NanoImpact 24 (2021) 100354

Contents lists available at ScienceDirect

NanoImpact

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

Research Paper

Safe-by-Design part II: A strategy for balancing safety and functionality in the different stages of the innovation process

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ARTICLE INFO

Editor: Bernd Nowack

Keywords:
Manufactured nanomaterials
Safe-by-Design
Safety
Functionality
Safe innovation
Stage-gate model

ABSTRACT

Manufactured nanomaterials have the potential to impact an exceedingly wide number of industries and markets ranging from energy storage, electronic and optical devices, light-weight construction to innovative medical approaches for diagnostics and therapy. In order to foster the development of safer nanomaterial-containing products, two main aspects are of major interest: their functional performance as well as their safety towards human health and the environment. In this paper a first proposal for a strategy is presented to link the functionality of nanomaterials with safety aspects. This strategy first combines information on the functionality and safety early during the innovation process and onwards, and then identifies Safe-by-Design (SbD) actions that allow for optimisation of both aspects throughout the innovation process. The strategy encompasses suggestions for the type of information needed to balance functionality and safety to support decision making in the innovation process. The applicability of the strategy is illustrated using a literature-based case study on carbon nanotube-based transparent conductive films. This is a first attempt to identify information that can be used for balancing functionality and safety in a structured way during innovation processes.

Information box: Definitions of terms used in the present article that may be interpreted in various ways. Definitions were retrieved using sources such as guidelines from international organisations (e.g. ISO, OECD), legal text of European regulations (e.g. REACH) and guidance/opinions from European bodies (e.g. ECHA). In addition, peer-reviewed scientific articles that are widely used and cited, were consulted as well as information from the International Union of Pure and Applied Chemistry (IUPAC).

Nanomaterials (NM): According to the Commission recommendation on the definition of a nanomaterial (2011/696/EU) a "nanomaterial" means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm – 100 nm (Commission Recommendation, 2011).

Risk: The probability that some adverse effect (e.g. skin irritation or cancer) will result from a given exposure to a chemical. The risk posed by a substance depends both on the intrinsic properties of the substance (hazard) and of exposure. (Corrigendum to Regulation (EC), 2006)

Hazard:Property or set of properties that make a substance dangerous (Corrigendum to Regulation (EC), 2006).

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Safety: Safety is the reciprocal of risk. It is the practical certainty that injury will not result from hazards and exposures under defined conditions. (Duffus et al., 2007)

Identity: The term identity is used to describe the sum of physicochemical characteristics of NM (the structure of NM). The identity can be described by different blocks of key parameters (composition, size, shape, surface, crystallinity, and perfection) that are connected hierarchically tier by tier to increasingly higher levels of complexity (Ozin, 2021).

Functionality: The term functionality is defined as the quality of being useful, practical, and right for the purpose for which something was made. It is neither a property nor an application itself. It is rather the relationship between the properties and the practical use of a material in such a way that the use of the NM has a positive influence on a task or a potential application.

Extrinsic properties: Properties of NM, which depend on the surrounding system and may be evaluated without consideration of any application of the final product. Properties such as stability, reactivity, agglomeration/aggregation state, dispersibility, hydrophilicity/ hydrophobicity, (bio)persistence/ (bio)degradation, and (bio)durability are members of this group.

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Abbreviations: NM, nanomaterials; NEP, nano-enabled products; SbD, Safe-by-Design; CNT, carbon nanotube; SWCNT, single-walled CNT; MWCNT, multi-walled CNT; ITO, indium tin oxide; TCF, transparent conductive films; CVD, chemical vapour deposition.

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https://doi.org/10.1016/j.impact.2021.100354
Received 10 February 2021; Received in revised form 12 August 2021; Accepted 23 August 2021
Available online 3 September 2021

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Use-oriented properties: NM tend to show very distinct magnetic, optical, electronic, mechanical, thermal, and chemical properties compared to their bulk counterparts due to higher surface-to-volume ratio and quantum confinement effects. These use-oriented properties are properties that make NM interesting for specific applications and are not necessarily related to safety aspects. They are defined by the identity of a specific NM.

Chemical properties: Chemical properties are defined as characteristics or behavior of a material that may be observed when it undergoes a chemical change or reaction. Examples are catalytic properties, super−/ ultra-hydrophobicity, corrosion/ oxidation resistance or flammability.

Electronic properties: Electronic properties of NM are defined as properties of a material which determine its response to an electric field. Examples are electronic transport, and electrical conductivity.

Magnetic properties: Various unique properties, which can be affected by using a magnetic field, are observed at the nanoscale. Examples are superparamagnetism and giant magnetoresistance.

Mechanical properties: Mechanical properties are physical properties of a material arising upon the application of forces (behavior under the action of loads on it). Remarkable improvements in mechanical properties of NM and nanocomposites like hardness, toughness, strength, elasticity, or adhesion provide new options for novel applications in many fields.

Optical properties: Optical properties describe the interaction of a material with electromagnetic radiation and the changes that light undergoes upon interacting. By carefully controlling the size, shape, and surface of NM, a wide range of optical effects can be generated. Examples are surface plasmon resonance, opacity and transparency.

Thermal properties: Thermal properties are properties of NM, which are influenced by temperature. Novel thermal properties arise in low dimensional NMs, such as abnormal heat conduction, high thermal stability, lower melting points, etc.

Safe-by-Design (SbD) actions: SbD actions are measures to improve safety in the context of the target innovation while maintaining functionality. The selection of the SbD action is based on the available information and should be suitable to design out hazard or to avoid release and exposure. Potential SbD actions are, for example, the use of alternative materials, changes in the production process or modification of the used NM.

Life-Cycle: The life-cycle comprises the consecutive and interlinked stages of a product system, from raw material acquisition or generation from natural resources to final disposal, including its production and use. The safe use of a substance during the whole life-cycle needs to be ensured. (Gottardo et al., 2016)

1. Introduction

Manufactured nanomaterials (NM) and nano-enabled products (NEP) have demonstrated a high potential for applications in fields such as medical and pharmaceutical industry, computing and electronics or food and consumer products (Dang et al., 2010; Piccinno et al., 2012; Peters et al., 2016; D'Mello et al., 2017). One of the main reasons for their use is the outstanding functional performance of these materials. Compared to their bulk counterparts, NM exhibit unique, size-dependent properties. These properties are in the first instance determined by the sum of their intrinsic physicochemical characteristics (their structure). However, the ability to predict structure-property relationships (the relationships between physicochemical characteristics and use-oriented properties) and property-application relationships at the nanoscale is still limited (see also sections 2.1 and 3.1.

Concomitantly, with the development of functional NM and NEP as key drivers for innovation, concerns about potential adverse health effects and environmental impact of NM and NEP have arisen over the years. (Teunenbroek et al., 2017; Krug, 2014) Besides increasing numbers of nanosafety-related studies, the design of safe(r) NM and NEP has gained increasing attention. To support this development, "Safe-by-Design" (SbD) approaches are currently under investigation. Despite being a rather novel concept in the context of nanotechnology, (Jacobs et al., 2010; Morose, 2010; Nath and Banerjee, 2013) SbD has become an important part of most European nanosafety projects (Hjorth et al., 2017; Lynch, 2017; Falk et al., 2021) and plays an important role in the EU's chemicals strategy for sustainability (Chemicals strategy (europa.eu)) (Gottardo et al., 2021). The SbD concept refers to identifying the risks and uncertainties concerning humans and the environment at an early phase of the innovation process so as to minimise uncertainties, potential hazard(s) and/or exposure. (OECD, 2020) The SbD approach addresses the safety of the material/product and associated processes through the whole life-cycle: from the Research and Development (R&D) phase to production, use, recycling and disposal (Salieri et al., 2021; Salieri et al., 2018; Bottero et al., 2017; Cobaleda-Siles et al., 2017). For SbD in nanotechnology, the NanoReg2 project specified three design pillars (Sánchez Jiménez et al., 2020; Soeteman-Hernandez et al., 2019).

I. Safe(r) material/product: minimising, in the R&D phase, possible hazardous properties of the NM or NEP while maintaining function;
II. Safe(r) production: ensuring industrial safety during the production of NM and NEP, more specifically occupational, environmental and process safety aspects; and
III. Safe(r) use and end-of-life: minimising exposure and associated adverse effects through the entire use life, recycling and disposal of the NM or NEP. This can also support circular economy.

SbD strives for negligible human and environmental safety risks through an acceptable balance between safety, product functionality, and, as far as possible, costs. Furthermore, the SbD approach helps to gather safety-related data needed in order to comply with regulatory requirements and to communicate on any remaining risks (OECD, 2020; Soeteman-Hernandez et al., 2019).

Although the need to address both safety and functionality, as well as implications of NMs through design has been established (Gilbertson et al., 2015), most approaches studied so far focus on the safety aspects, that is, by reducing either the hazard potential of NM and NEP or the release/exposure probability. (Ma et al., 2015; Xia et al., 2011; Libralato et al., 2017; Lin et al., 2018; Li et al., 2015) In fact, for the practical application of SbD, an equal focus on functionality and safety is needed to sustain or even improve the functional performance, while minimising the inherent hazard potential and avoiding exposure of humans and release into the environment at all stages of the life-cycle (Kraegeloh et al., 2018). Towards this aim, a first proposal for a strategy was developed on how to combine information on the functionality and safety early during the innovation process and onwards, and how to apply SbD actions for optimisation of both aspects throughout. This procedure can be supported by application of existing tools and approaches, e.g. SIA toolbox, LICARA NanoScan, SUNDS and GoNanoBioMat (van Harmelen et al., 2016; Jesus et al., 2019; Schmutz et al., 2020). In part I of this work, "Safe-by-Design part I: Proposal for nanospecific human health safety aspects needed along the innovation process" (Dekkers et al., 2020) a set of 17 questions were proposed that can help innovators to identify which type information is needed to asses and reduce or eliminate human health risks at each stage of the innovation processes. The questions may further help to decide if additional investments in a product are worthwhile, or if safe(r) alternatives exist. Here, in this second part of the work, the focus is set on NM functionality and the weighing of functionality and safety along the innovation process. It is important to note that both functionality and safety might be affected by any action taken during the innovation process resulting in changes of the materials physicochemical characteristics. Depending on the property to be exploited for a distinct application, it might not be possible to improve or even maximise both functionality and safety at the same time by application of one single SbD action. The underlying mechanisms that result in an improved functional performance or enhanced safety are often not systematically examined, and additional work is needed to reduce the existing knowledge gaps in the prediction of structure-propery and property-application relationships of NM and in assessing relationships between their functionality and safety. (Winkler, 2020)

The classical stage-gate model by Cooper (Cooper, 1990; Cooper, 2008), a model that describes the consecutive steps of information gathering and decision making during the innovation process from idea to launch, was applied to structure the SbD concept along the development of NM and NEP (Shandilya et al., 2020). A strategy for gathering and identification of information to be used for balancing safety and functionality aspects in order to support decision making at the decision points is introduced and potential SbD actions are discussed. To start, a clear differentiation between the intrinsic physicochemical characteristics of NM (the NM structure), their use-oriented properties and potential applications, and a concept for classification of the use-oriented properties is given.

2. Methods

A working definition of the term functionality was developed and discussed with experts from industry and academia of the NanoReg2 project, since an official definition is currently lacking. A scientific literature review was performed in PubMed and Web of Science with the keywords “nanomaterials”, “application”, “performance”, and “properties” to gather the most important applications of NM/NEP and the related properties. For every identified application and property, searches were conducted with different types of NM (e.g. carbon-based NM, noble metal NM, polymeric NM, metal oxide NM, etc.). All identified applications and properties were evaluated and ranked according to their importance and frequency. Each property was assigned to one of the following categories: chemical, electronic, magnetic, mechanical, optical and thermal. During a meeting of the NanoReg2 consortium, a questionnaire was provided to the participants, asking how functionality and safety aspects are related as well as how or more precisely by which actions SbD can be accomplished during innovation processes. The results clearly indicated the need to define and classify the different parameters and aspects in more detail and to develop a link between use-oriented properties, applications, and safety of NM/NEP.

2.1. Classification of NM properties to support SbD

The application of SbD demands the establishment of a link between safety and functionality of NM. This link is provided by the intrinsic physicochemical characteristics of NM determining safety as well as functionality. In order to better understand this relationship, in frame of this work, the concept of the NM identity (Ozin, 2021) was applied. Furthermore, the identity was differentiated from the use-oriented properties. A classification of use-oriented properties was introduced. SbD actions were exemplified enabling to optimise safety aspects considering the use-oriented properties based on state-of-the-art literature and including information on current regulatory practices.

The NM identity comprises the intrinsic physicochemical characteristics, which can be determined independently of the (biological) environment or test system. Contrary to the identity of a bulk material, which might be mainly determined by the chemical composition, the identity of NM is defined by a combination of various parameters (the composition, the size, the shape, the surface, the crystallinity, and the degree of perfection (e.g., intentional or unintentional presence of defects and impurities). These key parameters apply to all NM, but like the pattern of a kaleidoscope, they are linked to each other and influence and determine the resulting overall properties in a collective manner. (Ozin, 2021; Qian et al., 2015) The first five parameters are considered to be priority properties that influence functionality (Ozin, 2021) and safety (Arts et al., 2015) of NM and NEP equally and need to be characterised for regulatory purposes. (Aschberger et al., 2017; Comandella et al., 2020; Rasmussen et al., 2018; ECHA, 2017) In particular, the parameter perfection shows a strong influence on functionality and safety as revealed by information described in the literature. (Harper et al., 2014; Eixenberger et al., 2019; Llansola-Portoles et al., 2014; George et al., 2012) The six key parameters further comprise subparameters such as surface chemistry, surface area, surface allocation and surface charge (surface parameters) or density, core/shell structure, and doping (parameters of composition). Using the identity concept, each particular type of NM is precisely defined by one dataset, comprising information on these key parameters. Further modification of NM, their coating or their incorporation into specific matrices influence existing or even induce new properties and therefore result in a new dataset and a new identity of the materials.

In order to identify the most important use-oriented properties of NMs, a scientific literature search was performed and the results were used to develop an inventory of properties that provide parameters for functionality. The identity can also impact the safety-relevant properties of NM (Dekkers et al., 2020). However, this impact may be exerted indirectly as the intrinsic properties (NM structure) are affected by the given surroundings, resulting in extrinsic properties. Generally, the identity determines functionality and safety. However, both might not be modulated by the same parameter or might not correlate proportionally against variations of one parameter. Regarding safety, it is important to note that the identity might not only have an impact on the hazard potential of NM but also on release and exposure scenarios.

2.2. Stage-gate model

The Cooper’s stage-gate model, which originally is a model for structuring and optimising innovation processes without focussing on SbD, was applied and adapted to structure the course of action necessary to consider SbD along the innovation process. The original Cooper’s stage-gate-model divides the innovation process into a series of stages (work phases) followed by gates (quality checkpoints) that have been adapted in order to accommodate the development of NM and NEP by information gathering (stages) and evaluation of the gathered information (gates). Generally, starting from the idea and the first decision to conduct the project, five consecutive stages and gates are run through until market launch. The very first, preceding gate comprises the decision to start the process. Here, the stages and gates were combined into three phases (Table 1). The early phase (up to gate 3) comprises rather basic considerations, as far as possible based on already existing information, whereas the principal product development takes place during the middle phase (up to gate 4). Even later in the final phase (up to gate 5), upscaling of the process as well as field trials are performed, before the market launch takes place.

2.3. Strategy for weighing and decision making during the innovation process

The Cooper’s stage-gate-model comprises specific quality checkpoints at the consecutive gates. At each of these gates during the innovation process, the project is re-evaluated considering the information obtained in the preceding stage. This procedure was adapted by inclusion of safety and functionality as decisive parameters. For the application of SbD, information on safety and functionality needs to be collected throughout the innovation process for decision making and balancing at the various gates. As elaborated above, the identity was introduced as a link between safety and functionality. Decision making at the gates is performed by evaluation of qualitative indicators of each safety and functionality or ideally quantitative actual-values against predefined indicators or ideally quantitative set-values. Therefore, depending on the “weight” of this collected information or deviation of the actual values from set values, decisions either direct the process forward into the next stage (“go”) or make re-evaluation (“no go”) necessary. In case concerns regarding functionality or safety have been identified, these need to be addressed. As a result, at the gates the need for specific SbD actions is expressed and subsequently implemented in the previous or subsequent stages. The term SbD actions has been introduced in order to define the type of action to be taken. The current strategy does not allow for a general quantitative description of the weight of each safety and functionality aspect as these are case-specific and depend on the NM and its specific application. However, established

Table 1
Overview of the type of information needed to balance functionality and safety during the innovation process. Information gathering as well as application of SbD actions take place during the various stages/phases.

Stage	Functionality	Safety	SbD actions	Information & data gathering
1–2 (Early Phase)	Identification and definition of the identity, function-ality, and application field with the help of existing data (literature, databases).	First estimation of safety aspects (hazard and exposure) related to the NM and/or NEP with the help of existing data (literature, databases) including the identification of any restrictions related to the envisaged material or application. Qualitative tools to assess risk may be used at this point (e.g. control banding tools).	Identification and verification of potential SbD actions, based on the available information and suitable to design out hazard or to avoid release and exposure	No laboratory research is con-ducted at these stages, available data also on similar NM as well as predictive mod-elling approaches should be taken into account.
3 (Middle Phase)	Generation of a full set of data on the identity, extrinsic properties, functionality, use-oriented properties, durability, performance after processing.	More (semi)quantitative estimation of safety aspects (risk and life-cycle assessment) based on the actual NM/NEP, as well as first (semi)quantitative analysis of actual release and potential exposure scenarios.	Implementation of SbD actions for preparation of the actual NM/NEP at the lab-scale.	Laboratory research and mod-elling approaches are included at this stage. A prototype is developed.
4–5 (Final Phase)	Generation of a full set of data on all aspects of functionality, especially on the feasibility of the pilot/large-scale production.	Generation of data suitable for a complete risk and life-cycle assessment, including hazard potential of the final product, issues of occupational health, determination of potential release and exposure scenarios.	Implementation of SbD actions specifically for the pilot production, considering occupational health issues as well as the expected life-cycle of the NM/NEP.	Laboratory work and pilot-production are included at these stages. A preliminary or final production process is developed, detailed performance tests are performed, the whole life-cycle of the NM or NEP is taken into account.

innovation processes are based on the definition of quantitative requirement profiles specifying use-oriented properties of NM and NEP as a set value. These innovation processes could be developed further in order to also specify acceptable or non-acceptable safety aspects. In this work, the focus was put on functionality. As the original Cooper model was designed to support commercial launch of products, further economical aspects are also relevant in the context of innovation. However, these aspects have not been considered in this approach. The concept resulting from the adaption of the original model is elaborated in section 3.

2.4. Case study

To illustrate, which actions can be taken in order to implement the presented SbD concept into innovation processes, a literature-based case study was conducted. The study focuses on the early phase. During this phase, the NM or NEP are still under development and innovators will have the highest degree of freedom to apply any necessary SbD actions.

3. Results & discussion

3.1. The relationship between functionality and safety of nanomaterials

It is well known that NM of one elemental composition can fulfil various functions and therefore might be suitable for various applications. An example is nano-TiO_2, that is used as photocatalyst in photovoltaic cells and as UV absorber in cosmetic products. (Noman et al., 2019) Generally, the use-oriented material properties are not determined by one single physicochemical characteristic like elemental composition or surface chemistry. Similarly, various properties of NM can be expected to contribute to the initiation of a biological effect or the hazard potential. (Gerloff et al., 2017) Thus, defining the structure-property and the structure-safety relationship of NM is even more complex than for conventional chemicals (Gilbertson et al., 2015). Furthermore, safety and functionality might not be determined by identical physicochemical characteristics. Since the intrinsic, physicochemical characteristics of NM are an interrelated system, which cannot be considered isolated, the identity of a NM is used here as a more comprehensive descriptor. (Ozin, 2021) The identity depicts the sum of the intrinsic physicochemical characteristics (Fig. 1). It comprises a structured and hierarchical arrangement of these properties into key parameters (black bars in Fig. 1) and subparameters (white bars in

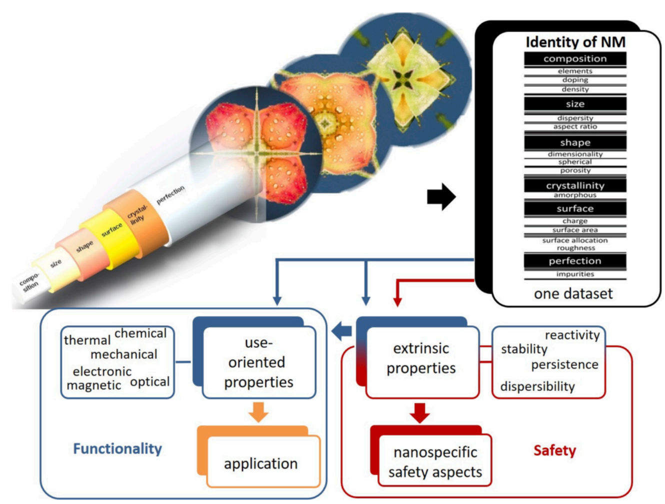

Fig. 1. The identity of NM and its relation to functionality and safety. The kaleidoscope illustrates the interlinkage of the intrinsic physicochemical characteristics of NM. Alteration of only one parameter results in a new pattern. The identity represents the sum of the intrinsic physicochemical characteristics (one pattern) and describes exactly one type of NM (Ozin, 2021). It determines the use-oriented properties of NM and their potential applications (functionality) as well as together with extrinsic properties, the safety-relevant properties of NM (nanospecific safety aspects (Dekkers et al., 2020)).

Fig. 1). As an example, for nano-TiO_2, the key parameter “composition” includes the main elements titanium and oxygen, as well as potential nonmetal, transitional metal and rare-earth metal dopants, or complex structuring like in a core-shell system, which might influence both the photocatalytic properties and the safety of the material. Furthermore, the key parameter “surface” can be divided into surface area, surface charge, and type and number of functional groups that influence the stability, dispersibility, and reactivity of the material. Thus, the identity (like a bar code) instead of one single parameter allows for an unambiguous identification of a NM. Using this concept, newly designed NM as well as existing NM can be exactly described and differentiated from each other by one set of parameters comprising specific descriptors. Although such specific descriptors are used for chemical molecules they have not been in practice for NM so far. (Gilbertson et al., 2015) In case of the above mentioned application of nano-TiO_2 in photovoltaic cells, the corresponding dataset at least requires information about the type of doping, the size, the shape, the surface properties, the crystallinity, and the structural defects (Huang et al., 2015; Bai et al., 2014).

The identity defines the use-oriented properties of a NM and relates to their function and potential applications (Fig. 1). Simultaneously, information on the NM identity is also important in hazard or risk assessment, mechanistic understanding, grouping or testing strategies, including predictions. However, safety-relevant properties of NM are not necessarily directly determined by their identity. Corresponding extrinsic properties, such as the stability (i.e. inertness against chemical reactions and external effects), the reactivity of NM, and resulting transformations, as well as release and exposure scenarios during manufacturing and along the whole life-cycle of the NM also play a role. A detailed overview on nanospecific safety aspects is given in the first part of this work. (Dekkers et al., 2020) In conclusion, the identity determines both the use-oriented properties and functional performance as well as safety-relevant properties and therefore can be regarded as link between them.

Here, the focus is set on the structure-property relationships in the context of SbD. Functionality describes the relationship between the use-oriented (functional) properties and potential applications of NM or NEP. The use-oriented properties make NM interesting for specific applications and are not necessarily related to their safety. For instance, the unique electronic and optical properties (i.e. high refractive index, UV absorption, photocatalytic activity, etc.) of nano-TiO_2 have led to its use in numerous fields of application (Gupta and Tripathi, 2011). The crystallinity of the material determines the photocatalytic activity and absorption capacity, due to different band gaps of the polymorphs (rutile-TiO_2 of 3.0 eV and anatase-TiO_2 of 3.2 eV), while size, shape, and surface of the material might influence the electron mobility. (Bai et al., 2014; Gupta and Tripathi, 2011) Defect engineering and doping of nano-TiO_2 also tune the band gap and improve the visible light-induced photocatalytic activity of the material (Khan et al., 2014). This example clearly illustrates the complex relationships between structure and use-oriented properties. Up to now, a classification of the use-oriented properties is missing, which would be needed as a basis to understand the structure-property relationships to support SbD.

The most important types of use-oriented NM properties were identified by a literature survey and then categorised (Fig. 2). Six main categories (chemical, electronic, magnetic, mechanical, optical, and thermal) of use-oriented properties were defined. These were further grouped into subordinate clusters (white (level 2) and grey (level 3) fonts in Fig. 2). This allows for a qualitative, relational categorisation of the functional performance of NM. Quantitative validity could be achieved through the input of collected data. For data collection, well-established or standardised methods should be used. (Johnston et al., 2020) Using quantitative data, the fuctional performance of various types of NM can be compared and evaluated. Such a comparative approach could be used in order to support the development of novel and tailored NM or the identification of alternative NM even for existing application fields.

Generally, quantitative data on the NM functionality could be contrasted with quantitative data determining safety-relevant aspects. However, the specification of quantitative set values for safety aspects still needs further development. Structured in this way, the categorisation scheme together with information about safety aspects could be integrated into existing physicochemical data collections. Although this might not have been achieved today (Winkler, 2020), the availability of such connected datasets would be necessary in order to further develop the current state of SbD.

The classification of the use-oriented properties and their differentiation from the identity and applications could further be expanded to

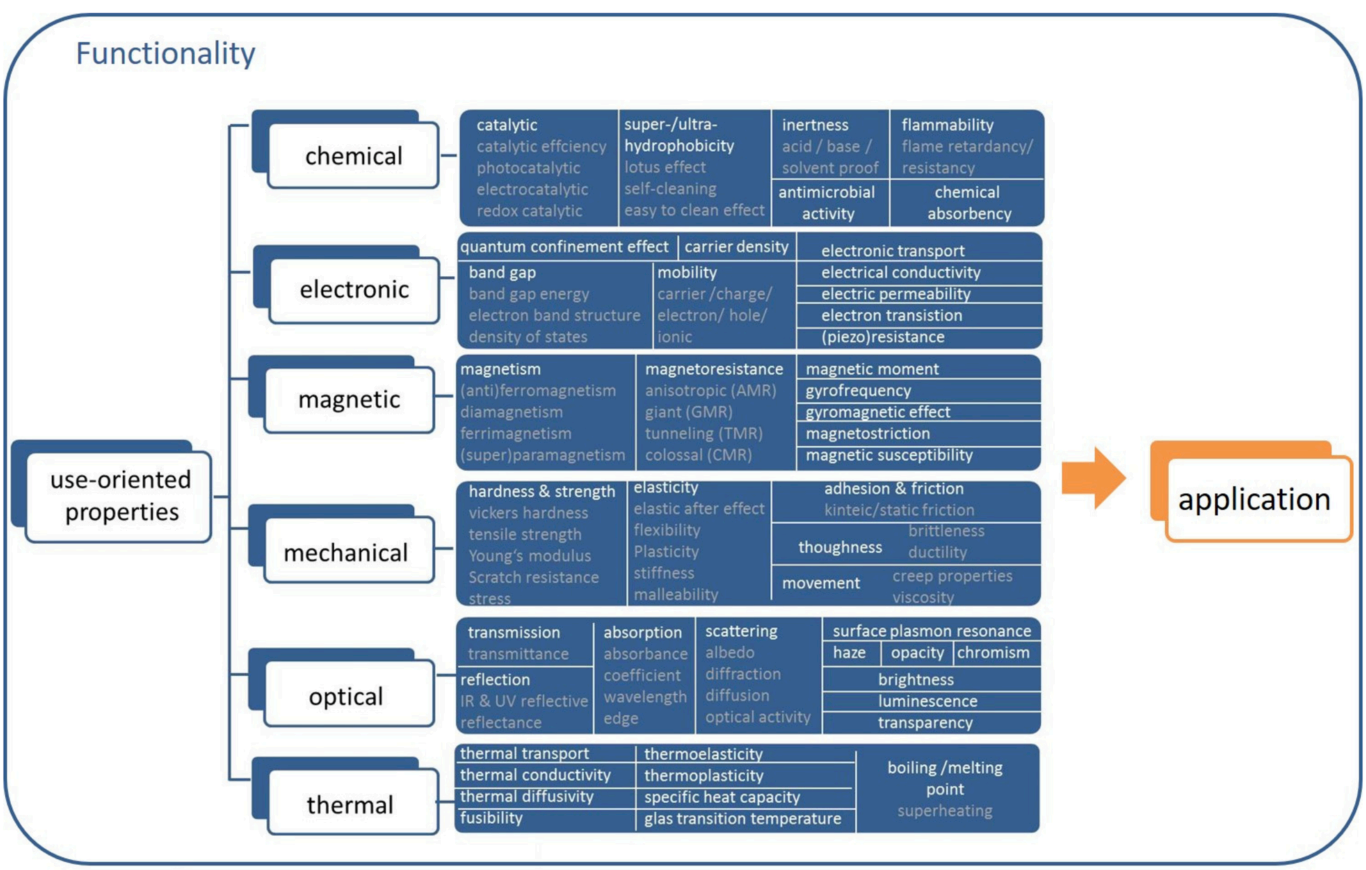

Fig. 2. Classification of the most relevant use-oriented properties of NMs based on a literature survey.

include information on the synthesis/processing (fabrication) as well as on characterisation methods, enabling coverage of all relevant aspects along the innovation process (Fig. 3). Given the vast number of NM, a systematic description of all these aspects could support early screening strategies in the context of SbD.

To the best of our knowledge, there is no freely accessible database that collects and summarises data on physicochemical characteristics, functionality, application and production of NM/NEP and simultaneously links this information with safety aspects. Such a database could enhance the awareness of relations between function and safety and thus support SbD. Furthermore, such a database might also be beneficial for regulatory processes by supporting regulatory preparedness. (Soeteman-Hernandez et al., 2019; Kraegeloh et al., 2018) Databases like eNanoMapper could enable such a modular integration of functionality information (Jeliazkova et al., 2015). In frame of the NanoReg2 project, the feasibility to integrate functionality data according to the above described scheme (Fig. 3) into such a database was demonstrated (data not shown). Clearly, the more comprehensive and complex such datasets become, the more awareness needs to be given to parameters like data completeness and data quality (Comandella et al., 2020; Marchese Robinson et al., 2016).

3.2. Balancing functionality and safety

The developed balancing strategy first combines information on the functionality and safety early in the innovation process and onwards. We propose that the evaluation of both parameters could be achieved by means of pre-defined qualitative and quantitative set-values used to specify acceptable functional performance compared to acceptable safety-relevant properties. If the set-values are not fulfilled, the subsequent application of proper SbD actions can allow for optimisation of both aspects throughout the innovation process. After introducing the NM identity and its interlinking role between functionality and safety, we subsequently illustrate how the presented strategy can be used to balance safety and functionality of NM to support the development of novel, tailored NM and NEP that are safe(r) by design. In general, SbD actions can be used to optimise NM or NEP as well as their production process (Examples of SbD actions are given in the supporting information). They should be ideally applied at the earliest stages (1 and 2) of the innovation process. At these stages, the highest degree of freedom prevails regarding the choice of a NM most suitable for the envisaged application, its modification, and processing. At later stages the scope for potential SbD actions becomes increasingly limited. An example would be the implementation of SbD after pilot production has already been started. At such a late stage, the production and processing has already been implemented and optimised, therefore the costs connected with alterations in the workflow would be enormous and probably not sustainable. Similarly, the early application of risk assessment tools (e.g. SIA Toolbox, SUNDS, GUIDEnano tool) (van Harmelen et al., 2016; Franken et al., 2020; Fadeel et al., 2018) and in silico methods (Basei et al., 2019; Burello, 2015; Baalousha et al., 2016) enable an early identification of potential safety issues already prior to the experimental phase. A thorough review of the state-of-the-art and search of (future) databases providing information on materials properties, functionality, safety, and fabrication would support the identification of potential SbD actions early in the innovation process.

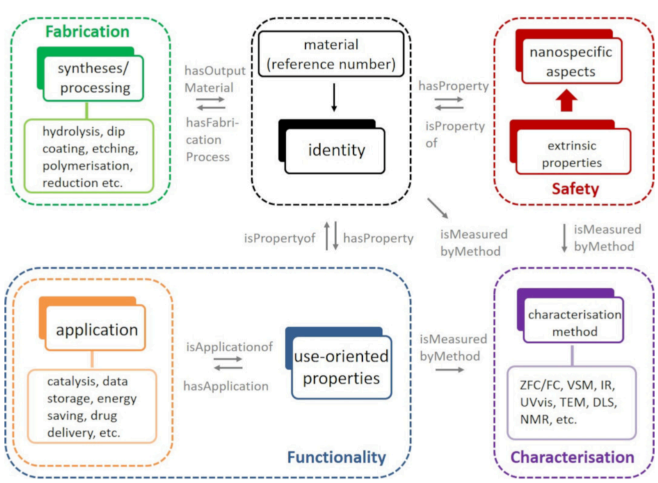

Fig. 3. The NM identity and the inventory of use-oriented properties are potential add-ons for existing databases to link the function of NM/NEP with their safety, fabrication, and characterisation methods. It is not a comprehensive overview of the different available modules and can be enhanced with further modules, i.e. end-of-life. Grey arrows indicate exemplary descriptors used to link the modules in ontologies.

3.3. Implementation of the balancing strategy by means of SbD actions

The implementation of SbD and the balancing of functionality and safety of NMs/NEP, can be seen as an add-on for existing industrial innovation processes. In order to integrate SbD into such a process, first of all a specification of the type and quality of information that can be used for balancing during the course of the innovation process is needed (Table 1). In order to support decision making at the different gates, functionality and safety aspects will have to be balanced according to the available information. This could be supported by definition of ideally quantitative set values, specifying minimal requirements for both aspects, safety and functionality. At the gates the set values could be compared to corresponding actual values, specifying the actual functional performance as well as safety-relevant aspects in order to define required improvements. At least for industrial developments, the specification of such set values is well established by definition of requirement profiles. At the early phase of the innovation process such information will be based solely on theoretical considerations, literature data, and empirical values, whereas at later phases specific information from the examination and characterisation of the prototype/product will be available (Table 1).

To gather the information needed for decision making at the various gates, all steps in the preceding stage should have been completed and information gaps should to be identified. Sets of questions on nano-specific safety aspects (Dekkers et al., 2020) and functionality of the NM/NEP (Table 2) may support decision making and can help innovators to decide which aspects have to be addressed before entering the next stage and if further investments in the product are economically reasonable. Furthermore, the questions may help to find alternatives that can be ranked or prioritised depending on the appearing problems.

Though functionality and safety are evaluated independently by different sets of questions, the overall decisions are based on the evaluation of both aspects (Fig. 4). The comparison of the results and the weighing of functionality and safety has to be performed on a case by case basis in accordance with the specified requirements. The outcome is a “go” or “no go” decision (Table S1 in the supporting information). For example, functionality requirements would be fulfilled, in case appropriate NM/NEP are available or can be produced. Expected performance deficiencies related to functionality need to be indicated. However, in order to proceed, such deficiencies might also be addressed later during the process and will in the first instance be handled as alarming information. For instance, if a known form of a NM/NEP does not fulfil the envisaged requirements, this severe deficiency makes it necessary to move back to the previous stage in order to identify a more suitable modification or an alternative material. In case a manufacturing route for a very similar NM/NEP is available, but has to be adapted, the issue is expected to become solved in the subsequent stages, but it needs particular attention. Comparably, information on a relevant hazard potential or potential release is considered as alarming. Quantitative estimation of such data needs to be based on toxicological evidence or

Table 2
Collection of functionality information needed to support decision making at the consecutive gates.

Functionality			
Early Phase			
Stage 1	Gate 2[a] **1)** Which **use-oriented properties** are needed to fulfil the requirements of the envisaged **application**? Which NM show these properties? How is their identity defined? **2)** Which **use-oriented properties** does the envisaged NM exhibit? Which **applications** are enabled by use of this NM? What are **existing applications** for the chosen NM? **3)** In **what form** can it be used for the envisaged application? Does it have to be modified? Which steps have to be performed to produce the envisaged NM/ nanoproduct? In which form will it be marketed? **4)** **What amounts** of the NM are needed for the application (s)?	Stage 2	Gate 3 **5)** What is the **identity** (composition/ size/shape/ surface/ perfection) of the used NM? Is the NM doped, surface treated or otherwised functionalised? Is anything known about the crystallinity of the NM? **6)** How are these properties linked to the **extrinsic properties**? Do transformations have an influence on the functionality? **7)** How is the NM **synthesized**? **8)** What are **the use-oriented properties** of the NM? How can these properties be determined? Which **characterisation methods** are needed? What **use-oriented properties** are needed for the envisaged application?
Middle Phase		Final Phase	
Stage 3	**Gate 4** **9)** Does the **prototype** fulfil the **requirements specified for functionality**? Is it suitable for the application? Does it exhibit the **desired identity/ use-oriented properties**? **10)** Is the real **functionality (after processing of the NM) still compelling**? Have all **functionality tests**, including indicators for robustness, transformation, and durability been performed? Do the results indicate that the requirements are fulfilled?	Stage 4	**Gate 5** **11)** Does **the upscaled process** influence the **material/ product parameters**? How are these differences defined? **12)** Does **the upscaled process** differ from **the lab scale process** in terms of grade and amount of raw materials, waste production, by-products, economics of the process, mechanical and thermal parameters (e.g. temperature or pressure)? **13)** Are there any potential **synergetic effects**? Do functionality and safety **influence** each other or are they **independent** from each other? **14)** Are the **process and the product reproducible**? (information on the reproducibility of physicochemical characteristics and low batch to batch variability)

[a] Gate 1 is not included here, as it precedes the first stage and mainly includes the initial decision to start the innovation process. Gate 1 is also named idea in Fig. 4.

appropriate correlation of in vitro to in vivo data as well as comparison with critical release or exposure data.

In the following sections, the consecutive stages and gates and corresponding actions along the innovation process are described. To further illustrate the presented concept, a case study is used, based on a literature survey. The case study covers only the early phases of the innovation process from the idea to the development of the prototype during stage 3. This restriction was set on purpose to underline the importance of an early application of SbD actions.

3.3.1. *Idea*

Independent from the use of the classical linear stage-gate model or other next-generation idea-to-launch systems, any innovation process is initiated by the discovery and scoping of a product idea. (Cooper, 2014; Cooper and Sommer, 2018) This idea must be screened conscientiously before deploying resources to the project. The screening includes a feasibility study, a socio-economic analysis, as well as technical aspects. Considering NM, two different types of innovation processes and products are conceivable. In the first place, the final product is in form of a powder or dispersion of a NM. In this case, the development of this specific NM with its unique properties is in focus, whereas potential future applications might be put into the background and maintained open. On the other hand, existing NM are used as raw material or component for the production of advanced NEP. In the latter case, at first the future application will be precisely specified. Thereby, also the product requirements are defined, limiting the range of potential material alternatives relevant for SbD to matrix variations or to NM with similar use-oriented properties.

For the illustrative case study, the second type of process was chosen. Here, the use of carbon-based NM (i.e., use of the NM as raw material) as alternative material to prepare transparent conductive films (TCFs) was selected. Such materials are used as components in touch screens, liquid crystal displays, and solar cells. (Hecht et al., 2011a; Yu et al., 2016) The functional performance of TCFs is determined by conductivity and optical transmittance. However, some of these films additionally require a remarkable mechanical flexibility and chemical/thermal stability in order to achieve future relevance in modern smart systems, e.g., when used as element of flexible displays or transparent heaters. (McCoul et al., 2016) To date, the industrial standard material used for transparent conductors is indium tin oxide (ITO). It exhibits the best combination of a high transparency (90%) and sheet resistance (10 Ω/square) compared to other already used materials. (Zhou and Azumi, 2016) However, ITO has some limitations such as the scarcity and high costs of indium as well as the brittle ceramic nature of the material. (Ellmer, 2012) Efforts to overcome these shortcomings by using alternative materials, have resulted in increased production costs and worse optoelectronic properties, since the optical transmittance and high conductivity often follow opposing trends. (Wang et al., 2019) Nevertheless, the market on TCFs will grow fast in the next years and the increasing demand for flexible and low weight optoelectronic devices makes the use of alternative TCFs indispensable for future developments.

3.3.2. *Early phase*

In the early phase of the innovation process (up to Gate 3), basic information on the identity, functionality, and application field of NM and/or NEP are gathered with the help of existing data (literature, databases) and without laboratory research (Table 1). Further, a first estimation of safety aspects (hazard and exposure) is performed at low cost and in short time.

3.3.2.1. Stage 1 (preliminary assessment). In the first stage of the innovation process, information on the functionality (what and for what?) of the NM or NEP is gathered to establish an initial requirement profile, specifying the decisive materials properties, e.g. conductivity and transmittance. Even though neither quantitative nor actual functional performance data might be available at this stage, the minimal requirements to achieve readiness for marketing need to be formulated. This requirement profile can be used in the following to match the

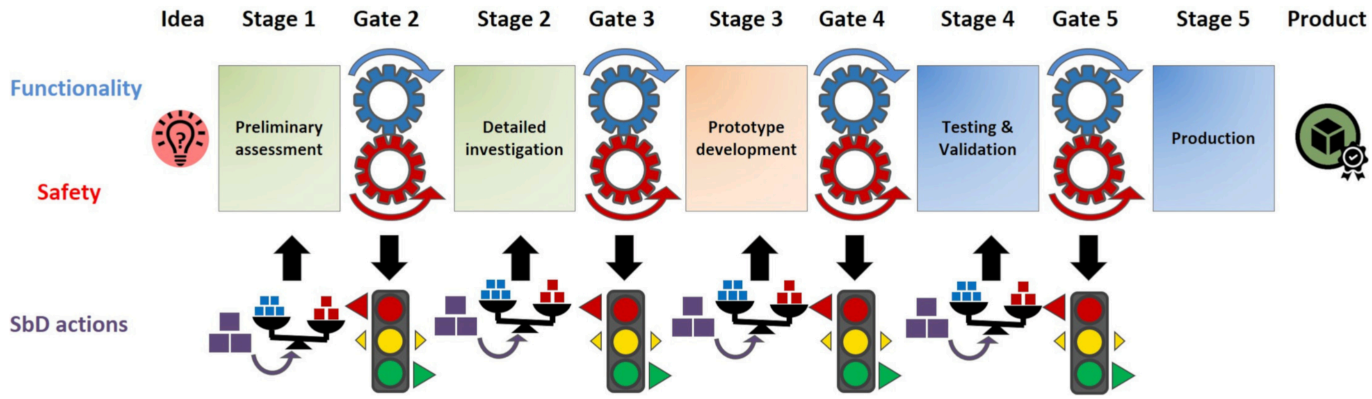

Fig. 4. Consecutive stages of the innovation process and actions to be taken after decision making at the gates. The innovation process is initiated by the idea including a first gate at which the decision to start the innovation process is made. Subsequently, 3 phases are run through (early = green, middle = orange, final = blue) prior to market launch of the product. At every gate the project is evaluated in light of the information obtained in the preceding stage by weighing of functionality and safety aspects. The outcome of weighing results in a "go" (green light) or "no go" (red light) decision. Yellow indicates a rising alarm, due to concerns on safety or deficiencies in functionality. In this case, either moving forward or back is possible, In any case, the concerns need to be addressed. Concerns are solved by implementation of SbD actions aiming at improving safety while keeping the functionality or vice versa. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

desired (set value) vs. actual material properties and functional performance (actual value).

At this early stage, only a brief screening is performed, based on existing information from literature and databases (Table S2 in the supporting information). With regard to functionality, TCFs at least require a high electrical conductivity and high transparency. The minimal requirements depend on the envisaged application. They vary regarding the sheet resistance and transparency between 500 Ω/square and 85% for touch panels and 10 Ω/square and 90% for photovoltaic electrodes. (Zhou and Azumi, 2016) Most thin films incorporating CNTs with a tube diameter in the range of 1–100 nm fulfil these requirements. Results of various research studies have shown that single-walled CNTs (SWCNTs) double-walled CNTs, and MWCNTs might be suitable. (He et al., 2017; Liu et al., 2011; Niu, 2011) However, the identity of CNTs, especially the wall number and diameter, has a strong impact on the electrical conductivity of films incorporating such NM. (Farbod et al., 2017; Hecht et al., 2011b) For instance, Mirri et al. presented conductive CNT films with a sheet resistance of 100 Ω/square and high transparency of 90% in the visible spectra. (Mirri et al., 2012) In another study Jiang and co-workers used a chemical vapour deposition (CVD) method to obtain a network of isolated SWCNTs with a low sheet resistance of 41 Ω/square at 90% transparency. (Jiang et al., 2018) Some other extraordinary use-oriented properties of CNTs, i.e. their high mechanical strength, flexibility and low weight, render them promising candidates for robust as well as flexible optoelectronic devices.

Likewise a preliminary estimation of potential hazard and risks related to the envisaged product and application field has to be performed at this early phase of the innovation process using existing data (Examples of safety data on CNTs are given in Table S3 in the supporting information using the questions provided in part I of this work (Dekkers et al., 2020)). Several safety aspects have to be considered for the use of CNTs in TCFs. One important exposure scenario is related to potential inhalation of CNTs during production. (Donaldson and Poland, 2013; Donaldson et al., 2013; Liu et al., 2013) In this context, characteristics like their high aspect ratio, (bio)persistence or metallic impurities remaining from the synthesis of CNTs have to be considered. (Ge et al., 2012) It is well known, that airborne CNTs are likely to be harmful at very low concentrations. Accordingly, various recommendations on exposure limits for CNTs have been published (Guseva Canu et al., 2020) (DGUV, 2021; Nanocyl, Responsible Care and Nanomaterials Case Study Nanocyl, 2009; Pauluhn, 2010). Such limits help to define quantitative safety-related requirements used for balancing.

The expected exposure scenario already needs to be considered for the selection and optimisation of the manufacturing process. CNT-based TCFs can be fabricated via different dry or wet processes, influencing the identity of the material. (Zhou and Azumi, 2016) Liquid-based processes, such as spin coating, spray coating or dip coating, are generally preferred for the fabrication of CNT-based TCFs at a large scale. (He and Tjong, 2016) However, TCFs fabricated by dry methods exhibit higher quality due to better separated CNTs, fewer defects and good adhesion of CNTs to the film substrate. (Abu-Thabit et al., 2020)

While manufacturing and processing are the most potent sources to direct environmental release and exposure for CNTs (Gottschalk et al., 2009), the third pillar of SbD (safe(r) use and end-of-life) has to be also evaluated at this stage. Human exposure during use might play a tangential role for TCFs, due to the fact, that the CNTs are embedded in a solid matrix and will not be released easily during normal use. (Nowack et al., 2013) However, mechanical abrasion or physicochemical alteration may cause unintentional release of CNTs into the environment. At the end-of-life the products are recycled or the waste is disposed through landfilling or incineration. Specific waste handling strategies, i.e. higher temperatures and longer duration in the incineration furnace, might be necessary to minimise the impact on the environment. Studies on life-cycle assessment and specific tools can be used to evaluate different scenarios and to study the potential impact on the environment and human health. (Jantunen et al., 2018)

Finally, restrictions related to the application of the envisaged NM or NEP by current European legislation (e.g. REACH, pesticides and biocides, food, cosmetics, medical devices) or national regulations should be identified in order to prevent non-marketable developments already at this early stage. For example, the ban of lead and cadmium in consumer electronics according to the Restriction of Hazardous Substances Directive will make it necessary to switch to alternative material types for quantum dots in consumer electronic applications. (Black, 2005) At the moment, there are no restrictions for the use of CNTs as NM or NEP in the EU, but recently the Swedish non-profit organisation *ChemSec* added CNTs as the first NM to its "Substitute It Now!" list that identifies substances of very high concern and is mainly based on their hazard potential. (Hansen and Lennquist, 2020) In contrast to the EU, the USA have strict notification requirements within the context of the "Toxic Substances Control Act" for CNTs, including information on manufacturing, use, personal protective equipment and the management of waste water. (EPA (Environmental Protection Agency), 2010)

3.3.2.2. Gate 2 (second screen). At the subsequent gate, decision making will be based on the information gathered in the preceding stage according to functionality and safety. Here, all three pillars of SbD should be considered, including safe(r) NM to generate safe products by design, safe(r) manufacturing/processing, and safe(r) use of NEP. A main reference for the functionality is the requirement profile. Besides the material itself, the used form of the NM (i.e. powder, liquid, embedded into a composite etc.), as well as future processing steps to produce the final product, and their potential effects on the functional performance of the product need to be considered. For example, if the elemental composition of the envisaged NM is banning its planned application due to legislative restrictions, this severe concern is suggesting a “no go” decision (red light in Fig. 4). In case the alarming safety information is expected to become solved in course of the process (indicated by the yellow light in Fig. 4), a “go” decision with reservation may result. Again, in this case the alarming issue needs particular attention. Although CNTs can be expected to fulfil the requirements for the use-oriented properties relevant for CNT-based TCFs, in this case safety concerns might raise an alarm. Since no legislative restrictions for the application or the material exist, a return to the previous stage is not mandatory. Moving forward with a “go” decision includes addressing the reservations by specific actions in the following stages, e.g. reduction of actual release and exposure scenarios during production and processing of the CNTs and minimisation of their actual hazard potential.

3.3.2.3. Stage 2 (definition and detailed investigation). In the second stage of the innovation process, the attractiveness and feasibility of the project is verified in more detail. At this stage, the NM identity, planned synthesis, processing, and production approaches, use-oriented properties and application fields have to be defined. Therefore, comprehensive information on the NM or NEP requirements as well as on the envisaged production or processing is gathered in order to specify the material as accurately as possible. However, still only theoretical information is gathered at this stage, unless the (pristine) NM is available. Read across or grouping and further predictive approaches might help to collect the needed information. (Stone et al., 2020; Lamon et al., 2018)

As stated above, the fibrous shape and aspect ratio of CNTs combined with biopersistence are the properties of highest concern regarding their safety. (Donaldson and Poland, 2013; Donaldson et al., 2013) To overcome these concerns, the use of CNTs with a lower aspect ratio might be a starting point. However, the CNTs length has to be carefully optimised as shorter tubes enhance dispersion, while longer tubes increase electrical conductivity. (Lee et al., 2012) For triple-walled CNTs an optimum length seems to be 200 μm whereas Farbod and co-workers reported for SWCNTs an optimum length between 168 nm and 1200 nm to achieve the needed functionality (high transparency and low sheet resistance). (Farbod et al., 2017) Modification of CNTs through doping or surface functionalisation has been described to enhance their degradability. (Liu et al., 2010) However, such modification might at the same time alter the resulting use-oriented properties, e.g. electrical conductivity and transparency. For instance, Gao et al. fabricated SWCNT-based TCFs with a relatively low sheet resistance of 82.6 Ω/square at 80.7% transparency and further improved the material (70.6 Ω/square; 81% transparency) through surface modification with poly(3,4-ethylenedioxythiophene):poly(styrene sulfonate). (Gao et al., 2013) In another study, Tsapenko and co-workers presented a simple method for aerosol doping of SWCNT-based TCFs, resulting in an alteration of sheet resistance from 79 to 3.2 Ω/square at 55% transparency. (Tsapenko et al., 2019) Therefore, the compliance with the specific requirements has to be reviewed after modification.

Another focus at this early phase of the innovation process is the analysis and optimisation of the production process through comparison with other methods and the search for alternative solutions. Typically, CNTs are synthesized by electric arc discharge, CVD or laser ablation. (Prasek et al., 2011) Among these synthesis approaches, CVD is the most promising one for producing high quantities of materials and is often used in industrial production. Through variation of reaction parameters, such as carbon precursor, catalysts, feed gas, reaction temperature, and reaction time, the identity and functionality of the CNTs can be tailored and optimised. (Brukh and Mitra, 2006) To narrow the size distribution and to reduce the amount of impurities, a purification step is generally employed after the synthesis. Here, machine learning techniques and other in silico approaches might help to study the influence of the different reaction parameters to obtain an optimised functional performance. (Khabushev et al., 2019) Harvesting from the CVD reactor and cleaning it, poses a high risk for exposure of workers and should be considered. (Lee et al., 2010) It is important to note that not only protective measures (i.e., ventilation/filtration of air) are suitable for mitigating any unacceptable emissions, but variation of the process itself might also help to minimise potential risks. In addition, the reduction of by-products (e.g. carbon black or metal impurities), analysis of the process parameters as well as understanding the growth mechanisms of CNTs are mandatory to select the optimal production process. For example, to minimise exposure of workers to CNTs during production, synthesis routes in liquids might be used. (Segawa et al., 2016) Such approaches might also be used to reduce by-products. (Yamagiwa and Kuwano, 2017)

Compared to ITO films, which are manufactured by an expensive sputtering technique at low pressure or by CVD at high temperatures, CNT based films can be produced by cheaper solution-phase coating processes. (Li et al., 2018; Siwal et al., 2021) Drawbacks of these methods are related to challenges in upscaling. A combination of these methods with printing techniques might solve this problem. To minimise the exposure of workers during the processing and fabrication of TCFs, Zhou and co-workers recently presented a combined spraying and roll-to-roll technique that might be fully programmable and automated. (Zhou et al., 2018)

The use of alternative materials might also be one promising approach to circumvent the hazard potential of CNTs. In a first step, these alternatives have to be reviewed for their compliance with the specific requirements for functionality. (Langley et al., 2013) A combination of conductive polymers and CNTs might lead to a better functional performance (sheet resistance 65 Ω/square and 92% transparency), including an improved resistance stability of the films. (Tian et al., 2019) To reduce the hazard potential, other carbon-based NMs, which are less biopersistent and do not fulfil the fiber paradigm might be used. For example, monolayered graphene exhibits a potential sheet resistance of 30 Ω/square and a transparency >97%. (Ma and Zhi, 2019) However, the conductivity and transparency of graphene-based TCFs are influenced by the number of graphene layers. A major drawback of graphene-based TCFs is still the challenge to produce large-area single-crystalline graphene without any defects and contaminants. (Liu et al., 2017) Furthermore, the use of metal oxides and metal nanowires for TCFs might impose further safety issues related to the release of toxic metal ions. ***3.***

3.3.2.4. Gate 3 (initiation of the project). At Gate 3, it needs to be demonstrated that the objectives identified before are met and that the planned steps from Gate 2 have been completed. The gate decision will be based on the evaluation of the available (usually still theoretical) information compared with the properties specified in the requirement profile (Table 2). Using the above described SbD actions might minimise the hazard potential of the material, but also influence the sheet resistance and therefore its functional performance. On the other hand, the sheet resistance has been shown to increase linearly with decreased tube length. (Mustonen et al., 2015; Pereira et al., 2009) In case no other options exist in order to reduce the hazard potential, protective measures for the workers need to be installed. This alarming information needs particular attention in the subsequent stages. Information on potential exposure scenarios during the further life-cycle, e.g. use and disposal, have to be considered and measures have to be taken in the next stage (“go” decision). A “no go” decision induces a repetition of stage 2 that put the focus on other SbD actions (different synthesis/processing approach or an alternative material).

3.3.3. Middle phase

After the preliminary definition and description of the NM and/or NEP, the development of a prototype is performed during this phase. Therefore, laboratory research and modeling approaches are used to obtain a full set of data on the actual NMs identity, functionality, and safety.

3.3.3.1. Stage 3 (development). At stage 3, the NM or NEP is developed, and experimental and more comprehensive data is generated. The information will be completed by quantitative data on the use-oriented properties, identity, and extrinsic properties. The focus at this stage is on the development of the product itself, including optimisation of the synthesis and preparation route, comprehensive material characterisation and initial functional performance and durability tests. In case of the proposed CNT based TCFs, not only the identity of the NM/NEP is analysed by suitable characterisation methods (Rasmussen et al., 2018), but also the sheet resistance and transparency of the obtained films are determined at this stage. (Kang et al., 2014) The obtained actual values are compared with the set values in the requirement profile. At this stage (semi)quantitative information on potential release and exposure and experimental data on the hazard potential of the NM/NEP is generated and used to determine alarming safety information. The prototype also allows for performance of more quantitative risk and life-cycle assessment to identify still existing data gaps and potential drawbacks.

3.3.3.2. Gate 4 (post-development review). At this gate the project is reevaluated according to the data obtained in stage 3 during the prototype development. The continued attractiveness of the prototype and its suitability for the envisaged application is checked (Table 2), taking the requirement profile into account. At this gate, the decision on upscaling of the production will be made. Comprehensive and at least semi-quantitative data documenting both the functional performance of the NM/NEP and safety is available. Data on the actual identity, use-oriented properties, extrinsic properties are available. First data has been collected indicating durability and robustness of the NM/NEP under use-conditions, release, and transformation.

3.3.4. Final phase

At the final stages 4 and 5, the production process and the final product are further improved and comprehensively tested. Therefore, information on the pilot-production and the whole life-cycle of the NM and NEP are considered and addressed by detailed testing.

3.3.4.1. Stage 4 (testing and validation). At stage 4, the work focuses on upscaling and the establishment of the pilot production. Not only the production process is developed, but also the final product is available. Test material is used to study the product functional performance by field trials on durability and/or release. It is checked whether the NM or NEP properties after upscaling are identical to the properties prior this step. It is also verified, whether the pilot production allows for manufacturing of the planned amounts of NM or NEP or if relevant variations of the production process are necessary. Further, a comprehensive assessment of potential risks, including data on hazard, release and exposure in particular at the workplace, is made in order to fill remaining data gaps that might not have been addressed before. Furthermore, regulatory relevant safety data needed for registration and/or approval of the final product should be gathered at this stage. Ideally, information (or part of it) could be used that was already gathered earlier. Therefore, awareness about the necessary regulatory information should be raised already in the beginning of the process.

3.3.4.2. Gate 5 (pre-Commercialisation). At the final gate prior to commercialisation the project is reevaluated according to the information on product functional performance and pilot production obtained in the previous stage 4. At this gate, the decisions will be based not only on the product functional performance, but also on the reproducibility of the production process as well as on the suitability, quality, and efficiency of the process itself. Especially the performance of the upscaled process will be evaluated (**Table 2**). Further, all regulatory relevant safety data has been compiled enabling risk assessment of all relevant exposed populations throughout the life cycle of the NM/NEP. (Dekkers et al., 2020; ECHA, 2017; ECHA, 2019)

At this gate, any reservations identified related to the functional performance of the NM/NEP or its safety should result in a “no-go” decision in order to ensure marketing of a high-quality and safe product: a product that is not only functional, but also SbD.

3.3.4.3. Stage 5 (full production and commercialisation). After the last decision, stage 5 includes the market launch of the NM and/or NEP and its production. At this stage, quality control ensures that key parameters in terms of identity, functionality, application, and safety are sustained.

4. Conclusion

Here we present a first proposal to a strategy aiming at balancing functionality and safety for SbD applicability during the various stages of the stage-gate and innovation process. This strategy combines information on the functionality and safety early in the innovation process and onwards, and then guides the application of SbD actions that allow for optimisation of both aspects throughout the innovation process. We acknowledge that this work is still under development and comprehensive advancements in predictive knowledge on how the physicochemical characteristics of NM are related to their functional performance as well as to potential hazard and risks for human health and the environment are still needed. Hence, the presented strategy integrating the NMs identity to safety aspects and functionality is a first step towards achieving the goal to design novel, tailored NM and NEP that are both functional and safe. Since the relationship between intrinsic physicochemical characteristics, functionality and safety are complex, studies on balancing functionality and safety as well as the search for potential SbD actions currently have to be performed on a case-by-case basis. Integration of functionality data into databases and tools might help to overcome this restriction. This is a first attempt to include functionality and safety into a structured model to implement SbD. Application of the developed strategy shows that by answering the sets of questions on functionality and safety, potential information gaps and concrete approaches for SbD actions are revealed. The case study demonstrates that potential SbD actions always depend on the target application and availability of alternatives. However, the presented SbD actions, such as analysis and optimisation of the production process, modification of the material, and search of alternatives are more effective and comprehensive than protective measures. It should also be noted that SbD actions should be performed as early as possible in the innovation process due to decreasing degree of freedom and increasing costs and effort when applied at later phases.

Funding sources

This work is part of the NanoReg2 project and has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement 646221.

Disclaimer

Any opinions expressed in this publication are those of the authors only. The paper does not necessarily present an official opinion or position of the European Commission.

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.

Acknowledgements

The authors like to acknowledge contributions of Araceli Sánchez Jiménez and Blanca Suarez-Merino in the development of this manuscript and like to thank the NanoReg2 partners for their useful feedback in the development of the Safe Innovation Guidance Manual. The authors also thank Christiane Petzold for proof-reading the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.impact.2021.100354.

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