NanoImpact 18 (2020) 100227

Contents lists available at ScienceDirect

NanoImpact

journal homepage: www.elsevier.com/locate/nanoimpact

Safe-by-Design part I: Proposal for nanospecific human health safety aspects needed along the innovation process

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ARTICLE INFO

Keywords:
Nanotechnology
Safe-by-Design
Safety
Human health
Safe innovation
Innovation model

ABSTRACT

Safe-by-Design aims to reduce uncertainties and/or increase the human health and environmental safety from already early in the innovation process onwards and will thereby contribute to increased innovation efficiency, economic viability, interdisciplinary collaboration, consumers trust and improve sustainability. Since most innovators or designers are neither toxicologists nor risk assessors, considering human health safety aspects within their innovation process may be challenging. This paper provides sets of questions that can help innovators to assess nanospecific human health safety aspects of their product or material along the various stages of the innovation process. Addressing these questions will facilitate innovators to identify which type of information may support decisions on how to address potential human health risks in the innovation process. The identified information on the human health safety aspects can help innovators to decide if further investments in the product or material are beneficial. It may allow them to rank, prioritize and choose safer alternatives early in the innovation process. This may enable innovators to better anticipate on potential safety issues in an early stage, preventing these safety issues to become an innovation killer in a later stage of the innovation process. This approach to identify potential nanospecific human health risks should be considered as complementary to current regulations. The applicability of this approach was evaluated using a few industrial case studies. To determine if the approach is applicable to the innovation of a broader group of nanomaterials and nano-enabled products, more experience within various industrial sectors is needed.

1. Introduction

The development, manufacture and use of nanomaterials (NMs) with novel properties and potentially novel risks are still growing rapidly. Unfortunately exploitation of the full economic potential of NM and nano-enabled product (NEP) investments is threatened by inadequate and/or unclear nanospecific provisions in the present regulatory frameworks. This means the regulatory information requirements may not always be adequate to fully address nanospecific human health and environmental risks. There are currently no indications that NMs will lead to other environmental or health effects (i.e. new toxicological endpoints or diseases) than those known for non-NMs (Donaldson and Poland, 2013; Gebel et al., 2014; Nel et al., 2006). However, the toxicological profile of a specific NM can be very different compared to that of the (bulk) material of the same chemical composition with a larger particle size, because NMs may distribute differently throughout the body or the environment, which may lead to toxicological effects at different dose levels and in other target organs or environmental compartments (Donaldson and Poland, 2013).

One of the greatest challenges of safety assessment of NMs is the rapid diversifying development and complexity of the manufactured NMs (Dekkers et al., 2016). Regulatory frameworks struggle to keep pace with innovation. One way to approach the gap between innovative materials and the present regulatory frameworks is by implementing Safe-by-Design (SbD) supported by the regulatory process (Nymark et al., 2020). The SbD concept aims to reduce uncertainties and/or increase human health and environmental safety of nanotechnology, by reducing hazards and risks starting as early as possible during the innovation process (Soeteman-Hernandez et al., 2019). The SbD concept intends to balance safety, functionality and cost in an integrated way (Kraegeloh et al., 2018), in order to improve innovation efficiency for the development process of better nanotechnology products,

Abbreviations: NM, nanomaterial; NEP, nano-enabled product; SbD, Safe-by-Design; C&L, classification and labelling

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https://doi.org/10.1016/j.impact.2020.100227
Received 2 March 2020; Received in revised form 23 April 2020; Accepted 13 May 2020
Available online 16 May 2020

considering all life-cycle steps, and not only the product or material development phase (Soeteman-Hernandez et al., 2019). A more detailed description of the structure-function relationship, the term functionality, as well as a decision model to balance the safety and functionality can be found in part II of this publication (Tavernaro et al., n.d.).

Assessing nanospecific human health safety aspects is a complex process and our paper provides an overview of the information needed to address nanospecific human health safety aspects of NMs and/or NEPs for the various phases of the innovation process. Here, we use the widely implemented Cooper's Stage-Gate model (Soeteman-Hernandez et al., 2019; Tavernaro et al., n.d.; Cooper, 2008) to describe the innovation process because it provides a supportive structure to identify the relevant safety information needed to make decisions on how to proceed with innovations within the various stages of the innovation process. In short, the underlying, classical stage-gate model by Cooper consists of five main stages in which a set of parallel activities must be completed prior to entering the next step of the innovation process. Between the stages, gates are used to make decisions to move forward or to return to the previous stage while improving the product. The first two stages comprise the scoping and building of the business case, whereas the principal product development takes place at stage 3. After building the prototype, upscaling of the process and testing and improving of the product are performed at stage 4. The market launch takes place at the last stage. Although the focus of this paper is on nanospecific human health risks, a similar approach can be applied for environmental risks.

The information needed to address the nanospecific human health safety aspects proposed in this paper do not replace the current regulatory requirements and should be seen as additional information. There is some overlap between the human health safety aspects described in this paper and the regulatory information requirements of different regulatory frameworks. However, since the emphasis of the human health safety aspects described in this paper is nanospecific, they do not include human health safety aspects addressing more general non-nanospecific risks.

SbD can be better applied when innovators know which type of information is needed to assess nanospecific human health risks in each stage of the innovation process. This enables the elimination or reduction of potential human health risks from an early phase of the innovation process onwards, maximising use of resources, and expediting the development of new NMs and NEPs.

2. Methods

The most relevant overviews and approaches for the identification of information needed to address potential nanospecific risks in the various stages of the innovation process were considered to be two deliverables D1.1 and D6.4 (www.nanoreg.eu) and one publication (Dekkers et al., 2016) from the EU 7th framework NANoREG project in which new testing strategies for NMs were developed. Although these documents have developed within the community of the NANoREG project several years ago, several elements within these approaches are still utilised and supported by other scientific and regulatory stakeholders (EFSA, 2018; Oomen et al., 2018; Rasmussen et al., 2019; SCCS, 2019). D1.1 describes the most important questions and issues in the area of regulatory toxicology and risk assessment of NMs. D6.4 gives an inventory of existing regulatory accepted toxicity tests applicable for safety screening of manufactured NMs and the publication by Dekkers et al. describes a strategy to efficiently assess the nanospecific issues within the human health risk assessment of NMs. Therefore, these documents were used to select the human health safety aspects or safety questions that would support decisions on how to address potential human health risks for each stage of the innovation process. In this selection, not only the potential nanospecific human health risks, but also the expected availability or feasibility to generate the information were taken into account for each stage of the innovation process. For each safety aspect, the information needed to address that aspect (or answer that question) was identified. A general description of the methods that can be used to obtain this information is provided, but no recommendations for specific experimental assays are given, as the most suitable experimental assay to be used also depends on the type of nanomaterial and the expected exposure scenario, transformation, translocation and potential target organs. Furthermore, a short explanation with respect to the relevance of each safety aspect for the human health risks was given.

As the information needed address the human health risks safety aspects is proposed from a risk assessment perspective in combination with the expected availability or feasibility to generate the information in each stage of the innovation process, the question arises whether the proposed information is indeed available and whether they are considered relevant by innovators. Therefore, the practical feasibility of the approach, including the relevance and availability or feasibility to generate the information needed to address the nanospecific human health safety aspects in the decision making, was investigated with cooperation of several industrial partners involved in the EU Horizon 2020 NanoReg2 project (www.nanoreg2.eu). The NanoReg2 project developed new principles and ideas to establish SbD, based on data from case studies on NMs or NEPs developed by industrial partners (Soeteman-Hernandez et al., 2019; Salieri et al., n.d.; Sanchez Jiménez et al., n.d.). A custom made questionnaire was made and completed during a video or teleconference call with several industrial partners. The companies involved were mostly large and medium sized companies, including one large company and four small and medium-sized enterprises (SMEs). In the questionnaire, the industrial partners were first asked how they would evaluate the relevance of the information needed to address the proposed human health safety aspects in the decision making process in each stage of their innovation process, based on the experience with their case study. Secondly, they were asked if the information needed to address the proposed human health safety aspects was available or feasibility to generate in the indicated stage of their innovation process.

3. Results

3.1. Human health safety aspects in stage 1

The first stage of the innovation process is the scoping stage. At this stage a quick, inexpensive preliminary assessment of the product under development is performed, including the scoping of the idea – largely desk research – to better define the concept, assess technical feasibility and to gain insights into commercial prospects. Inclusion of human health safety aspects into this assessment requires a preliminary estimation of potential hazard and risks related to the envisaged product and application field. For this estimation basic information on the hazard potential of the NM, the type of incorporation of the NM into the product and potential release and exposure routes is needed. This first estimation of the potential hazard and exposure related to the NMs and/or NEPs is mainly based on theoretical information on the desired physicochemical characteristics of the NM or NEP and existing data (literature, databases) on the chemical components of the NM or NEP, including classification, labelling and any restrictions related to the envisaged material or application (see Table 1). No laboratory research (i.e. no new experimental data generation) is anticipated at this stage.

Information on the desired primary particle size will determine the need to look into nanospecific human health safety aspects. In general, (nano)materials with a primary particle size in the nanorange (i.e. smaller than one or a few hundred nm) are expected to have a different hazard profile than (bulk) materials of the same chemical composition with a larger primary particle size (larger than one or a few hundred nm). Nanoparticles require extra attention because they may be more reactive due to their relatively higher surface area and their small size

Table 1
Human health safety aspects and information needed to address these aspects in Stage 1.

Human health safety aspects	Information needed
1a) Is it a NM?	Desired physicochemical properties: primary particle size (within the nanorange and aspect ratio).
1b) Does it look like asbestos (HARN)?	Shape (sphere, rod, fibre, etc.).
1c) Is it persistent?	Solubility (highly soluble: e.g. sea salt, soluble: e.g. Ag NPs, insoluble: TiO_2 NPs, or highly insoluble: e.g. CNTs).
2) Which routes of exposure can be expected?	Production process and product description (how it is produced and used)?
3) How are the chemical components of the (pristine) NM labelled? Are there any restrictions?	Chemical composition of the nanomaterial. Toxicity, C&L of these chemical components.
4) Which types of exposure and release scenarios can be expected?	Qualitative description of intended production process and use of the product, including the expected waste disposal of the product.
5) What is the toxicity of the (pristine) NM or similar (N)Ms	Physicochemical properties of NM (e.g. as obtained from manufacturing): primary particle size, shape, dissolution rate (water) and surface chemistry. Toxicity, C&L of the NM or similar (N)Ms.

may enable them to reach (parts of) organisms that are out of reach for bulk chemicals (Donaldson and Poland, 2013).

Rigid, persistent, fibre-like materials with high aspect ratios (> 1:5), require additional attention because of their resemblance to asbestos (Donaldson et al., 2010).

Also persistent NMs that do not look like asbestos (non-fibre like materials, including spheres and rods) require additional attention because of their potential to accumulate in the environment and the human body. On the other hand, if a NM is not persistent and has a very fast dissolution rate (i.e. close to instantly dissolved), the NM will probably convert into its molecular or ionic form before it reaches its potential target (Arts et al., 2015; Wohlleben et al., 2019). These NMs can be evaluated using the information on the chemical composition(s) of the non-NM. The solubility of the chemical components of the NM in water may give a first indication of the persistence of a NM.

Information on the production process and product description (how it is produced and used) will give a first indication on which routes of exposure in humans and release to which environmental compartments can be expected. The (anticipated) route of exposure gives information on which hazard data needs to be collected. For example, information on dermal sensitisation is only relevant if exposure to the skin is expected.

The chemical composition of the core as well as any surface coating or functionalisation of the particle may contribute to the hazard profile. It can be expected that any known hazard or classification (e.g. as a 'respiratory sensitiser') of the chemical components of a NM are also relevant for a NM itself. If there are any legislative restrictions related to the envisaged material/application these are usually related to safety concerns and such a material/applications should not be further developed. Suitable information on chemical substances is provided by ECHA on www.echa.europa.eu. Information on legislative restrictions is also included in the Safe by Design Implementation Platform (https://temas.taglab.ch/SbDimplementation/). In the course of the innovation process, it will become more and more important, what type of information has to be provided for launch, registration or approval. The Safe-by-Design Implementation Platform has been designed to support acquisition of such safety data according to the stage gate model.

Based on the intended production process, product use and waste disposal, a rough indication of the expected types of exposure scenarios can be given. Information on the exposure scenarios gives an indication which hazard data needs to be collected.

Using information on the physicochemical properties of the NM enables to collect hazard information on NMs or larger sized materials with similar physicochemical properties, assuming that this kind of information is existing. Safety information on similar materials can be found using the eNanomapper database (http://www.enanomapper.net/) or other databases providing information on the identity, toxicity, and/or exposure.

3.2. Human health safety aspects in stage 2

In the second stage of the innovation process the Business Case is build. At this stage, a more detailed investigation is performed involving primary research and experiments – both market and technical – leading to a Business Case, including product and project definition, project justification, and the proposed plan for development. With respect to safety, this would include the identification of any potential hazards and risks related to the envisaged product and application field. Unless the (pristine) NM is available, no new laboratory research is anticipated at this stage. Physicochemical properties, modelling approaches and existing experimental data on the pristine or similar NMs, similar larger sized materials or chemical components are used (see Table 2). Although approaches for read across or grouping for NMs are still under development, some basic principles for grouping and read

Table 2
Human health safety aspects and information needed to address these aspects in Stage 2.

Human health safety aspects	Information needed
6) Which transformations of the NM can be expected throughout the life cycle (focus on dissolution, aggregation, agglomeration)?	Physicochemical properties of the NM throughout the life cycle of the product: primary, aggregated and agglomerated particle size, surface chemistry and dissolution rate (relevant media) (experimental or else theoretical information).
7) What is the reactivity, accumulation, immunotoxicity, and/or genotoxicity of the pristine or similar (N)Ms.?*	Hazard information on the reactivity, absorption (e.g. *in vitro* cellular uptake or barrier crossing), immunotoxicity and/or genotoxicity of the pristine or similar NMs (experimental or else theoretical information).
8) What are the most relevant exposure and release scenarios (throughout whole life cycle stages), in terms of exposure level, exposure duration and exposed populations?	Exposure scenarios of hotspots and associated forms of NM throughout the production process and downstream use of the products, including waste disposal (theoretical information).
9) What are relevant exposure reduction measures?	Relevant exposure reduction measures and their efficiency.
10) How are chemical components of the doping, coating, surface treatment or other functionalisation labelled? What is the C&L of the different crystalline forms?	Chemical composition of the doping, coating, surface treatment or other functionalisation. Toxicity, C&L of these chemical components.

* Please, select the most important endpoints based on the type of NM and expected exposure.

Table 3
Human health safety aspects and information needed to address these aspects in Stage 3.

Human health safety aspects	Information needed
11) What are the estimated doses/magnitudes of all relevant exposure scenarios?	Estimated production volume, production process and uses (PROCs).
12) What is the reactivity, accumulation, immunotoxicity and/or genotoxicity of the relevant nanoforms?*	Hazard information on the reactivity, absorption, immunotoxicity and/or genotoxicity of the exposure relevant nanoforms or similar NMs for the exposed populations (experimental or else theoretical information).

* Please, select the most important endpoints based on the type of NM and expected exposure.

across are already incorporated in existing predictive models and tools. These basic rules for grouping and read across and further predictive approaches might help to collect the needed information as well as to gather preliminary information for a screening risk assessment. Several predictive approaches, models and tools for such a screening risk assessment can be found in the Safe Innovation Approach Toolbox (https://www.siatoolbox.com/). Available data on similar materials can be found in databases, e.g. using eNanomapper.

Transformation: Physicochemical properties of NMs, and therefore also their hazard profile, often change throughout their life-cycle, due to changing environmental factors that they may encounter. Dissolution of the NM may lead to the release of toxic ions, while aggregation and agglomeration, may lead to different behaviour in terms of distribution of the NM through the environment (e.g. sedimentation) or organism (e.g. deposition and uptake).

Reactivity: Reactive materials may trigger the generation of reactive oxygen species (ROS), leading to oxidative stress and subsequent inflammation in biological tissues. For metals and metal oxides, the reactivity and subsequent inflammatory effects after inhalation, can for example be predicted using the conduction band energy levels in combination with the solubility (Zhang et al., 2012). For other NMs and other exposure routes, the reactivity of NMs can be obtained by using acellular assays (Arts et al., 2015; Hsieh et al., 2013; Nel et al., 2013).

Information on cellular uptake, attachment, and interaction gives a first indication on the possible mechanisms of toxicity, such as damaging different cellular targets through the release of ions, the generation of ROS or the binding and interaction with intracellular proteins (Frohlich, 2013; Nel et al., 2009). For example, direct interaction of a NM with DNA can only occur if the NM is taken up by the cell and is able to reach the DNA within the nucleus.

Information on the translocation of the NMs through biological barriers (skin, lung, gastrointestinal tract, blood-brain-barrier, and placenta) gives an indication of the possible absorption and distribution and translocation of the NM to relevant target organs. This information can be used to select relevant cell types for *in vitro* assays. When, for example, a NM is likely to reach the systemic circulation, *in vitro* blood-brain or placental barrier models might be relevant, though it should be noticed that such *in vitro* models cannot distinguish between low and no translocation. For NMs that are likely to be distributed to the liver, hepatic cell lines should be considered for *in vitro* genotoxicity testing.

For some materials, there are many exposure scenarios possible, for example, if the material goes through a lot of different production steps or is used in a range of very different consumer products. It is recommended to first perform preliminary risk assessment for the most relevant exposure scenarios (or hotspots) which result in: i) the highest exposure levels, ii) the longest exposure duration, or iii) exposure to sensitive groups (e.g. children). In case the NM undergoes changes in its physicochemical properties, it is recommended to consider these three scenarios for each exposure relevant form.

Health risks may be significantly reduced with the use of appropriate exposure reduction methods. It is recommended to check the efficiency of different exposure reduction measures, according to the SbD principles and addressing the foreseen life-cycle of the NM, since not all methods may be effective for NMs.

Introducing other chemical components can affect the fate, toxicokinetics and toxicity of a NM, even if it concerns only small amounts (e.g. doping or impurities). Therefore, not only the main chemical components, but also the chemical constituents of the doping, impurities, coating, surface treatment should be taken into account. When a NM is made of a core-shell structure, both the C&L of the core and the shell should be taken into consideration, because under certain circumstances, the shell might be separated from the core, making both bioavailable. For some chemical components, the crystalline form also determines its toxicity.

3.3. Human health safety aspects in stage 3

In the third stage of the innovation process, the development stage, the project gets into realisation, including the design and development of the new product, the production process required for eventual full scale production and several alpha iterations of the prototype. The NM or NEP is developed and experimental and comprehensive data on the NM or NEP is generated (i.e. new laboratory research is performed). The availability of test material at this stage also allows for a more elaborated hazard assessment of the envisaged NM or NEP, comprising for example, reactivity, (bio)persistence, cytotoxicity, immunotoxicity and/or genotoxicity, indicators for acute or chronic toxicity, or data on the potential release into the environment (see Table 3). Again, *in silico* data will support the generation of datasets on the safety of the NM or NEP.

The production volume, production process and uses (PROCs) may be helpful in deriving a first (semi)quantitative estimate of the exposure levels to NMs.

Physicochemical properties of NMs, and therefore also their hazard profile, often change throughout their life cycle, due to changing environmental factors that they may encounter. Therefore, information on the reactivity, absorption, immunotoxicity and/or genotoxicity is not only needed for the pristine NMs, but also on all exposure relevant nanoforms. Furthermore, a more quantitative life-cycle assessment should be performed taking into account humans as well as the environment.

3.4. Human health safety aspects in stage 4

The fourth stage of the innovation process is the testing and validation stage. At this stage, the product is tested in the marketplace, lab, and plant to verify and validate the proposed new product, brand/marketing plan and production, including several iterations of the beta prototype. Not only the test material is available, but also the final production process is developed. Therefore, a comprehensive assessment of potential risks is possible, including data on hazard, release, specifically, release at the workplace (see Table 4). Release, exposure and transformation scenarios along the future life-cycle of the NM or NEP should be modelled.

A change in production scale may result in different exposure scenarios in terms of levels and duration, sometimes even exposure routes. Different exposure reduction methods may be needed after upscaling of the manufacturing process.

If hazard information exists on similar NMs, it is recommended to check whether the properties of the NM for which this information exist

Table 4
Human health safety aspects and information needed to address these aspects in Stage 4.

Human health safety aspects	Information needed
13) Does occupational exposure increase due to the upscaled process?	Update of relevant exposure reduction measures in occupational setting in response to up scaling.
14) Is it possible to use read across or grouping of relevant forms to fill remaining data gaps for risk assessment?	Earlier obtained information for read across or grouping as described in the ECHA guidance (i.e. phys-chem and *in vitro* data of relevant nanoforms and phys-chem and hazard information of similar nanoforms).
15) What is the outcome of the risk assessment of the relevant nanoforms for the relevant exposed populations throughout the life cycle of the product? What are the uncertainties in this assessment? Are there still important data gaps (e.g. advice for further testing)?	Earlier obtained information for the risk assessment of all relevant nanoforms for all relevant exposure scenarios (e.g. exposure quantities of relevant exposure scenarios and hazard information on relevant or similar nanoforms).
16) Is the quality of the production process sufficient?	Information on the reproducibility of physicochemical properties and low batch to batch variability.

is sufficiently similar to the NM in development. If so, this data can be used instead of generating new data.

At this point, all potential risks throughout the life-cycle of the product should be assessed. Information collected in earlier stages can be used, and any large uncertainties and data gaps should be filled by generating new data.

Many NMs are heterogenous in their properties, but the quality control of the production process should be sufficient to keep these properties within specific ranges to ensure that the hazard information is still applicable to the NM.

3.5. Human health safety aspects in stage 5

The fifth stage of the innovation process is the launching stage. This stage includes the full-scale production, commercialisation and market expansion of the NM and/or NEP. This is the transition from the innovation to the Product Lifecycle Management process, including post market monitoring. Regular checks need to be performed to determine if the risk assessment needs to be updated due to changes in the production volume, production process or use of the NM or NEP (see Table 5).

3.6. Additional information

Sometimes, additional relevant information which is not included in the human health safety aspects will be available. For example, when measured (experimental) data on exposure levels or *in vivo* toxicity of the pristine NMs and/or its exposure relevant nanoforms is available, this should be used to address the human health safety aspects (or answer the questions). However, the absence of information on the proposed human health safety aspects in a specific stage within the innovation process, does not have to impede decision-making. Furthermore, any information needed in a later stage in the innovation process that is already available in an earlier stage may also be used to address the human health safety aspects in this earlier stage. The approach is intended to give guidance on what human health risk-related information to collect at various stages of the innovation process, but does not dictate the decisions to be made in case the information is unavailable or indicates a risk. Rather, the approach is intended to facilitate the user to decide either to continue to the next stage of the innovation process, to obtain more information, to apply safe by design (SbD) actions to reduce the hazard potential or exposure, or to stop the innovation process. The actual decision on how to move forward is left to the user.

3.7. The practical feasibility

In general, the industrial partners considered the proposed human health safety aspects relevant for risk assessment purposes, but indicated that the timing of the proposed information needed to address these human health safety aspects (i.e. in which stage of the innovation process the human health safety aspects are addressed) also depend on how likely it is that the NM within a NEP might change. Basic information on particle characteristics are available in the first two stages of the innovation process. However, in the first three stages of the innovation process the future application and therefore also the characteristics of the NM may still change. There are some differences between the large company and the SMEs. First, at the large company sophisticated techniques to measure NM characteristics are available in house. Second, the large company has enough in house expertise to perform risk assessment for workers, consumers and the environment at the various stages. Third, the large company already has developed a structured stepwise innovation approach that takes safety into account. The SMEs do not have these in house facilities and expertise and therefore rely on cooperation with universities and external experts. According to the SMEs it is challenging but feasible to obtain most information needed within each stage of the innovation process via cooperation with universities. For the large company it would be feasible to generate all information in house, however the likelihood of changes in the future application of a NM should be taken into account when deciding in which stage of the innovation process to invest in data generation. Once all data would be available, the SMEs would need expert advice how to interpret the results and how to perform and interpret the risk assessment, including the uncertainty. At the large company interpretation of risk assessment results is performed in house and uncertainties are taken into account. Concepts like grouping and read across are considered relevant for both the large company and the SMEs, but difficult to implement for SMEs without in house expertise.

In a publication by Soeteman-Hernandez et al. (Soeteman-Hernandez et al., 2019) these and several other challenges for the implementation of SbD by innovators are described, including: i) limited resources of SMEs; ii) lack of guidance on how to implement SbD; iii) lack of information; and iv) lack of trust for information sharing. These challenges illustrate that the implementation of SbD is currently in a transition phase where SbD is an accepted strategy for reducing the uncertainties of NMs, but not yet fully applied in practice. To facilitate

Table 5
Human health safety aspects and information needed to address these aspects in Stage 5.

Human health safety aspects	Information needed
17) Does the risk assessment need to be updated?	Regular checks of exposure levels and physicochemical properties, especially in case of a change in production volume or process (e.g. using different starting materials).

SbD implementation, policy strategies need to be directed to supporting innovators, particularly SMEs to apply SbD. The current Horizon2020 projects Gov4Nano, NanoRigo and RISGONE are working towards a future-proof operational Nano Risk Governance Model (NRGM) that addresses the needs of the transdisciplinary field and innovative (and key enabling) character of nanotechnology. The novel governance model might address issues of providing the necessary expertise and facilitating SbD application in SMEs.

4. Discussion and conclusion

Most innovators or designers focus on the development of a product that fulfils a specific set of requirements related to the functionality or application of the product. Safety is addressed during the innovation process but in many cases only just before entering the market. With the SbD concept, safety is addressed early during the innovation process. This is beneficial for industry since this may increase the efficiency of the innovation process and may enable the elimination or reduction of human health and environmental risks of the material or product without losing its functionality. Additional benefits include increased economic viability, consumers trust, responsible innovation, improve sustainability, a better reputation and interdisciplinary collaboration and transparency (Soeteman-Hernandez et al., 2019; SusChem, 2019).

As most innovators are neither toxicologist nor risk assessors, considering human health safety aspects within their innovation process may be challenging. This paper provides sets of questions that can help innovators to assess the nanospecific human health safety aspects of their product during the various stages of their innovation process. Addressing these questions can facilitate innovators to identify which type of information may support decisions on how to address potential human health risks for each stage in the innovation process. The identified information on the human health safety aspects can help innovators to decide if further investments in the product or material are beneficial. It may allow them to rank, prioritize and choose safer alternatives early in the innovation process. This may enable innovators to better anticipate on potential safety issues in an early stage, preventing these safety issues to become an innovation killer in a later stage of the innovation process.

This easy to use, practical and user-friendly approach maximises resource use and expedites the development new NMs and NEPs that are safer by design. The approach should be considered as complementary to existing regulations, to identify potential nanospecific risks that cannot always be fully addressed using the regulatory information requirements. The sets of questions can be used alone as a basis for assessing the human health safety aspects during the various stages of the innovation process, but also in conjunction with the assessment of the functionality aspects in a decision model as presented in part II of this publication (Tavernaro et al., n.d.).

The practical feasibility of the approach as first explored in collaboration with industrial partners of the H2020-project, indicated that some innovators of SMEs may need expert advice on how to interpret the information on the various human health safety aspects, including how to perform and interpret risk assessment, grouping and read across. Additional knowledge and expertise may be obtained through consultants, knowledge exchange (within and/or across supply chains and sectors and between larger industry and SMEs or start-ups) or via education and skills development of (future) innovators on human health safety aspects and the implementation of SbD (SusChem, 2019). Furthermore, the industrial partners indicated that the likelihood of changes in the future application of the NM, should also be taken into account when deciding in which stage of the innovation process to investment in data generation. The decision model described in part II of this publication (Tavernaro et al., n.d.) may help innovators in balancing safety, functionality and costs.

In addition, practical case studies as described in the publications by Sanchez et al. (Sanchez Jiménez et al., n.d.) and Salieri et al. (Salieri et al., n.d.) indicate that the innovation process is not a linear process following the five stages described in the Stage-Gate model, but rather an iterative process in which some of the information becomes available at an earlier stage, while other information becomes available at a later stage (or not at all) due to practical reasons. The human health safety aspects described in this paper can also be used in such an iterative innovation process. Any information needed to address human health safety aspects linked to a later stage in the innovation process can also be used in an earlier stage. In case information on one of the human health safety aspects is lacking, the innovator can also decide to continue to the next stage of the innovation process and obtain more information at a later stage. The approach does not dictate, but only proposes the order in which the human health safety aspects can be addressed. It is only intended to give guidance on what nanospecific human health risk-related information may support decision making in the various stages of the innovation process. The applicability of the approach was evaluated using a few case studies by a small group of industrial partners. To determine if the approach is applicable to the innovation of a broader group of NMs and NEPs, more experience within various industrial sectors and a larger group of SMEs as well as larger companies is needed.

CRediT authorship contribution statement

Susan Dekkers: Conceptualization, Methodology, Investigation, Writing - original draft, Visualization. **Susan W.P. Wijnhoven**: Conceptualization, Methodology, Investigation, Writing - review & editing. **Hedwig M. Braakhuis**: Conceptualization, Methodology, Investigation, Writing - review & editing. **Lya G. Soeteman-Hernandez**: Conceptualization, Writing - review & editing. **Adrienne J.A.M. Sips**: Conceptualization, Writing - review & editing. **Isabella Tavernaro**: Conceptualization, Writing - review & editing. **Annette Kraegeloh**: Conceptualization, Writing - review & editing. **Cornelle W. Noorlander**: Conceptualization, Methodology, Investigation, Writing - review & editing, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors like to acknowledge contributions of the industrial partners in NanoReg2 to the evaluation of the practical feasibility, including the relevance and availability or feasibility to generate the information needed in the decision making in the innovation process. The authors also like to thank the NanoReg2 partners for their useful feedback.

Funding

This work was supported by the Horizon 2020 Framework Programme of the European Union under Grant Agreement Number 646221 (NanoReg2) and the Dutch Ministry of Infrastructure and Water Management (IenW, project number M260105).

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