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Evaluating environmental risk assessment models for nanomaterials according to requirements along the product innovation Stage-Gate process

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Abstract

Nanomaterial risk governance requires models to estimate the material flow, fate and transport as well as uptake/bioavailability, hazard and risk in the environment. This study assesses the fit of such available models to different stages during the innovation of nano-enabled products. Through stakeholder consultations, criteria were identified for each innovation stage from idea conception to market launch and monitoring. In total, 38 models were scored against 41 criteria concerning model features, applicability, resource demands and outcome parameters. A scoring scheme was developed to determine how the models fit the criteria of each innovation stage. For each model, the individual criteria scores were added, yielding an overall fit score to each innovation stage. Three criteria were critical to stakeholders and incorporated as multipliers in the scoring scheme; the required time/costs and level of expertise needed to use the model, and for risk assessment models only, the option to compare PEC and PNEC. Regulatory compliance was also identified as critical, but could not be incorporated, as a nanomaterial risk assessment framework has yet to be developed and adopted by legislators. In conclusion, the scoring approach underlined similar scoring profiles across stages within model categories. As most models are research tools designed for use by experts, their score generally increased for later stages where most resources and expertise is committed. In contrast, stakeholders need relatively simple models to identify potential hazards and risk management measures at early product development stages to ensure safe use of nanomaterials without costs and resource needs hindering innovation.

Introduction

Advances in nanotechnology over the past decade have enabled the production and use of engineered nanomaterials for different products and applications, representing an estimated global annual market value of $1 trillion.[1] The number of nano-enabled consumer products available to European consumers has increased noticeably over this time covering a variety of product categories from sporting goods to personal care and cleaning products.[2] The added benefits of nanomaterials are often ascribed to their unique characteristics. By engineering key features, such as coating, size or shape, it is possible to change properties, such as reactivity and dispersion stability to support specific applications relevant to use in various products.[3] However, the potential for such highly engineered nanomaterial properties to cause toxicity in organisms following deliberate or accidental release to the environment has been a cause for public and political concern. This has resulted in scientific and regulatory community calls for timely risk assessment to identify and manage any potential adverse effects to human health and the environment from engineered nanomaterials.

Currently, the environmental risk assessment of nanomaterials is based on procedures originally conceived for the risk assessment of conventional chemicals,[4] although the field is developing. Approaches used for conventional chemicals consist of four main steps: hazard identification, hazard characterisation, exposure assessment and risk quantification. For nanomaterials, each of these steps presents challenges. The hazard identification is often based on inherent physical and chemical properties, which differ for nanomaterials compared to conventional chemicals.[5] In the hazard assessment, establishing concentration-response relationships for nanomaterials is more challenging because particle-specific processes such as agglomeration and sedimentation often will cause exposure concentrations to fluctuate during incubation.[6] The exposure assessment is also challenged by particle-specific processes such as homo- and heteroagglomeration, dissolution and reactivity, as well as the scarcity of available data on nanomaterial use and production volumes and also issues with reliable detection methods for model validation.[7] As the final risk characterization phase compiles information from all the previous steps, the limitations of each step towards the final assessment add to the overall uncertainty of the final calculated risk quotient.[5] The challenges in conducting nanomaterial environmental risk assessment using traditional paradigms have led to the development of alternative nano-specific modelling and decision support tools. Examples include the "Precautionary Matrix for Synthetic Nanomaterials"[8] and the LICARA nanoSCAN.[9] Furthermore, modelling approaches and tools originally developed for chemicals, such as the species sensitivity distribution (SSD) and multimedia environmental fate models, have been refined in the attempt to accommodate certain nanomaterial-specific properties and behaviours in the environment, such as agglomeration and dissolution.[10–14]

Several reviews of decision support tools or environmental assessment models available for nanomaterials are published.[15–24] In 2012, Brouwer[16] discussed similarities and differences between six control banding approaches proposed for nanomaterials, Grieger et al.[15] evaluated eight alternative tools proposed for environmental risk assessment of nanomaterials against ten criteria cited as important by various sources, including transparency, precaution and life cycle perspective, and Hristozov et al.[18] discussed the value of tools for risk assessment and management of nanomaterials considering limitations and uncertainties in key areas such as data availability. Later in 2016, Hristozov et al.[17] extended their analysis to 48 tools, assessing potential utility for different aspects of risk assessment against 15 published stakeholder needs including nano-specific requirements, life cycle approach, pre-assessment phase, and exposure-driven approach. No single tool was found to fully meet the criteria, leading the authors to call for the development of a new tool that integrates data and current models to support nanomaterial risk assessment and management. This conclusion was broadly supported by Arvidsson et al.,[19] following a review of 20 risk assessment screening methods. Also in 2016, Baalousha et al.[21] focused on the state-of-the-art of models assessing nanomaterial fate and transport as well as uptake and accumulation in biota and found that available models require calibration and validation using available data, rather than extension to higher complexity and inclusion of further transformation processes. In line with this, Nowack[23] evaluated environmental exposure models within a regulatory context in 2017. The review concluded that some of the available fate models for nanomaterials are built on concepts accepted by regulators for conventional chemicals, increasing the likelihood that such nano-models will be accepted. It was found that a critical issue for all models is the missing validation of predicted environmental concentrations by analytical measurements; however, validation on a conceptual level was found to be possible.

Romero-Franco et al.[20] in 2017 evaluated the applicability of 18 existing models for assessing the potential environmental and health impacts of nanomaterials based on six decision scenarios, describing common situations of different stakeholders from manufacturers to regulatory bodies who need to make decisions in matters concerning environmental health and safety of nanomaterials. For all decision scenarios, at least one existing tool was identified as capable of partly meeting the needs. Also with a focus on stakeholders, Malsch et al. 2017[25] presented a mental modelling methodology for comparing stakeholder views and objectives in the context of developing a decision support system. A case study was conducted among prospective users of the SUNDS decision support tool, mainly from industry and regulators, which showed a greater interest in risk assessment decision support than in sustainability assessment.

Some of the most recent reviews of nanomaterial environmental risk assessment methods is that of Trump et al.[26] and Oomen et al.[22] from 2018. Trump et al. 2018 reviewed the nanomaterial tool development over time, and found that tools based on metrics of risk (hazard and exposure assessment) have been the most common over the last 14 years, control banding became more popular during the period of 2008-2012, whereas LCA and decision analytical tools emerged most recently. The authors state that “no method dominates in applicability and use over the others, within all context. Instead time, resource availability, along with perceived stakeholder need, should guide which tool(s) should be used in a given context”.[26] Oomen et al.[22] considered 14 models or tools for prioritisation, ranking or assessing nanomaterial safety, according to their fit to OECD defined criteria for regulatory relevance and reliability. All except one tool were found to lack criteria enabling actual decision-making and the authors suggest the development of an international pragmatic decision framework that is only partially scientifically based. The scope is decision-making in regulatory contexts and in the product development chain, and although conclusions briefly touch upon applicability of the tools in the innovation chain, a complete matching of tools and Stage-Gates was not conducted. An innovation chain Stage-Gate model, such as that presented by Cooper in 1990[27], is a structured approach for bringing a product idea to market launch as effectively as possible while driving down the risk of spending resources on developing products, that will never make it to market launch. Since its initial publication, the Stage-Gate model has become an industrial standard for managing new product innovation processes.[28] In the Stage-Gate approach, the overall innovation process is divided into discrete work stages, each ending in a decision point (gate), where the process is reviewed against pre-defined decision criteria and a decision is made on whether to terminate, continue, hold or recycle the product innovation process (Figure 1). Usually the amount of resources committed increases along the stages, and the quality of the information generated also becomes higher. As a result, the risk of making incorrect decisions on the development of a product after having spent a great amount of resources is lowered, as decisions can be made with increased certainty.[27]

To our knowledge, none of the numerous reviews published have assessed nanomaterial environmental assessment models against stakeholder needs for different applications during specific stages of the product innovation chain, although a case-study focusing on graphene, provides an overview of actions and actors during different stages of innovation that may help achieve safe development of products including this nanomaterial.[29] In this study, we apply such coupling of modelling tools to the Stage-Gate concept to enable the identification of tools or approaches best suited at specific stages of innovation. At the different stages, stakeholders need different model estimates, features and output for decision-making, and they have varying resources allocated for risk assessment and safety-related work. Therefore assessing how currently available models or tools match the needs of individual stages, allows structured and effective use of the available tools to ultimately ensure safe use and development of nanomaterials and nano-enabled products, without hampering innovation or financial growth. Furthermore, the present study, conducted within the H2020 project caLIBRAte, provides a semi-quantitative assessment, whereas most published reviews are qualitative or narrative. We focus on selected environmental risk assessment models and evaluate these according to requirements in the Stage-Gate process using input obtained through a stakeholder consultation exercise. In total, 38 models/tools focused on the assessment of nanomaterial flow, fate and transport, hazard, uptake/bioavailability or risk in the environment, were assessed against 41 criteria. Feedback from 18 stakeholders assisted the design of a scoring scheme to comparatively assess the model suitability to stakeholder requirements at different stages of the innovation chain. The scoring scheme considers both the fit against the defined criteria and weights model fit to stakeholder needs according to the identified criteria.

Methods

Overall concept for model assessment

Published models or tools proposed for the assessment of nanomaterial flow, exposure, hazard, uptake/bioavailability and risk in the environment were assessed against requirements at different stages in product conception, development and application for nano-enabled products. We used the Stage-Gate concept[27,28] as an approach to track the suitability of different models at different stages of innovation during potential product development. From the EU FP7 project "Nanoreg II", descriptions of the safety-related activities in the various stages have been obtained. An overview of the product innovation and safety activities in each stage is provided in Figure 1.

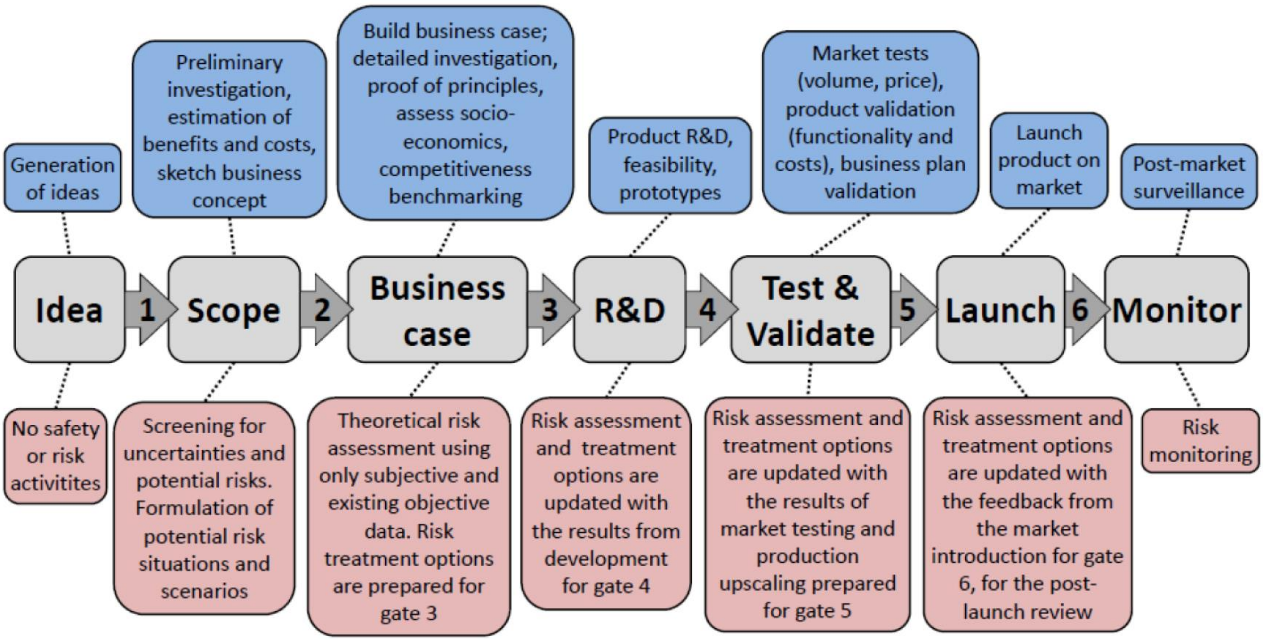

Figure 1. Overview of product innovation (blue) and safety-related (red) activities reported by the EU FP7 project "Nanoreg II" at the different stages of the product innovation process (grey) presented by Cooper (1990)[27] and Edgett (2015)[28].

Within the chain, the level of information both needed for and required from models for environmental risk assessment increases at each stage. In early stages, with little information available about the materials or products in question, risk evaluation tools that can operate with limited data may fit the needs of decision-makers better than at later stages, where models with more extensive and specific data needs may be better suited. Hence, different models may be required by users at different stages, with no single tool likely to be appropriate for all potential needs within the chain. Identification of the tools best fitted to each stage can facilitate optimal use of resources to enable efficient risk assessment.

Identification of stakeholder needs along nanomaterial innovation

To identify different stakeholders' needs from nanomaterial environmental assessment models, a generic questionnaire was distributed to a selection of stakeholders to engender a diversity of structured feedback. The questionnaire was prepared by listing potential criteria/requirements for nanomaterial environmental assessment models based on previous work and existing narrative literature on tool fit to stakeholder needs such as Hristozov et al., 2016.[17] The questionnaire contains two parts identifying requirements in two areas:

1. General model features, relevant to all model types, concerning applicability such as required user resources and model features.
2. Model output parameters and features affecting the output of exposure, hazard and risk assessment models, respectively.

The criteria for model output parameters were categorized as relating to aspects of material flow, fate and transport, hazard, uptake/bioavailability or risk, recognizing though, that some of the risk assessment models include sub-model(s) relating to one or more of the other categories. As the purpose of the interviews was to identify what stakeholders need from nanomaterial environmental assessment models during decision-making processes, the criteria focus on model *outcome* parameters/information, although these outcomes are obviously governed by input parameter availability and quality.

The questionnaire lists criteria (vertically) against product innovation stages (horizontally), thus forming a table that stakeholders were each asked to complete. This allowed stakeholders to provide feedback on their needs and requirements for each of the criteria at the individual stages in Figure 1. If key criteria were found missing, the stakeholder could add these. For each criterion, the response options used restricted selection, defined depending on the question asked, including; yes/no, pick lists, tick off lists, and the rating of a criterions' importance from 0 (not important) to 5 (essential), rather than free text options. Stakeholders were encouraged to provide comments on these default response options to allow modification if necessary. The questions and response options distributed to stakeholders are included in the electronic supplementary information (ESI), Table S1a-d. Along with the questionnaire, stakeholders were asked to indicate and rank the three most important criteria for nanomaterial environmental assessment models, regardless of innovation stage considerations.

The questionnaire was distributed to 60 potential stakeholders targeted within the network of the 24 partner institutes involved in the H2020 project caLIBRAte, and come from sectors including chemical and environmental regulatory bodies; innovators; large and small/medium-sized commercial enterprises; industrial sector bodies; insurers; and consumers. Regulators were specifically included as they directly influence the regulatory frameworks governing the risk assessment of nanomaterials during innovation. Of invitees, 18 (30%) agreed to participate and provide feedback. Most participants agreed to complete the questionnaire as sent, however, some asked to provide verbal feedback in teleconferences both instead of and in addition to filling in the questionnaire. An anonymized overview of the number and type of stakeholders involved and feedback received is presented in Table 1. To maintain confidentiality, specific stakeholders and feedback are reported anonymously throughout this work, according to the numbers assigned in Table 1. All stakeholders gave their informed consent by participating in teleconferences or returning questionnaires. The authors comply with EU and national laws as well as institutional guidelines, including the “Act on Processing of Personal Data” and the ”Danish Code of Conduct for Research Integrity” describing data collection, storage and retention.

Table 1. Overview of the number and type of stakeholders involved and feedback received.

No.	Stakeholder group	Type of feedback	Part(s) of questionnaire addressed	Stage-specific feedback
1	Regulator	Questionnaire	General part	Yes
2		Questionnaire	All	No
3	Industry (Association)	Questionnaire	General part	Yes
4		Teleconference	All	Yes
5	Industry (Large enterprises)	Teleconference	General part	Yes
6		Questionnaire, teleconference	General part	Yes
7		Questionnaire	General part	Yes
8	Consultant	General comments by mail/phone	Not Applicable	No
9		General comments by mail/phone	Not Applicable	No
10		Questionnaire	General part	Yes
11	Industry (SME)	Questionnaire	General part	Yes
12		Teleconference	General part	No
13		Questionnaire	All	Yes
14		General comments by mail/phone	Not Applicable	No
15		General comments by mail/phone	Not Applicable	Yes
16		General comments by mail/phone	Not Applicable	Yes
17		General comments by mail/phone	Not Applicable	Yes
18	Research organization	Questionnaire	General part	Yes

Identification of relevant nanomaterial environmental assessment models

Considering there are currently more than 500 tools available for nanomaterial safety assessment[30], the present study is delimited to consider the following five categories of models relevant for environmental risk assessment of nanomaterials:

1. Material flow models simulating nanomaterial flows into the environment from different sources and their transport between different environmental compartments
2. Fate and transport models simulating nanomaterial movement within and between compartments, and nanomaterial transformations that may affect their state and form in the environment
3. Hazard assessment models estimating the effects of nanomaterials on environmental species
4. Uptake/bioavailability models assessing nanomaterial uptake and accumulation in environmental organisms

5. Risk assessment models providing estimates for the potential environmental risk of nanomaterials

Moreover, models/tools described in peer reviewed literature were targeted. In practise, published models/tools relevant to each category were identified through a literature search using Web of Knowledge and Google Scholar, as well as any information from the authors that may identify additional models published in the international or national grey literature (including project progress reports). All identified publications presenting a model/tool/method within these defined categories were included, not just models that had been fully developed into ready-to-use software or tools. In total 38 models relevant for environmental risk assessment were identified, including seven material flow models, eight fate and transport models, seven hazard assessment models, four uptake/bioavailability models and 12 risk assessment models (listed in Table 4). It must be noted that this list is not static over time and not necessarily exhaustive.

Development of scoring scheme for models along innovation stages

To allow a systematic assessment of the suitability of different models to different stages (Figure 1), a scheme was designed to score the models against the stage-specific criteria using input from the stakeholder consultation. All identified models were then categorised (cf. categories 1-5 above) and the fit of each model against the features desired by stakeholders, was assessed as exemplified in Table 2 (The full list of assessment criteria are available in Table S2). For this assessment, the primary literature relating to each model was reviewed, and the accordance of the model to the specific identified features recorded. In those cases where the characteristics of each model relevant to a criterion could not be discerned from published information, model owners were contacted to provide details on model format, structure and outputs. Using this approach, it was possible to provide a complete assessment record for each model (not shown).

Table 2. Examples of assessment criteria and response categories for nanomaterial environmental assessment models (see Table S2 for full list of criteria).

Assessment criteria	Description of criteria	Response categories
Time/cost to parameterise model	What are the maximal costs to calculate and input all of required parameters into the model?	Minutes-Hours, Hours-Day, Days-Weeks, Weeks-Moths
Level of expertise	What level of expertise is needed by the user running the model, can it only be operated by experts or is the structure and guidance of sufficient quality that a non-expert would be able to use the tool with minimal training?	Novice, Intermediate, Expert
Time/cost to run model	What is the maximal time running the model may take, including the iterative process or running the model and updating input parameterss to gain the desired result?	Minutes-Hours, Hours-Day, Days-Weeks, Week-Months
Approval status	What is the scientific and regulatory approval status of the model, has it been peer reviewed, is it widely used and accepted in the scientific community, has it been the subject of standardisation and/or regulatory approval?	Standardised, Peer reviewed, In development
Format	What is the format of the model, is it available in a stand alone format, is it a web based tool or does it have another non-software format?	Online, Stand alone, Not software
Guidance available	Is there guidance on how to parameterise and operate the model available for potential users?	Yes, No

In order to quantitatively rate and compare the suitability of models at different innovation stages (Figure 1), a scoring scheme was developed, based on the assessment records:

1. Numerical values were assigned to each assessment criterion and stage combination to reflect where in the innovation process different model features are suitable. The large majority of criteria were scored 0, 0.5 or 1 depending on whether they were: not required/necessary (score 0), desirable/valuable but not essential (score 0.5), or required/preferred (score 1). Generally, criteria involving greater operational complexity were assigned higher scores for the later stages where greater resource commitment is likely to be needed and justifiable.
2. Three assessment criteria were recognized as being of particular importance based on the stakeholder feedback; 1) “Time/cost to parameterize the model”, 2) “Levels of expertise needed to operate the model”, both of which were applicable to all of the model types and 3) “Presents comparison of PEC and PNEC” which was relevant only

to models in the risk assessment category. For these three “priority criteria” a more refined set of scoring categories were used whereby models were allocated a score of 0, 0.1, 0.25 0.5, 0.75 or 1.

Examples from the scoring scheme are listed in Table 3, with the full scoring scheme available in the ESI (Table S3). For all the identified models, the features associated with each model were transformed to numerical values according to the scheme in Table S3. This resulted in a scoring scheme for each model by stage (not shown).

Table 3. Examples from the scoring scheme used to assess suitability of nanomaterial environmental assessment models according to each assessment criteria and stage. The full scoring scheme is available in the ESI (Table S3).

Criteria		Idea	Scope	Business case	R&D	Test & Validate	Launch	Monitor
Time/cost to parameterise model	Minutes-Hours	1	1	1	1	1	1	1
	Hours-Day	0.5	0.75	1	1	1	1	1
	Days-Weeks	0.25	0.25	0.5	0.5	1	1	1
	Week-Months	0.1	0.25	0.25	0.25	0.5	1	1
Level of expertise	Novice	1	1	1	1	0.75	1	1
	Intermediate	0	0.25	0.5	0.75	1	0.75	0.5
	Expert	0	0	0	0.5	0.75	0.5	0.25
Time/cost to run model	Minutes-Hours	1	1	1	1	1	1	1
	Hours-Day	0	0	1	1	1	1	1
	Days-Weeks	0	0	0	1	1	1	1
	Week-Months	0	0	0	0.5	0.5	0.5	0.5
Approval status	Standardised	1	1	1	1	1	1	1
	Peer reviewed	1	1	1	1	0	0	0
	In development	0.5	0.5	0.5	0	0	0	0
Format	Online	0	0	0	0	0	0.5	0.5
	Stand alone	1	1	1	1	1	1	1
	Not software	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Guidance available	Yes	1	1	1	1	1	1	1
	No	0.5	0	0	0	0	0	0

Lastly, an algorithm was developed to calculate an overall “assessment score” for each model and stage. The algorithm was specifically designed to make the assessment in a semi-quantitative manner (as it is based on criteria), and calculated in two steps:

1. For each model and stage, the criteria scores were summed excluding the three “priority criteria”.
2. To reflect the importance of the priority criteria, these were assigned greater weight in the assessment score calculation. The sum from step 1 was multiplied with the score for each priority criteria in turn. The product values obtained by these three multiplications were then added together and that sum divided by the number of priority criteria that were relevant to each model type, namely two for the material flow, fate and transport, hazard and uptake/bioavailability models (Equation 1) and three for the risk assessment models (Equation 2).

   Equation 1:

   Assessment score for each flow/fate/hazard/bioavailability model at each stage =

   $\sum \text{criteria scores} \cdot (\text{priority criteria 1} + \text{priority criteria 2})/2$

   Equation 2:

   Assessment score for each risk assessment model at each stage =

   $\sum \text{criteria scores} \cdot (\text{priority criteria 1} + \text{priority criteria 2} + \text{priority criteria 3})/3$

The resulting assessment scores allow comparison of models *within* each of the five model categories (flow, fate, hazard, uptake/bioavailability and risk assessment) to develop ranking lists to identify which models are most suited the requirements of stakeholders for each stage. Comparison of assessment scores *between* model categories was not feasible, as models in this case have different application fields, and hence, can achieve different scores. Moreover, the scoring scale differs between model categories, as not all 41 identified criteria apply to all five categories of models and because the additional priority criterion applies for the risk assessment models.

Results and discussion

Stakeholder requirements along nanomaterial innovation

It proved difficult to achieve the desired stakeholder participation number of 60, as only 30% of invitees agreed to participate. This is, however, consistent with return rates published for user surveys of this type and design.[31] Also, limited time availability of the stakeholders, resulted in different levels and types of feedback (Table 1), although always based on the generic questionnaire (Table S1a-d). Different approaches and methodologies have been applied for stakeholder elicitations and analysis of feedback.[25,32] In the present study, the stakeholder feedback was collected as input for the development of the scoring scheme, not for the comparison or weighing of stakeholder views. Therefore, specific stakeholder analysis methodologies as such were not applied, For the sake of transparency, general trends and divergences between stakeholder individuals/groups are discussed in the following.

In general, the stakeholder (SH) feedback illustrated that the Stage-Gate approach applied in this work (Figure 1) was not always recognized among responders. In some cases, this is because the stakeholder is not directly involved in innovation of nanomaterials and nano-enabled products, as reported by one of the regulators. For other stakeholders, especially small/medium-sized enterprises (SMEs) involved in innovation, development and production of a single nanomaterial product or process, the Stage-Gate system is not applied, although some of the guiding philosophy was clearly recognised. Some stakeholders involved only partly in the innovation process, may be involved only in initial stages, and not the later stages leading to launch (as reported by SH18: a research organization collaborating with SMEs). Others, especially large industrial companies, confirmed that they recognize and use the Stage-Gate approach, although the specific activities and decisions of the various stages and gates may differ from those described within the classic model. For example, SH14, 15 and 16 (SMEs) reported conducting legislative safety assessments mainly in the research and development (R&D) stage, whereas SH5 and 6 (large enterprises) reported a focus on the “Test & Validate” stage, or in some cases even in the initial part of the “Launch” stage. Overall, the stakeholder feedback indicates that the middle to late stages (“Business Case”, “R&D”, “Test & Validate”, and “Launch”) are those of primary importance for safety and risk-related work, such as testing, risk assessment and establishing regulatory compliance. Even within these limitations, the majority of responders clearly considered the Stage-Gate model as a suitable framework within which to assess nanomaterial environmental assessment models, as they reported different needs at the different innovation stages in questionnaire responses.

The stakeholders were asked to indicate one to three of the most important criteria for risk assessment models, regardless of innovation stage. This information was compiled both as requested feedback to questionnaires or from direct discussions in teleconferences. The large industries generally considered the format of the tool, especially whether it is online or stand-alone, as of key importance. The importance of a stand-alone format which can be incorporated into existing company managed systems was stated as being critical, as compared to web-based systems, because it ensures secure handling of confidential information. Compared to the larger corporations, SMEs had greater problems in completing some of the aspects of the needs questionnaire. This was principally due to a lack of in-house experts in safety and regulatory compliance issues, causing them to often hire consultants to undertake such activities. Thus, an easy to operate decision support tool, that clearly lists the data/information needs along Stage-Gates and outlines a simple and easy to parameterise set of data needs and requirement was identified as valuable for SMEs.

Different stakeholders including regulators, SMEs and a research organization independently reported the need for precautionary measures, i.e. some type of “worst-case scenario” consideration, either during the innovation process; related to any default model values (in case of data gaps) or in the way a model deals with the input data. It was also reported across stakeholder groups that the costs and efforts to run the model must be kept minimal until the R&D stage. This reflects the potential to stop innovation progression after this stage. Low effort in these early stages, thus, encourages innovation, while minimizing resource commitment to the environmental assessment of nanomaterial products that do not enter production. Finally, any regulatory requirements related to the risk assessment of nanomaterials and products need to be incorporated into the system, for example so that the needed input data to run the model rely only on data that are required by regulatory frameworks such as PEC and PNEC data. Indeed, this regulatory compliance was identified as a critical need among almost all responding commercial organisations. Currently, the nanomaterial specific regulatory requirements are being developed and no environmental assessment models have yet been specifically approved. For this reason, although an important criterion, no model currently meets this requirement. Consequently, the assessment reported here develops quantitative information to allow the selection of models to fit this need, rather than it being driven by it.

Several stakeholders reported no or very limited safety activities at the initial stages and SH6 (large enterprise) explicitly said that there is no need for risk assessment in the initial “Idea” and “Scope” stages. Still, some stakeholders mentioned the importance of identifying any potential hazard or “red flags” as early as possible during innovation. This issue may be solved through the use of some very simple models capable of providing “red flags”, while still recognizing the limited resources allocated for risk assessment in the initial stages. Models that score highly in these early stages could, therefore, be expected to present features that support easy parameterization and rapid use by non-experts.

The commonly stated concept of “safe-by-design” that is frequently mentioned in the nano-safety assessment community[33] was not mentioned explicitly by stakeholders suggesting that it is not a major explicit consideration for those actually involved in innovation or product development. However, some stakeholders did indicate a need for early advice to prevent or reduce product-related risks in cases where these are foreseeable. This could include, for example, support in the selection of the final product matrix into which nanomaterials are incorporated early in design (SH12, SME). While a safe-by-design approach could assist in preventing risks related to nanomaterials and nanomaterial-enabled products, in practice this is not a straight-forward task. The underlying identification of the characteristics, related to nanomaterial hazard, exposure, fate, and transport, needed for safe-by-design represents a major knowledge gap in nano-safety research[33].

Suitability of environmental assessment models for each innovation stage

The calculated assessment scores for each identified nanomaterial environmental assessment model along the innovation stages in Figure 1 are presented in Table 4, with colours indicating low (red) or high (green) fit of models with the needs and requirements at each stage as expressed by the stakeholders.

Material flow models

Available material flow models all have a similar overall structure that combines usage information with flows between different environmental compartments. This results in a broadly similar pattern of scores across successive stages. The assessment score is relatively low in early stages and increases to peak in the “Test & Validate” and “Launch” stages, followed by a slight decline for the “Monitor” stage (Table 4). Being priority criteria and multipliers in the scoring algorithm, the time and expertise needed to run material flow models generally lead to low scoring of the fit to stakeholder needs, especially in the early stages. At later stages, where speed and ease of use are less important, other common model characteristics, such as the flexibility for use for different nanomaterials and products, and the ability to predict nanomaterial concentrations across different media and environmental compartments, increases scores as these are desirable features for such assessment. The score peaks at the “Test & Validate” stage. As this is the critical stage in product development, this is also were the greatest investment of time and engagement of experts in nanomaterials environment assessment is likely to take place. Hence, it is also the stage at which the greatest amount of resources is likely to be committed. In the “Launch” and “Monitor” stages, the main priority changes from initial establishment to product stewardship. Hence, the desire may be to use reduced resources and to use less experienced staff to support a sustained need for continuous assessment, making these more complex models less well suited to these ongoing requirements.

Across all models, the PFMA Version 1 model[34] was consistently the best scoring of the available material flow models. The feature of this model combined the incorporation of complexity, such as inclusion of dynamic and probabilistic assessment and consideration of the movement of nanomaterials to all relevant environmental compartments, with relative ease of use, a key assessment criterion and multiplier in the appraisal. Thus, this later characteristic was, of critical importance in driving the relatively high score given to this model, as compared to less user-friendly models in this category.

Table 4. Assessment scores by innovation stage for identified nanomaterial environmental assessment models. The assessment score colours represent the level of fit between models and stage-specific needs, ranging from low (red) to high (green).

	Environmental assessment model	Reference	Idea	Scope	Business case	R&D	Test & Validate	Launch	Monitor
MATERIAL FLOW	PMFA	35	1	2	2	8	14	16	13
	PMFA Version 1.0.0	34	4	8	13	18	23	18	16
	DPMFA	36	1	2	2	9	15	17	14
	Spatial-PMFA	37	1	2	2	8	12	14	12
	MFA	38	2	5	10	13	22	17	14
	Tiede et al. 2010	39	3	2	5	9	14	12	10
	LearNano	40	2	4	10	12	18	15	12
FATE	SimpleBox4Nano	14	4	9	15	18	22	17	14
	NanoDUFLOW	41	2	2	4	9	15	12	11
	Rhine model	11	2	2	4	8	14	11	9
	MendNano	42	1	2	2	7	12	14	11
	WSM/WASP7	43	1	2	2	7	13	15	12
	Rhone Model	44	2	2	4	8	14	11	9
	RedNano	45	1	2	2	8	13	15	12
	GWAVA with water quality module	46, 47	2	2	4	9	14	12	10
HAZARD	US EPA SSD Generator	48, 49	2	4	9	13	21	17	14
	SSWD	10	1	1	2	8	13	14	12
	NanoQSAR model	50, 51	7	8	12	14	14	11	9
	Framework for oxidative stress potential	52	8	7	6	10	9	6	4
	nanoSAR	53	4	5	6	10	9	6	4
	nano-SAR (OCHEM, WEKA)	54	2	2	5	9	13	10	8
	Nanoprofiler 1.2	55	2	2	4	9	13	10	8
UPTAKE	Kinetic model/BCF	56	6	11	16	17	16	12	10
	Two component Efflux/uptake model	57	6	11	16	17	16	12	10
	Biodynamic model	58	6	11	16	17	16	12	10
	BLM concept model	59	6	11	16	17	16	12	10
RISK	FINE	60	6	6	8	12	14	15	13
	Precautionary Matrix for Synthetic Nanomaterials	8	22	20	19	17	13	14	13
	Tervonen et al. 2009	61	8	9	15	16	18	14	13
	SUN, 2016	34	7	8	14	20	27	23	21
	pERA	13	6	6	9	16	20	21	19
	LICARA nanoSCAN	9	9	11	14	16	16	13	11
	nanoinfo	62	6	6	10	17	25	22	19
	Topuz and van Gestel, 2016	63	5	6	8	16	19	20	18
	GUIDEnano tool	None	6	6	10	18	26	22	20
	SUNDS 2nd tier	None	5	5	9	17	25	22	20
	SUNDS 1st tier	9	9	11	14	16	16	13	11
	GUIDEnano tool intermediate	none	8	11	18	23	28	23	21

Environmental fate and transport models

The environmental fate and transport models followed a similar pattern of scoring across stages as the material flow models, with lower scores in early stages. The common pattern in scores between the different fate and transport models across stages reflects a common set of shared features. These include representations of key nanomaterial processes, such as homo- and heteroagglomeration, sedimentation, and dissolution, as the major features driving fate and transport, especially in aquatic environments. With a number of relatively complex features, these models are often rather time-consuming to parameterise and operate and also require a high level of expertise to identify parameters and interpret outputs. This translates to relatively poor scores in the earlier stages, whereas in later stages where increase resource investment is more often warranted, the penalty arising from the required resource commitment reduces and scores consequently rise (Table 4).

The SimpleBox4Nano model[12,14] scores the highest of the fate and transport models across all stages. Indeed the calculated scores for SimpleBox4Nano are in some cases two-times higher or more than those awarded for any of the alternative fate and transport models in some stages (e.g. “Scope” and “Business case”). The key characteristics underlying the higher scores achieved for SimpleBox4Nano include its open availability for use, full guidance availability, and estimation of nanomaterial fate and transport across a range of environmental compartments (air, soil, water and sediment). The model is Excel-based and, hence, requires a lower level of expertise than some of the other models presented in code-based formats. As a critical assessment multiplier, this relative ease of use has a major impact on the Stage-Gate scores.

Uptake and bioavailability models

To date, only few models have been proposed for modelling the uptake and bioavailability of nanomaterials in ecological assessments, as methods for such studies remain in their relative infancy. One of these models is the biotic ligand model (BLM), which has been widely used for modelling metal bioavailability. It has recently been proposed for use with silver nanoparticles in initial studies, although challenges have been identified.[57] Also, three toxicokinetic modelling approaches are included in this category; “Kinetic model/bioconcentration factor”, “Two component efflux/uptake model”, and “Biodynamic model”, which are all based on modelling the influx/uptake and efflux/elimination of nanomaterials for organism tissues to consider bioaccumulation. The use of bioaccumulation factors requires equilibrium partitioning, which is not considered relevant for nanomaterials, due to the kinetic nature of many processes affecting internal fate, such as attachment, dissolution, and chemical transformation.[21] Rather than a single model, these approaches all represent a family of models with different complexities. For example, they may consider the organism as one or more compartments in the model, depending on available information on internal anatomy and metal handling characteristics. Only the BLM is designed to consider speciation and bioavailability. Thus, a significant research gap remains in this area.

The four models are awarded the same scores across stages. Scores are low in the early stages, driven primarily by a somewhat restricted scope and range of settings in which these models can currently be used, in addition to intermediate or high level of expertise needed to parameterize and run each model. In the “Business case” and “R&D” stages, scores increase as the greater resource requirements mean the requirements of time and expertise is no longer extensively penalised. In later stages, scores decline again as the models lack considerations of nonspecific properties. Hence, it remains uncertain whether they will fully capture the characteristics of a nanomaterial affecting bioaccumulation. Indeed initial efforts to use the BLM for nanomaterials have recognized problems, such as the potential for exposure to occur through ingestion, which is an exposure route not routinely considered in this model structure.[57,64]

Environmental hazard models

Seven environmental hazard models relevant for use with nanomaterials were identified, covering two main approaches;

1) Species sensitivity distribution (SSD) models that estimate the hazardous concentration for a certain percentage of species based on the distribution of toxicity data from laboratory field tests (or potentially field based assessments).
2) Quantitative structure activity relationship (QSAR) models that aim to predict the toxicity of untested nanomaterials based on chemical/structural descriptors.

In environmental risk assessment, both SSD and QSAR models are essential components of current regulation as they can extrapolate from known data to untested species and substances. Given the number of different nanomaterials that can be produced from combinations of core chemistry, size, shape, surface functionalization etc., and the need to protect the range of untested species in ecosystems, such extrapolation models are likely to remain an important component of any future nanomaterial management system.

Of the two SSD tools available, the US EPA SSD generator scored higher than the "species sensitivity weighted distribution" (SSWD) approach in all stages. This is driven by the relative ease of the US EPA tool compared to the SSWD, which is more complex and time-consuming, as besides species sensitivity, it also considers species relevance, trophic level abundance and the level of nano-specific characterisation accompanying the toxicity data. This greater level of complexity could be warranted in later stages as these considerations can benefit from a more complete assessment. However, even though the scores for both tools do rise along stages, the US EPA tool always outscores the SSWD tool based on ease of use weighting. However, given the efforts that may be committed to assessments at this stage, this outcome may not preclude the selection of more complex tools for later stages if deemed appropriate.

The five QSARs identified apply various approaches to use nanomaterial properties and features as predictors of effects, either on biochemical related endpoints, such as oxidative stress potential, or on measured endpoints such as cell viability. These models generally require a high level of expertise to operate, as they require input of a range of nano-specific properties that are both difficult to derive and complex to interpret and ultimately parameterise. Consequently, all nanoQSAR models score rather low in all stages. A common feature of the nanoQSAR models is that the score does not greatly increase towards later stages (i.e. the rise in the score for each model is less pronounced than for other model types). Because they make use of prior information in the absence of specific hazard information, nanoQSAR models are most applicable to assessment in the early developmental stages, where stakeholders expressed a clear demand for early “red flags” relating to potential hazard. This is similar to the QSAR strategies applied for organic chemicals. Hence, although they clearly require development, especially relating to the ease of use, there remains a potential role for reliable nanoQSAR models in environmental risk assessment. Among nanoQSAR models, the method of Puzyn et al. (2011) received the highest score. The model is designed to predict the bacterial toxicity of metal oxide nanoparticles based on a single descriptor; their enthalpy of formation of a gaseous cation having the same oxidation state as that in the metal oxide structure. This is to date, the most well-known and established nanoQSAR. It is, however, restricted in its domain being applicable only to metal and metal oxide nanomaterials; suitable for predicting effects only for materials with different pristine core chemistry (and not variations in properties such as size, shape, and coating); and applicable only for the bacterial species with which it was developed. Expanding the domain space of nanoQSAR models is, thus, recognised as a research priority. For all hazard models, the issue of data availability are an additional uncertainty. This means that models may be assessed fit for purpose, although adequate data may not be available to actually run them.[65,66]

Environmental risk assessment models

The environmental risk assessment models comprise both the hazard and exposure assessment of nanomaterial related risks. In total 12 tools were identified, ranging from screening levels methods (e.g. LICARA nanoSCAN, Precautionary Matrix for Synthetic Nanomaterials), to complex tools covering all aspects of fate and transport, and hazard assessment, e.g. the GUIDEnano tool and the SUN discussion support tool (SUNDS). A particular challenge when assessing the risk assessment models was that some contain different material flow, fate and transport, and hazard assessment tools embedded within their overall structure. For example, the SUNDS tool include the LICARA nanoSCAN (named 1st tier in the results section) and the pERA developed by Gottschalk et al. in 2013[13], whereas the LICARA nanoSCAN includes parts of the Precautionary Matrix for Synthetic Nanomaterials[8], NanoRiskCat[67] and StoffenManager Nano[68]. As a result, the tools can be used in different ways. This creates a specific challenge regarding the scoring of model features, such as ease of use and functionality. Similarly, many risk assessment tools include different methods for estimating hazard including SSDs. When this is the case, models may be well suited for particular criteria, i.e. they may take different nanomaterial properties into account. However, the use of an SSD module that does not account for nano-specific properties may mask the value of such features, if a lack of consideration of nano-specific features in the hazard module influences the overall model score. It should be noted that several tools are not yet fully developed and may differ in later versions to be released. Additionally, we differentiated GUIDEnano into GUIDEnano and GUIDEnano-intermediate that accounts for the user experience by recommending default values.

Score comparison between models along stages indicated that principally, the ERA tools can be differentiated into two categories: applicable to early stages and applicable to late stages. Three tools, the Precautionary Matrix for Synthetic Nanomaterials, the LICARA nanoSCAN and SUNDS 1st tier (equal to LICARA nanoSCAN), score higher than other models in the earlier stages. These tools apply a risk screening (Precautionary Matrix) and risk-benefit assessment (LICARA/SUNDS 1st tier) to nanomaterials evaluation. Such screenings require less data and information about the nanomaterial allowing the (unexperienced) user to apply these tools easily and with minimal time requirements. The results of these tools indicate where further investigations or information are required to proceed further in the stages. By doing so, such methods apply a less evidence-driven approach to assess potential risks and benefits without achieving a complete risk assessment. These tools scored lower in the later stages due to the increasing demands on evidence of data and information, which is accompanied by the need for expert knowledge and more time-consuming and comprehensive assessments.

The remaining nine risk assessment models each score lower in the early stages, driven predominately by the need for expert parameterisation and relative high time requirements for successful parameterisation and operation. The majority of these models peak in the “R&D” stage before declining slightly. Among these models, the GUIDEnano-intermediate tool version scored the highest in the “R&D” and “Test & Validate” stages as it provides a pre-parameterized tool for intermediate users, while the SUNDS tool only gives (and learns) by scenarios entered into the tool. In the end, both tools may be on the same score level depending on how well the database is managed and updated. Although the scores are similar, differences are found in the possibilities to adjust environmental compartments and regions (i.e. GUIDEnano) and the determinations of PEC values for the complete range of applications (SUNDS) vs. the contribution of a single application to the PEC (GUIDEnano). Also, the data handling and evaluating of data in GUIDEnano is more guided than in the SUNDS tool. A challenge for the evaluation of the nanoinfo tool, was obtaining information on how the algorithms work behind the web interface. Here, we used the published articles that constitute the modules of the tool. Particularly, the hazard assessment module is still being developed to apply QSARs for hazard assessment. However, it must be stressed that for the mentioned tools development is ongoing and the evaluation should be repeated in the future.

Conclusions

We evaluated the fit of 38 models relevant for assessing the fate, exposure, hazard or risk of nanomaterials to the innovation stages, considering 41 criteria reflecting needs and requirements obtained by consultations with 18 stakeholders of six different groups.

Important stakeholder criteria for environmental risk assessment models include the required time/costs and level of expertise needed for model parameterisation and operation. For risk assessment models specifically, also the generation of PEC/PNEC was a key requirement. All stakeholders identified regulatory compliance as a critical criterion, which is presently difficult to incorporate into models as frameworks for nanomaterial risk assessment has yet to be developed and adopted. Also, the availability of data to run the models is a prevailing issue for nanomaterials. Consequently, the generation of model input data and development of regulatory requirements for nanomaterials will likely have a significant influence on the future selection as well as development of tools.

Within the five model categories, similar model features often resulted in similar scoring profiles across stages. The majority of models are relatively complex tools developed by experts for use in a research context and, therefore, generally score higher at later stages where the greatest amount of resources and expertise are allocated during product innovation. This is driven by the stakeholder requirements to limit investments in risk management to the stages after initial innovation but prior to “Launch”. Models requiring less time and user expertise, such as nanoQSARs and the less complex risk assessment models, fit stakeholder needs for early stages, as they aim to identify potential hazards and provide risk management measures, without substantive early resource investments. Refinement of tools over the next few years may change the balance in scoring and assessment between particular tools. A flow-through from research tools to simplified and easily operationalized systems may ultimately deliver the balance between rigor and ease that is needed.

Conflict of interest

There are no conflicts to declare.

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Notes and references

(1) Roco, M. C. The Long View of Nanotechnology Development: The National Nanotechnology Initiative at 10 Years. Nanotechnology Research Directions for Societal Needs in 2020; Science Policy Reports, Vol 1. **2011**, 1–28.

(2) Hansen, S. F.; Heggelund, L. R.; Revilla Besora, P.; Mackevica, A.; Boldrin, A.; Baun, A. Nanoproducts – What Is Actually Available to European Consumers? *Environ. Sci. Nano* **2016**, *3*, 169–180.

(3) Stark, W. J.; Stoessel, P. R.; Wohlleben, W.; Hafner, A. Industrial Applications of Nanoparticles. *Chem. Soc. Rev.* **2015**, *44* (16), 5793–5805.

(4) WHO. *Nanotechnology and Human Health: Scientific Evidence and Risk Governance. Report of the WHO Expert Meeting 10-11 December 2012*; Bonn, Germany, 2013.

(5) Syberg, K.; Hansen, S. F. Environmental Risk Assessment of Chemicals and Nanomaterials - The Best Foundation for Regulatory Decision-Making? *Sci. Total Environ.* **2016**, *541*, 784–794.

(6) Sørensen, S. N.; Holten Lützhøft, H.-C.; Rasmussen, R.; Baun, A. Acute and Chronic Effects from Pulse Exposure of D. Magna to Silver and Copper Oxide Nanoparticles. *Aquat. Toxicol.* **2016**, *180*, 209–217.

(7) Wigger, H.; Wohlleben, W.; Nowack, B. Environmental Science Nano Redefining Environmental Nanomaterial Flows : Consequences of the Regulatory Nanomaterial. *Environ. Sci. Nano* **2018**, DOI: 10.1039/C8EN00137E.

(8) Höck, J.; Epprecht, T.; Hofmann, H.; Höhner, K.; Krug, H.; Lorenz, C.; Limbach, L.; Gehr, P.; Nowack, B.; Riediker, M. *Guidelines on the Precautionary Matrix for Synhtetic Nanomaterials, Version 2*; Berne: Swiss Federal Office for Public Health and Federal Office for the Environment, 2010.

(9) Van Harmelen, T.; Zondervan-Van Den Beuken, E. K.; Brouwer, D. H.; Kuijpers, E.; Fransman, W.; Buist, H. B.; Ligthart, T. N.; Hincapié, I.; Hischier, R.; Linkov, I.; et al. LICARA NanoSCAN - A Tool for the Self-Assessment of Benefits and Risks of

Nanoproducts. *Environ. Int.* **2016**, *91*, 150–160.

(10) Semenzin, E.; Lanzellotto, E.; Hristozov, D.; Critto, A.; Zabeo, A.; Giubilato, E.; Marcomini, A. Species Sensitivity Weighted Distribution for Ecological Risk Assessment of Engineered Nanomaterials: The n-TiO2 Case Study. *Environ. Toxicol. Chem.* **2015**, *34* (11), 2644–2659.

(11) Praetorius, A.; Scheringer, M.; Hungerbühler, K. Development of Environmental Fate Models for Engineered Nanoparticles - A Case Study of TiO2 Nanoparticles in the Rhine River. *Environ. Sci. Technol.* **2012**, *46* (12), 6705–6713.

(12) Meesters, J. A. J.; Quik, J. T. K.; Koelmans, A. A.; Hendriks, A. J.; Van De Meent, D. Multimedia Environmental Fate and Speciation of Engineered Nanoparticles: A Probabilistic Modeling Approach. *Environ. Sci. Nano* **2016**, *3* (4), 715–727.

(13) Gottschalk, F.; Kost, E.; Nowack, B. Engineered Nanomaterials in Water and Soils: A Risk Quantification Based on Probabilistic Exposure and Effect Modeling. *Environ. Toxicol. Chem.* **2013**, *32* (6), 1278–1287.

(14) Meesters, J. A. J.; Koelmans, A. A.; Quik, J. T. K.; Hendriks, A. J.; Van De Meent, D. Multimedia Modeling of Engineered Nanoparticles with SimpleBox4nano: Model Definition and Evaluation. *Environmental Science and Technology*, **2014**, *48*, 5726–5736.

(15) Grieger, K. D.; Linkov, I.; Hansen, S. F.; Baun, A. Environmental Risk Analysis for Nanomaterials: Review and Evaluation of Frameworks. *Nanotoxicology* **2012**, *6* (2), 196–212.

(16) Brouwer, D. H. Control Banding Approaches for Nanomaterials. *Ann. Occup. Hyg* **2012**, *56* (5), 506–514.

(17) Hristozov, D.; Gottardo, S.; Semenzin, E.; Oomen, A.; Bos, P.; Peijnenburg, W.; van Tongeren, M.; Nowack, B.; Hunt, N.; Brunelli, A.; et al. Frameworks and Tools for Risk Assessment of Manufactured Nanomaterials. *Environ. Int.* **2016**, *95*, 36–53.

(18) Hristozov, D. R.; Gottardo, S.; Critto, A.; Marcomini, A. Risk Assessment of Engineered Nanomaterials: A Review of Available Data and Approaches from a Regulatory

Perspective. *Nanotoxicology* **2012**, *6* (8), 880–898.

(19) Arvidsson, R.; Furberg, A.; Molander, S. *Review of Screening Risk Assessment Methods for Nanomaterials. Report No. 2016:12*; Gothenburg, 2016.

(20) Romero-Franco, M.; Godwin, H. A.; Bilal, M.; Cohen, Y. Needs and Challenges for Assessing the Environmental Impacts of Engineered Nanomaterials (ENMs). *Beilstein J. Nanotechnol.* **2017**, *8* (1), 989–1014.

(21) Baalousha, M.; Cornelis, G.; Kuhlbusch, T. A. J.; Lynch, I.; Nickel, C.; Peijnenburg, W.; van den Brink, N. W. Modeling Nanomaterial Fate and Uptake in the Environment: Current Knowledge and Future Trends. *Environ. Sci. Nano* **2016**, *3* (2), 323–345.

(22) Oomen, A. G.; Steinhäuser, K. G.; Bleeker, E. A. J.; van Broekhuizen, F.; Sips, A.; Dekkers, S.; Wijnhoven, S. W. P.; Sayre, P. G. Risk Assessment Frameworks for Nanomaterials: Scope, Link to Regulations, Applicability, and Outline for Future Directions in View of Needed Increase in Efficiency. *NanoImpact* **2018**, *9*, 1–13.

(23) Nowack, B. Evaluation of Environmental Exposure Models for Engineered Nanomaterials in a Regulatory Context. *NanoImpact* **2017**, *8*, 38–47.

(24) Quik, J. T. K.; Bakker, M.; van de Meent, D.; Poikkimäki, M.; Dal Maso, M.; Peijnenburg, W. Directions in QPPR Development to Complement the Predictive Models Used in Risk Assessment of Nanomaterials. *NanoImpact* **2018**, *11*, 58–66.

(25) Malsch, I.; Subramanian, V.; Semenzin, E.; Zabeo, A.; Hristozov, D.; Mullins, M.; Murphy, F.; Linkov, I.; Marcomini, A. Comparing Mental Models of Prospective Users of the Sustainable Nanotechnology Decision Support System. *Environ. Syst. Decis.* **2017**, *37* (4), 465–483.

(26) Trump, B. D.; Hristozov, D.; Malloy, T.; Linkov, I. Risk Associated with Engineered Nanomaterials: Different Tools for Different Ways to Govern. *Nano Today* **2018**, *21*, 9–13.

(27) Cooper, R. Stage-Gate Systems: A New Tool for Managing New Products. *Bus. Horiz.* **1990**, No. May-June, 44–54.

(28) Edgett, S. J. Idea-to-Launch (Stage-Gate ®) Model: An Overview. *Stage-Gate*

International. 2015, pp 1–5.

(29) Park, M. V. D. Z.; Bleeker, E. A. J.; Brand, W.; Cassee, F. R.; van Elk, M.; Gosens, I.; de Jong, W. H.; Meesters, J. A. J.; Peijnenburg, W. J. G. M.; Quik, J. T. K.; et al. Considerations for Safe Innovation: The Case of Graphene. *ACS Nano* **2017**, *11* (10), 9574–9593.

(30) Jantunen, A. P. A.; Gottardo, S.; Rasmussen, K.; Crutzen, H. P. An Inventory of Ready-to-Use and Publicly Available Tools for the Safety Assessment of Nanomaterials. *NanoImpact* **2018**, *12* (May), 18–28.

(31) Sheehan, K. B. E-Mail Survey Response Rates: A Review. *J. Comput. Commun.* **2001**, JCMC621, https://doi.org/10.1111/j.1083-6101.2001.tb00117.x
.

(32) Linkov, I.; Bates, M. E.; Canis, L. J.; Seager, T. P.; Keisler, J. M. A Decision-Directed Approach for Prioritizing Research into the Impact of Nanomaterials on the Environment and Human Health. *Nat. Nanotechnol.* **2011**, *6* (12), 784–787.

(33) Hjorth, R.; van Hove, L.; Wickson, F. What Can Nanosafety Learn from Drug Development? The Feasibility of “Safety by Design.” *Nanotoxicology* **2017**, *11* (3), 305–312.

(34) SUN. *Deliverable D 3.6. Development of Modelling Tools to Predict Release and Transformation of NOAA. SUN-Sustanable Nanotechnologies, Grant Agreement Number 604305*; 2016.

(35) Gottschalk, F.; Scholz, R. W.; Nowack, B. Probabilistic Material Flow Modeling for Assessing the Environmental Exposure to Compounds: Methodology and an Application to Engineered Nano-TiO2 Particles. *Environ. Model. Softw.* **2010**, *25*, 320–332.

(36) Bornhöft, N. A.; Sun, T. Y.; Hilty, L. M.; Nowack, B. A Dynamic Probabilistic Material Flow Modeling Method. *Environ. Model. Softw.* **2016**, *76*, 69–80.

(37) Gottschalk, F.; Ort, C.; Scholz, R. W.; Nowack, B. Engineered Nanomaterials in Rivers – Exposure Scenarios for Switzerland at High Spatial and Temporal Resolution. *Environ. Pollut.* **2011**, *159*, 3439–3445.

(38) Mueller, N. C.; Nowack, B. Exposure Modeling of Engineered Nanoparticles in the

Environment. *Environ. Sci. Technol.* **2008**, *42* (12), 4447–4453.

(39) Tiede, K.; Westerhoff, P.; Hansen, S. F.; Fern, G. J.; Hankin, S. M.; Aitken, R. J.; Chaudhry, Q.; Boxall, A. *Review of the Risks Posed to Drinking Water by Man-Made Nanoparticles. Food and Environment Research Agency, Sand Hutton, York, YO41 1LZ*; 2010.

(40) Keller, A. A.; Lazareva, A. Predicted Releases of Engineered Nanomaterials: From Global to Regional to Local. *Environ. Sci. Technol. Lett.* **2014**, *1*, 65–70.

(41) de Klein, J. J. M.; Quik, J. T. K.; Bäuerlein, P. S.; Koelmans, A. A. Towards Validation of the NanoDUFLOW Nanoparticle Fate Model for the River Dommel, The Netherlands. *Environ. Sci. Nano* **2016**, *3* (2), 434–441.

(42) Liu, H. H.; Cohen, Y. Multimedia Environmental Distribution of Engineered Nanomaterials. *Environ. Sci. Technol.* **2014**, *48* (6), 3281–3292.

(43) Dale, A. L.; Casman, E. A.; Lowry, G. V.; Lead, J. R.; Viparelli, E.; Baalousha, M. Modeling Nanomaterial Environmental Fate in Aquatic Systems. *Environ. Sci. Technol.* **2015**, *49* (5), 2587–2593.

(44) Sani-Kast, N.; Scheringer, M.; Slomberg, D.; Labille, J.; Praetorius, A.; Ollivier, P.; Hungerbühler, K. Addressing the Complexity of Water Chemistry in Environmental Fate Modeling for Engineered Nanoparticles. *Sci. Total Environ.* **2015**, *535*, 150–159.

(45) Liu, H. H.; Bilal, M.; Lazareva, A.; Keller, A.; Cohen, Y. Simulation Tool for Assessing the Release and Environmental Distribution of Nanomaterials. *Beilstein J. Nanotechnol.* **2015**, *6*, 938–951.

(46) Dumont, E.; Johnson, A. C.; Keller, V. D.; Williams, R. J. Nano Silver and Nano Zinc-Oxide in Surface Waters – Exposure Estimation for Europe at High Spatial and Temporal Resolution. *Environ. Pollut.* **2015**, *196*, 341–349.

(47) Johnson, A. C.; Bowes, M. J.; Crossley, A.; Jarvie, H. P.; Jurkschat, K.; Jürgens, M. D.; Lawlor, A. J.; Park, B.; Rowland, P.; Spurgeon, D.; et al. An Assessment of the Fate, Behaviour and Environmental Risk Associated with Sunscreen TiO2 Nanoparticles in UK Field Scenarios. *Sci. Total Environ.* **2011**, *409* (13), 2503–2510.

(48) US EPA. Species Sensitivity Distribution (SSD) Generator. United States Environmental Protection Agency 2016.

(49) Garner, K. L.; Suh, S.; Lenihan, H. S.; Keller, A. A. Species Sensitivity Distributions for Engineered Nanomaterials. *Environ. Sci. Technol.* **2015**, *49* (9), 5753–5759.

(50) Puzyn, T.; Rasulev, B.; Gajewicz, A.; Hu, X.; Dasari, T. P.; Michalkova, A.; Hwang, H.-M.; Toropov, A.; Leszczynska, D.; Leszczynski, J. Using Nano-QSAR to Predict the Cytotoxicity of Metal Oxide Nanoparticles. *Nat. Nanotechnol.* **2011**, *6* (3), 175–178.

(51) Mu, Y.; Wu, F.; Zhao, Q.; Ji, R.; Qie, Y.; Zhou, Y.; Hu, Y.; Pang, C.; Hristozov, D.; Giesy, J. P.; et al. Predicting Toxic Potencies of Metal Oxide Nanoparticles by Means of Nano-QSARs. **2016**, *10*, 1207–1214.

(52) Burello, E.; Worth, A. P. A Theoretical Framework for Predicting the Oxidative Stress Potential of Oxide Nanoparticles. *Nanotoxicology* **2011**, *5* (2), 228–235.

(53) Liu, R.; Zhang, H. Y.; Ji, Z. X.; Rallo, R.; Xia, T.; Chang, C. H.; Nel, A.; Cohen, Y. Development of Structure-Activity Relationship for Metal Oxide Nanoparticles. *Nanoscale* **2013**, *5*, 5644–5653.

(54) Chen, G.; Peijnenburg, W. J. G. M.; Kovalishyn, V.; Vijver, M. G. Development of Nanostructure–activity Relationships Assisting the Nanomaterial Hazard Categorization for Risk Assessment and Regulatory Decision-Making. *RSC Adv.* **2016**, *6* (57), 52227–52235.

(55) Ambure, P.; Aher, R. B.; Gajewicz, A.; Puzyn, T.; Roy, K. “NanoBRIDGES” Software: Open Access Tools to Perform QSAR and Nano-QSAR Modeling. *Chemom. Intell. Lab. Syst.* **2015**, *147*, 1–13.

(56) Isaacson, C. W.; Sigg, L.; Ammann, A. A.; Stadnicka-Michalak, J.; Schirmer, K. Interactions of TiO2 Nanoparticles and the Freshwater Nematode Plectus Aquatilis: Particle Properties, Kinetic Parameters and Bioconcentration Factors. *Environ. Sci. Nano* **2017**, *4* (3), 712–719.

(57) Khan, F. R.; Paul, K. B.; Dybowska, A. D.; Valsami-Jones, E.; Lead, J. R.; Stone, V.; Fernandes, T. F. Accumulation Dynamics and Acute Toxicity of Silver Nanoparticles to

Daphnia Magna and Lumbriculus Variegatus: Implications for Metal Modeling Approaches. *Environ. Sci. Technol.* **2015**, *49* (7), 4389–4397.

(58) Croteau, M. N.; Misra, S. K.; Luoma, S. N.; Valsami-Jones, E. Silver Bioaccumulation Dynamics in a Freshwater Invertebrate after Aqueous and Dietary Exposures to Nanosized and Ionic Ag. *Environ. Sci. Technol.* **2011**, *45* (15), 6600–6607.

(59) Sakamoto, M.; Ha, J.-Y.; Yoneshima, S.; Kataoka, C.; Tatsuta, H.; Kashiwada, S. Free Silver Ion as the Main Cause of Acute and Chronic Toxicity of Silver Nanoparticles to Cladocerans. *Arch. Environ. Contam. Toxicol.* **2015**, *68* (3), 500–509.

(60) Money, E. S.; Reckhow, K. H.; Wiesner, M. R. The Use of Bayesian Networks for Nanoparticle Risk Forecasting: Model Formulation and Baseline Evaluation. *Sci. Total Environ.* **2012**, *426*, 436–445.

(61) Tervonen, T.; Linkov, I.; Figueira, J. R.; Steevens, J.; Chappell, M.; Merad, M. Risk-Based Classification System of Nanomaterials. *J. Nanoparticle Res.* **2009**, *11* (4), 757–766.

(62) UC CEIN University of California, Center for Environmental Implications of Nanotechnology. CEIN Integrated Nanoinformatics Web-Portal www.nanoinfo.org (accessed June 20, 2018).

(63) Topuz, E.; van Gestel, C. A. M. An Approach for Environmental Risk Assessment of Engineered Nanomaterials Using Analytical Hierarchy Process (AHP) and Fuzzy Inference Rules. *Environ. Int.* **2016**, *92–93*, 334–347.

(64) Diez-Ortiz, M.; Lahive, E.; Kille, P.; Powell, K.; Morgan, A. J.; Jurkschat, K.; Van Gestel, C. A. M.; Mosselmans, J. F. W.; Svendsen, C.; Spurgeon, D. J. Uptake Routes and Toxicokinetics of Silver Nanoparticles and Silver Ions in the Earthworm Lumbricus Rubellus. *Environ. Toxicol. Chem.* **2015**, *34* (10), 2263–2270.

(65) Hjorth, R. The Shortfall of Risk Assessment for Decision-Making. *Nat. Nanotechnol.* **2017**, *12* (12), 1109–1110.

(66) Hjorth, R.; Skjolding, L. M.; Sørensen, S. N.; Baun, A. Regulatory Adequacy of Aquatic Ecotoxicity Testing of Nanomaterials. *NanoImpact* **2017**, *8,* 28-37.

(67) Hansen, S. F.; Jensen, K. A.; Baun, A. NanoRiskCat: A Conceptual Tool for

Categorization and Communication of Exposure Potentials and Hazards of Nanomaterials in Consumer Products. *J. Nanoparticle Res.* **2014**, *16:2195*.

(68) Van Duuren-Stuurman, B.; Vink, S. R.; Verbist, K. J. M.; Heussen, H. G. A.; Brouwer, D. H.; Kroese, D. E. D.; Van Niftrik, M. F. J.; Tielemans, E.; Fransman, W. Stoffenmanager Nano Version 1.0: A Web-Based Tool for Risk Prioritization of Airborne Manufactured Nano Objects. *Ann. Occup. Hyg.* **2012**, *56* (5), 525–541.