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Environmental Significance Statement

While there is a suite of new, emerging tools to evaluate potential health and environmental risks of engineered nanomaterials (ENMs), there has not yet been adequate testing or validation of these tools. This study tests a subset of ENM risk screening tools using a common case study focused on ENMs for water treatment technologies. Key findings from this analysis include that these tools can be used in a complementary manner, underlying data and information often play large roles in generated outcomes, multidisciplinary teams are essential for completion, and further testing and validation of risk analysis tools for ENMs continues as an important research need.

Application and Testing of Risk Screening Tools for Nanomaterial Risk Analysis

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Abstract

The field of engineered nanomaterial (ENM) risk analysis has matured significantly in the past decade. While there is a suite of new, emerging tools to evaluate ENM risks and make decisions regarding these risks, there has not yet been thorough testing of these tools. This analysis applies and tests three risk screening tools (NanoRiskCat, LICARA nanoSCAN, NanoGRID) using a common case study focused on ENMs designed for water treatment technologies, compares results generated, and highlights key lessons learned and best practices for stakeholders involved in developing and/or applying ENM risk screening tools. NanoRiskCat was found to be most useful for providing a visual aid to characterize the potential exposure and health impact profiles of the ENMs, while LICARA nanoSCAN was most useful for providing guidance on proceeding with ENM-enabled innovations. NanoGRID was helpful for characterizing data on potential ENM exposure and hazards and providing detailed guidance for subsequent laboratory-based testing. At the same time, several key challenges were identified during tool application and testing phases, ranging from minor inconveniences to more complex, foundational issues. Key lessons learned and potential best practices gleaned from this analysis include: i) risk screening tools can be used together in a complementary manner; ii) risk managers and other users should be clear on the selection of underlying data and impacts on results; iii) multidisciplinary teams are essential for tool completion; and iv) continued testing and validation of emerging risk analysis tools for ENMs is a continued research need.

Keywords: Engineered nanomaterials, decision support, risk analysis, tool, validation

1. Introduction

Over the past 10-15 years, risk assessment for engineered nanomaterials (ENMs) has undergone several revisions and transformations, moving from attempts to apply traditional regulatory risk assessment frameworks towards new tools for ENM-specific risk analyses and decision support. This transition started after initial attempts to apply chemical-based risk assessment frameworks to ENMs were met with numerous challenges and obstacles noted by various authors[1-3]. Given the expected time and resources needed to adapt regulatory risk assessment frameworks for ENMs[4,5], it became clear that other risk-based approaches for risk analysis and decision support would be necessary to make informed decisions regarding ENM risks, particularly in the short-term[1, 6-10]. This need for alternative models and methods to assess risks of ENMs and formulate decisions regarding these risks is due to the extensive uncertainties and complexities related to understanding ENMs[11-13] and how they interact with biological and environmental systems[10, 14, 15]. Given the challenges to using traditional risk assessment frameworks for ENMs and the need for alternative approaches for ENM risk evaluations, suggestions are numerous and include risk-screening tools, preliminary risk evaluations, control banding, grouping and read-across approaches, decision support tools, and governance frameworks. Several of these have been reviewed in previous work[1, 16-18]. In addition, the European Commission recently published a comprehensive compilation of tools for ENM risk evaluations (i.e., NanoReg Toolbox), which include nano-specific risk assessment, safe-by-design, life cycle assessment, and cross screening and control banding[19]. To the best of the authors' knowledge, the NanoReg Toolbox represents the most comprehensive compilation of tools, methods, and approaches for ENM risk evaluations at this time.

While there now exists a suite of potential tools to evaluate ENM risks and make decisions regarding these risks (and benefits), these tools have yet to be thoroughly tested, validated, or applied to a common case study, which may be helpful for inter-tool comparisons. Furthermore, external users (i.e., users who were not involved in the tools' design or development) may likely run into different issues and obstacles compared to those faced by tool developers and innovators, including e.g., challenges related to simply learning how to use the tool, handling uncertainty and/or lack of data, and handling conflicting data. It is also still relatively unclear which tool(s) may be best suited for different users or for different case studies, since there are no established overarching guidance or recommendations developed thus far to recommend the most appropriate tool(s) for a given purpose.

This study addresses these challenges and tests a subset of emerging ENM risk screening tools using a case study focused on ENMs innovated for use in water treatment technologies. This work is part of a larger project aimed at developing and innovating ENMs for water treatment technologies through a collaboration between North Carolina State University (NC State) and RTI International located in the United States[20]. The results of this analysis will feed into material innovation processes used within the project, essentially providing risk screening information and decision support to researchers and engineers at early innovation stages to help ensure safe and sustainable ENM design. Sustainability in this project draws from the "triple bottom line" approach[21] that includes considerations of environmental, social, and techno-economic factors, and in this project these factors are related to ENMs and their use[22].

The ENMs selected for the case study include ENM candidates for use in water treatment technologies within the NC State-RTI collaborative project[20]. ENMs have the potential to address several aspects of sustainable water supplies, including but not limited to water quality and availability. For example, unique aspects of ENMs such as high specific surface area and enhanced reactivity can occur at the nanoscale, enabling a greater potential for adsorption and removal of target contaminants[23, 24]. Recognizing these opportunities, the US National Nanotechnology Initiative issued a multi-agency Nanotechnology Signature Initiative whitepaper highlighting possible nanoscale solutions to global-scale water challenges[25]. Concomitantly, potential environmental, health, and safety concerns regarding ENMs have led to the need for safe and sustainable innovation of the ENMs in this domain. As a first step, this analysis focused on the application of risk screening tools to a set of eight ENMs proposed for use in water treatment technologies. Subsequent stages of the project will incorporate of the results of this analysis into a larger decision support framework to help guide ENM selection decisions.

The objectives of this analysis are therefore to: 1) test a subset of risk screening tools proposed for ENMs selected in the case study; 2) evaluate each screening tool according to its intended purpose, scope, utility, functionalities, and generated output; 3) document the processes used to test the screening tools and identify key challenges and outcomes; and 4) highlight key lessons learned and potential best practices for stakeholders involved in developing and/or applying risk screening tools for ENMs. Finally, we discuss how the results of this work will be fed back into ENM innovation processes and cycles.

2. Experimental

2a Case study. The collaborative NC State-RTI project, entitled "Water Sustainability through Nanotechnology," began in early 2017 and is expected to be completed in early 2020. This project is a large, interdisciplinary seed research project that aims to develop ENMs for use in sustainable water treatment systems, focusing on nutrient and contaminant removal among other project objectives[20]. One task of the project aims to link ENM risk research scientists and decision support experts with materials developers early in the design phase to better support the development of safe and sustainable solutions. Throughout this task, material scientists, innovators, environmental engineers, and risk and decision support experts interact and communicate regularly. This communication helps ensure an iterative feedback cycle in the project between ENM developers and risk and decision experts. The work presented in this analysis documents the first step towards ensuring sustainability in the materials solutions developed by innovators in the GRIP project and focuses primarily on the environmental, health, and safety impacts of the selected ENMs. Subsequent stages of the project will incorporate societal and techno-economic factors in a decision-making process, following the "triple bottom line" approach, prior to ultimate selection of ENMs for use in water treatment systems. To apply the selected risk screening tools, a multidisciplinary team was formed and utilized through the data collection and application phases of the risk screening tools. The multidisciplinary team included experts within ENM risk analysis, decision support, ENM-specific risk screening tools, life cycle analysis, and material scientists.

While this case study is based on a "real world" scenario in which different ENMs are evaluated according to their suitability in sustainable water treatment systems for use within a larger project, a specific ENM-containing water treatment application has not yet been identified at this innovation stage. This is intentional and is a result of the focus on early Technology Readiness Levels (TRLs). Early TRLs in this domain involve the selection of the best performing ENMs or a subset of ENMs considering specific sustainability factors. In this analysis, it is assumed that the ENMs evaluated in this project will be used in a water treatment application that involves water flowing through ENMs in a closed container. It is not envisioned for consumer use at this stage. It is envisioned that later stages of the project (higher TRLs) would include the development of the water treatment application, during which additional reviews of the selected ENMs and other factors would be performed to promote sustainability within the project[20].

2b. Selected ENMs. Eight ENMs are selected for this analysis. These include the following materials with reported nanoparticle (NP) size from the commercial supplier: Al NP (60-80nm), Al_2O_3 NP (60nm), CuO NP (30-50nm), Fe_2O_3 NP (3nm), MnO_2 NP (50nm), MgO NP (100nm), TiO_2 anatase NP (15nm), and ZrO_2

NP (<100nm) (Table S-1 in Supplementary Information). These ENMs were initially selected by material scientists, developers, and environmental engineers as viable candidates for use in water treatment systems based on promising water treatment performance studies found in available literature. All NPs except for MnO_2 were purchased from chemical suppliers. MnO_2 NPs were grown on nanofibrous filter media by NC State researchers. Table S-1 in the Supplementary Information provides more details of the selected ENMs, including information on their specific surface area, volume/mass/quantity available, price, and supplier information.

2c. Risk screening tools. Three risk screening tools were selected for testing and application. These tools provided evaluations of potential environmental, health, and safety impacts of the selected ENMs for use in the case study. The selected risk screening tools include NanoRiskCat[26, 27], LICARA nanoSCAN[28-30], and NanoGrid[31, 32]. The tools were chosen based on their: i) intended scope and suitability for evaluating health, environmental, and safety impacts of the selected ENMs; ii) expected output in terms of guidance on potential impacts and risks of the selected ENMs; iii) documented applications to other case studies involving ENMs; and iv) availability of communication with tool developers to enable clarifications regarding proper intended use of the tools and their underlying assumptions. While this analysis focused on testing and applying these risk screening tools, other analyses that utilize different screening tools or frameworks could also be useful in subsequent work (e.g., Precautionary Matrix[33, 34], Nano Risk Framework[35], Green Screen for Safer Chemicals[36]). Furthermore, the approach and generated results presented in this analysis could be used as a foundation for future evaluations of other tools as well.

A step-by-step description of these tools is provided in subsequent sections along with Tables S-2 to S-4 in the Supplementary Information.

2d. Tool testing and analysis. After the selection of the eight ENMs and three risk screening tools, data and information were collected on each of the ENMs for use within the tools. This included information on ecological and health impacts, worker health and safety, potential release and exposure pathways, life cycle impacts, regulatory requirements, as well as physio-chemical parameters related to the ENMs. Data and information were obtained from peer-reviewed journal articles, reports, databases, and safety data sheets (SDS) available from the ENM suppliers. Data collection occurred independently by team members and results were later compared and coalesced to compile a data set for each material.

After the data were coalesced and compiled for each material, the same set of data and information for each ENM was used to complete the evaluations using the three risk screening frameworks. Additional data and information were occasionally added or supplemented when needed, as some of the data/information requirements differed between tools. For example, NanoRiskCat was the only tool that required information on the EU's Classification, Labelling, and Packaging (CLP) Regulation of the bulk form of the ENM (based on the widely-used Globally Harmonized System (GHS) of Classification and Labelling of Chemicals), LICARA nanoSCAN required detailed life cycle impact information (e.g., emissions of hazardous substances), and NanoGrid required Predicted Environmental Concentration (PEC)/ Predicted No Effect Concentration (PNEC) ratio data that were not required in the other tools.

Through the process of testing each risk screening tool, several questions and challenges arose. These included practical questions about the tools (e.g., required web browser for proper tool functionality, accessing the most current version of the tool) as well as questions related to guidance on best practices to use the tools (e.g., selecting data points in cases of conflicting data or studies, details regarding underlying calculations used in models). In cases when it was not clear how to proceed with a given portion of the tool, the developers of the tools were contacted to provide insight. None of the responses or feedback provided by the tool developers changed the results or outcomes of the analysis. Rather additional clarification or acknowledgement of the identified challenge or issue was provided by the tool developers in some instances (e.g., guidance on correct web address link for tool access or supporting information).

In the case of LICARA nanoSCAN, the questions on environmental, economic, and societal benefits of the ENM-enabled product (termed nanoproduct in LICARA nanoSCAN) are determined based on comparison against a conventional product or material that is larger than the nanoscale size range (i.e., micrometer size). In this analysis, activated granular carbon was chosen as the conventional product due to its use in similar applications as flow-through filter media. Also, the "Use phase" and "End-of-life" phase of LICARA nanoSCAN indicates that they are only for the final products and articles, while additional guidance specifies that answering these questions will help improve the quality of decision support. For this reason, these questions were answered drawing on expertise from life cycle experts on the team to enhance the realistic decision support output from the tool, albeit that the case study does not yet involve a completed product or application for water treatment. This was also done to more fully test the functionalities and utility of LICARA nanoSCAN as a screening level risk tool for the current case study.

After all the ENMs were assessed using each of the screening level tools, a compilation of all results according to each risk screening tool was developed to make comparisons between ENMs.

3. Results

3a. Description of risk screening tools. The following provides a brief overview of the risk screening tools selected and tested in this analysis. See also Tables S2-4 in the Supplementary Information for detailed step-by-step descriptions of the tools.

NanoRiskCat. NanoRiskCat is a first-tier risk screening and communication tool that focuses on exposure potentials for professional end-users, consumers, and the environment, as well as health and ecological hazards[26, 27] (see Table S-2 in Supplementary Information for details). Exposure potentials are primarily based on the location of the ENM in the end product using the Hansen et al.[37] categorization framework (e.g., ENM used on a structured surface, NPs suspended in liquids, NPs suspended in air, etc.) and the final end product or handling of the ENM. Evaluations of health and ecological hazards are based on a decision tree that includes decision nodes on regulatory classifications, acute toxicity data, as well as other toxicity/ecotoxicity endpoints. The user evaluates the exposure potentials and hazard evaluations for a given ENM-enabled product based on available data and information, such as e.g., ecotoxicity, toxicity assessments and environmental fate studies as well as a description of the ENM-enabled product.

For evaluating the exposure potential for the three sub-populations, the user indicates whether the exposure potential is expected to be high, medium, low, or unknown on a qualitative judgement basis following the Hansen et al.[37] framework. For the hazard evaluations, the user follows a decision tree provided in Hansen et al.[26, 27] that contains a series of questions or decision nodes that are associated with high, medium, low, or unknown hazard evaluation outcomes. The overall end result is the generation of five colored dots that correspond to exposure potential levels (for the three populations) and hazard evaluations (health, environmental). Each of the dots are colored, where red indicates a high exposure or hazard potential, yellow indicates medium exposure/hazard potential, green indicates low exposure/hazard potential, and grey indicates unknown exposure/hazard potential. The output is intended to assist in the overall communication regarding potential risks of an ENM-enabled product.

LICARA nanoSCAN. This web-based tool evaluates the benefits and risks of ENM-enabled products over life cycle stages (i.e., manufacturing, use, end-of-life)[28-30] (see Table S-3 in Supplementary Information for details). It was developed out of the European Framework 7 project "Life Cycle Assessment and Risk Assessment of Nanoproducts"[29]. To access the tool, the user first creates an account on the LICARA nanoSCAN site, located: https://diamonds.tno.nl/licara/index.php#/introduction. After logging in, the user is then able to start a new evaluation (termed "nanoSCAN") or review a saved evaluation.

The LICARA nanoSCAN tool includes six tabs (termed "Box" within the tool) that are divided into benefits (i.e., environmental (Box 1), economic (Box 2), social (Box 3)) and risks (i.e., public and environment (Box 4), occupational (Box 5), consumers (Box 6)) regarding the ENM-enabled product. Each Box has a list of questions and the user selects a response from a drop-down menu. In the case of the occupational risk tab (Box 5), users are directed to a separate web-based tool (Stoffenmanager Nano 1.0[38]). To access Stoffenmanager Nano, the user clicks on a link (located: https://nano.stoffenmanager.nl/), creates an account and logs in, starts a new evaluation (termed "risk assessment"), and selects the appropriate responses in a drop-down menu to questions categorized in six separate steps (1. General, 2. Product characteristics, 3. Handling/Process, 4. Working area, 5. Local controls measures and personal protective equipment, 6. Risk assessment). The output is a summary of calculated exposure-hazard-class and risk scores that are then fed back into Box 5 under the appropriate life cycle stage (i.e., manufacture, processing, application). Box 6 evaluates consumer health risks based on exposure potential using the Hansen et al.[37] framework. This Box is only relevant for consumer or consumer/professional products. After completing all six Boxes, a final decision support tab shows an overview of the benefits and risks of the ENM-enabled product and guides the user on proceeding with the ENM-enabled innovation or product in the form of a decision support matrix of benefits-risks. Options include "Go ahead," "Cancel/rethink," "Further research needed," "Other benefits required," and "Undecided." Error bars are included along with the final benefit-risk matrix to indicate any ambiguity or unknown responses. The user is also able to save the scenario and export results (i.e., PDF and text files), but exported results do not include the final decision matrix.

Throughout the tool, guidance is available in each tab that provides additional detail on the underlying questions, intended purpose, and scoring scheme. In total there are 88 possible questions, and 75 of them are mandatory to complete an evaluation. Questions within each Box are divided into different groups whereby each group is equally weighted to other groups in the same Box with regard to their impact on the final score; similarly, each question within each group is also equally weighted to the other questions in the same group. LICARA nanoSCAN compiles the results from the benefit evaluation Boxes (1-3) using a normalized scale from -1 (lowest possible benefit) to 1 (highest possible benefit). Scores of 0 indicate that a nanoproduct is "as good as" a conventional product for the benefit evaluations. Unanswered questions are given a score of -1 by default. In the risk evaluation Boxes (4-6), the results are represented in a normalized scale from 0 (lowest possible risk) to 1 (highest possible risk). Unanswered questions or "unknown" responses are given a score of 1 by default, using a worst-case principle. In the occupational and consumer health risk tabs (Box 5, 6), a scale from 1 to 8 is used whereby values 1-3 indicate "low" risk, 4-5 indicate "medium" risks, and values 6-8 indicate "high" risk.

These values are then normalized. If the total normalized risk score is $\geq$ 0.67, it is considered as a high risk level that is fed into the final evaluation. The final output assumes each benefit and risk evaluation is weighted equally.

NanoGRID. The Nano Guidance for Risk Informed Deployment (NanoGRID) tool is a Microsoft Excel application that uses a tiered approach to characterize the environmental, health, and safety impacts of an ENM-enabled product and provides guidance on additional testing approaches that may be needed[31, 32] (see Table S-4 in Supplementary Information for details). To access the tool, the user can download NanoGRID via the web after creating an account (located: https://nano.el.erdc.dren.mil/nanogrid_toolx.aspx). Once downloaded, a user can start a new evaluation (termed "profile") of a given ENM-enabled product. Throughout an evaluation, the user is guided through the tool via completing separate tabs or tiers, with a maximum of 5 tiers to complete. Using the tiered approach, the user is guided to a next tier only if a potential risk exists related to the ENM or ENM-enabled product. If no risk is likely, the evaluation does not continue.

Tier 1 focuses on basic information regarding the ENM and ENM-enabled product, including detailed information on the ENM, ENM definition, physico-chemical properties, and the location of the ENM in a product based on the Hansen et al.[37] framework. The user can then proceed to the next tier if the ENM adheres to ENM definitions, based on scientific literature, proposals by regulatory agencies or international organizations. In this step, references are provided in the margin of the tool as guidance. As long as the ENM of interest adheres to one or more of the provided definitions, then the user can proceed to Tier 2. Tier 2 focuses on release potential of the ENM from the ENM-enabled product. This is based on the release potential using Hansen et al.[37] (e.g., product class 3B, nanoparticle suspended in liquid matrix), ENM release scenarios (e.g., release of 100% of ENM from product), and hazard identification information including comparisons between a PEC and PNEC. At the completion of Tier 2, the user is advised on whether a potential risk or concern is present and whether fate testing is needed to better understand the release potential of the ENM. If there is potential for the ENM to be released or if the user would like to better characterize the environmental, health, and safety impacts of the ENM-enabled product, the user is directed to Tier 3. Tier 3 evaluates the environmental fate and persistence of ENMs in aqueous media. This tier includes an introduction tab that provides guidance to the user, and four evaluation tabs (Levels 1-4) provide a structured methodology to characterize and evaluate the environmental fate and persistence of ENMs in aqueous media. As noted in the tool, the outcomes from Tier 3 depend on the range and behavior of ENM concentrations tested. The authors note "it is possible that Tier 3 guidance will suggest that, at the higher concentration the assessment should proceed directly to Tier 4 and should focus on sediment hazard tests, whereas the lower concentration dispersion should be analyzed to determine particle size and size distribution, and settling and dissolution potentials." If the released ENMs are suspected to persistent in the environment, then the user advances to Tier 4 which evaluates the environmental health and/or human health hazards of the ENMs. This tier guides the user towards various environmental hazard and human health hazard tests to be conducted based on various guidelines generated from international bodies and the scientific community (e.g. The Organisation for Economic Co-operation and Development (OECD), International Organization for Standardization (ISO), US Environmental Protection Agency (EPA)). This includes acute toxicity, chronic toxicity, and elutriate assessments as well as a flow chart for human health exposure scenarios and toxicity bioassays. Finally, Tier 5 aims to provide an in-depth product investigation, although this final tier is not yet functional in the current version of the tool. Tiers 2, 3, 4, and 5 all require experimental work to be completed if there are no screening values already available.

The final output from NanoGRID includes a PDF file that provides an overview of the evaluation according to each tier and guidance towards testing that may be needed related to the selected ENM. Throughout the tool, the user can save the evaluation (profile) and generate a report. In addition, there is detailed guidance available in each tab that provides the user with additional details to the underlying questions and associated rationale to complete an evaluation.

3b. Tool testing and generated results. The eight selected ENMs were analyzed by each of the risk screening tools. The results of applying NanoRiskCat to the selected ENMs are shown in Table 1. Additional details, justifications for the resulting risk profiles and associated references are provided in Table S-5 in the Supplementary Information.

All the selected ENMs are associated with high potentials in at least one of the exposure or hazard evaluations following the guidelines and decision trees in the NanoRiskCat methodology. All the ENMs except MnO_2 NP have high exposure potentials for the professional end-users given that they are loose (unbound) NPs and their intended use in a water treatment application. The ENMs were purchased from a supplier and handled by end-users (researchers) in laboratory settings with the use of a fume hood. In the case of MnO_2, there is a medium exposure profile for professional end-users since the ENMs are grown on nanofibrous filter media and there could potentially be release of the ENMs from the fibers given the state of the ENM on the fibers and no release studies have yet been performed. All ENMs were considered to have a medium level of exposure potential for consumers and the environment given the loose (unbound) state of the NPs, their intended use in a water treatment application, and that it is possible that ENMs may be released from the envisioned application. For human health evaluations, all of the ENMs except ZrO_2 and Al were considered to have a high hazard potential in light of data and information in the literature that triggered a high risk profile designation (e.g., suspected human carcinogen for inhalation, serious eye damage, cytotoxicity and DNA damage, etc.; see Table S-5 for details). ZrO_2 and Al triggered medium hazard potential designations in light of available studies (Table S-5). For ecological hazard evaluations, all ENMs - except ZrO_2 which triggered a low risk profile- triggered high hazard potentials due to data and information in the literature (e.g., LC50 values < 10mg/L, Bulk form of material with Level A CLP classification) (Table S-5). Across all NanoRiskCat results for the eight ENMs, ZrO_2 had the lowest overall risk profile followed by Al and MnO_2. The remaining five ENMs (Al_2O_3, CuO, Fe_2O_3, MgO, and TiO_2) all had similar risk profiles that could not be distinguished from each other using this methodology.

Table 1. Results from NanoRiskCat applied to ENMs in case study according to exposure and health/ ecological hazard potentials (red = high potential; yellow = medium; green = low); NP = nanoparticle

	Exposure Potential			**Hazard Evaluation**	
ENM (NP)	**Professional End-User**	**Consumers**	**Environment**	**Health**	**Ecological**
Al	🔴	🟡	🟡	🟡	🔴
Al_2O_3	🔴	🟡	🟡	🔴	🔴
CuO	🔴	🟡	🟡	🔴	🔴
Fe_2O_3	🔴	🟡	🟡	🔴	🔴
MgO	🔴	🟡	🟡	🔴	🔴
MnO_2	🟡	🟡	🟡	🔴	🔴
TiO_2	🔴	🟡	🟡	🔴	🔴
ZrO_2	🔴	🟡	🟡	🟡	🟢

The results of applying LICARA nanoSCAN to the selected ENMs are shown in Figure 1. Additional details, justifications for the resulting risk profiles and associated references are provided in Table S-6 and Table S-7 in the Supplementary Information. Applying the LICARA nanoSCAN methodology regarding the potential benefits and risks of the ENMs in the ENM-enabled product (early innovation stage, hypothetical water treatment application), all the selected ENMs fall within or close to the "Other benefits required" or "Undecided" categories in LICARA nanoSCAN's final decision support matrix profile (i.e., in the lower left quadrant of the matrix). TiO_2 was the worst performing material, with a decision matrix closer to the "Cancel/rethink" category, and none of the ENMs fell within the "Go ahead" decision category. All other materials have a benefit-risk profile that falls close to "Other benefits required" and "Undecided," with minor differences observed. For example, ZrO_2 has a smaller uncertainty bar and falls in the "Other benefits required" category, and MnO_2 has slightly more benefits than the other materials and is moved towards the "Go ahead" area of the profile although it is situated between "Other benefits required" and "Undecided." This result is partially driven by the fact that without an actual ENM product to evaluate, it is not possible to meaningfully evaluate the potential benefits in the use and end-of-life phases of the product compared to an equivalent activated carbon-based product. Existing life-cycle data on ENMs is limited, but studies have generally shown that manufacturing phases are more energy- and emissions-intensive in ENMs than their conventional counterparts[39].

As discussed above, Box 5 of LICARA nanoSCAN directs the user to Stoffenmanager Nano 1.0, which involves answering additional sets of questions regarding occupational risks (details are shown in Table S-7). Six out of the eight ENMs had similar risk assessment profiles using Stoffenmanager (Hazard class B, Exposure class 1, Risk score III). The resulting risk assessment profile of MnO_2 was slightly worse, with a Hazard class C, Exposure class 1, and Risk score III, and TiO_2 NP had the worst risk assessment profile of Hazard class D, Exposure class 1, and Risk score III. It should be noted that Box 6 was not evaluated for consumer risks since the case study involves an ENM-enabled product for professional use only (Table S-6). All eight ENMs had similar decision matrix profiles that could not be easily distinguished from each other using this methodology (see Figure 1).

[Insert Figure 1 here]

Figure 1. Results from LICARA nanoSCAN applied to ENMs in case study.

The results of applying NanoGRID to the selected ENMs are shown in Figure 2. Additional details, justifications for the resulting risk profiles and associated references are provided in Tables S-8 and S-9 in the Supplementary Information. Tier 1 and Tier 2 assessments were completed for all selected ENMs. The output from Tier 1 show that all ENMs adhere to a regulatory definition for engineered nanomaterials, as expected, following definitions from European Commission[40], US EPA[41] and other references (i.e., Kreyling et al.[42]) used as guidance in NanoGRID. It was recommended to continue to Tier 2 to test the ENMs for potential release from the ENM-enabled product.

Results from Tier 2 for all ENMs indicate potential environmental, health, and safety risks could not be dismissed or neglected and therefore further assessments of the environmental fate and stability should be performed in Tier 3. This recommendation was based on Tier 2 results that showed PEC/PNEC ratios were > 1 for ENMs that had published PEC values from the literature (Al_2O_3, Fe_2O_3, TiO_2) (Table S-8) or conservative assumptions using the NanoGRID methodology. While PNEC values were available for all ENMs using literature values (Table S-8), PEC values were not available for five of the eight ENMs (Al, MnO_2, CuO, MgO, ZrO_2). In these cases, the NanoGRID methodology takes a conservative approach and estimates that PEC/PNEC > 1 for these ENMs using a worst-case scenario. If these PEC values become available, NanoGRID evaluations may be updated with this new information.

After evaluating if there is a potential risk based on PEC/PNEC ratios, NanoGRID then evaluates a potential for release from the ENM-based product. This release potential is based on Hansen et al.[37]. All the evaluated ENMs were assumed to have 100% release from the water treatment application (not yet developed at this early innovation stage). This is due to the categorization of the ENMs as either category IIIB (NP suspended in liquids) for all ENMs except for MnO_2 which is categorized as IIIA (surface bound NP) and the intended product which envisions the incorporation of loose (unbound) NPs. For the selected ENMs in category IIIB, NanoGRID assumes that there is potential for 100% of the ENMs to be released from the product and therefore there is no need to perform a laboratory release test. For MnO_2 NP (category IIIA), the potential for release is mainly related to aqueous- and corrosion-related releases (Table S-9). Potential release from aging processes were also scored highly for MnO_2, although aging is not well-defined in NanoGRID and it is not related to any specific release tests. For this reason, release tests using different aging times has been recommended in NanoGRID before proceeding with the MnO_2 NP evaluation. Subsequent sections discuss the selection of ENM release tests further using the NanoGRID methodology. For the other ENMs, given the potential for 100% of the ENMs to be released from the product and the PEC/PNEC values were estimated to be > 1, NanoGRID therefore concludes that a potential risk may be present, and the user should proceed to Tier 3 which focuses on environmental persistency. Tiers 3 and 4 evaluations were not yet possible, however, given the early innovation stage of this case study and Tier 5 is not yet functional in NanoGRID. These subsequent Tiers may be completed once a final water treatment application that uses ENMs is designed or developed for use and a revised version of NanoGRID is available.

[Insert Figure 2 here]

Figure 2. Results from NanoGRID applied to ENMs in case study.

3c. Tool evaluation. Each of the risk screening level tools generated different final results, as expected and as described in the previous section. NanoRiskCat produces five color-coded dots that characterize a level of exposure and health impacts for an ENM-enabled product, LICARA nanoSCAN produces a benefit-risk matrix with decision support recommendations for an ENM-enabled product, and NanoGRID provides a final compilation of the risk screening framework (and guidance on subsequent testing if the user proceeds to additional Tiers). See Table 2 for a comparative overview of the risk screening tools.

For this case study that focuses on the selection and use of ENMs in water treatment technologies, the application of these three risk screening tools helped characterize the overall environmental, health, and safety profiles of the selected ENMs that can be incorporated into a larger decision-making framework to help aid in the selection of sustainable ENMs. To this end, NanoRiskCat was found to be most useful for providing a relatively straight-forward visual aid to characterize the potential exposure and hazard impact profiles of each material. These results can be easily communicated to various stakeholders and users. LICARA nanoSCAN was found to be most useful for providing overall guidance on whether the ENM-enabled product is “worthwhile” to pursue compared to using a conventional based material that is larger than nanoscale (i.e., activated carbon). LICARA nanoSCAN was also very practical in having a web-based tool with final output that could be exported. NanoGRID was found to be most useful for compiling and characterizing data on potential exposure and hazard data and could provide detailed guidance for subsequent laboratory-based testing in future analyses once the final water treatment application is designed.

Table 2. Comparative overview of the selected risk screening tools used in case study. NRC=NanoRiskCat; LNS=LICARA nanoSCAN; NG=NanoGRID; NM = engineered nanomaterial; NP = nanoparticle

Risk Tool	Objectives	Output	Advantages	Limitations	Additional Comments	References
NRC	• First-tier assessment and communication tool for exposure, health, and environmental effects of ENMs	• Five color-coded dots that represent high, medium, low, and unknown risk levels	• Relatively straight-forward, easy-to-use • Incorporates uncertainty, (via precautionary approach) • Results easily communicated	• Tends towards conservative, precautionary results • Challenges to handling divergent data points or data sources • Potential for different users to produce different outcomes (reproducibility issues) • Not a user-friendly tool or format; user should carefully document decisions and references in own format	• In this analysis, NRC allowed for most differentiation between ENMs, primarily based on hazard evaluations • Questions or comments were directed to the developers (Hansen, S.F. and colleagues), including e.g. questions on handling divergent data points or information on environmental persistency of ENMs	26, 27
LNS	• Web-based tool to assess benefits and risks of ENM-enabled product over life cycle	• Decision support matrix comparing benefits-risks • Guidance on proceeding with ENM-enabled innovation • Output as PDF file, text file, and Word document from Stoffenmanager[38]	• Easy-to-use, web-based tool that the user “clicks” through and reaches final decision matrices • Detailed questions over life cycle • Incorporates uncertainty (via precautionary approach) • Provides final decision support on ENM-enabled innovation • Guidance available in	• Requires life cycle stage data/info that may not be available to all users • Best suited for multidisciplinary team of experts, that may not be available to all users • Can be very time-consuming (> 1-4 hrs) • Closer investigations on underlying scoring methodology	• In this analysis, the LNS developers were contacted for guidance and response to various questions and issues encountered. • Responses were helpful but did not end up changing any of the results of this analysis	28-30

Risk Tool	Objectives	Output	Advantages	Limitations	Additional Comments	References
			tool • Exportable output	recommended • May periodically delete users' saved evaluations without notification		
NG	• Microsoft Excel based, tiered framework to characterize environmental, health, and safety impacts of ENM-enabled products • Guidance on subsequent laboratory-based testing	• Generated PDF file that provides overview of tiered evaluation and guidance towards testing	• Somewhat easy-to-use spreadsheet tool that the user "clicks" through • Detailed risk evaluation • Incorporates uncertainty (via precautionary approach, use of safety factors) • Detailed guidance available in tool • Exportable output	• Best suited for multidisciplinary team of experts, that may not be available to all users • Best suited for users with testing capabilities • Challenging to have access to all possible questions in tool without conducting full analysis • Tier 2 risk decision based on PEC/PNEC ratios, but no guidance to assess PEC values if not available in literature • Guidance information available in various documents • Tiers 4 and 5 still under development	• In this analysis, the NG developers were contacted for guidance and response to various questions and issues encountered, including e.g. website issues, location of guidance documents, Tier 2 and 3 data requirements. • Responses were helpful to understand how to successfully complete NG evaluations for select ENMs	31, 32, 50

Across the three tools, the results from NanoRiskCat allowed for more differentiation between the ENMs compared to LICARA nanoSCAN and NanoGRID. Out of the eight selected ENMs, three ENMs were shown to have either slightly better performance regarding potential health and ecological impacts or exposures compared to the other ENMs (i.e., ZrO_2, Al, MnO_2) (Figure 1). The results from LICARA nanoSCAN showed similar decision profiles for the selected ENMs across the benefit-risk matrices (Figure 2), and therefore the "least" or "most" risky ENMs were not easily distinguished using this methodology. This is partially because in early-phase research (before the application is designed and developed), the results differed only in the selection of the incorporated ENM, some with similar exposure and hazard profiles. Additionally, the benefit questions and scoring in LICARA nanoSCAN are all based on a comparison to a conventional product with particles larger than the nanoscale (e.g. activated carbon), and therefore the ability to compare across ENMs is limited. For example, the environmental benefits for each of the ENMs could be significantly different, but if they were all better or worse than activated carbon, then the final scoring would show very few differences among them. The NanoGRID methodology also did not allow for clear distinctions between the ENMs using output from PEC/PNEC ratios in Tier 2, primarily due to a lack of PEC data on five out of eight of the ENMs. However, the ENMs could be ranked according to their PNEC values, if deemed useful, since this tool essentially helps compile this information based on literature sources (i.e., TiO_2< Al< MnO_2< CuO< ZrO_2< Al_2O_3< MgO < Fe_2O_3) (see Table S-8 for details). In addition, the use of NanoGRID seems to be best suited for ENM-enabled products and applications that are in more mature innovation stages than the present case study in which the ENMs are essentially being vetted for use in subsequent steps.

Throughout the application and testing phases using the risk screening level tools, several key challenges arose. These ranged from minor inconveniences in correctly completing the evaluations to more complex, theoretical issues within each risk screening tool. In the case of NanoRiskCat, one of the main practical challenges is that there is no user-friendly tool or software package as in the case of LICARA nanoSCAN or NanoGRID. Rather, the user follows Hansen et al.[26, 27] as guidance throughout the evaluation process. For this reason, the user needs to document all decisions and associated references in their own documentation and supporting files, which could differ between users and applications of the tool. For example, there may be instances when a complete evaluation may be revised in light of new or revised data or if multiple users wish to complete an evaluation using the same data set and compare findings. Another main challenge to NanoRiskCat is that it is possible that different users may produce different results depending on their handling of existing data points, diverging findings between studies, or in some cases the use of judgment in following the tool. For example, in the case of evaluating the human health impact of ZrO_2 NPs, there were conflicting findings between published studies, since some studies found no or low toxicity[43, 44] while other studies documented some potential for neuronal developmental toxicity, behavioral changes, impacts on reproduction, and cytotoxicity and genotoxicity[45-47] and bulk ZrO_2 may cause irritation (eyes, skin, ingestion, inhalation)[48]. In this analysis, these findings led to a medium (yellow) human health hazard evaluation (Table S-5), although other users could potentially produce other hazard results depending on the data used to trigger the resulting hazard profile for this material.

The application of LICARA nanoSCAN also involved challenges that ranged from minor questions and issues such as using the on-line tool to more fundamental questions concerning the underlying scoring methodology and overall utility of the tool. One of the most significant challenges experienced is that the developers indicate that the tool can be used with little data and applied in approximately 1-4 hours[30]. However, based on our experience, the completion of a profile in LICARA nanoSCAN requires the involvement of a multidisciplinary research team-with experts in ENMs, regulation, market/economics, life cycle concepts, ENM-specific hazard and exposure information-to answer all questions in a meaningful way (i.e., 88 possible questions, 75 of these are mandatory for tool completion). It seems likely that this will involve substantially more than the original 1 to 4 hour estimate for many users. For example, answering the 20 questions in Box 1 (Environmental Benefits) could easily take 1-2 working days if the user attempts to search for data on each of the questions for both the ENM in question and the conventional alternative, especially given the limited life cycle data related to ENMs[39]. In fact, it seems as if the results from a Life Cycle Assessment (LCA) would ideally be needed to complete the Box 1 questions in LICARA nanoSCAN, and if so, then feeding the LCA results back into the tool does not appear to be an optimal use of time for ENM-decision support overall, especially for a screening-level evaluation. Our analysis took substantially more than 4 hours to complete, even with guidance from experts. Access to a multidisciplinary team also may not be possible to all stakeholders or users. While it is possible to answer "unknown" to many questions in the tool, this may also sway the results of the evaluation (e.g., "unknown" is scored equal to "worse" in some cases), and therefore more information will lead to more meaningful results.

Furthermore, there seem to be a few issues that could benefit from further investigation regarding the underlying scoring methodology in LICARA nanoSCAN. First, each Box is equally weighted to the other Boxes, even though some Boxes have more questions than others (i.e., Box 3 has three questions compared to nine questions in Box 4) (Table S-3). This means that a single question in one Box (i.e., Box 3) would have greater overall weight than a question in another Box (i.e., Box 4) in the final decision profile. Further, we also investigated the scoring methodology to explore how different hypothetical scenarios that use different maximum and minimum benefit-risk profiles compare in the final decision profile after changing different input parameters. This type of "sensitivity analysis" revealed some unexpected findings, including counterintuitive results in the final benefit-risk matrices in scenarios that had i) minimum benefits and maximum risks and ii) minimum benefits and minimum risks. In the former scenario, the benefit-risk profile resulted in "Further research needed" rather than a "Cancel/rethink" conclusion, and the latter scenario resulted in "Go ahead" rather than "Other benefits required(results not shown here, but communicated with the tool developers). Meanwhile, on the practical side of the analysis, several of the saved nanoSCANs were periodically deleted from the on-line site without any prior notifications or messages. In these cases, the deleted nanoSCANs were recreated afterwards, and all generated output including text files that could be re-uploaded and screenshots of the results were saved, although it can easily be imagined that some users could lose their saved evaluations without notification. There were also website issues with the site at one time during the evaluation, in which all saved nanoSCANs were not accessible through one web browser (i.e., Internet Explorer) and had to be recreated in another web browser (i.e., Google Chrome).

Similar to the experiences of using other risk screening tools for ENMs, the most significant challenge to using NanoGRID was the time, resources, and reliance on a multidisciplinary team to complete an evaluation. In fact, NanoGRID was considered to be the most detailed and complex of all three screening tools tested. When starting an evaluation, it was difficult to have an overview of all possible questions or to be able to count, list, and/or compile all questions in the tool since the user must complete some questions in a Tier before subsequent questions are available or shown to the user, and some questions are dependent upon past selection (Table S-4). In other words, there are different "paths" the user can take within NanoGRID, depending on the responses to each question and therefore getting an entire overview of the number and breadth of underlying questions was challenging. Another challenge experienced with NanoGRID is that it seems better suited for stakeholders with access to ENM-specific testing capabilities, either in-house or through collaborations. While this case study could include subsequent testing through the NC State-RTI project (e.g., ENM-release from the developed water treatment device(s), ENM-exposure testing in workplace settings), it may not be reasonable to assume that these resources will be available, especially for a screening-level analysis. It should be noted that some of the NanoGRID developers offered to provide testing or share their existing data for our analysis, which was helpful but may not be possible for every potential user. A third main challenge experienced with NanoGRID is that the risk evaluation decisions are heavily weighted on PEC/PNEC ratios, and therefore the final results could be shifted depending on which values are selected and included from the literature. This is similar to the issues described above with NanoRiskCat, whereby the final outcome could be heavily dependent upon which data points or results from the literature the user selects for inclusion. Also, specific guidance on the use of NanoGRID is somewhat divided across several different documents and files, including the NanoGRID tool (as instructions and help text[32]), and on-line documentation[49, 50]. This resulted in a less streamlined process of applying and testing the tool compared to having a more user-friendly format with compiled guidance for the tool's completion. Finally, if a final ENM-enabled product was defined, Tiers 4 and 5 are still under development in the tool and therefore unable to be further evaluated.

4. Discussion

To the best of the authors' knowledge, this analysis is the first published study that tests a subset of newly emerged risk screening tools for ENMs using a common case study. Three risk screening tools were evaluated using eight ENMs that are being vetted for use in a project focused on sustainable water treatment solutions[20]. The main findings in this work show the output from applying each of the risk screening tools along with key limitations and outcomes. One key insight from this work is that the risk screening tools can be used together in a complementary, or even sequential, way to aid decision-making involving ENMs in a case study. In other words, the main advantages and utility of each of the tools can be coalesced with the complementary use of the other tools for decision support. For example, NanoRiskCat can provide a visual aid to characterize ENM potential exposure and health impact profiles, LICARA nanoSCAN provides overall guidance on proceeding with the ENM-enabled product, and NanoGRID helps compile and characterize data on potential exposure and hazard data and provides guidance on specific laboratory-based testing.

In subsequent stages of the project, a decision support framework will be developed to help guide ENM selection and research prioritization and other risk management decisions. The decision support framework will incorporate these findings on the environmental, health, and safety impacts of ENMs along with additional parameters such as ENM performance (e.g., technical viability, performance, scale-up), cost (e.g., material costs, profitability), as well as social and ethical concerns (e.g., public perceptions and concerns). One option to factor in multiple decision criteria in a larger decision support process is to use decision support tools such as Multi-Criteria Decision Analysis (MCDA) and Value of Information (VoI). For example, Linkov et al.[51] suggest the use of MCDA and VoI to help maximize the utility of both qualitative and quantitative information, prioritize future research needs for a given decision context, and aid in the identification of the best performing ENMs and/or ENM-related factors under conditions of high uncertainty. Interestingly, NanoGRID also includes a type of MCDA component in Tier 2's ENM release tab, whereby the user can select various ENM release parameters of interest and the MCDA tool to help select the best test or sets of tests based on the user's unique needs.

Throughout this analysis, several key lessons learned and potential best practices for stakeholders involved in applying risk screening tools for ENMs were identified. First, this analysis focused on the application of three risk screening tools, although there could also be other risk screening tools potentially suitable for the NC State-RTI project, such as e.g., Green Screen for Safer Chemicals[36] for screening level hazard evaluations. As mentioned earlier, there are no established overarching guidance or recommendations developed thus far to recommend the most appropriate tool(s) for a given purpose. Therefore, while this analysis could be expanded upon or used as a foundation for future evaluations of other tools, it would be helpful for stakeholders to have more formal guidance, recommendations, and/or instructions for which risk analysis or risk screening tool or set of tools would be most applicable or helpful for a certain case study. Some research initiatives are currently testing and vetting different risk analysis tools for ENMs and formulating recommendations for different stakeholders, such as the European H2020 project, caLIBRAte[52], although these guidelines are not finalized or made available as of the time of this analysis. In addition, efforts are also underway in caLIBRAte to coalesce different tools for ENM risk screening to enhance user accessibility through the development of a "systems of systems" approach.

It should also be mentioned here that each of the screening tools evaluated in this analysis uses the Hansen et al. (2008)[37] framework to evaluate exposure potential, primarily based on the location of the ENM in a product. We recognize that there are potential limitations to this approach, such as the omission of ENM concentrations which would inform exposure evaluations for consumers, professional end-users, and ecological recipients. More sophisticated tools and approaches to assess environmental exposures have recently become available and could be included in the further development of risk screening tools, including e.g. dynamic probabilistic material flow[53] models, MendNano[54], SimpleBox4nano[55], and nanoFate[56].

Second, risk managers and other users of these risk screening tools should be clear about the selection of the underlying data and their potential impacts on the final results. As noted above, there is little guidance provided in the risk screening tools on best practices for choosing data points when there are conflicting or divergent data points from different studies or within a database. In the selected risk screening tools, the tools often had precautionary or worst-case scenario-based approaches, whereby the most precautionary data point or value would trigger more serious risk outcomes or indicators from the tools. This is logical given the application of worst-case scenarios or the use of precautionary approaches under conditions of extensive uncertainties for emerging technologies and ENMs[6, 57]. The main point here is that users of the tools should be aware of these decisions and potential impacts when applying risk screening tools with diverging data points. It is recognized that other approaches have been proposed to help ensure the quality of ENM ecotoxicity and toxicity peer-reviewed publications (e.g., NanoCRED[58], DaNa 2.0 frameworks[59]), however these are not suggested, incorporated, or required by these risk screening tools for completion and entail additional investments of time and resources to understand, apply, and interpret the results.

Third, it was also very valuable to be able to contact and receive feedback from the tool authors or developers to ask questions on various details and aspects related to the tools. Not only did it help clarify some questions and issues the project team had in applying the tools, but it also confirmed that the tools were used and applied appropriately, and the final results were correctly interpreted.

Fourth, it became apparent throughout the tool testing and analysis stage that a multidisciplinary team was needed to properly complete the ENM evaluations. This was due to the breadth and depth of the questions within the tools, such as ecological and health impacts, worker health and safety, potential release and exposure pathways, life cycle impacts, regulatory requirements, as well as physio-chemical parameters related to the ENMs. Other stakeholders or users of these tools will likely need a multidisciplinary team or access to experts in these various fields to complete the evaluations. The breadth and depth of the questions within the tools also highlights the often time-consuming nature of completing risk screening evaluations (including the collection of supporting data and information); where the tools must strike a balance between being straight-forward and easy to use while at the same time providing meaningful results.

Finally, it is clear that the field of ENM risk analysis has matured significantly in the past decade, with the movement from traditional, chemical-based risk assessment to more ENM-specific risk analyses and decision support tools. Moreover, many of the risk screening tools that have emerged for ENMs could also be useful for risk governance as well as risk evaluations, as highlighted by others[60-62]. The next step is therefore to test and validate these emerging risk analysis tools for ENMs or ENM-enabled products and help identify those best suited for different stakeholders or different decision contexts.

5. Conclusion

While there is a suite of new, emerging tools to evaluate ENM risks and make decisions regarding these risks (and benefits), there has not yet been thorough testing of these tools using a common case study. This study therefore tested a subset of emerging tools for ENM risk analysis using a case study focused on ENMs designed for water treatment technologies. Results will be fed back to material innovators in the project at subsequent stages, essentially providing risk screening information and decision support to ENM researchers and engineers at early innovation stages to help ensure safe and sustainable ENM design.

In this analysis, eight selected ENMs were evaluating with three separate risk screening tools (NanoRiskCat, LICARA nanoSCAN, NanoGRID). Results from applying NanoRiskCat showed that ZrO_2 NPs have the lowest overall risk profile, followed by Al and MnO_2 NPs. Results from LICARA nanoSCAN showed all the selected ENMs fall within or close to the “Other benefits required” or “Undecided” categories in the final decision matrix profiles, and the ENMs were not easily distinguished from each other using this methodology. Results from NanoGRID showed that all ENMs should proceed to Tier 3 testing for environmental fate evaluations, and release testing should be performed for MnO_2 NPs. Across the risk screening tools, NanoRiskCat was found to be most useful for providing a relatively straight-forward visual aid to characterize the potential exposure and health impact profiles of each material. LICARA nanoSCAN was found to be most useful for providing overall guidance on whether the ENM-enabled product is “worthwhile” to pursue compared to using conventional materials (i.e., activated carbon). NanoGRID was found to be most useful for compiling and characterizing data on potential exposure and hazard data and could provide detailed guidance for subsequent laboratory-based testing in future analyses once the final water treatment application is identified. At the same time, several key challenges arose throughout the application and testing phases using the risk screening tools. These ranged from minor inconveniences to correctly completing the evaluations to more complex, foundational issues within each risk screening tool.

Key lessons learned and potential best practices gleaned from this analysis include: i) the risk screening tools could be used together in a complementary manner to aid in decision support regarding the ENMs; ii) risk managers and other users of risk screening tools should be clear about the selection of the underlying data and their potential impacts on the final results, iii) multidisciplinary teams are essential to properly complete evaluations using these tools, due to the breadth and depth of the questions including ecological and health impacts, worker health and safety, potential release and exposure pathways, life cycle impacts, regulatory requirements, as well as physio-chemical parameters related to the ENMs; and iv) there is a sustained need for continued testing and validation of emerging risk analysis tools for ENMs and the identification of those best suited for different stakeholders or different decision contexts.

Conflicts of interest

It is recognized that one of the coauthors of this analysis, Steffen Foss Hansen, is also one of the developers of NanoRiskCat[26, 27]. However, the work presented in this paper aims to provide an objective application and review of the NanoRiskCat methodology through the utilization and reliance on the other authors in this paper which have no previous connections or review of this tool.

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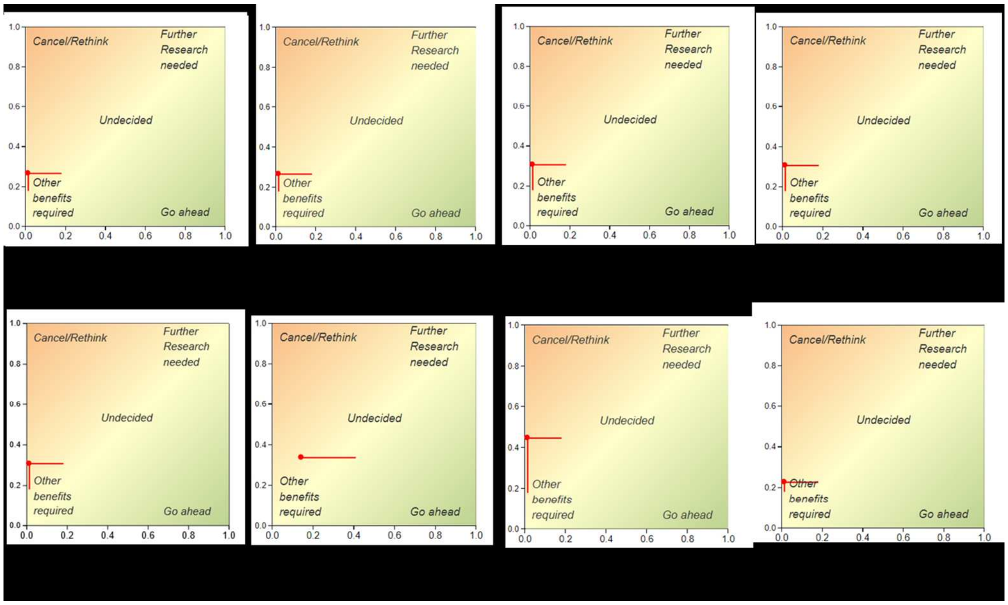


Results from LICARA nanoSCAN applied to ENMs in case study.

248x148mm (150 x 150 DPI)

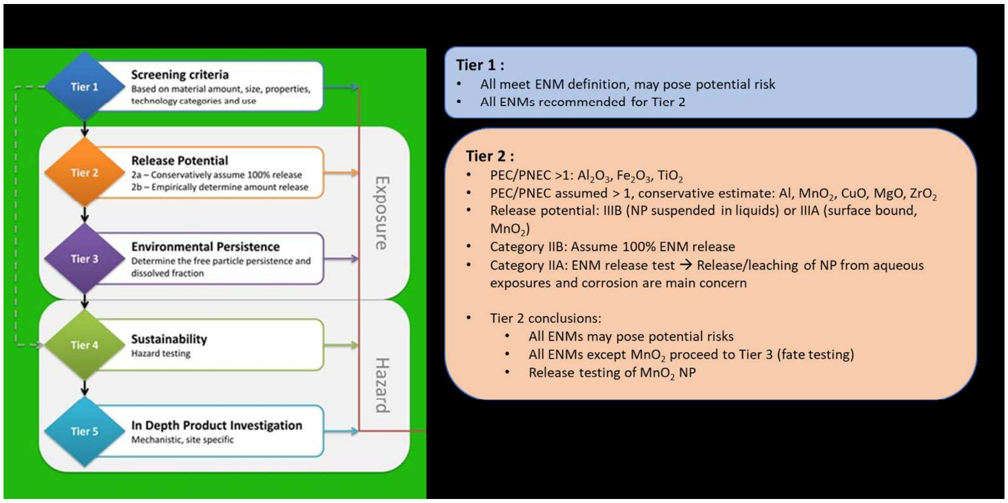
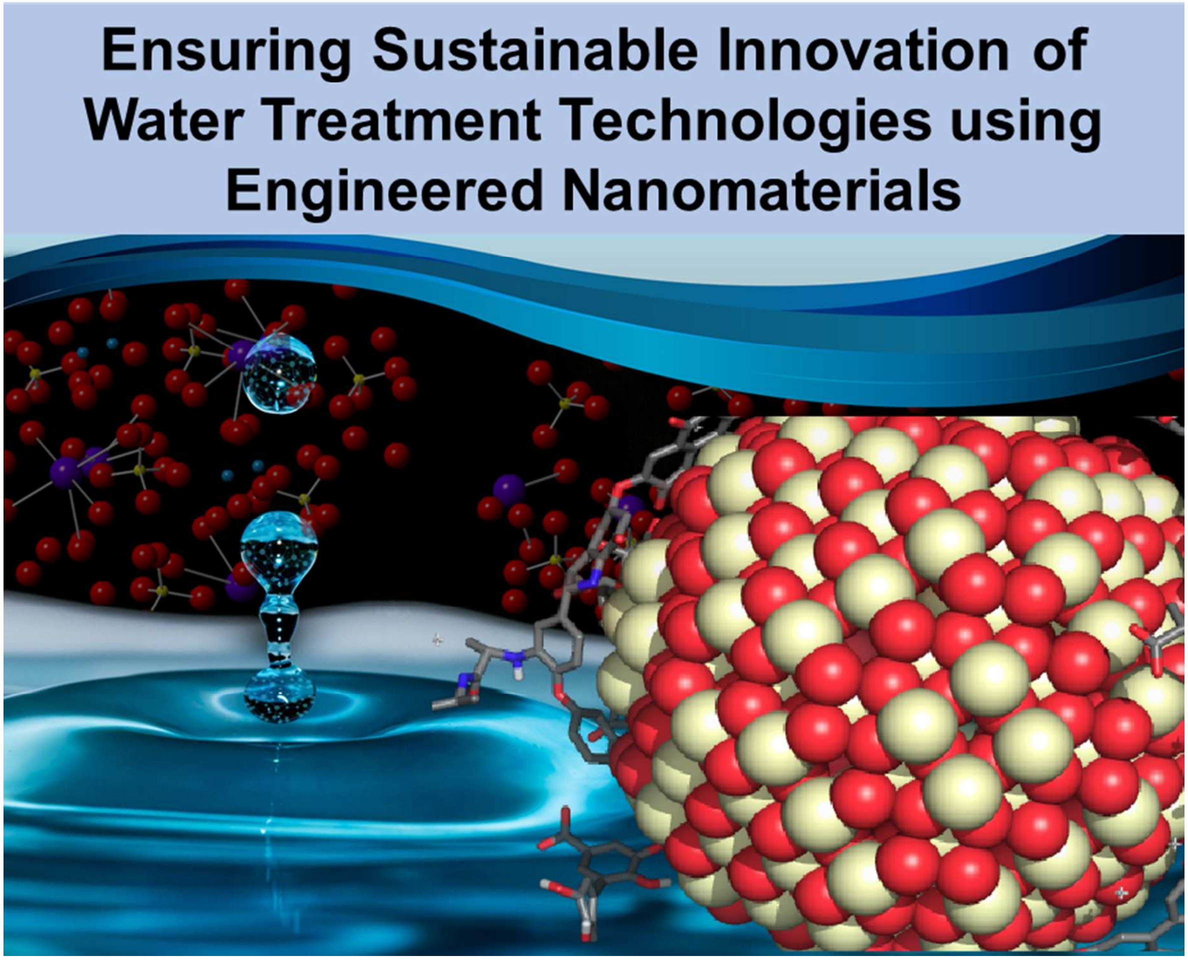


Figure 2. Results from NanoGRID applied to ENMs in case study.

329x163mm (150 x 150 DPI)



This study is applies and tests new risk screening tools for engineered nanomaterials and highlights key findings.