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Supporting Safe-by-Design of Multi-Component Nanomaterials by Linking Functionality-Related Properties with Potential Safety Issues

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Abstract:
Advanced materials, including multicomponent nanomaterials (MCNMs) are designed to show specific new or enhanced functionalities. They may contribute to solutions to current societal challenges, yet they represent a challenge themselves to safe innovation and risk assessment. One challenge is the lack of available toxicological information at early innovation stages. Instead, information on functionality and material properties is generally available at early innovation stages, but such information is typically not used in safety assessments. Safe-by-Design aims to improve the safety of materials and products by integrating safety considerations with functionality as early as possible in innovation. Here a conceptual approach is presented that uses functionality-related material properties to flag potential impacts on risks and guide Safe-by-Design. This approach relies on relations between material properties and their potential impact on release, fate/toxicokinetics and toxicity. These relations are illustrated for 21 new or enhanced material properties of MCNMs. Applicability of this approach was explored through several case-studies. The presented approach is designed to 'flag' potential aspects of risk for further consideration. Identified aspects may support application of Safe-by-Design for MCNMs, including grouping approaches to enable sharing of safety information. The approach is relevant at early innovation stages where toxicological information is largely absent.

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Supporting Safe-by-Design of Multi-Component Nanomaterials by Linking Functionality-Related Properties with Potential Safety Issues

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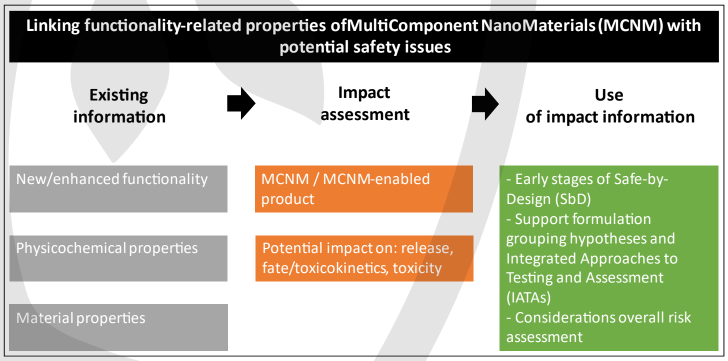
SIGNIFICANCE (max 590 characters)

Advanced materials are increasingly being developed. It is critical that these new materials are not only functional but also safe. Safe-by-Design principles have been developed to support safer innovation of chemicals and materials. Applying such principle and tools is essential for operationalizing the Sustainable Development Goals set by the United Nations. We propose that, at very early innovation stages, before safety information is available, that physicochemical and functionality information can be used to flag the potential for safety issues. Here we demonstrate the use of such information for multicomponent nanomaterials.



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ABSTRACT

Advanced materials, including multicomponent nanomaterials (MCNMs) are rationally designed to show specific new or enhanced functionalities. They are considered key in solving current societal challenges such as the energy transition, yet they represent a challenge themselves to safe innovation and risk assessment. One challenge is the lack of available toxicological information at early innovation stages. Instead, information on functionality and related material properties is generally available at these early innovation stages, but such information is typically not used in safety assessments. Safe-by-Design (SbD) aims to improve the safety of materials and products by integrating safety considerations with functionality as early as possible in the innovation. To exploit the information on functionality for SbD purposes, here a conceptual approach is presented that uses functionality related material properties to flag potential impacts on risks and guide SbD. This approach relies on insights into relations between material properties and their potential impact on release, fate/toxicokinetics and toxicity. These relations have been illustrated for 21 new or enhanced material properties that are incorporated in the design of MCNMs. For example, a set of 'mechanical properties' were identified as likely to have an impact on release and fate/toxicokinetics of MCNMs, while 'reactive properties' were expected to be able to affect their toxicity. Applicability of this approach was briefly explored through several case-studies. The presented approach is designed to 'flag' potential aspects of risk that require further consideration. These identified aspects can then support the application of SbD for MCNMs, including grouping of similar MCNMs to enable sharing of safety information. The approach is relevant at early stages in the innovation process where toxicological information is still mostly absent.

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Introduction

Over the last two decades, manufactured nanomaterials (NMs) have been a key driver of material innovation. These versatile and diverse materials can be tailored to exhibit specific desirable functionalities with applications ranging from medical and pharmaceutical, electronics, paints and coatings to food and consumer products.[1-5] Quick progress in nanotechnology has resulted in the development of even more complex and advanced materials. For example, multicomponent nanomaterials (MCNMs) have been generated in a wide variety of forms, ranging from simple core-shell structures, to complexes of two or more different nanomaterials.[6-7] These structures may be included within a matrix to generate a MCNM-enabled product. Some of the most widely used components are (combinations of) carbonaceous (e.g. fullerenes, carbon nanotubes, graphene) or inorganic (metal or metal oxide) NMs with or without organic coatings (e.g. polymers, macromolecules and enzymes).[6] MCNMs are typically designed to create or improve functionalities of a material. The functionality may result from the interaction between NMs and/or the structuring of materials within the MCNM. As a result, the properties of these MCNMs may differ (in part) from the intrinsic properties of the individual components.

Although there are still considerable knowledge gaps for many single component NMs, information on NM safety is increasingly available, for example within the data repository eNanoMapper.[8] However, due to their novel functional feasibilities and their multicomponent nature, MCNMs present an additional challenge in ensuring safety for human and environmental health compared to single component NMs.[9] For instance, the release, fate and toxicokinetics of active substances encapsulated in nanocarriers are different from the corresponding characteristics of the active substance.[10-11] Moreover, when MCNMs (partly) degrade, dissociate or transform in a cell, tissue or organ, concurrent exposure to the individual component(s) may result in mixture effects.[12] The safety assessment is further complicated by the lack of fundamental toxicological research on MCNMs. It is possible that new feasibilities result in new hazards. For example, much material innovation research is being done to obtain MCNMs with electromagnetic properties.[13] Yet, it is not clear if and how such properties have an impact on hazard and whether existing test methods are sufficiently equipped to measure potential adverse effects. Taken together, the implications for safety of combining different substances into an MCNM with new or improved functionality are not well-understood.

Over recent years, several test guidelines and test standards specific to NMs have been developed, such as those available within the Organisation for Economic Co-operation and Development (OECD). Also modifications to legislation have been introduced to accommodate NMs. For example, in the EU, REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) annexes currently have NM-specific clarifications and provisions.[14] However, most of these adaptations have been made with 'simpler' NMs in mind, and it remains unclear to what extent these adaptations are sufficient to address specific issues of MCNMs.[15] Uncertainty regarding the critical safety issues of these complex materials and the validity of existing regulatory test methods could affect the regulatory acceptance of MCNMs. This uncertainty regarding regulatory acceptance may, in turn, result in uncertainty for innovators who develop MCNMs, which could act as a barrier for innovation.[16-17]

Some of these uncertainties may be reduced when safety is specifically considered as early as possible in the innovation. This can be seen as a complementary and preventative strategy prior to legal safety obligations (e.g., as those laid out in REACH in the EU) at the near-market stage. To that end, the concept of 'Safe-and-Sustainable-by-Design' (SSbD), which considers both safety and sustainability from an early innovation stage on, has been developed over the last several years (e.g., within the European Commission (EC)[18-20], European projects[21-22], OECD[23], European Environment Agency (EEA)[24], Cefic[25-27] and ChemSec[28]). SSbD is a central component of the EC Chemicals Strategy for Sustainability[18] and a framework has been proposed by the EC's Joint Research Centre (EC-JRC)[19, 20] and discussed with stakeholders to support the design and development of safe and sustainable chemicals and materials. SSbD goes beyond Safe-by-Design (SbD), as also sustainability considerations are included. SSbD encourages scientists, innovators and industry to integrate safety and sustainability with the desired functionality of the chemical/material and economical aspects, in an iterative way during the innovation process.[1,29-35] SSbD efforts are most beneficial when applied at early Research and Development (R&D) stages because the possibility to make changes to a product decreases with the maturation of an innovation.[36-37] Specific tools for SSbD/SbD for NMs become more and more available due to current developments.[36-38] A SSbD tool can be more or less specific to elements in SSbD – such as only covering safety aspects (SbD) – or to specific innovation stages. It it can be assumed that multiple tools are needed to gather the information to support decision making moments during innovation. An example includes an approach for applying SSbD early in the innovation process tailored towards small and medium enterprises (SME).[31] Thus far, most of these approaches and tools rely on toxicological information of the material or final product for the assessment of the safety. However, toxicological information for a specific material is often unavailable, especially at the initial design stages. The toxicity of a material is driven by its physicochemical properties and route of exposure/environmental compartment, toxicokinetics and dose reaching target organ(s) or species. However, due to novelty of advanced and nanomaterials and the ongoing process of developing test guidelines and guidance documents for these materials, limited data and even fewer in silico predictive models such as QSARs and other machine-learning (nano) models are available.[39-41] Furthermore, innovators of materials in many cases do not design materials for their specific physicochemical properties per se, but rather for the function that can be achieved by altering material properties (such as specific mechanical or optical properties), which in turn are determined by their physicochemical properties. It can be presumed that typically innovators have some, but limited information on physicochemical properties (like elemental composition, general information on size and morphology) at initial innovation stages, while also the type of material properties that underlie the intended functionality are known. A tool that uses the functionality as starting point for SbD will thus be a valuable complementary approach that is particularly relevant at early design stages.

Here, we argue that in absence of specific toxicological information, indications for potential safety issues of a MCNM (or any advanced material) can be inferred by examining the material properties that enable a certain functionality. Such indications could then be used by innovators to better consider safety in their innovation and for targeting specific safety testing. As an example, it has been reported that elasticity of (nano)materials can affect the uptake into cells.[41] Therefore, when a MCNM that is designed to achieve a certain (high or low) elasticity, one could expect that these design choices may impact their fate and toxicokinetics, and thereby the risk of the materials. Further, we foresee that such information may also inform the development of grouping and read-across arguments of MCNMs. For example, if the impact on release, fate/toxicokinetics or hazard is potentially high, this should be considered in grouping hypotheses and assessed via Integrated Approaches to Testing and Assessment (IATAs).[43-46] Risk assessors can benefit from a better general understanding of the functionality in relation to toxicity. Such insights based on functionality are typically not used in risk assessment, but we argue that they can help regulators to evaluate possible hazards associated with new or enhanced functionalities of specific materials, and to consider whether current regulations are adequate for such materials.

In this paper we describe a novel conceptual approach that uses material properties to guide the identification of possible risks at early innovation stages in order to support safer development of MCNMs. Although the focus of this approach is on MCNMs, the principle of the approach may also be applicable to other advanced materials or 'simple' NMs like spherical single-component NMs. The approach should be regarded as conceptual, aiming to demonstrate that functionality and related material properties may be used as a starting point in the safer design of materials. Further work at later innovation stages would be required for a more informed approach to SbD, and of course to meet chemical regulatory requirements. In the current manuscript we focus on how information on functionality can be used in the early innovation stages of 'Safe-by-Design (SbD)', i.e., without considerations on sustainability. The approach can be used along other tools and approaches that support SbD or SSbD.

Outline and application of a material property-guided approach

In the following sections, first, the general outline of the approach is explained. In the section that follows, the potential impact of 21 material properties on key aspects of risk is qualitatively assessed. This list can be expanded to include additional properties in future. Lastly, the approach is briefly applied in several case-studies to further demonstrate the use of the approach for SbD of MCNMs.

Functionality links to material properties and physicochemical properties of a material. In the context of this paper functionality relates to the intended use of the materials such as insulation, CO_2 storage, imaging. To achieve a certain functionality, specific material properties can be modified (see Table 2 for the material properties considered). For example, the material property 'heat conductivity' can be modified to improve thermal insultation of a material. Material properties are in turn determined by physiochemical properties, like the elemental composition. The term physicochemical properties is currently used for those physicochemical properties that are used in risk assessment of nanomaterials. These include, but are not limited to elemental composition, shape, size distribution, crystallinity, specific surface area, and surface chemistry.[47-48]

The approach and its content was developed through literature searches and group discussion between the authors and within the EU Horizon project SUNSHINE (www.h2020sunshine.eu). The expertise covered by the authors include human health and environmental risk assessment, material science, chemistry, physics, biology, European chemical legislation, and SSbD .

Outline of the approach

The material property-guided approach consists of three main phases: 'existing information', 'impact assessment' and 'use', as depicted in a schematic overview in Figure 1. Details of the different phases are explained in the following sections. Briefly, the 'existing information' part collects information on the functionality and material and physicochemical properties that are already available for the MCNM (or its enabled product) that is being developed at a very early innovation stage. The aim of the 'impact assessment' is to link specific material properties to potential impacts on three 'aspects of risk'. These key aspects are 'release', 'fate/toxicokinetics' and 'toxicity'; see Table 1 for what in this paper is meant by these terms. Each of these 'aspects of risk' is an element that may influence the risk. In this paper we refer to the links between material properties and aspects of risk as (potential) 'material property – risk relations'. Note that the approach does not predict the risks of a MCNM. Rather, it assesses whether an impact should be considered on one of the key aspects of risk. Also note that such an impact can be both positive or negative, meaning that the risk can increase or decrease. Once the relations between material properties and aspects of risk are understood then this information can be fed into the decision making process that underlies the safer development (or use) of an MCNM. For example, this approach can be used for several purposes, i.e., as input for SbD of the MCNM via risk mitigation or targeted testing, or as input for the grouping and read-across of MCNMs. The obtained insights can also provide additional understanding relevant to the risk assessment.

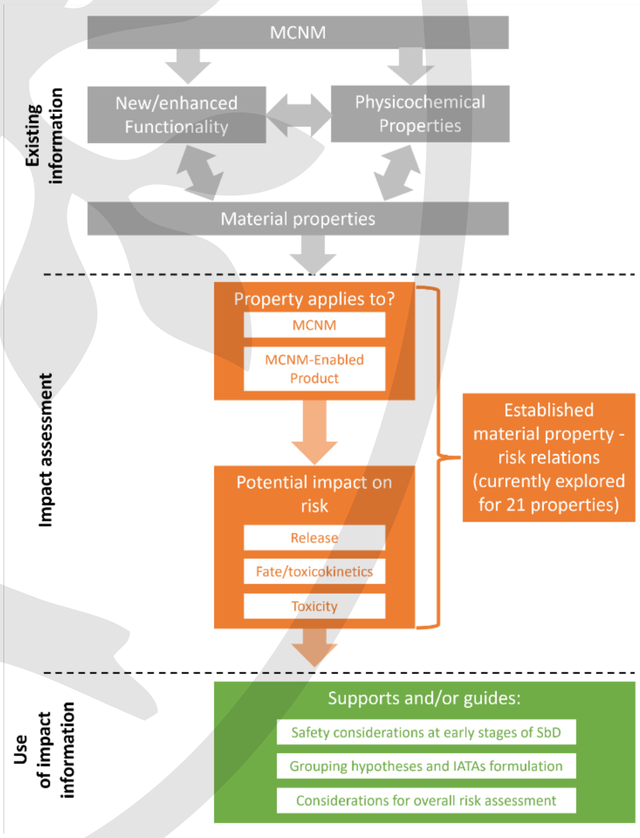

Figure 1: Outline of the material property-guided approach to support SbD for MCNMs at early innovation stages. Three phases are distinguished: existing information, impact assessment and use. The left side of the section 'impact assessment' shows the steps used here to assess the impact of material properties on aspects of risk (for description of aspects of risk, see Table 1) that can be used to flag potential issues that can guide further investigations. This assessment results in qualitative material

property–risk relations, as depicted on the righthand side of the impact assessment section.

Table 1: Potential 'aspects of risk'. The impact of material properties related to new or enhanced functionality is assessed on different aspects of risk: 'release', 'fate/toxicokinetics', and 'toxicity'. These aspects are similar to those applied by the approach to risk assessment and grouping developed by the EU H2020 project GRACIOUS.[48]

Aspects of risk	Description	Justification of use in this approach
Release	'Release' relates to the environmental compartment into which the MCNM (or its components) are released, as well as the form and extent of release.	The most relevant environmental compartments and human routes of exposure determine the context for potential risks. The extent of release provides information on the exposure level.
Fate/toxicokinetics	The 'fate' in the environment relates to mass flows in environmental compartments. 'Toxicokinetic behaviour' focusses on uptake, distribution, accumulation in the human body and potential target organs.	In the present context the focus is on how the material property related to new or enhanced functionality affects bioavailability, accumulation and distribution in the environmental compartments and the environmental species to consider. Fate and toxicokinetics determine the actual or internal exposure and thereby the toxicity.
Toxicity	'Toxicity' relates to the endpoints of toxicity of interest (e.g. oxidative stress, genotoxicity).	A specific endpoint for human or environmental toxicity may arise, increase or decrease as related to a material property.

Existing information

In this phase the existing information related to functionality, material properties and physiochemical properties is collected (Figure 1). MCNMs or MCNM-enabled products are designed to exhibit specific functionalities. To achieve a certain functionality material properties such as electrical conductivity, light absorption or tensile strength of the material are considered. These material properties that underlie the intended functionality are therefore typically known at very early stages of innovation. In addition, some physicochemical information like elemental composition, general information on size and morphology is often also known.

Note that many material properties are interrelated meaning that modifications of certain intended material properties may also have an inadvertent effect on other material properties. For example, changing the porous structure to achieve better insulation properties may also affect the availability of reactive sites and thereby the reactivity of the materials.

Thus, the existing information phase of the approach requires the user to identify and describe the intended functionality, the underlying material and physicochemical properties that are known. Also any inadvertently altered material properties (if known) should be described in this phase.

Impact assessment

First, as depicted in Figure 1, it should be considered whether the material property applies to the MCNM itself, the MCNM-enabled product or both. This is relevant to consider because it could impact the associated risks. For example, embedding a MCNM into a product can affect the release of (components of) MCNMs to the environment, and thereby potentially impact risk. Note that not all materials properties apply to both the MCNM itself and the MNCM-enabled product. For example, MCNMs may be added to a medium to alter the viscosity of the final product. However, MCNMs themselves do not inherently exhibit viscosity, as it is a macroscopic property of a fluid. Thus, the material property viscosity is only relevant for MCNM-enabled products and not MCNMs themselves.

Next, the potential implications of a material property on aspects of risk for the MCNM and/or MCNM-enabled product should be assessed. This impact is assessed for three key aspects of risk: 'release', 'fate/kinetics' and 'toxicity' (see Table 1 for details on the meaning of these terms in the context).

There are several approaches by which these material property – risk relations can be evaluated. For example, these relations may be estimated based on literature searches and/or expert judgement. In some cases predictive models, when available, can be used to assess property – risk relations.[49-50] As an example, Banerjee and co-workers used predictive models to demonstrate that electronic properties contribute to cytotoxic properties of MCNMs.[50] However, in most cases the impacts are qualitatively considered. Consequently, the overall impact of a material on risk is also qualitative and not quantitative.

In this paper, a set of 21 'material property – risk relations' were explored to allow for direct application. These relations were determined through literature research and expert assessment. For our work on the considered properties, three levels of impact were used: 'large', 'medium' and 'small'. Arrangement into these three levels was for pragmatic reasons in order to establish a principle, i.e. no formal criteria were applied.

Use of impact information

Applying this approach results in the identification or flagging of aspects of risk for specific material properties (related to new/enhanced functionalities) that could potentially impact risk. The resulting estimations of the impact assessment can be used to guide SbD in the following ways (Figure 1).

For entirely novel materials with a specific functionality and material properties, identified flags (i.e. aspects of risks for which large potential impacts are identified) could either be prioritized in safety tests during innovation, or used in selection or considerations of alternatives, as relevant in SbD. In particular, the proposed approach can be used in the very early stages of technological innovation i.e. before the strategic decision to start the development of a new MCNM/MCNM-enabled product (Technology Readiness Levels (TRL) 1 – 3).[51] Therefore, the approach provides input to support decision making on continuation, termination or changes to the innovation process using the limited information available. The approach can also provide input during the early development stages (TRL4), without incurring too much cost. This can facilitate the development of safer materials/products, thereby supporting effective SbD MCNM innovation.

The information on potential impact could also help in grouping and read-across, that could be used to steer SbD based on existing information of similar materials. Strategies built to support the process of grouping and read-across, as developed within GRACIOUS[48], use grouping hypotheses and IATAs to gather the information needed to substantiate grouping and read-across.[32-34] Information from material properties can offer insights and can be used to formulate grouping hypotheses and data collection via application of tailored IATAs. For example, if an MCNM exhibits enhanced elasticity due to the combination of components, its potential for uptake by animals or plants can be increased as compared to its single components. This would mean that a similarity assessment of a MCNM and its single-components should include uptake as criteria to accept or reject the grouping hypothesis. When knowing the potential impact of the introduction of, or change in material properties on a certain risk aspect, it becomes easier to judge whether a grouping hypothesis is relevant to pursue.[46] Further, the overall risk assessment can benefit from an additional perspective to consider the available information.

Estimations of the impact on aspects of risk for 21 material properties

To demonstrate the feasibility of the approach detailed above, and to aid in the practical application of the approach, an extensive but non-exhaustive overview is provided of the potential impact of in total 21 material properties on aspects of risk.

Selection and definition of the material properties

Material properties that are potentially exploited to enhance functionalities of MCNMs were identified through literature review and expert assessments. This resulted in the identification of in total 21 material properties which are described in see Table 2 and Table S1 of the Supplementary Information. Many of the identified properties were also independently identified by Tavernaro et al.,[1] whose research in part examines the relation between NM functionality and material properties at a more conceptual level. The identified new or enhanced properties are currently organized into one of seven types: 'electromagnetic', 'heat and thermodynamics', 'optical', 'surfaces', 'liquid media', 'mechanical' and 'reactive´. The 21 identified properties set the scope for this work on material property-risk relations. It is acknowledged that there are more properties that may be relevant to MCNMs that are not considered in this paper. The potential impact of such additional properties may be assessed by innovators, researchers and/or risk assessors through use of the approach described here.

Applicability of material properties to MCNM and/or MCNM-enabled product

As explained in the above section, the properties related to new or enhanced functionality might apply to the MCNMs themselves and/or in MCNM-enabled products. By our judgement and based on literature studies, for 11 of the 21 identified material properties, the property related to new or enhanced functionality apply to MCNM themselves and in the MCNM-enabled product. Five properties were judged to only apply to MCNM, while five different properties apply to MCNM-enabled product. Supplementary information Table S1 provides an overview whether a property applies to the MCNM and/or the MCNM-enabled product, including a rationale.

Qualitative assessment material properties – risk relations

For each of the 21 properties qualitative estimations of the impact on the release, fate/toxicokinetics and toxicity of a MCNM were made, based on examples from literature, where available, or based on expert assessment (Table 2). Note that an impact of the introduction of, or change in a material property can either have a decreasing or increasing effect on risk, which is not specified in this work. When a large impact on, for example, release is possible for a given changed property this does not necessarily mean an increased risk is associated with these MCNMs, but rather that this potential impact should be taken into consideration for further safety assessment or for grouping and read-across. In fact, if further studies demonstrate that a given change in a certain property results in lower release of the MCNM (or components thereof) a reduced risk may be expected. Thus, the approach presented here aims to flag potential safety issues so that they can be assessed. It does not aim to make a statement on the actual impact on risk itself. Further information and support for the assessment of the 21 properties can be found in Supplementary information Tables S2.1 to S2.7.

Table 2: Overview of material properties relevant to MCNM function and their estimated potential impacts on the aspects of risk: release, fate/toxicokinetics and toxicity. A small impact refers to when the impact is considered not relevant in terms of risk. A large impact refers to when the impact can potentially have a considerable impact on risk, whereas the medium impact refers to the situation in between. The Supplementary Information provides details on these material properties (**Table S1)** and the rational for the qualitative impact assessment (**Tables S2.1 to S2.7)**. Studies that contributed to the assessment are referenced. Assessments for which no literature reference is provided were made on the basis of expert judgements only.

Material property	Applicable to	Release	Fate/ toxicokinetics	Toxicity
Electromagnetic				
Electrical conductivity	MCNM-enabled product	Medium [52]	Large [53]	Large [54-56]
Electrical capacitance	MCNM-enabled product	Medium [52]	Small	Large
Magnetism	MCNM	Small	Large [57-58]	Medium [59-60]
Heat and thermodynamics				
Thermal conductivity	MCNM	Small	Small	Small or Large[a] [61-63]
	MCNM-enabled product	Small	Small	Small or Large[a] [61-63]
Heat capacitance	MCNM-enabled product	Small	Small	Small or Large[b] [64]
Optical				
Light absorption	MCNM	Small	Small	Small[c] or Large [65-66]
	MCNM-enabled product	Small	Small	Small[c] or Large [65]

(includes photoconductivity, photothermal effects and plasmonic effects)				
Luminescence	MCNM	Small	Small	Small[c] or Large [67]
	MCNM-enabled product	Small	Small	Small[c] or Large [67]
Surfaces				
Pore characteristics	MCNM	Small	Small	Large
	MCNM-enabled product	Medium	Medium	Large [68-70]
Wettability and surface tension	MCNM	Small	Large [71-72]	Small
	MCNM-enabled product	Large	Medium	Small
Relative permeability	MCNM	Small	Small	Medium
	MCNM-enabled product	Medium	Small	Small
Adhesion/cohesion	MCNM	Large [73]	Large [74]	Medium [74]
	MCNM-enabled product	Large	Large	Small
Liquid media				
Dissolution rate	MCNM	Large	Large [75-76]	Large [76-77]
	MCNM-enabled product	Large [78]	Large [79]	Large
Dispersibility	MCNM-enabled product	Large [80]	Large [81-85]	Small [85-86]
Viscosity	MCNM-enabled product	Medium	Medium [87]	Small
Mechanical				
Tensile strength	MCNM	Small	Large	Small or Large[d] [88]
	MCNM-enabled product	Large	Large	Small or Large[e] [89]
Ductility	MCNM	Small	Large	Small or Large[d] [88]
	MCNM-enabled product	Large	Large	Small or Large[e] [89]
Elasticity	MCNM	Small	Large [42,88,90-96]	Small or Large[d] [88]
	MCNM-enabled product	Large	Large	Small or Large[e] [89]
Reactive				
Oxygen vacancies	MCNM	Small	Small	Large [92-96]
Reactive sites	MCNM	Small	Small	Large [97-98]
Redox reactivity	MCNM	Small	Small	Large [99]
Metal oxide acid-base reactivity	MCNM	Small	Small	Large [100-102]

[a] For applications with increased thermal conductivity as their primary goal, for example medical applications, the impact is considered to be large. Typically an external energy source is required for materials to display thermal conductivity.

[b] For certain medical applications where increased heat capacitance is a primary goal, the impact on toxicity can be large.

[c] In the absence of light. In the presence of light, impacts on toxicity may be large (e.g. through generation of creating reactive oxygen species).

[d] High aspect ratio materials like fibers may induce frustrated phagocytosis due to their stiffness.

[e] In case of application as a medical implant, i.e. MCNM-enabled product applied in the body.

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Based on Table 2, some general observations can be made for the estimated potential impact on aspects of risk for the property classes focused on. First, for MCNMs and MCNM-enabled products that have intended new or enhanced functionalities related to 'heat and thermodynamics' and 'optical' properties, in general, we expect no or a small impact on related risk aspects. One possible exception where the impact may be large for optical properties is for either intentional dermal applications or inadvertent release of MCNMs to the environment or contacting skin. In such cases the optical properties may result in photoreactivity resulting in toxicity. Another exception for properties related to heat and thermodynamics may occur where there is an external energy source that can trigger heating of the MCNM or the MCNM-enabled product, as for example may be the case for certain medical applications, which may damage biological molecules and/or kill cells.

Impacts on risk aspects for properties dealing with 'liquid media' are considered to be medium or large for release and fate/toxicokinetics, whereas the impact on toxicity can be small or large. The impact of dissolution rate on toxicity is considered to be potentially large, as toxicity can differ between materials and the corresponding solutes (molecules, ions). Overall, this suggests that researchers, innovators, and risk assessors should pay attention to the impacts on risk aspects for MCNMs and MCNM-enabled products that have intended new or enhanced functionalities related to dissolution rate, dispersibility or viscosity.

Impact on risk aspects for 'electromagnetic' properties and properties related to 'surfaces' may be considerable. However, by our judgement, which risk aspect is impacted seems property dependent. Large impacts on risk for electromagnetic properties are mostly expected on fate/toxicokinetics and toxicity, whereas for surfaces the potential impact is even more property specific. For example, both electrochemical activity (conductivity and conductance) and pore characteristics may have an impact on toxicity by affecting the reactivity of a material through the potential to produce reactive oxygen species. When the properties related to magnetism or adhesion/cohesion are altered, this may impact on the agglomeration behavior of the material, which is likely to have an impact on fate/toxicokinetics.

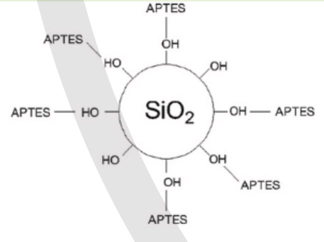
Our assessment also shows that MCNMs having new or enhanced functionalities related to 'mechanical' properties may have a large impact on fate/toxicokinetics. For MCNM-enabled products (but not MCNM themselves), mechanical properties may also have a large impact on the release of (components of) MCNMs. Here we hypothesize that mechanical properties mostly affect the extent or form of release from a MCNM-enabled product due e.g. to abrasion, weathering, use or end-of-life. Further, when materials are sufficiently elastic, the uptake kinetics into an organism of a material might be altered, which in turn might increase or decrease the potential risk of a material. When mechanical properties are introduced or changed through combination of single components (be it as MCNMs themselves or in an MCNM-enabled product), the risk assessment of these materials should specifically address potential issues related to fate/toxicokinetics.

When MCNMs are designed to have altered 'reactive' properties this can, by our judgement, affect toxicity. A common mechanism by which these properties may affect toxicity is through altering the production of reactive oxygen species. When reactive properties are introduced or changed through combination of single components (be it as MCNMs themselves or in an MCNM-enabled product), the risk assessment of these materials should specifically address potential issues related toxicity.

Case-studies

To further demonstrate its feasibility for early innovation, the material property-guided approach was applied in several case-studies of MCNMs that are in use or are being developed within the EU Horizon 2020 project SUNSHINE [22]. These case study MCNMs include two materials with a mesoporous silica core (i.e. SiO_2-APTES, SiO_2@ZnO), and a core-shell SiC@TiO_2. For each case study, the relevant intended application, functionality, physicochemical and material properties were identified. Following the approach (Figure 1), the material property – risk relations were applied and the potential implications from a functionality point of view were considered. These considerations can be used in early stages of innovations, and complemented with other considerations, e.g. related to toxicological information from components of the MCNM. Results of these case studies are reported in Table 3.

Table 3: Application of the material property-guided approach (**Figure 1**) to SUNSHINE MCNM cases and the potential implications for innovation and research, e.g. for SbD. The indicated potential implications are relevant at early stages of innovation and only relate to the listed material properties from a functionality point of view, and not to existing toxicological information for components of material (for which a few footnotes are included in the table).

MCNM, physicochemical information and application	Information on material properties related to new or enhanced functionality	Potential impact on aspects of risk related to material property[b]	Potential implication for innovation and research (SbD)
SiO_2-APTES[b] Spherical 20 nm mesoporous SiO_2 with covalently bound APTES[a] NPs  **Application:** Cement additive (<5%)	**Liquid media (dispersibility):** The amine groups of the APTES provide polarity, which improves the dispersibility in ionic media, such as Portland cement pastes **Material property applies to**: MCNM itself and MCNM-enabled product **Mechanical properties (tensile strength and ductility of MCNM-enabled product):** The SiO_2-APTES promotes change in the microstructure of cement pastes by delaying the initial hydration reactions, but promoting the pozzolanic reaction later. The changed porous structure improves the mechanical performance of the resulting concrete.[101] **Material property applies to**: MCNM itself and MCNM-enabled product	**Release**: large Extent and form of release of MCNM from cement and concrete can be changed as compared to single components. The use of the additive can change the release of particles from concrete in general. **Fate/kinetics:** large If the form of release is changed, there can be a major change in fate/toxicokinetic behaviour. **Toxicity:** small To our knowledge there is no evidence that suggests that an impact can be expected.	Consider the form of release during manufacturing, abrasion/weathering and at end-of-life, and their consequent fate/toxicokinetics in view of potential risk.
SiO_2@ZnO (core-shell) 15-20 nm mesoporous SiO_2 core particles with a thin ZnO layer resulting in almost spherical, highly	**Optical (photocatalytic reactive properties):** Chemical reaction (oxidation of NO_x) is facilitated in the presence of light (photocatalytic	**Release**: small To our knowledge there is no evidence that suggests that an impact can be expected.	Consider if dermal exposure to SiO_2@ZnO is possible, e.g. during manufacturing, use or

agglomerated particles. The overall constituent particle size are 19 ± 4 nm. The ZnO shell structure is non-homogeneous. **Application:** Mortar additive in buildings for photocatalytic oxidation of NO_x	effects are considered under 'light absorption'). The use of the additive results in better selectivity towards the formation of nitrates instead of NO_2^-. **Material property applies to**: MCNM itself and MCNM-enabled product	**Fate/kinetics**: small To our knowledge there is no evidence that suggests that an impact can be expected. **Toxicity**[c]: small or Large There can be a major change in toxicity, e.g., via ROS formation in case of the presence of light (e.g. dermal exposure) as compared to the single components or the absence of the additive.	end-of-life, and if so, consider potential phototoxicity/ROS formation.
$SiC@TiO_2$ (core-shell) In-house produced TiO_2, 100% anatase. Two types: - $SiC@TiO_2$_60: 48-75 nm almost spherical particles - $SiC@TiO_2$_500: 530-640 nm particles of irregular morphology **Application:** Applied on aluminum molds for bread production (as alternative to fluorinated polymers), providing hydrophobic and anti-stick properties	**Surfaces (adhesion/cohesion; wettability and surface tension)**: a mixture of two different nanoscale dimensions of $SiC@TiO_2$ MCNMs in ceramic matrix is used to develop rough fractal surfaces (at the nanoscale), thereby increasing hydrophobicity and providing anti-stick properties. **Material property applies to**: MCNM-enabled product **Liquid media (dispersibility)**: TiO_2 shell is used to improve compatibility with the ceramic sol-gel matrix. This allows use of the SiC properties in the product such as chemical and heat resistance, thermal conductivity and mechanical resistance. **Material property applies to**: MCNM-enabled product	**Release**: large Extent and form of release of MCNMs and other fragments from the product may be changed (to a greater or smaller release) as compared to the use of single components. **Fate/kinetics**[d]: large If the form of release is changed, there can be a major change in fate/toxicokinetic behaviour. Improved dispersibility can also lead to a change in fate/toxicokinetics. **Toxicity:** small To our knowledge there is no evidence that suggests that an impact can be expected.	Consider the form of release during manufacturing, during use and at end-of-life, and their subsequent fate/toxicokinetics in view of potential risk.

[a] See **Table 2** and **Tables S2.1** to **S2.7** for further details.

[b] APTES: 3-aminopropyltriethoxysilane.

[c] As a general consideration of using SiO2@ZnO, note that the ZnO coating may result in Zn-ion release that may be hazardous to the environment.

[d] As a general consideration of using SiC and/or TiO2, note that SiC, TiO2 and SiC-TiO2 can be very persistent. This may result in accumulation, provided that there is release from the MCNM-enabled product.

Discussion

Next to many promising benefits from material innovations, the development of increasingly complex (nano)materials, including MCNMs and other advanced materials, poses a challenge to safe innovation and risk assessment. One of the key challenges in identifying SbD considerations for early stages of the innovation is the lack of low cost and easily accessible information regarding the safety of advanced materials. Here, it is argued that when specific toxicological information is yet unavailable, potential safety issues of MCNMs (and other advanced materials) can be identified by examining the material properties linked to the new or enhanced functionality of the material. This study therefore provides an outline to a novel material property-guided approach to support SbD. The approach presented complements existing SbD and SSbD tools and methods. It may assist innovators, researchers and risk assessors in identifying flags based on limited existing information related to functionality, that can trigger further evaluation or decision making at these very early innovation stages. Other tools can be used to identify other aspects relevant for decision making in innovation, for example related to sustainability. Ultimately, the current approach aims to support the development of MCNMs and other advanced materials according to SSbD principles.

As detailed in the above sections, the basis of the approach is to assess 'material property – risk relations'. In this study, 21 of these relations were qualitatively estimated on the basis of literature studies and expert assessment. However, the conducted literature studies were not-exhaustive and should therefore be considered as preliminary findings, demonstrating the concept of taking functionality and material properties into account in SbD of materials. We encourage innovators, scientists and risk assessors to become familiar with the approach and suggest modifications and refinements e.g. by further investigating specific 'material property – risk relations' of the properties relevant to the functionality of their materials. The better these relations are known, the more effective the tool can be to steer towards safer materials in early innovation stages.

Over the last decades, much of the nanotoxicology research has been focused on how nanomaterials behave in environmental media and the human body, and how nanomaterials react with cells, organs and individuals, and subsequently cause toxicity. As a result, for some material properties that are key to both functionality and risk, there is currently a considerable knowledge base. For example, information is available on how properties like dissolution, dispersibility and reactivity affect the release, fate/toxicokinetics and toxicity of nanomaterials.[75-76,81-85,92-102] Other properties such as heat and thermodynamics and some optical properties have received much less toxicological examination. Consequently, there is less certainty on the potential impact of these properties on release, fate/toxicokinetics and toxicity. The uncertainty in the relations between material properties and risk therefore varies. Assessing the level of uncertainty for different material properties – risk relations was beyond the scope of this study and requires additional investigation. However, it is encouraged to consider the uncertainty of any identified 'material property – risk relations', for example by analyzing the existing information on this relation.

Furthermore, some of the properties mentioned are interrelated, meaning that a change in one property also affects another property. An example is that the pore characteristics of a material also directly affect the mechanical strength of the material (see Table S2.4 and Table S2.6 in Supplementary Information). Such interrelations are not always obvious. This underlines the continued need for safety testing of MCNMs that should be part of further stages of innovation, which our approach cannot substitute.

The current list of material properties related to new or improved functionality of MCNMs is not exhaustive. Instead, the list focused on properties commonly used in MCNM applications or those expected to influence aspects of risks. Innovators, researchers or risk assessors could take this list as a starting point, and are invited to assess the potential impact on risk for additional relevant material properties. For example, many carrier materials can be considered MCNMs. These materials are specifically designed to facilitate the precise delivery of active ingredients like medicines or pesticides. The carriers can therefore significantly influence fate and toxicokinetics.[10-11] The current approach does not (yet) consider carrier functionality but presents an opportunity for its inclusion in assessments.

While this approach focused on safety, it is recognized that a full SSbD approach should address (environmental) sustainability as well. Modified or new properties can affect sustainability, along different stages of the life cycle of a MCNM or MCNM-enabled product, for example regarding impact categories related to pollution [20]. Hence, although out of scope of the present work, the impact of material properties related to new or enhanced functionalities on sustainability aspects may be considered for a MCNM, or any other advanced material, in the context of SSbD. Sustainability and further safety considerations in the innovation process may (also) be addressed by other existing or to be developed tools.

Conclusions

In this work we have outlined a material property-guided approach to estimate impacts on aspects of risks linked to new or enhanced functionality in MCNMs. These relations may be used in SbD of new materials in very early innovation stages where toxicological information is (mostly) absent. By identifying potential flags, potential risks can be mitigated and further evaluation can be triggered in a targeted manner. They may also support grouping and read-across of MCNMs as well as overarching considerations in risk assessment. Our preliminary findings, for example, indicate that mechanical properties may have an impact on fate/toxicokinetics, while reactive properties are expected to affect toxicity. It is important to note that the estimated impact can be both positive or negative, meaning that the risk can increase or decrease. For both directions of the impact, this information may help regulators, scientists and innovators in the assessment of safety of their materials and thereby, our approach may facilitate SbD, especially at early innovation stages. Through the approach several potential implication for innovation and research were identified for several case study MCNMs which, when sufficiently addressed, may contribute to safer use of MCNMs in society. These potential implications could be used along information from other tools, approaches that can support SbD. Further research should consolidate the reported relations (including uncertainties) via additional information from literature or experimental and/or modelling studies.

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Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

Author's contribution

Petra van Kesteren, Nynke Krans, Vicki Stone and Agnes Oomen conceptualized the paper, and formulated research goals and aims. Danail Hristozov, Lya Soeteman-Hernández, Vicki Stone and Agnes Oomen were involved in funding acquisition. Research, i.e. identification of properties, literature studies, impact assessments) were performed by Elena Badetti, Andrea Brunelli, Virginia Cazzagon, Petra van Kesteren, Teresa Fernandez, Nynke Krans, Anniek Gielen, Hubert Rauscher, Vicki Stone and Agnes Oomen. The methodology was developed by Elmer Swart, Jan Harm Westerdiep, Petra van Kesteren, Nynke Krans, Elena Badetti, Andrea Brunelli, and Agnes Oomen. Writing and editing was performed by all authors, with original drafts by Elmer Swart, Jan Harm Westerdiep and Agnes Oomen.

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