Also in this case, the existence of similar conventional applications can support the definition of specific MNM-related issues. In all other cases, reasonable assumptions have to be made.

Information	Why
Type of product	The type of product/application (e.g. powder, mobile phone, solar panel, medicine) is essential to identify potential exposure pathways and the main target. It also can give an indication of the potential market and level of use.
Similar conventional	Useful to support the collection of data.

products	
Frequency of use	It gives an idea of the frequency of contact with the product/application.
MNM properties	MNM phys-chem properties and MNM form are useful to evaluate exposure (e.g. dustiness, powder or liquid form), and at the same time to potentially evaluate hazardous properties. MNM may change form during its LC, and this has to be considered.
Wastes	How are wastes handled? Can the MNM end up in the environment?

2.3.4.2 Exposure Scenarios

Once the Life Cycle profile of the Target Application/s is defined, a set of Exposure Scenarios (ES) are built. This step concerns the organization of the information in scenarios that are developed taking into account the technology description and the Life Cycle profile. This phase requires a creative thinking, because wild cards (unexpected events) should be factored in the scenarios in some way. Different expertise sources can give this kind of input and diversity across the expertise base can facilitate creativity. Since innovative applications are not fully known in terms of characteristics and use profile, information on comparable applications can be useful to fill in the gaps and predict elements of the ES.

As shown in Figure 7, the Exposure Scenarios are defined with three main elements:

1. Source: this element describes what is the source of the MNM (i.e. the stressor), how the MNM is released, and in which environmental compartment (e.g. air, surface water, groundwater, sediments, soil) or matrices (e.g. food). A Source can be the point of Application production, the MNM processing, the Application/product itself during use;
2. Pathway: this element characterizes the pathway that the MNM takes to reach the target, and what happens to the MNM along the way. From the point of release to the target, through the environmental compartment or in matrices, the MNM can be physically and chemically modified, it can be diluted, or remain unchanged until reaching the target. In this element all these processes are taken into account, including the time to reach the target, aiming at identifying the actual stressor form to which the target is exposed to. This part of the Exposure Scenario is difficult to elaborate for MNM, since apart from generic environmental processes, and the growing knowledge on MNM aging, very little is known on MNM transformations, especially for novel nanomaterials not included in the “usual suspects” category (e.g. TiO_2, SiO_2, Ag). However, the main scope of Exposure Scenario is to identify where is the MNM going to, and how it is reaching the target. For missing data, reasonable assumptions can be made, and in any case lack of knowledge can be managed by transparently highlighting the potential for unknown risks.
3. Target: the last element is the target, which includes workers, consumers, and environment. “Workers” are only the industry workers, i.e. people producing MNM and related Applications, or intermediate products going to other industries. “Consumers” includes both generic consumers, using the final product, and professional users. The profile of the professional user is considered different than the one of workers, since there is lower possibility to control exposure, also due to the potential lack of a safety management system. Professional use is also the professional applying a nano-paint in a household: the user in this scenario may not be aware of the additional safety precaution to be taken, and not only for his health, but also for the environment (e.g. cleaning the paint container in a sink not connected to the wastewater treatment plant). Environment here is considered as a target, and not as a pathway. Therefore, the MNM ending up in water can cause adverse effects on the water biota, but also to humans via food chain, or ending up in drinking water via rivers or groundwater pollution (this is a common scenario for conventional chemicals).

2.3.4.3 Preliminary Risk Hypotheses

Once developed, the ES are combine with information about hazard of MNM included in the Application/s. Hazard data will probably be not available for the specific MNM. However, as established for other risk management approaches, CLP-like hazard classification schemes can be applied on the basis of other data.

This kind of approach will probably not be applicable to completely new nanomaterials, for which a bulk counterpart does not exist.

The combination of exposure scenario for each relevant the Life Cycle stages, and the Hazard information (when available), leads to the formulation of a set of Preliminary Risk Hypotheses (PRHs). A Risk Hypothesis is the proposed answer to questions risk assessors have about what responses targets will show when they are exposed to stressors and how exposure will occur. In other words, they represent assumptions about the potential risks for the selected targets. Assumptions can be based on theory and logic, empirical data, mathematical models, or probability models. Risk hypotheses are formulated using a combination of professional judgment and available information, integrating the results of the first two SRA steps (i.e. Life Cycle profile and Exposure Scenarios, i.e. potential sources of MNM, MNM characteristics, and observed or predicted adverse effects on potential targets.

Therefore, to formulate a Risk Hypothesis, it is necessary to use tools to elaborate the available information. In the Foresight System, the input information is semi-quantitative at best; therefore, it is not possible to expect the application of sophisticated models. However, a set of qualitative tools were developed to rank and categorize risks posed by MNM. For example, NanoRiskCat, Stoffenmanager Nano, etc. Also in NANoREG, there are some tools such as the D3.1, where critical exposure potential in the value chain was identified for the project core nanomaterials. This work can be used as basis to evaluate the exposure potential of MNM on the basis of similarity with the MNM used in the Target Application/s.

Graphical Risk Hypotheses are accompanied by a text explaining in the highest possible detail the data that were used, the quality of such data, the related uncertainty, and the justification for the selection of that specific Hypothesis.

2.3.4.4 Final Risk Hypotheses

A set of PRHs is identified on the basis of data collected from different sources. However, it is always possible that this process would miss some key information, maybe available only to experts and industry directly involved in the field and that were not included in the HS or SRA process until this time. Therefore, the PRHs should ideally be evaluated by a group of experts, to identify missing points, such as potential uses, MNM transformation, and potential adverse effects. A workshop is organized with a limited number of experts of the different aspects of the PRHs, including MNM applications, uses, environmental behaviour, and toxicity. To this panel it is possible to add representatives of regulators, ideally the regulator that asked the application of the NANoREG foresight system in the first place, to give an impression about the ability of the PRHs to answer the question asked. In a half day discussion the generated Hypotheses are assessed and the result will be a list of Final Risk Hypotheses (FRHs), which should include all possible reasonable scenarios, as well as some less likely hypotheses. The FRHs are evaluated again, looking for additional data and information, and the results are then included in the Final Report.

2.3.4.5 Final Report

The information generated in the whole NANoREG foresight system is summarised in the Final Report. The Report is organized with the following content:

1. Technical description of the Application and the associated MNM life cycle;
2. Why was the Application selected (criteria used);
3. Regulatory framework;
4. What are the data sources;
5. Description of evaluated Risk Hypotheses;
6. Where are the data coming from, and what is their quality;
7. The result of risk assessment
8. Summary Conclusion and Recommendations

The Report aims at being short and effective, as a text useful for regulators. Besides the Report, all the information collected during the assessment will be kept and provided if requested as a technical file.

2.4 Case study

To evaluate the NANoREG foresight system proposal, a case study was identified. The case study will allow describing in a more practical way the different parts of the proposal, without any proposed methodology validation purpose.

The selected case study is **graphene**. This case study represents an example of the MNM entry point. The first aspect to consider is to justify the selection of graphene as interesting for regulators. The second aspect is to focus the analysis on the target applications, taking into account the fact that the proposed NANoREG foresight system has to concern the future applications.

Disclaimer: the case study is described on the basis of the knowledge of the report writer only, which is limited to risk assessment of nanomaterials. Therefore, the case study will lack the insight provided by experts in graphene application, toxicity, and life cycle. In reality, applications and risk assessment has to be performed by a group of experts in different related fields.

2.4.1 Graphene relevance for regulators

To justify the selection of graphene as a case study, we will focus on market, technological considerations, and investments level. The sources of this information are summaries of market studies and published reviews on growth of graphene market and related nanomaterials (e.g. graphene oxide), and a list of all potential graphene uses. These two aspects can justify a potential interest by regulators for graphene because they entail the assessment of the amount of graphene available on the market, the diffusion in different and strategically relevant industry sectors, and the possibility to evaluate future applications beforehand.

2.4.1.1 Market studies

Market studies available on the internet show a significant expected growth of the global market, with a range of foreseen Compounded Average Growth Rate (CAGR). There are different predictions, as listed below, for graphene as such, graphene-based products, and specific sectors. The data shows that the foreseen economic growth for graphene and graphene applications is considered significant in the next 5 to 10 years.

- 46.8% in the period 2014-2020 for graphene (http://www.marketsandmarkets.com/PressReleases/graphene-electronics.asp, accessed 06/09/2016);
- 46.3% in the period 2016-2015 for graphene-enabled products (http://www.hawaiinewsnow.com/story/32718525/global-graphene-based-products-market-to-reach-21-billion-by-2025-capacitors-worth-625-million-by-2025-research-and-markets, accessed 06/09/2016);
- 42.1% in the period 2014-2022 for graphene (http://www.marketresearchstore.com/report/graphene-market-outlook-global-trends-forecast-and-37805, accessed 06/09/2016);
- 60.7% in the period 2014-2015 for global graphene electronic market (http://www.transparencymarketresearch.com/pressrelease/global-graphene-electronics-market.htm, accessed 06/09/2016);
- 44.0% in the period 2014-2020 for graphene (http://www.azonano.com/news.aspx?newsID=31314, accessed 06/09/2016).

Another way to look at growth is to summarize the actual value of the graphene market. However, to collect detailed data about this kind of information is difficult. Since all market reports are available only after purchase and they are quite expensive, the information reported here is taken from what's available in the report summary on the website. Some figures are reported in Table 5. The figures for graphene as nanomaterial are quite variable, ranging for 2020 forecast (rather close horizon), from 125 M$ to 278M$ (roughly a 2x difference), and for around 10 years from now, from 160 M$ to 400 M$. For comparison, the global value of titanium dioxide nano in coatings and paintings is forecasted to grow from 56.8 M$ in 2015 to 99.50 M$ in 2020, while a growth to 189 M$ in 2020 is expected for use in personal care products (http://www.businesswire.com/news/home/20160902005029/en/Titanium-Dioxide-Nanomaterials-Market-Witness-Dominance-Personal, accessed 06/09/2016). It is also important to look at the graphene-enabled product market. For example, BCC research (Table 4) shows a global value of products around 2.1 B$ by

2025, and that the graphene electronic market will reach 1.2 B$ in 2025 (Transparency Market Research, 2015).

Table 5. Some examples of graphene market values forecasts included in market forecasts.

Company	2015	2020	2025	Amount produced	Notes
BCC research[1]	1.5 M$	310.4 M$	2.1 B$		
IDTechEx[2]			220 M$ (2026)	3.8 kt/y (2026)	Energy storage and composites will grow to be the largest sectors, controlling 25% and 40% of the market in 2026, respectively.
Global Industry Analyst[3]		125 M$			Figure 9 for a summary.
Markets and Markets[4]		278.45 M$			
Allied Market Research[5]		149.1 M$			Figure 10 for details
Transparency Market Research[6]			159.2 M$ (2023)		The electronics segment is leading the global graphene market. As of 2014 this segment held a leading share of 32.5% in the overall market, which is expected to reach 34.7% by the end of 2023.
Global Market Insight[7]			400 M$ (2023)	9 kt/y (2017)	
Grand View Research[8]				Around 500 t/y (2020 in USA). (Figure 8)	

[1]: http://www.bccresearch.com/market-research/advanced-materials/graphene-technologies-applications-markets-report-avm075d.html, value of graphene-based products; [2]: http://www.idtechex.com/research/reports/graphene-2d-materials-and-carbon-nanotubes-markets-technologies-and-opportunities-2016-2026-000465.asp, graphene value; [3]: http://www.strategyr.com/MarketResearch/Graphene_Market_Trends.asp, graphene value; [4]: http://www.marketsandmarkets.com/PressReleases/graphene.asp, graphene value; [5]: https://www.alliedmarketresearch.com/graphene-market, graphene value; [6]: http://www.transparencymarketresearch.com/graphene-market.html, graphene value; [7]: https://www.gminsights.com/industry-analysis/graphene-market-, graphene value; [8]: http://www.grandviewresearch.com/industry-analysis/graphene-industry, graphene value;

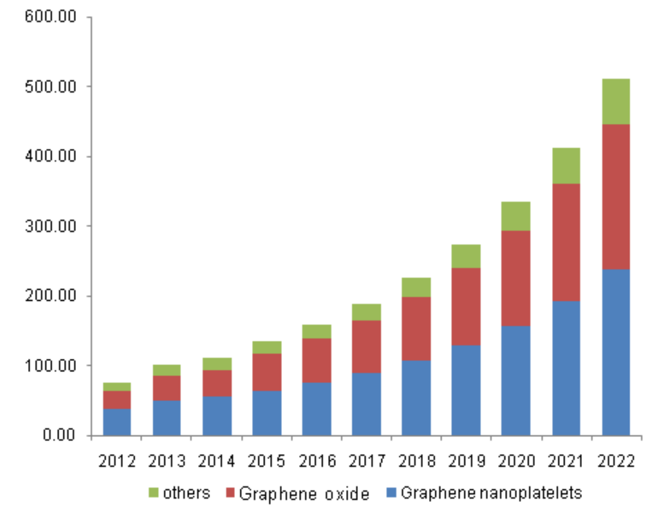


Figure 8. U.S. graphene market volume, by product, 2012 - 2022 (Tons)

2.4.1.2 *Expected applications*

Graphene is considered the “wonder material”, because its properties allow for improvement of different industrial applications. According to Ferrari et al. (2015), graphene has the potential to become a disruptive technology, i.e. to be able to create its own *not incremental* applications. Graphene is expected to have a major impact on electronic applications (e.g. high-frequency devices, touch screens, flexible and wearable devices, ultrasensitive sensors), energy field (e.g. supercapacitators), and medicine (e.g. diagnosis and drug delivery). According to Global Industry Analyst, the faster growing applications for graphene in 2020 are super capacitators, sensors, and high strength composites (Figure 9), while for Allied Market Research the main applications by sectors are energy, life sciences, coatings, defence, electronics, aerospace, automotive, composites, and sensors (Figure 10). Also, IDTechEx Research forecasts that energy storage and composites will grow to be the largest sectors, controlling 25% and 40% of the market in 2026, respectively.

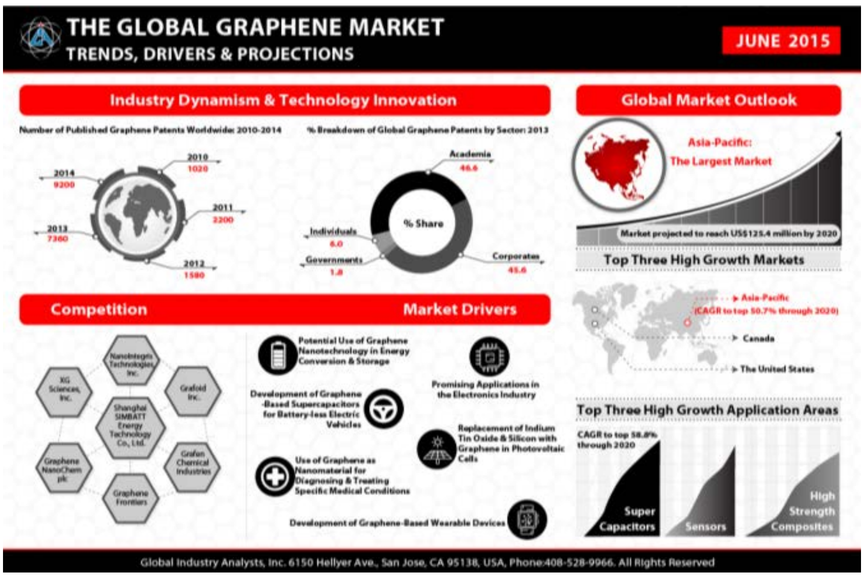


Figure 9. Summary of most promising applications (http://www.strategyr.com/MarketResearch/Graphene_Market_Trends.asp)

Zurutuza and Marinelli (2014), reports some niches applications of graphene:

- DNA sequencing: nanopores in graphene could enable the sequencing of DNA.
- Membranes and filtration system for water purification: graphene could provide both chemical and mechanical filtering.

- Thermal management applications: graphene-containing metal, ceramic and polymer matrix composites could provide thermal interface materials and heat spreaders.
- Photodetectors: graphene could enable high-responsivity detectors for light harvesting and ultrafast detectors for digital photon counting in medical imaging.
- Organic LEDs (OLEDs) and displays: graphene-based transparent conductors could add flexibility in OLEDs, displays and touch-screen applications.
- III–V semiconductor growth: graphene could be used as a substrate for growing high-quality semiconductor materials such as gallium nitride (GaN).
- Anticorrosion coatings: graphene-enabled anticorrosion coatings could provide a replacement for carcinogenic chromate-based primers in steel and aluminium materials.
- Novel lubricants: graphene could be a dry, thin-film lubricant used in low-wear and high-precision components such as ball bearings, watch mechanisms, sealed mechanical systems and engine components optimized for harsh environments.

Figure 10. Summary of most promising applications (https://www.alliedmarketresearch.com/graphene-market).

All these potentially disruptive applications can bear huge technological benefits for society, but not all of them are at the same stage of technological readiness level (TRL). According to Deloitte (2015), the status of graphene development is mostly at the research stage, while market applications will reach their maturity in the next ten years. Also Ferrari et al. (2015) shows that consumer products can be expected by 2025-2030. A commentary by Zurutuza and Marinelli, published in 2014, shows a graph reporting the TRL level of different potential applications of graphene (Figure 11).

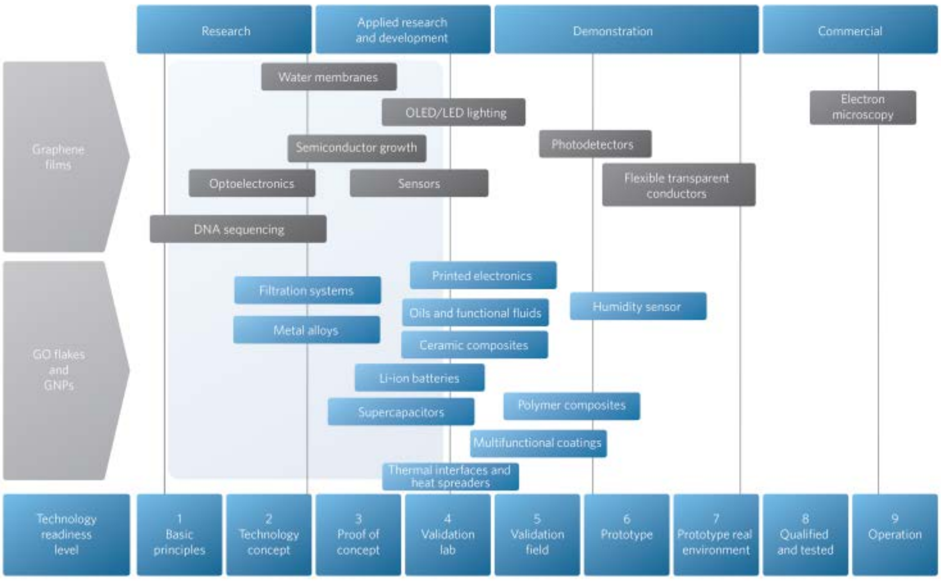


Figure 11. TRL of graphene applications (Zurutuza and Marinelli, 2014).

2.4.1.3 Research and patenting

Graphene and its derivations (e.g. graphene oxides) are increasingly being proposed, in research laboratories around the world, as a good material useful to generate a variety of beneficial applications. A 2014 commentary, by Zurutuza and Marinelli, shows a steeper increase of patents from 2010 to 2013 with respect to other benchmark materials such as carbon nanotubes (Figure 12).

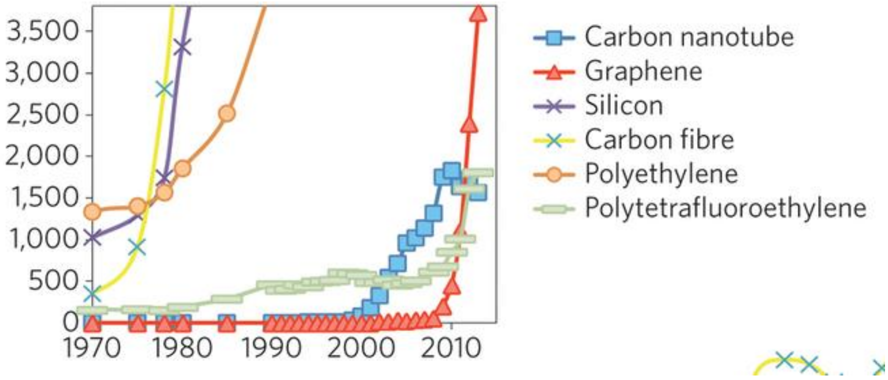


Figure 12. Number of patent applications and granted patents by first publication date (adapted from Zurutuza and Marinelli, 2014).

A search carried out on patents granted globally on Espacenet website (https://www.epo.org/searching-for-patents/technical/espacenet.html#tab1), from 2010 to 2016, showed the following results (Figure 13):

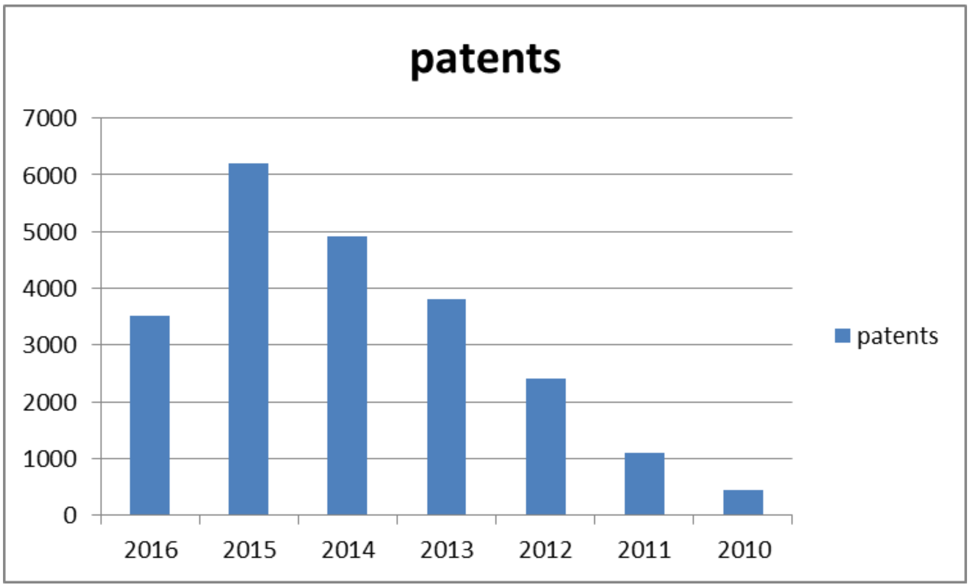


Figure 13. Number of patents in Espacenet, containing the word "graphene" in the title or abstract.

Ferrari et al. (2015) published a similar analysis of the sectors of patents up to July 2014, obtaining the following figure (Figure 14):

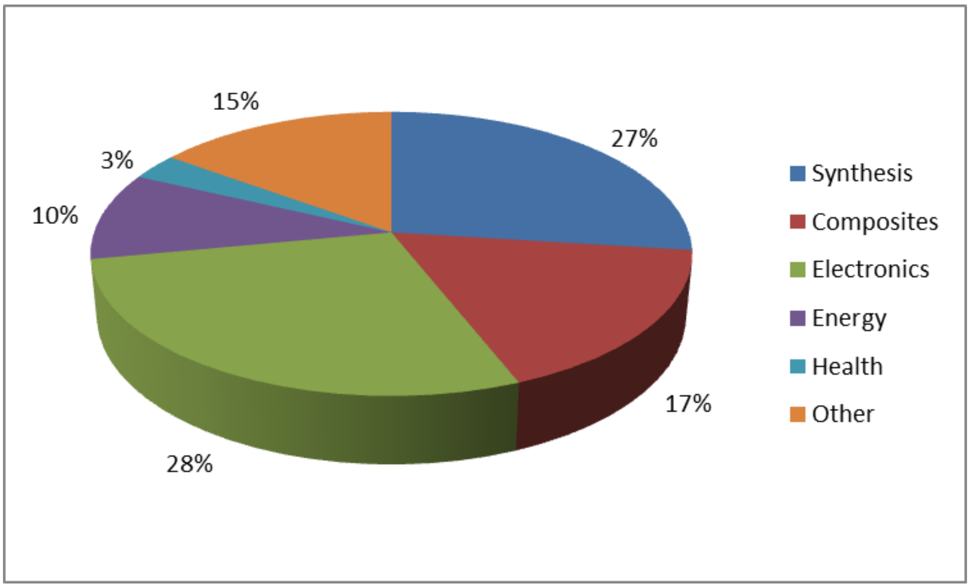


Figure 14. Sectors of patents up to July 2014. Adapted from Ferrari et al., 2015

Finally, another indicator about the growing interest in graphene, especially at research stage, is shown by the growth of publications (Figure 15). The research was carried out in Scopus, by searching papers for the word "graphene". In the same research, an indication of covered subjects in the period 2010-2016 is shown (Figure 16).

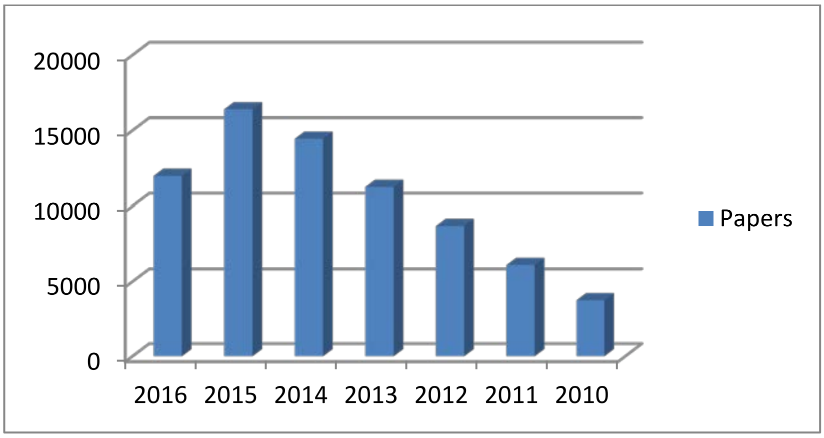


Figure 15. Number of papers in Scopus containing the word "graphene" in title, abstract or keywords.

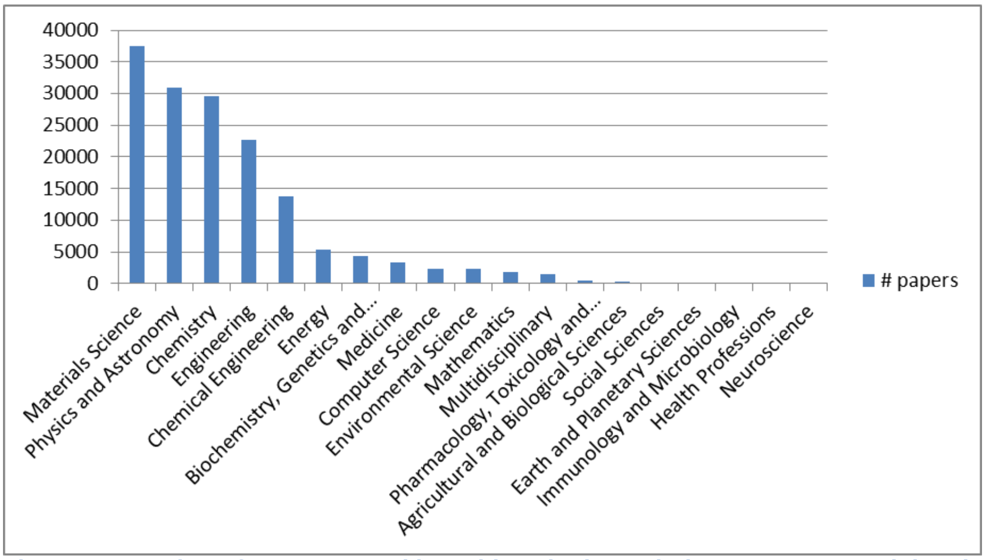


Figure 16. Number of papers sorted by subject, in the period 2010-2016, containing the word "graphene" in the title, abstract, or keywords. Search in Scopus.

2.4.1.4 Regulatory relevance of graphene for future innovation

Overall, taking into account all the reported data and information, graphene is a material that is showing a growing interest at research level, with an increasing number of both research publications and patents. The main fields of application are electronics, composites, and energy, followed by medicine and biosciences and environmental applications.

The expected market in the next 10 years will be covered mostly by applications related to energy, sensors, and composites. Medical applications, while still as niche, is relevant because of the potential benefits for the patients and the societal impact on target groups such as elderly, e.g. for personalize medicine and sensors for on-line diagnosis.

The European Commission (EC) launched in 2013 the Graphene Flagship, a Future and Emerging Technology initiative which has the scope of bringing together academic and industrial researchers to take graphene from the realm of academic laboratories into European society in the space of 10 years, thus generating economic growth, new jobs and new opportunities. The initiative has a budget of 1 B€.

From a regulatory safety perspective, graphene represents a potentially disruptive technology creating its own applications (therefore, not comparable to existing applications), with a full market potential achievable in 10-15 years, and with a spectrum of applications that can potentially reach a wide portion of the population.

The investment of resources both by the EC and private enterprises requires a proactive approach, carrying out an assessment of the potential adverse impacts of foreseen applications, to assure a good social and economic return.

2.4.2 Horizon scanning: Identification of Target Applications

The first phase of the NANoREG foresight system is the identification of the target application/s. Since we are dealing with a MNM that has a set of potential applications, there is the need to evaluate the range of applications to identify what can be of interest for stakeholder, regulators *in primis*. The main source of information to draw the whole picture of graphene applications is the graphene European strategic roadmap written by Ferrari et al. (2015) in the context of the European graphene flagship. The selection of this source is based on the credibility of the content, the amount of reviewed papers and sources (2344), and the link to a European initiative.

An overall picture of the uses of graphene and the timeline for their implementation is in Figure 17.

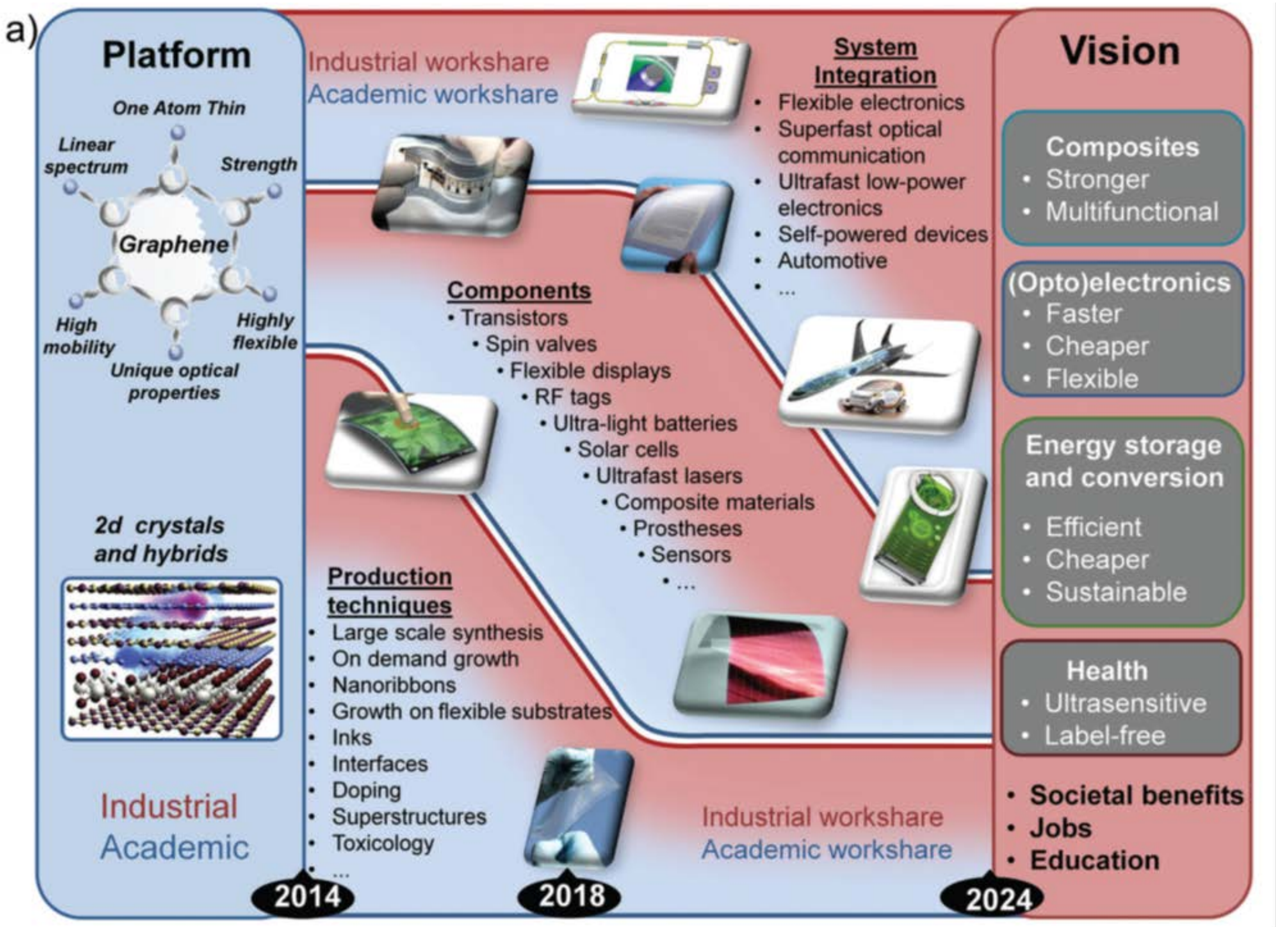


Figure 17. Summary of graphene applications and timeline for their implementation. From Ferrari et al., 2015.

Without entering into details that can be retrieved from the roadmap, the main application fields are: electronics, energy, and composites. In turn, the products and applications that can be foreseen may find place in different industry sectors, such as automotive, sport goods, health and medicine, environmental monitoring and remediation, ITC, consumer electronic devices, military and defence, just to name few. Looking into the roadmap, a summary table with all applications and timeline was compiled (Table 6).

Table 6. Overview of development of graphene applications, and examples of industry sectors.

Sector	2018	2020	2024 and >	Industry sectors
Electronics	Flexible screens and foils (e.g. OLED)	Flexible screens and foils (e.g. OLED)	Transistors	Electronic consumer goods (mobile phones, computers, wearable electronics, ITC) Electronic industry applications
Spintronics		CMOS devices, data storage	CMOS devices, data storage	Electronic consumer goods (mobile phones, computers, wearable electronics, ITC) Electronic industry applications
Photonics and optoelectronics	Photodetectors	Fibre lasers Photodetectors Plasmon detectors	Systems implementation (e.g. spectrometers, optoelectronic systems)	
Sensors	Mass sensors	Pressure sensors Chemical sensors	Plasmonic read sensors Piezoresistive devices Capacitative devices Magnetic field sensors	Environmental monitoring Health and Safety Defence Biological safety
Flexible electronics	Wearable smart devices for sensing and connectivity Chemical and biosensors	Flexible and portable devices Flexible energy harvesting and storage devices	RFD connectivity Flexible mobile phones Integrated smart sensors units	Consumer electronics Domotic Personal healthcare Industrial processes Internet of things Printed sensors and antennas Food traceability Photovoltaic panels Inks
Energy Storage and conversion		Fuel cells Photovoltaic cells	Flexible photovoltaic cells Flexible energy and H_2 storage Super capacitators	Renewable energy production Smart energy grids Fully electric cars

Composites	Functional composites for packaging Hybrid composites		Functional composites for mechanical, photonic and energy applications	Avionic/space Automotive Security Sport goods Food, pharmaceuticals, and cosmetic packaging Lab on chip devices
Biomedical applications		Delivery systems Electrochemical sensors	Imaging platforms Delivery systems	Diagnosis Theranostic Therapy Targeted drug delivery Prostheses, implantable medical devices

2.4.2.1 List of applications

The first result of the horizon scanning should be a list of applications, with a detailed description of each one of them, as reported in § 2.3.3. However, for this case study, which may include a lot of potential applications, it does not make sense to list all of them and devote resources to the identification of the information to describe each single application. The adopted strategy is to directly describe the target applications, identified by using the criteria as modified from AHRQ (2013), and listed in page 37 of this report. Table 6 can be considered a good list to allow for the selection of the target applications.

2.4.2.2 Target applications

To select the target applications, it was used the Table 6 list and the main field of development of graphene in the next 5 years (see Figures 10 and 11). Three target applications are selected, trying to cover the three main sectors as identified by Global Industry Analyst: energy, composites, and electronics. For the scope of the NANoREG foresight system implementation, only potential applications, in a very low TRL (1-3), should be selected (see Fig. 11).

Taking into account the selection criteria for target applications, which are listed here (page 37), the three following specific applications were selected:

1. **Energy**: <u>supercapacitators</u>. The growth of renewable energy production, both household and industrial, the trend toward the development and use of full electric mobility, would need the production of better, more flexible, energy storage solutions, able to store energy in excess and release it when needed (e.g. lack of light, wind), to reduce weight of energy storage systems in automotive, and to allow the development of smart grids. Also mobile electronics could benefit from the development of smaller "energy units", with a faster charge time. These applications would point toward a widespread use. The affected population is including workers and consumers, while it is difficult to identify a specific sensitive population for this application. The disposal of electronic devices is a point in the life cycle of the application that has to be evaluated, due to the potential impact on the environment. There is a clear economic relevance, from both industry and governments, as a component of the new energy infrastructure, at a global scale. The public perception is not clear, but usually, innovation in the energy sectors related to the renewable and green energy production are seen as beneficial.
2. **Composites**: <u>filtration membranes</u>. In this case, filtration membranes are used in environmental settings, to clean-up contaminated water and soils. For example, membranes composed by hybrids of

graphene (G) and layered double hydroxides (LDHs) possess increased adsorption properties (a 62% increase with only 7% addition of graphene), and it has a large surface area and mesoporous characteristics. The nano-hybrid adsorbent can also be regenerated. This polymer can be used to remove heavy metals and organic compounds from water. Other applications are linked to the creation of composites to generate steam and drinkable water, by using bio-foams with embedded graphene oxide. Other material scan also be embedded in to the aerogel to act on harmful bacteria and contaminants present in water. The potential level of use is not entirely clear, but applications in contaminated sites (industrially polluted soils), to make water potable in difficult geographical areas (e.g. removal of arsenic from naturally polluted groundwater) can be envisaged. Small scale applications (like households systems) can be possible, but there is no information right now to evaluate this possibility. The main target besides workers making the filters is the environment, both through direct and indirect exposure (disposal). Consumer exposure is possible in theory, considering that graphene may be released from the polymer, but this hypothesis has to be evaluated. Concerning the economic relevance, clean and drinkable water available for all is one of the main issues of global disparity.

3. **Electronics**: sensors. Sensors can be use in a variety of applications, from mobile communication to chemicals and radiation detection. In this case, the specific application is the development of sensors to detect pesticides in food. This application is part of the 2050 food system guideline promoted by the European Commission. Biosensors may allow faster and more reliable analysis, with cheaper and portable tools. In this case, we are talking about electrochemical sensors that allow detection of pesticides in food at low concentrations (from 10^{-7} to 10^{-15} M). Validation of sensors is not available yet, but it is a promising application. Portable systems made by printing technology can be used in situ, directly in the farm or in industry, to identify critical quality conditions in raw food, without extraction. Also, lab-o-chip applications in laboratory could allow for High Throughput analysis lowering the overall cost of the quality controls. This kind of sensors are potentially a game changer in food industry, since their incorporation into the production line could allow a real time control, cheaper and faster than the current quality control process. Therefore it is possible to infer a widespread use, in the field and in industry, but also on smart and intelligent packaging, thus reaching the consumer market and a larger diffusion. While nanomaterials as food components are not positively accepted by consumers, the position toward nanotechnology in food packaging and to assure food safety is less critical in the public opinion.

For each application a template is filled in as shown below. One example is made here for the water filtration application. The reason for this selection is that according to a study of 2013 (Gupta et al., 2013) comparing the perception of different nanomaterial applications (i.e. targeted drug delivery, smart pesticide, nano food, food packaging, water filtration), water filtration was considered by 67 experts coming from different countries: the second mostly beneficial (close to drug targeted delivery), lowest risk perception, second in necessity perception, with a medium high concern about coming in contact with the nanomaterials, and a low to medium time to market. Therefore it represents an application of graphene that can be of interest for a regulator.

Table 7. Case study summary information: water filtering membrane

Industry sector	Novel materials, Water treatment
Generic application name	Nanocomposites
Products already or close to the market	e.g. G2O water membranes (coating existing membranes with graphene oxide) (http://g2o.co/); it is a start-up.
Nanocomposite production method	Starting from graphene, different approaches are used to link graphene to polymer, and in case, to functionalize the graphene layer. An example is The “graft to” method uses the functional groups of polymers to attach graphene to the polymer matrix, via regular chemical reactions or thermal treatment. The “graft from” methods include polymerization, chemical oxidation, and electrochemical polymerization
Nanocomposite production scale	Currently mostly lab scale. No scale up hypothesis available at this point.
Foreseen use	Mainly Industrial and Professional, less for Consumers at this stage

MNM	Graphene, Graphene Oxide
MNM function	Act as sorbent for chemicals (heavy metals) from water increasing the adsorption properties and the reusability of the composite
MNM production method	Graphene can be produced in many different ways. A detailed list of methods is reported in Ferrari et al. (2015)
Sources of information	Peer Reviewed literature; News services (see Nanowerk).
Source Quality	Papers are very recent, and more than one paper was selected to cover different aspects of the specific application. Impact factors of the journals varied a lot, from 6.18 of the journal Carbon to 1.025 of the Journal of water and health, to 0 for Nano LIFE.
Information type and quality	There are several publications on this topic, but more technical in nature, without much information on potential impacts (e.g. release from polymers). The technical information (production process, performances) is usually very detailed.
Regulatory context	There is no nano-specific environmental legislation. In case of release in water, there are no environmental concentration limits for graphene. Graphene is not in REACH yet, while CLP is available on ECHA website.

For this specific graphene application on water filtration, the risk assessment approach will be applied.

2.4.3 Screening Risk Assessment

The screening risk assessment is applied to a group of applications, i.e. the water filtration through membranes. There are different approaches to make graphene membranes, from very complicated to very simple and different properties are obtained at the end.

Therefore, the overall assessment will be based on general assumptions about membranes uses and properties, trying to address the properties differences when possible.

2.4.3.1 Life cycle profile

The overall simplified life cycle of a hypothetical water filtration membrane can be constructed as follows:

1. Production of graphene or graphene oxide
2. Production of the membrane:
    a. Incorporation of graphene oxide into polymers
    b. Generation of filter
3. Use (scale)
    a. Desalinization (industrial)
    b. Water purification (industrial, household)
    c. Decontamination (industrial, household)
4. End of life

For each step, few considerations are reported in the following paragraph. The scope is to identify information useful for the formulation of the risk hypotheses.

2.4.3.1.1 Graphene and graphene oxide production

The production approaches of graphene and graphene oxide are well known, and information can be found in several papers, as well as in the Ferrari et al. (2015) report about the European graphene roadmap. As an example, few approaches are reported here:

- Dry exfoliation: it is performed in vacuum, air, or inert environment, splitting of LM into atomically thin sheets via mechanical, electrostatic, or electromagnetic forces. These methods can be used both at lab scale and at industry scale to produce graphene.
- Liquid exfoliation: it is done in both aqueous and non-aqueous solvents, exploiting ultrasounds to extract individual layers. The LPE process generally involves three steps: (1) dispersion in a solvent; (2) exfoliation; (3) “purification”. The third step is necessary to separate exfoliated from un-exfoliated flakes, and usually requires ultracentrifugation. LPE is cheap and easily scalable, and does not require expensive growth substrates. It is used for composites. LPE is a versatile technique and can be exploited not only for the exfoliation of pristine graphite, as reported in section 4.1.2.1, but also for the exfoliation of graphite oxide and graphite intercalated compounds (GICs), which have different properties with respect to pristine graphite.
- Growth on SiC: it is performed at high temperature, and the graphene sheet is formed due to Si sublimation. A drawback for this technology for large scale production is the SiC wafers cost and their smaller size compared to Si wafers.
- Growth on metals by precipitation: this is the mostly used industrial approach, and it includes flash evaporation, physical vapour deposition (PVD), Chemical Vapour Deposition (CVD), and spin coating. The carbon source can be a solid, liquid, or gas. In the case of a pure carbon source, flash evaporation or PVD can be used to deposit carbon directly on the substrate of interest.
- Chemical vapour deposition: Chemical vapour deposition is a process widely used to deposit or grow thin films, crystalline or amorphous, from solid, liquid or gaseous precursors of many materials. The main difference in the CVD equipment for the different precursor types is the gas delivery system. The process is carried out in a closed system.
- Chemical synthesis: graphene can be chemically synthesized, assembling benzene building blocks, starting from graphene-like molecular precursors in the form of polyphenylenes. Chemical graphene tend to form insoluble aggregates.

Transfer of the graphene layer is part of the production process, and it is performed both in dry and wet conditions, often in open systems. Dry approaches are the best to be used for large graphene surfaces.

The potential impacts of the production phase are mostly concerning workers. While environmental release from production site is possible, there are no studies on the subject.

There are very few available studies for workers exposure assessment in this phase: one for the industrial production, and one for the lab production. These data will be used to evaluate the potential exposure and impact for workers and researchers.

2.4.3.1.2 Membrane production

In this case, there are several examples in the literature. Some examples relevant for the case study are reported here:

- Graft-to method: it links the graphene oxide to the polymer support, making use of polymers functional groups. This approach is building an ordered structure, bottom-up, in steps, through normal chemical reactions. There are no industrial scaled-up processes at this time, but the process is normally done in liquid environments. The technical nature of the procedure does not allow a better understanding of the potential exposure for workers and researchers (Huang and Chen, 2014).
- Graft-from method: this approach is a creation of the nanocomposite by mixing together graphene oxide or functionalized graphene with the monomers, and going through the polymerization process. This is also a wet chemistry approach. The resulting structure can be an ordered structure with graphene oxide with linked polymerized chains, or a co-polymer with graphene oxide dispersed into the matrix (Huang and Chen, 2014).

- Graphene/LDH: this approach is used to synthesize graphene/layered double hydroxides nanocomposites. The approaches used for this synthesis are all in wet chemistry, and are based on, for example: co-precipitation, hydrothermal reaction, exfoliation-restacking synthesis, and layer-by-layer assembly. There is no indication about scale up production.
- Nanoporous graphene: this approach is used to produce reverse osmosis membranes, creating nanopores in graphene sheets (Cohen Tanugi and Grossman, 2012). Earlier approaches relied on electron beam exposure, but the most recent methods make use of diblock copolymer templating, helium ion beam drilling, and chemical etching to achieve both higher porosity and a more precise pore size distribution.
- Biofoam: The last production method is dedicated to a steam-generation membrane, produced by mixing together nanocellulose produced in situ by bacteria, and reduced graphene oxide flakes mixed in the cell culture media. By freezing the obtained hydrogel, a aerogel composed by nanocellulose and reduced graphene oxide flakes is obtained (Jiang et al., 2016).

Production of membranes seems to be limited to wet approaches. Once graphene is fixed in polymers, there should be no risk of exposure for workers, as experience with other nanocomposites may suggest. However, there is no direct information about graphene release from finished products.

Since we have no information about scale-up processes for the methods shown here, or in general for the preparation of industrial scale amounts of membranes, exposure in this phase is difficult to estimate. The target is anyway the workers.

2.4.3.1.3 Use

Use can be inferred by use of conventional membranes having the same function. For example, Lawler et al. (2012) in the context of reverse osmosis membranes disposal, foresee that in 2015 around 12000 tons have to be disposed of globally. Therefore, a potential massive use of graphene in such products is foreseeable if all conventional membranes are substituted by graphene-based membranes. The use of membranes is mostly for water desalination, while uses for water purification and decontamination are also reported in the literature. However, the use as contaminant adsorbent would be limited to small areas, and limited time, such as for example oil spills, or groundwater contamination. It is also likely that the adsorbent material would not be freely dispersed in the environment, but used in filtering systems where the graphene membranes are contained. However, there is a lack of information about the potential release of graphene during use,

2.4.3.1.4 End of life

Disposal of membranes can be done in different ways, as reported by Lawler et al. (2012) for reverse osmosis membranes. A normal life span for a reverse osmosis membrane is 5 years. Since the main use of the graphene membranes is similar, the basic disposal options should be the same. Reuse in other contexts is a growing possibility: if the performance of the membrane is not useful anymore for the task at hand, residual performances can be useful in other conditions. Another option is the membranes conversion, with modification into ultra and nanofiltration films. Recycling of the materials is complicated, since the membranes have a complex composition, and there can be a contamination after the extensive use. Therefore, mechanical recycling can be costly and resources intensive. The best way to dispose of the membranes is thermal processing. The graphene-based membranes are stable, and can be regenerated, but a robust estimation of their operational life span is not yet available.

2.4.3.2 Exposure scenarios

Since the lack of data about the graphene release in different contexts, especially from the final product, the exposure scenarios for the specific application are going to be very simple, stating the potential sources, pathways and targets. In the formulation of exposure scenarios there is a lot of expert judgement, and the uncertainty will be high especially for some scenarios. Not for all pathways data will be available, not even qualitative ones. Scenarios are described for each target: workers, consumers, and environment.

1. Workers: workers as potential targets are exposed during production phase of both the MNM and the nanocomposite. The main route of exposure is inhalation.
    a. Graphene: the two available papers show that the exposure is possible, even if at lower levels than exposure limits for particles, especially when operator intervention is necessary. In a laboratory setting, measured exposure was negligible in different production operations.
    b. Exposure during production of nanocomposites is not quantifiable, but given the product6on methods, it is possible that during some operations exposure occurs, especially if dry graphene material is used to be incorporated into the polymer. It is likely that apart from the mixture phase, no other steps of the production process will lead to workers exposure.
2. Consumers: exposure from the use of the membranes is unlikely, because the main use is likely to be in industrial settings such as desalination plants and water/groundwater decontamination operations. It is foreseeable a more household-type of use, in filters used to clean water locally, or in portable systems. This kind of application is likely more limited, in certain countries and extreme situations (e.g. lack of potable water in isolated areas in developing countries). The indirect exposure through release of graphene in water is a possibility, but there are no literature studies (to the best of the writer knowledge) reporting on this specific issue.
3. Environment: environmental exposure is a possibility. MNM can be released into the environment during the production process, through air, water, and wastes. There is no available information about this exposure, but in general the management of risks related to environmental release and waste is normally performed in chemical industries. Environmental release during use of the product may result from the decontamination of polluted waters. The MNM can be released from the polymer, but as for the consumers, no information is available. Also, not much is now about the fate of graphene in water. A main concern is the release after disposal in landfills.

2.4.3.3 MNM toxicity

Human toxicity

Graphene toxicity is described in different literature reviews (Guo and Mei, 2014; Arvidsson et al., 2013; Jastrzebska and Olszyna, 2015). In vitro studies show concentration and time dependent cytotoxicity (apoptosis) in lung cells (BEAS-2B), ROS generation, cytotoxicity and mitochondrial injury in neural cells (PC12), macrophages, and epithelial cells. Also inflammation was observed in THP-1 cells. Functionalization of graphene decreases the toxicity compared to the bare counterpart. Dimension is also a factor, where smaller sheets are more toxic than larger sheets with the same thickness. The cell internalization mechanism of different graphene family compounds (e.g. graphene, graphene oxide, reduced graphene oxide) can be different. Genotoxicity in human fibroblast cells was also observed for graphene oxide.

According to Arvidsson et al. (2013), the in vitro cells No Observed Effect Concentration ranges between 0.01 mg/L for metabolic activity to 20 mg/L for human fibroblast cells viability. However, functionalized graphene family compounds usually show a lower toxicity.

Ecotoxicity

Jastrzebska and Olszyna (2015) published a review about ecotoxicological effects of graphene family nanomaterials. The finding shows that:

- Bacterial metabolic activity, bacterial viability, and biological removal of nutrients, such as organics, nitrogen, and phosphorus, were significantly impacted by the presence of Graphene Oxide (GO) in the activated sludge at a concentration of 50 mg/L. Also, GO interaction with wastewater produced significant amount of reactive oxygen species (ROS), which could be one of the responsible mechanisms for the toxic effect of GO.
- Graphene was found toxic to the algae *Dunaliella tertiolecta*.
- Authors also showed the presence of graphene aggregates into the gut of crustacean *A.salina*. A 48-h exposure experiment revealed an altered pattern of oxidative stress biomarkers, resulting in a significant increase of catalase activities in graphene 1 mg/L treated *A.salina* and a significant increase of glutathione peroxidase activities. Increased levels of lipid peroxidation of membranes were also observed by authors. However, despite the toxic-suggestive results, no acute toxicity was demonstrated by the authors with respect to *A. salina*. Tests on *Amphibalanus amphitrite* (cirripedia, crustacea) larvae in two phases of development: cyprids and naupilius, showed that the increasing

concentrations of GO (0.01, 0.1, and 0.5 mg/mL) and increasing exposure times (24, 48, and 72 h) lead to decreases in the swimming speed of nauplii and to increases in their mortality.

- GO studies on zebrafish embryos showed that GO can cause actual toxicity to organisms inducing slight hatching delay of zebrafish embryos at a high dosage of 50 mg/L. Authors demonstrated that embryos exposed to GO exhibited more moderate toxic effects. The overt morphological malformation was bent spine, minor tail malformations and body degradation and opaqueness in yolk which may be an indicative of apoptotic tissue in zebrafish embryos.
- Combined morphological and physiological analyses on plants indicated that after 20 days of exposure to 500 to 2000 mg/L of graphene caused a significant inhibition of plant growth and biomass level. Significant effects were also detected showing a concentration-dependent increase in ROS and cell death as well as visible symptoms of necrotic lesions, indicating graphene-induced adverse effects on cabbage, tomato, and red spinach mediated by oxidative stress necrosis. Significant negative impacts of GO concentrations starting at 100 mg/L were observed in germination of *V. faba* seedlings. Effects included decreases in growth parameters and the activity of H_2O_2-decomposing enzymes (ascorbate peroxidase-APX, catalase-CAT) and by increases in the levels of electrolyte leakage (EL), H_2O_2 and lipid and protein oxidation.
- Absence of acute toxicity in vivo, for all tested concentrations (50 to 250 μg/ml) of graphite nanoplatelets was observed in nematode *Caenorhabditis elegans*. On the other hand, high doses of nanosheets (10 and 20 μg/mL) triggered an increase in ROS accumulation in the worms over 75 %, showing the ability of nanosheets to induce oxidative stress.

The fate of graphene in water is linked to the shape (it can lose the 2D structure in favour of smaller particle-like structures) and hydrophobicity (Arvidsson et al., 2013). However, there is the possibility of interaction with natural organic matter, as reported by Wang et al. (2016), causing a better dispersion and higher toxic effects on environmental organisms.

The diversity of graphene size, functionalization, and oxidation state, to name few parameters, as well as the different systems in which the toxicity is exerted, do not allow generalizing about graphene family materials hazard. However, taking into account the precautionary principle, from the toxicity data available, it can be concluded that graphene can cause toxicity (cytotoxicity and genotoxicity, inflammation and immunotoxicity) through different exposure routes to humans. It also shows some degree of toxicity toward water organisms, and plants in soil compartment.

2.4.4 Preliminary risk assessment and risk hypotheses

Given the available information on exposure scenarios, hazard properties of graphene family materials, in this last phase of the case study, the qualitative risk assessment with the preliminary risk hypotheses will be formulated. No final report will be produced, since expert intervention and interaction with stakeholders to support the identification of final risk hypotheses is not possible at this time.

Risk hypothesis 1: workers exposure. The available studies on **workers exposure** show that there is some exposure to graphene family materials, especially at industrial level, and for the operations where human intervention is necessary (Spinazzè et al., 2016). However, the level of exposure is lower than the reference level for the Time Weighted Average for particles in air, and the actual amount of graphene was not verified in the samples. Therefore, more work has to be done in terms of exposure assessment, also for different industrial production methods. Despite the low possibility for exposure, this risk hypothesis is considered for evaluation because data are lacking, and the toxic potential of graphene family materials inhalation. This hypothesis is also valid for the production process of the membrane.

Risk hypothesis 2: environmental exposure during use for decontamination. This hypothesis covers the environmental exposure occurring during the use as decontamination. This application is not well characterized yet, and a widespread use is not foreseen at this time. However, localized applications can lead to release into the environment of graphene material due to unintentional dispersion (e.g. loss of adsorbent material in oil spill recovery). In time, degradation of polymers can release graphene, which is persistent and bioavailable and could cause adverse effects on ecological targets, also due to the very absorption of toxic metals and substances that can be concentrated and carried into the organisms. Indirect humans exposure is also possible through the food chain.

Risk hypothesis 3: environmental release after disposal. Disposal of the membranes at their end of life is mostly related to the industrial applications. In some papers it is highlighted that graphene-based membranes are stable and can be easily reactivated and reused. Also, it seems that incineration is the best solution for the elimination of membranes that are not useful anymore, eliminating the risk of release of graphene. However, there is the possibility of landfill disposal, which poses the issue of long term release into soil and groundwater.

Risk hypothesis 4: direct consumer exposure. Direct consumer exposure may happen due to release of graphene into the purified water. Despite the expected low use of graphene membranes for this kind of consumer application, also in relation to the larger amount potentially used at industrial level, this hypothesis is relevant because of the possible direct impact on consumers. A continuous use of these membranes could lead to a low but continuous exposure to graphene-like compounds, and likely to sensitive population already under stress situations for other factors.

2.4.4.1 Preliminary conclusions

The assessment of the application of graphene family material for the water treatment and purification resulted in the identification of main issues to be addressed to evaluate early on its potential impact. Graphene-based membrane properties make them a potential candidate to substitute current water treatment methods, with a potential global diffusion in high amount (thousands of tons). Also, the efficacy and simplicity of certain systems (e.g. the biofoam) can lead to diffusion among consumers of portable systems. On one hand, effective and cheap systems to clean water and produce drinkable water both at general service and personal level is an important achievement toward sustainable and just society. On the other hand, the knowledge about the possible abundant use of graphene in composites, its persistence and hydrophobicity, as well as its substantial toxicity according to conducted studies, implies that graphene should be regarded as a potential environmental and health hazard.

According to the 4 preliminary risk hypotheses, from a foresight point of view, there is the need to have more data on (in order of priority):

- Emission of graphene form nanocomposites has to be studied in realistic conditions, simulating potential use and accelerated wear. Even indicative measurements can improve the preliminary assessment of adverse impacts.
- Workplace emissions have to be better measured characterized at different level (from lab to industry), for the main production methods, those eligible for scaling-up, in order to exclude workers as specific target as well as to identify the need of risk management measures.
- Toxicity studies on graphene family materials are still lacking, in number and quality. The European flagship initiative should allow filling the gap by using regulatory acceptable methods. However, there is a very strong focus on development of technical applications, and more investment on the side of safety is needed.

From a regulatory point of view, to address the graphene safety, if the production amount will reach the predicted level, there will be a REACH dossier, but it is not clear the level of detail that it will have depending on the tonnage/year of each company. If the number of companies is limited as it seems, it is likely that a detailed dossier will be available in the next 5 to 10 years. However, in the meantime, the only obligation for graphene is in CLP regulation. Water framework directive do not have a reference value for graphene to perform the chemical status assessment, but it can be included implicitly in the ecological status assessment. Concerning worker exposure, the regulation is covering the safety of workers. The fact that graphene is still outside the conditions of REACH for the compilation of a dossier is worrying, but the European graphene flagship initiative should help identify potential risks associated with graphene uses in time. The main issue is the coordination with regulators, to provide the robust and appropriated information that decision-makers need.

2.5 Evaluation and conclusions

The proposed NANoREG foresight system makes use of well-known and accepted concepts to assess the potential impacts of future innovations linked to new nanomaterials. The framework and the system are a first step toward nanotechnology innovation monitoring. The reference to methods, models and tools developed or applied in NANoREG represents a first idea of what kind of approaches can be used to carry out the analysis. The case study exercise also highlighted that to implement such a system for innovation monitoring it is necessary the cooperation of experts in different fields, in order to collect and evaluate data and information which are qualitative in nature. Also, a great deal of expert judgement is necessary to evaluate the risk hypotheses and define the priorities. The work done in D6.1 is linked to SbD, and in a RRI context, it is placed as analysis tool to assess potential applications of nanomaterials, up to the idea stage of the innovation stage-gate approach. Also, the inclusion of regulators and other stakeholders in this system is supporting the following Trusted Environments creation which is part of the regulatory preparedness of the Safe Innovation Approach.

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