TRAAC framework for regulatory acceptance and wider usability of tools and methods for safe innovation and sustainability of manufactured nanomaterials

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Abstract

There has been an unprecedented use of advanced materials, particularly manufactured nanomaterials, in industrial applications and consumer products across several sectors in the last two decades. It has instigated concerns about the sustainability, in particular, risks and uncertainties regarding the interactions of the manufactured nanomaterials with humans and the environment. Consequently, significant resources in Europe and beyond have been invested into the development of tools and methods to support risk mitigation and risk management, and thus facilitate the research and innovation process of the manufactured nanomaterials. The level of risk analysis is increasing, including assessment of socio-economic impacts, and sustainability aspects, moving from a conventional risk-based approach to a wider safety-and-sustainability-by-design perspective. Despite these efforts on tools and methods development, the level of awareness and use of the majority of such tools and methods by stakeholders is limited. Issues of user-friendliness, trust, implementation training, regulatory or authority compliance needs, regulatory acceptance and unsuitability to the users' needs are some of the factors which have been traditionally known to hinder their widespread use. Therefore, a framework is presented to quantify the readiness of different tools and methods towards their wider regulatory acceptance and downstream use by different stakeholders. The framework diagnoses barriers which hinder regulatory acceptance and wider usability of a tool/method based on their Transparency, Reliability, Accessibility, Applicability and Completeness (TRAAC framework). Each TRAAC pillar consists of criteria which help in evaluating the overall quality of the tools and methods for their (i) compatibility with regulatory frameworks and, (ii) usefulness and usability for end-users, through a calculated TRAAC score based on the assessment. Fourteen tools and methods were assessed using the TRAAC framework as proof-of-concept. The results provide insights into any gaps, opportunities, and challenges in the context of each of the 5 pillars of the TRAAC framework.

1. Introduction

In the last two decades, a considerable rise of interest in manufactured nanomaterials (MNMs) has occurred (OECD 2016; EC 2012). Labelled by the European Union (EU) as a Key Enabling Technology, the use of MNMs allows for considerable innovation in a variety of sectors such as healthcare, energy, aerospace, cosmetics, and electronics (EC 2018). Their potential to improve the performance and quality of some products and processes have led to the rise of a global market which is projected to reach 30 billion euros by 2030 (Tewari 2021).

In the EU, MNMs are regulated under several legislative frameworks: the Registration, Evaluation, Authorization, and Restriction of Chemicals framework REACH 1907/2006, Classification, Labelling, and Packaging regulation CLP 1272/2008, European Food Safety Authority EFSA 2015/2283 and other EU regulation frameworks which address the case of MNMs specifically for several product types, e.g. biocides EC 528/2012, medical devices EC 178/2002 and EC 1223/2009 and cosmetics EC 1223/2009.

Within the REACH framework, MNMs have until recently been treated as conventional substances. However, scientific evidence showed a need for a nano-specific approach for materials identification and risk assessment (Dekkers et al. 2016; EFSA Scientific Committee 2009; EFSA Scientific Committee 2018; Gottardo et al. 2017; SCENIHR 2009). To meet the new needs, the European Commission (EC) amended the REACH regulation EU 2018/1881 to address nanoforms, which came into effect on January 1, 2020. Consequently, industries and importers must make registrations of specific nanoforms and their nano-specific human and environmental risk assessments.

So far, compliance with the new regulatory requirements, set out by the EC, has proven to be challenging for industries. According to the European Chemical's Agency (ECHA), the lack of validated tools and methods (e.g. manuals, instructions, guidances) for the characterization, testing and risk assessment of MNMs plays a significant role in the low compliance rate to the legal obligations (ECHA, 2020). In addition, lack of knowledge about the tools, user capacity, training and usage difficulty impede the successful implementation of the new regulatory requirements among industrial users (Kirkegaard et al., 2020). Despite this, large and diverse type of tools and methods dealing with the assessment of risks, as well as sustainability aspects, and socio-economic impacts of MNMs, have been developed and published in the last decade by national and international research organizations, companies, government agencies and other actors. In the context of this study, 'tool' can be interpreted as an instrument (e.g. computational model, database) to obtain a specific result and a 'method' as a description of the process to achieve the result (e.g. risk assessment framework, technical and procedural guidance, standard).

There currently is a demand for validated regulatory-oriented tools and methods (T&M) to carry out the assessments of MNMs for their potential risks and socio-economic impacts. Thus, we focus on T&M dealing with the risk assessment, risk management, socio-economic impact assessment and sustainability of MNMs which are some of the essential aspects of the safe innovation of MNMs.

'Regulatory orientation' of the research data and the results provided by the T&M have constantly been highlighted in the scientific literature as a key component (and sometimes main deterrent) to the wider use of these T&M (van Teunenbroek et al., 2017; Porcari et al., 2019; Sørensen et al., 2019; Halamoda-Kenzaoui et al., 2019). Regulatory needs entail well defined, standardized, reliable, reproducible and exchangeable results, and implies that the T&M must be aligned with- and support the regulatory frameworks in place and should be widely used and accepted by different stakeholders (regulators, end-users, and the scientific community) (van Teunenbroek et al., 2017; Porcari et al., 2019). However, as demonstrated by Halamoda-Kenzaoui et al. (2019), new state-of-art methods, instruments, approaches or tools have not yet sufficiently proven their reliability and relevance for the purpose of assessing risks and socio-economic impacts of MNMs and nanotechnology-enabled products. Recently, however, an OECD initiative assessed a large set of tools for their regulatory preparedness based on analysis of the tools' accessibility, sensitivity and performance in regards to nano-specific environmental, consumer and occupational exposure assessment (OECD 2021).

Besides regulatory orientation or acceptance, the T&M should also demonstrate their alignment with specific needs of their end-users/stakeholders, such as public research and/or manufacturing companies, regulators, policy makers, service providers/consultancy and supra-national organizations dealing with the issues related to the safety of MNMs. As shown by a recent study (Porcari et al. 2020), stakeholder needs include extended functionality, (easier) accessibility, (easy) usability, affordability and more efficient available (limited) data exploitation. In addition, the role of the T&M with respect to different factors or aspects

of the safe innovation of MNMs (e.g. risk assessment, risk management, risk-benefit analysis, socio-economic impact assessment) are also of prime interest to the stakeholders. The lack of both proper guidance and training is a recurrent issue which hinders the wide usability of the T&M (Kirkegaard et al., 2020).

In the present study, a framework is proposed which contributes to the identification of the T&M that could reach regulatory acceptance and wider stakeholders use for the safe innovation of MNMs by evaluating their compatibility with regulatory orientation or requirements, their usefulness and usability for T&M end-users, and their overall quality. The framework is composed of five core pillars: Transparency, Reliability, Accessibility, Applicability, and Completeness (i.e. TRAAC). The TRAAC framework is intended to help (i) regulators by pointing out the most appropriate and relevant T&M (i.e. regulatory orientated) for the safe innovation of MNMs; (ii) aforementioned end-users of T&M by selecting the most appropriate options for their specific needs; (iii) industries by increasing their trust and confidence around the T&M and thus accompanying them with the regulatory compliance process; (iv) T&M developers by compiling end-users' needs into an easy-to-use framework, which may help them to improve their T&M.

The paper describes the development of the TRAAC framework and results of a test of the framework on a selection of 14 different T&M which include various nano-specific qualitative and (semi) quantitative tools and methods, such as LICARA NanoSCAN, Precautionary Matrix for synthetic nanomaterials, Stoffenmanager Nano, NanoSafer CB etc. These T&M show potential to meet the industry and regulatory needs for decision support as well as risk assessment and management (Liguori et al., 2016).

This work builds upon the work conducted in former EU H2020 projects such as caLIBRAte in which a web-based Nano Risk Governance Portal (NRGP) was launched, NANoREG (and NanoReg2) in which a Safe Innovation Approach (SIA) framework for MNMs was developed and subsequently refined and the ongoing Gov4Nano project which aims to develop a Nano Risk Governance body to improve safe governance of MNMs and specific NRGP with T&M.

2. Traac Framework

The TRAAC framework was developed in several steps, as further elaborated below, which consisted of:

i. a literature search of general issues and "themes" with regards to regulatory acceptance and wider usability of T&M;
ii. development of the different pillars and criteria within the framework structure;
iii. multi-stakeholder workshop to present the framework structure and further improve it based on received feedback;
iv. test examples of existing T&M to demonstrate the use of the framework as a case study.

2.1 Literature search

A literature search with regards to risk and sustainability aspects of MNMs (i.e. risk assessment, risk governance, functionality, economic impact and societal impact) and available T&M helped to identify the key elements needed to design the TRAAC framework. In addition, attention also was given to the REACH regulation EC 1272/2008 and its recent amendments, as well as to the reports of previous EU funded projects, such as caLIBRAte and NanoReg2, which intensely analyzed topics of risk assessment, material/product functionality and nano-risk governance. Additionally, relevant material published by governmental agencies (e.g. EPA, 2017; ECHA, 2011; EUON, 2020) and international organizations (e.g. OECD, 2005; IOMC, 2016) about REACH requirements for environment and human health assessments of MNMs was considered. The views and perspectives of stakeholder needs on the risk governance of MNMs and nano-related products (as identified by Kirkegaard et al. 2020 and Porcari et al. 2020), based on selected EU funded projects, initiatives and literature resources, were further used to support the applicability of the framework.

2.2 Workshop

An interactive workshop was organized involving 36 stakeholders from different EU countries, including researchers, academics, industry, regulators, consultants and government (European Commission). The objectives of the workshop were to demonstrate the TRAAC framework, be recognized by a wider audience and to incorporate their feedback to further refine the framework. Built upon the literature search, a draft framework was presented and, for each of the five pillars, the participants were asked to vote and rate pre-selected criteria (detailed in following sections) using Mentimeter (https://www.mentimeter.com/) in the order of their significance to the given pillar and propose additional criteria. The participants could see the number of received votes for each criterion in real-time which fostered lively discussion among them.

2.3 Structure

As shown in Figure 1, the framework follows a multi-faceted approach aiming to evaluate the regulatory readiness of T&M and their alignment with the stakeholder needs. It rests on five pillars:

i. Transparency: Ownership, clear communication about development, methods, strengths and limitations (i.e. boundary of use);
ii. Reliability: Quality, correctness and consistency of output;
iii. Accessibility: Usability, findability and user experience evaluation;
iv. Applicability: Applicability domain and adequacy to address user need(s);
v. Completeness: Comprehensiveness in regard to EU regulatory frameworks and requirements for MNMs.

Each of these five pillars consists of several multi-weighted criteria (on a scale of 1 to 5). The weight assigned to a criterion signifies its importance in defining the feature and scope of the pillar, with 5 being the most important and 1 being the least. The criteria and their respective weights in each pillar are shown in Tables 1-4. The weight of these criteria are derived on the basis of their significance found during the literature search and workshop.

As described more in the subsequent sections, the criteria in turn are comprised of three scoring options which evaluate the degree of their fulfilment: 0.1- unfulfilled, 0.5- partially fulfilled and 1-completely fulfilled. There are certain criteria for which there are two scoring options, 0.1- unfulfilled and 1-completely fulfilled, as partial fulfilment for such criteria is not possible (more details in subsequent sections).

2.3.1 Transparency

Transparency towards the scientific community, regulators, and end-users is an important factor for the stakeholders' acceptance of T&M. As underlined by Hristozov et al. 2012, EC 2019 and EU 2019, transparency is a prominent part of the risk governance process. In the context of the T&M, it implies a clear information about the authors/developers, the methods and data (and their scientific evidence) used for their development, and the communicated uncertainties with regards to the tools' output.

A multi-stakeholder study has shown that 38% of policymakers and 24% of the industry have only a basic to intermediate understanding of MNMs (Porcari et al. 2019). A transparent approach to risk assessment from the tool developers helps these stakeholders to better understand the risk assessment and safe innovation process for MNMs, increases their trust and confidence in the tools and technology, and enables potential downstream users to interpret and communicate risks clearly (Isigonis et al., 2019; EC 2012).

The TRAAC framework takes transparency into account by answering three underlying questions (EC 2019; Gomez-Diaz and Recio 2019; OECD 2005), which lead to the development of four transparency related criteria in Table 1.

- Who created the T&M? This allows for accountability, facilitates collaboration, and enables regulators and industries to directly get in touch with the T&M developers.
- Why was the T&M created? A clear scientific rationale and publicly defined purpose for T&M is necessary in order for end-users to assess the appropriateness of the T&M for their intended purpose, e.g. risk assessment, socio-economic impact assessment.
- How does the T&M work and what are the restrictions of use? A detailed description of the tool helps end-users understand how the tool works, how relevant it is for them, and how reliable the T&M approach is, by addressing uncertainties, strengths, and limitations.

Table 1: Criteria in the transparency pillar

Criteria ref	Criteria name	Description	Assigned weight (out of 5)	Scoring options
T.1	Clear mention of developers and affiliations	The T&M (or its guidance) provides information about developers, contributors, and funding when applicable.	3	**Score 1**: The developers of the T&M, contributors, and institutions involved are fully disclosed in the documentation. Funding when applicable is also publicly disclosed.
				Score 0.5: Developers, contributors, institutions, and funding are partially disclosed.
				Score 0.1: Developers, contributors, institutions, and funding are not disclosed.
T.2	End-users communication with developers or project team	End-users are able to get in touch with the developers for feedback, questions, or to request additional guidance.	2	**Score 1**: End-users are able to get in touch or communicate actively with the developers of the T&M or the project developing the T&M in order to provide feedback, obtain additional information, and receive guidance.
				Score 0.5: End-users are able to submit remarks and comments to the developers or the project developing the T&M but cannot engage into active communication and receive guidance.
				Score 0.1: No contact information is provided for any purpose to the users.
T.3	Publicly available detailed description	The aim of the T&M, scope, source, processing of the data, applicability, and endpoints are addressed by developers.	5	**Score 1**: Aim of the T&M, scope, source, and processing (when applicable) of the data, methodology, applicability, endpoints, and decision criteria are described in detail. Contribution of the T&M to the assessment process is clearly stated. Comprehension, use, and/or replication are possible.
				Score 0.5: The description of the T&M includes some of the considerations listed above but lacks key information. Comprehension, use, and/or replication is possible but difficult.
				Score 0.1: The description of the T&M includes few or none of the considerations listed above. Comprehension, use, and/or replication is either not possible or very difficult.
T.4	Fully disclosed strengths and limitations	The strengths and limitations of the T&M are fully disclosed by the developers (e.g. in a user guidance or separate research paper).	4	**Score 1**: The strengths and limitations of the T&M are addressed by the developers and clearly known to the users.
				Score 0.5: The strengths and/or limitations of the T&M are partially addressed or partially known to the user.
				Score 0.1: The strengths and limitations of the T&M are not addressed or unknown to the user.

2.3.2 Reliability

Reliability is often considered as the pre-requisite for regulatory acceptance and stakeholders. Results from T&M need to be reliable, accurate (e.g. in line with reality or a realistic worst-case estimate) and the uncertainty of the estimates needs to be dealt with. The uncertainty is generally reflected by model uncertainty and can be expressed as a certain percentile (e.g. the 90th percentile) in which case the user knows that the T&M estimates are intended to be conservative. Additionally, between- and within-user variance provides additional insights in the uncertainty and can be used to calculate different percentiles. The reliability pillar of the TRAAC framework focuses on aforementioned aspects by assessing the correctness and consistency of the tools' outputs (see Table 2). Three underlying questions are addressed (Aerts 2017; EPA 2017; Gomez-Diaz and Recio 2019; Hristozov et al. 2016; Isigonis et al. 2019; JRC 2018; Morris et al. 2010; OECD 2005; Sørensen et al. 2019) when considering the reliability of the T&M, which lead to the development of six reliability related criteria in Table 2.

- Have the T&M been verified and received support within the scientific community? For scientific knowledge to be approved and accepted by regulators, their quality must be high, and their findings should be approved and supported throughout, for instance, peer reviewing approaches involving the scientific community of reference (EC, 2019).
- Has the scientific quality of T&M been assessed/measured? Documented applications, validating the T&M results against results from other tools or (preferably) measurements, and evaluation of the quality of the data used are important reliability evaluation criteria for stakeholders (EPA, 2017; Hristozov et al., 2016; Isigonis, 2019; OECD, 2005; Porcari et al., 2019).
- Is the uncertainty of the T&M assessed or dealt with? Information with regards to the uncertainty of a T&M outcome or result is considered crucial to assess the reliability.

Table 2: Criteria in the reliability pillar

Criteria Ref	Criteria Name	Description	Assigned weight (out of 5)	Scoring options
R.1	Testing or validation of the T&M	The T&M has been tested by comparing its output with preferably MNMs measurement studies or in case data was lacking similar tools/methods and the comparison shows that the output is reasonable (e.g. a strong Pearson correlation coefficient between estimated and measured values).	5	**Score 1**: The T&M has been tested/validated against MNMs specific data.
				Score 0.5: The T&M has been tested against outcomes of tested/validated models.
				Score 0.1: The T&M has not been tested.
R.2	Peer-review	The development of the T&M is published in a scientific journal and the work is peer-reviewed. Unlike other criteria which have three scoring options (0.1, 0.5 and 1), there are only two scoring options here because the T&M can either be peer-reviewed or not. There is no partial peer-review.	2	**Score 1:** The scientific publications of the developers about the T&M are peer-reviewed. This also includes reports/documents issued by governmental organizations (e.g. OECD, ECHA), regulatory authorities (e.g. RIVM, BAuA) or public standards organization (e.g. CEN) which are often based on peer-reviewed scientific publications.
				Score 0.1: The scientific publications of the developers about the T&M are not peer-reviewed or there is no scientific publication.
R.3	Quality of the data	Measurement data used for the development of the T&M has been collected with use of validated measurement methods (published by renowned institutes) and the contextual information is of high quality.	5	**Score 1:** The T&M developers address data quality in a guidance document or a scientific article. The data used during the development is well documented, measurements are performed with validated measurement methods (or closely resembling methods), and contextual adequacy is addressed.
				Score 0.5: The data quality and measurement methods are either not addressed by the T&M developers or are unknown. **Score 0.1 or N/A:** The T&M is developed without the use of available measurement data.
R.4	User variability and clear decision making	The required information by the T&M is clear, and multiple users of the T&M, with the same set of required information to execute the T&M, reach the same output with an unambiguous interpretation.	3	**Score 1:** A study was conducted, and user variability was concluded to be acceptable by the authors.
				Score 0.5: A study was conducted, and user variability was concluded to be high.
				Score 0.1: No study was conducted to investigate the user variability.
R.5	Uncertainty analysis	The uncertainty of the output has been properly dealt with in the T&M. Like R.2, the uncertainty of T&M can either be dealt with or not, hence two scoring options.	4	**Score 1:** The T&M includes an uncertainty analysis (wherever applicable) with its output (percentile of certainty) in order to help the decision-making process.
				Score 0.1: The T&M does not include an uncertainty analysis with its output.
R.6	Collaborative effort	The T&M was developed with different stakeholders (e.g. research community, industry, regulatory institutions). There can either be a collaborative effort or not and thus there are only two scoring options like R.2 and R.5.	2	**Score 1:** The T&M was developed and funded with partners and collaborators from the research community, the industry, and the regulatory institutions. It can also be the product of a research project.
				Score 0.1: The T&M was not developed or funded with partners and collaborators from different communities.

2.3.3 Accessibility

The Accessibility pillar of the TRAAC framework evaluates the T&M in terms of user experience (see Table 3). It assesses the usability and findability of the T&M by users particularly in accordance with the stakeholder needs as described by Porcari et al. 2020, FAIR principles (Jeliazkova et al. 2021; Wilkinson 2016) and other relevant studies (Aerts 2017; EC 2019; Gomez-Diaz and Recio 2019; Hristozov et al. 2016; Isigonis et al. 2019; JRC 2018; OECD 2005; Soeteman-Hernández et al. 2019; Sørensen et al. 2019; Trump et al. 2018).

A large part of the organizations developing and producing MNMs are Small and Medium Size Enterprises (SMEs) (Teunenbroek, 2017). Accessibility of relevant T&M can influence the choice of T&M, as most T&M require some training and a certain degree of expertise. Consequently, the more complex a T&M is to use, the more resource demanding and difficult is its use. As SMEs often do not have in-house expertise about potential environmental and human health risks of MNMs and work with limited budgets, accessibility of a T&M in terms of its use is important to consider (Kirkegaard et al., 2020; Porcari et al., 2019). Three underlying questions help to determine the seven criteria for this pillar:

- how easily findable is the T&M?;
- how easily accessible (in terms of use) is the T&M?;

- what type of additional resources (e.g. guidance, training) do the developers provide to users?

Ideally, a T&M should be easy to use, understandable, and compatible with different levels of expertise (Isigonis et al., 2019; Sørensen et al., 2019). Amongst other criteria, as mentioned in Table 3, quality guidance material, a user-friendly interface, and built-in case studies can help accelerate the learning period. When assessing accessibility, other aspects are also to be looked at, for example, availability of licenses for redesigning or reusing the existing T&M in a new project/work, citations for scientific credibility and recognition by a wider stakeholders community, and availability of the T&M (or its guidance material) in different languages for a wider audience for whom the default language of the T&M can be a deterrent feature.

Table 3: Criteria in the accessibility pillar

Criteria Ref	Criteria Name	Description	Assigned weight (out of 5)	Scoring options
A.1	Quality guidance material	Up-to-date guidance for use of the T&M is provided and includes study-cases, access information, audio visual resources, FAQs…	4	**Score 1:** The user is provided with up-to-date guidance material for basic and/or advanced features of a T&M. The guidance material is complete and clear. The guidance material includes case studies, and information for accessing the T&M. Additional resources (e.g. guidance, training) are listed on the platform or within the T&M itself. The user guide is task oriented and features illustrations and examples for each step. Audio visual guides (e.g. Webinars, tutorials) or FAQs can also be considered as guidance material.
				Score 0.5: The user is provided with some guidance material. The guidance material mainly addresses basic features of a T&M and lacks clarity. Additional material such as other resources or audio-visual guides are not included or are not currently available.
				Score 0.1: No or very few guidance is provided to the users.
A.2	Compatibility with different levels of expertise	Basic and more advanced features of the T&M are understandable and usable without a high level of expertise.	3	**Score 1:** The basic and advanced features are easily understandable and usable without a high level of expertise. The results and decision-making criteria are clear and can be interpreted by a wide range of end-users.
				Score 0.5: The basic and advanced features are understandable and usable with a moderate level of expertise. The results and decision-making criteria are clear and can be interpreted by most end-users.
				Score 0.1: The basic and advanced features are understandable and usable with a high level of expertise. The results and decision-making criteria cannot be easily interpreted and require substantial expertise.
A.3	Availability of the T&M in more than one language	The T&M (or its guidance material) is available in English and in other languages. As previously observe for the Reliability pillar, this criterion also has only two scoring options because T&M can either be present in more than one language or not.	1	**Score 1:** The T&M (or its guidance material) is available in English and additional languages.
				Score 0.1: The T&M (or its guidance material) is only available in English.
A.4	Inclusion of a license	The T&M includes a license determining conditions for usage, reproduction, modification, and distribution of the T&M.	1	**Score 1**: The T&M includes a license addressing (i) authorship, (ii) conditions for usage, (iii) reproduction and modification, (iv) distribution, and (v) liability.
				Score 0.5: The T&M includes a license. Only some of the aspects listed above are addressed.
				Score 0.1 or N/A: The T&M is not accompanied by any license or its development is not advanced enough to include a license.
A.5	Citations/mention in scientific, regulatory, or industry publications	The T&M is cited or mentioned in publications from the industry, the scientific community, or governmental agencies.	2	**Score 1**: The T&M is cited/mentioned in at least 3 scientific, regulatory, or industry publications (excluding publications from the developers or associated project).
				Score 0.5: The T&M is cited/mentioned in at least 1 scientific, regulatory, or industry publication (excluding publications from the developers or associated project).
				Score 0.1: The T&M is not cited/mentioned in publications other than the ones by its developers or associated project.
A.6	Findability and accessibility	The T&M is accessible online or through download. The T&M can either be easy or difficult to find and access. Thus, there are only two scoring options.	4	**Score 1:** The T&M is easily accessible to end-users on the web, either on a web platform or through download.
				Score 0.1: The T&M is difficult to access or is only available upon request.
A.7	User-friendliness	The T&M is easy to operate and navigate. In some cases, the T&M can be used in combination with other T&M or databases.	5	**Score 1:** The T&M is user friendly: the GUI (Graphical User Interface) or the step by step methodology is clear and simple. Information is easily findable. When applicable (for a GUI), inputs controls and navigation components are easy to understand and interact with. In some cases, and when applicable, the T&M is inter-operable and can be used in combination with other T&M.
				Score 0.5: The T&M is somewhat user-friendly and relatively easy to navigate.
				Score 0.1 or N/A: The T&M is not user-friendly or is still in an early development stage to consider user-friendliness.

2.3.4 Applicability

The applicability pillar addresses two aspects of the T&M: (i) their applicability domain and (ii) the extent to which they fulfill some specific stakeholders' needs as identified in previous works (Beaudrie and Kandlikar 2011; Franken et al. 2020; Isigonis, 2019; Porcari et al. 2020). The criteria evaluating the T&M applicability are shown in Table 4 and they are determined based on three underlying questions in line with Hristozov et al. 2016; Isigonis et al. 2019; JRC 2018; Morris et al. 2010; OECD 2005; Porcari et al. 2019; Sørensen et al. 2019; Teunenbroek et al. 2017; Trump et al. 2018:

- Are the T&M nano-specific? Unlike conventional chemicals, MNMs require T&M to consider nano-specific parameters, such as additional physico-chemical characteristics.
- What are the specific usage-relevant characteristics of the T&M? Due to the data gaps for MNMs, the capacity of T&M to work with low number of input data is desirable for potential end-users. Quantitative types of T&M and risk management options also ease the risk assessment and safe innovation process by providing end-users with more specific information for making decision depending on the innovation stage. Moreover, continuous support and development of the T&M is useful for them to stay relevant and up to date. A 'one-size-fits-all' approach of the T&M, measured in terms of their comprehensiveness for different population (worker, consumer, general population, environment), exposure routes and life cycle stages, is certainly a factor that also increases their applicability. A T&M can be highly effective and useful in a single process, life cycle stage, population or exposure route for which it was developed. However, its inability to be applicable to other processes and/or life cycle stages, populations or exposure routes limits its general applicability.
- Does it cost a lot of resources (money and time) to work with the T&M? Efficiency is measured by evaluating the time and costs implied by the use of T&M. Sometimes, it can be a trade-off between saving time and spending money (in the form of a user fee). For example, a T&M can ask for a user fee for the easy management of risk assessment files for REACH registration which ultimately saves time in building REACH dossiers compared to free versions.

Table 4: Criteria in the Applicability pillar

Criteria Ref	Criteria name	Description	Assigned weight (out of 5)	Scoring options
P.1	Applicable life cycle stage(s)	The T&M is applicable to all life cycle stages of a product.	1	**Score 1:** The T&M is applicable for all the following life cycle stages: (i) R&D/Synthesis, (ii) Manufacturing, (iii) Use, (iv) End of life.
				Score 0.5: The T&M is applicable for two or more life cycle stages (listed above).
				Score 0.1: The T&M is applicable for one life cycle stage (listed above).
P.2	Applicable exposure routes and/or population types	The T&M is applicable to all exposure routes and/or exposed populations.	4	**Score 1:** The T&M is applicable to all routes of exposure and/or applicable populations. Applicable routes of exposures include i) inhalation, ii) dermal, iii) ingestion. Applicable populations are i) consumers, ii) workers, iii) environment, iv) general population.
				Score 0.5: The T&M is applicable to 2 or more routes of exposure and/or 2 or more populations (see above).
				Score 0.1: The T&M is very specific in its application and allows for one applicable route of exposure and/or one applicable population.
P.3	Nano-specificity	The T&M considers relevant physico-chemical properties and endpoints for MNMs specific behaviour. As previously seen for several other criteria, this criterion also has only two scoring options because the T&M can either be nano-specific or not.	5	**Score 1:** The T&M is developed with the purpose of being applicable to MNMs' specific behaviour and physiochemical properties.
				Score 0.1: MNMs are out of the scope of the T&M or its applicability to MNMs is not yet known.
P.4	Quantitative output	The output of the T&M enables end-users to quantify risks.	3	**Score 1:** The T&M has a quantitative output.
				Score 0.5: The T&M has a semi-quantitative output (i.e. relative scores).
				Score 0.1: The T&M has a qualitative output.
P.5	Handling data gaps	The T&M can be executed despite limited data/information being available. This criterion has also two scoring options because the T&M can either handle the data gaps or not.	4	**Score 1:** The T&M can be executed despite limited information availability. When insufficient information is available to the user, some required information can be left blank, and a result can still be obtained. It takes into account worst-case estimates or uses typical default inputs based on expert judgement.
				Score 0.1: The T&M requires the user to fill in all the input fields in order to carry on to the next steps and generate a result.
P.6	Time and cost efficiency	The T&M is considered time and cost efficient for users depending on the innovation stage. For the early innovation stages (ideation/scope/business case/R&D), which focus on ideas screening and building up the concept, the T&M should not need more than a few minutes for the assessment. For the later stages (test & validation/launch/monitoring), which require more in-depth assessment, the T&M should not need more than a few hours for the assessment. The T&M can either be time and cost efficient or not, and thus there are two respective scoring options.	3	**Score 1:** The T&M is time and cost efficient depending on the innovation stage.
				Score 0.1: The T&M is not time or cost efficient. The T&M requires substantial training and/or time, even for early innovation stage.
P.7	Continuously	The T&M stays up to date with new requirements, new data, and studies. It is	3	**Score 1:** The T&M is

	supported by developers	updated when needed. The continuous support from T&M developers can either be there or not, and thus there are two respective scoring options.		continuously supported by developers: it stays relevant and takes into consideration new studies, data, or regulatory requirements. It is updated when needed. Continuous support of the T&M also includes updates for the T&M interface/user experience.
				Score 0.1 or N/A: The T&M is not continuously supported by developers.
P.8	Advice for improving the output	The T&M provides end-users with advice on how to improve the assessment output to an accepted level (e.g. for exposure assessment that would be lowering the estimated exposure). The two respective scoring options for this criterion represent the ability of the T&M to either generate the advice or not.	2	**Score 1:** The T&M is able generate advice to the user on the measures to take to improve the assessment output to an accepted level.
				Score 0.1: The T&M simply provides an output with no such advice.

2.3.5 Completeness

The last pillar of the TRAAC framework evaluates the comprehensiveness of the T&M and methods in relation to EU regulatory standards and requirements for MNMs, as mentioned in modified REACH Annexes I, III and VI-XII in EC Regulation (EU) 2018/1881. There cannot be a universal set of completeness criteria which are applicable to all types of T&M because the input parameters in a T&M depend on the type of the assessment it does (e.g. assessment of risk, exposure, hazard, socio-economic impact). Thus, unlike the previous four pillars, the Completeness pillar follows a modular approach. Within its current scope, there are 5 modules in the pillar (as shown in Figure 1) with each module representing a specific aspect which is relevant for the safe innovation/safety-by-design of MNMs: (i) Human risk assessment (ii) Environmental risk assessment (iii) Human exposure assessment (iv) Socio-economic impact assessment (v) Environmental impact assessment. Each of the required parameters in a module (e.g. C.1.1 to C.1.27 criteria for human risk assessment, C.1.1 to C.1.14 and C.2.1 to C.2.6 criteria for environmental risk assessment) serves as the completeness evaluation criterion with all criteria having the same assigned weight (i.e. 1). There are only two scoring options for all criteria, i.e. Yes (1) and No (0.1). If 'Yes' is selected for a particular parameter and for a particular T&M, it implies that particular T&M addresses that particular parameter. The option 'No' implies otherwise. Since each module has its own set of parameters/criteria, it is important to know that each T&M can be evaluated based on the module to which it is applicable.

The human exposure assessment is known to be a part of the human risk assessment in which exposure and hazard levels are combined to assess the overall risk. However, it has been kept separate within the TRAAC framework. This can be clearly seen in Figure 1 in which the modules 1 and 3 share parameters C.1.1 to C.1.22 but are still separate modules. The reason behind this separation is that there are several T&M which are developed to focus only on the human exposure assessment and exclude the hazard assessment. Scoring them for their completeness on the basis of risk assessment parameters/criteria will unjustifiably lower their Completeness score. Thus, it was decided for human exposure assessing T&M to have their own Completeness module with the parameters/criteria dedicated to human exposure assessment.

In addition to the aforementioned regulatory frameworks addressing MNMs, the criteria/parameters in the completeness pillar are also based on the regulatory guidance documents, including EUON's summary of the new REACH requirements, ECHA Guidance R.14 (ECHA 2016a) and Appendix R14-4 (ECHA 2016b), an EU H2020 caLIBRAte project report on quality criteria for data (Nymark et al., 2017), and ECHA's Socio-Economic Analysis guidance report.

2.4 Scoring system

To allow for a comprehensive and objective assessment (as much as possible), the framework is designed to yield a score per pillar as well as an overall score combining the individual scores per pillar. Figure 2 shows the scoring system considered in the TRAAC framework schematically.

Within each pillar, as mentioned earlier, two or three scoring options (1, 0.5 and 0.1) are available when attributing a fulfillment score to a criterion (Tables 1-4). For instance, the criterion T.1: "Clear mention of developers and affiliations" in Table 1 has an assigned weight of 3 and offers three scoring options to the user:

- **Score 1**: The developers of the T&M, contributors, and institutions involved are fully disclosed in the documentation or within the T&M. Funding when applicable is also publicly disclosed. For instance, developed by A. Dupont, in collaboration with B. Dupont, working for Institution N, and funded by Organisation A.
- **Score 0.5:** Developers, contributors, institutions, and funding are partially disclosed. For instance, developed and funded by Institution N in partnership with Organisation A.
- **Score 0.1:** Developers, contributors, institutions, and funding are not disclosed.

If the second option is valid for a given T&M, the score for the given criterion is equal to 1.5 (=0.5x3). A similar procedure is followed for each criterion to obtain individual scores. A weighted mean of the individual scores is taken, as shown in equation 1, to obtain a final score of the T&M per pillar. In equation 1,

is the assigned weight to the criterion, is the scoring option valid for the criterion and is the number of criteria in a pillar. An arithmetic mean of the individual scores from equation 1 is taken to provide an overall score for the T&M which measures the readiness of the T&M for its regulatory acceptance and stakeholder use. Therefore, in the end, the framework provides a score per pillar and an overall average score for a T&M (both scores varying from 0.1 to 1) where the pillars themselves all contribute to the final score equally.

$$Score\ per\ pillar = \frac{\sum_{i=}^{n} W_i S_i}{\sum_{i=}^{n} W_i} \qquad (1)$$

To determine what could be considered a good performance for a T&M in terms of regulatory acceptance and stakeholder use (also called TRAAC performance), performance ranges are also shown in Table 5.

Table 5: Performance ranges of the T&M as a function of their overall TRAAC score

Overall score	TRAAC Performance
>0.9	Perfect/Excellent
0.7 to 0.89	Good
0.4 to 0.69	Average
≤0.39	Poor

2.5 Evaluation of T&M using TRAAC framework

To demonstrate the TRAAC framework and the way it ranks some of the existing T&M according to their regulatory acceptance and stakeholder use readiness, several T&M were selected and evaluated with the proposed TRAAC framework. The T&M were selected from a comprehensive inventory of 160 state-of-the-art and emerging T&M candidates for the NRGP (Shandilya et al., 2020a). Evaluating all 160 T&M using the TRAAC framework was not practical due to the limited resources. Therefore, to demonstrate the generalizability of the TRAAC framework, we selected 14 T&M which represent a general sub-set of this inventory and are diverse in terms of their nano-specificity, type, application domains, applicable routes of exposure and populations, as shown in Table 6. To make the general sub-set of the T&M, certain selection boundaries had to be established too by excluding the following types of T&M (nevertheless, it does not imply that the excluded T&M cannot be evaluated using TRAAC framework):

i. The T&M which are not publicly available, have a broken access link, or are in a language other than English;
ii. The T&M classified as “regulatory documents” or “standards documents” and published by governmental agencies or governments for which regulatory acceptance is already established;
iii. The guidance T&M, databases, system of T&M and web platforms compiling T&M and data, which are either meant as strictly informative for the process (providing guidance), uses several T&M to provide an assessment or simply serve as a library of T&M to guide a user to an appropriate T&M;
iv. The T&M requiring a fee for access or considered a service, and thus requiring the intervention of a third party to carry out an assessment;

3. Traac Framework Performance

3.1 Diversity of selected T&M

The selected 14 T&M are diverse in terms of their nano-specificity, type, applicable exposure route and population, as shown in Table 6.

Table 6
List of selected T&M for their evaluation using TRAAC framework

Selected T&M		Nano-specific	Type	Application domain	Route of exposure	Applicable population
1	NanoSafer Control Banding	Yes	Tool	Risk assessment and management	Inhalation only	Worker
2	Stoffenmanager Nano	Yes	Tool	Risk assessment and prioritization	Inhalation only	Worker
3	MARINA Framework	Yes	Method	Risk assessment	All routes	Environment, Worker, Consumer, General population
4	LICARA NanoScan	Yes	Tool	Socio-economic impact assessment, Environmental impact assessment, Risk-benefit analysis	Inhalation only	Environment, Worker, Consumer, General population
5	LRI Ambit 2	Partly	Tool and method	Risk assessment	All routes	Environment, Worker, Consumer, General population
6	Advanced REACH Tool (ART)	No	Tool	Exposure assessment	Inhalation only	Workers
7	NewHoRRIzon Societal Readiness Thinking (SRT)	No	Method	Social-economic impact assessment, Environmental impact assessment	N/A	N/A
8	ECETOC TRA	No	Tool	Exposure assessment	Inhalation, Dermal	Environment, Worker, Consumer
9	RiskofDerm (ROD)	No	Tool	Exposure assessment	Dermal only	Worker
10	Future Nano Needs Bayesian Belief Network (FNN-BBN)	Yes	Tool	Exposure assessment	Inhalation only	Worker
11	Precautionary Matrix for synthetic nanomaterials	Yes	Tool	Exposure assessment	All routes	Environment, Worker, Consumer
12	SimpleBox4Nano	Yes	Tool	Exposure assessment	N/A	Environment
13	ConsExpo nano	Yes	Tool	Exposure assessment	Inhalation only	Consumer
14	NanoDUFLOW Model	Yes	Tool	Exposure assessment	N/A	Environment

3.2 Score per pillar

The results of the evaluation on the basis of the 5 TRAAC pillars and the overall score for the 14 T&M are shown in Figure 3.

3.2.1 Transparency

The transparency scores obtained for the tested T&M range from 0.46 to 1 (Figure 3). Overall, the T&M perform relatively well for this pillar as the average score is equal to 0.81 which is highest compared with the other 4 pillars. The details on the calculated scores for each T&M are provided in the Supplementary Information (Table S1). There are 3 T&M which score particularly higher than 0.9: FNN-BBN (1), SimpleBox4Nano (1), and ART (0.93). The other 9 T&M (i.e. LICARA, ECETOC TRA, PM, NanoSafer CB, ROD, ConsExpo nano, SRT, NDF and MARINA) score between 0.7 and 0.89 and 2 T&M (i.e. STMn and LRI Ambit2) score 0.69 and 0.4 respectively.

During the analysis, it was observed that while most T&M provide contact details for end-users and a detailed description of the T&M, the developers and partners associated with a T&M are not always clearly disclosed. This is more noticeable for industry developed T&M, such as LRI AMBIT 2 and ECETOC TRA, which disclose organization affiliations rather than the names of the developers in most cases. The T&M score generally low for criteria T.4 (regarding the disclosure of the strengths and limitations).

3.2.2 Reliability

With regards to reliability, scores range from 0.33 to 0.93, with an average of 0.6 (see Figure 3). The details on the calculated scores for each T&M are shown in the Supplementary Information (Table S2). The top three scoring T&M in terms of reliability are ART (0.93), RiskofDerm (0.93), and Stoffenmanager Nano (0.7).

The socio-economic impact assessment and risk-benefit analysis T&M (i.e. LICARA NanoScan and SRT), as well as MARINA framework, generally do not perform well in this pillar, with results below average, ranging from 0.33 to 0.49. For the MARINA framework, its lowest score (0.33) is largely due to its early development phase and conceptual nature, which makes it difficult to validate using data, or quantify uncertainty. As for T&M like LICARA NanoScan, and SRT, their lack of testing as well as their inability to consider uncertainty affect their performance. While the T&Ms score generally good (or above average) for most of the criteria, for criteria R.4 and R.5 which refer to the user variability and uncertainty, their performance is rather poor because of the absence of studies on the user variability (i.e. R.4) or a lack of description of the output uncertainty (R.5).

3.2.3 Accessibility

The scores in the accessibility pillar range from 0.33 to 0.96, with an average score of 0.69. As shown in Figure 3, the top three scoring T&M are ECETOC TRA, PM and LRI Ambit 2, with scores ranging between 0.88 and 0.96. The details on the calculated scores for each T&M are shown in the Supplementary Information (Table S3). It can be observed that these three highest scoring T&M were not developed within the research community but involved either the industry (i.e. LRI Ambit 2, ECETOC TRA) or a governmental agency (i.e. PM). While most T&M are easily findable (A.6) and often cited (A.5), inequalities in the quality of the guidance material have been noticed (A.1). User friendliness (A.7) is also an additional area for improvement. The three criteria where the T&M particularly lag are A.2, A.3 and A.4. Almost all T&M need some level of expertise in a relevant domain (e.g. material science, exposure science, toxicology) to be able to use them (criterion A.2). With regards to the other two criteria, A.3 (multiple languages) and A.4 (availability of a license), most of the T&Ms are not available in multiple languages and do not have a license of use agreement.

The T&M with high complexity of use (e.g. SimpleBox4Nano), conceptual frameworks or methods (e.g. MARINA Framework), and which are only available and detailed within academic research papers (e.g. NanoDUFLOW model) typically rank lower in this pillar. Operationalizing and using these T&M require a greater effort on the part of end-users, making them less accessible as a result.

3.2.4 Applicability

The scores range between 0.4 to 0.88 in the Applicability pillar, with an average score of 0.67 (Figure 3). The details on the calculated scores for each T&M are shown in the Supplementary Information (Table S4). The top three scoring T&M within the applicability pillar are LICARA, ECETOC TRA and PM, with scores ranging from 0.83 to 0.88. The top ten ranking T&M of the pillar are all nano-specific, with the exception of ECETOC TRA. This is expected as 9 of the 14 T&M are nano specific and nano-specificity (i.e. P.3) is the heaviest weighted criterion (i.e. 5). ECETOC TRA performs well for every criterion due to having a very broad applicability domain, with the exception of P.3 (nano-specificity). Majority of the T&M and methods generally score lower for the criterion on applicable exposure routes and/or population (P.2) because they are specific to either one exposure route (e.g. inhalation, dermal) or one population type (e.g. worker, environment, consumer). Similarly, providing some advice on relevant measures to improve the assessment output to accepted level is out of scope for a lot of T&M due to which they score poorly for the criterion P.8 (advice on improvement of the result).

3.2.5 Completeness

The general scores of the T&M and methods for the completeness pillar range from 0.3 to 0.96, with an average score of 0.55 (Figure 3) which is lowest among all 5 pillars. The details on calculated scores for each T&M are shown in the Supplementary Information (Table S5). The overall top three scoring T&M are LICARA NanoScan, NanoSafer CB and LRI Ambit 2 with scores between 0.77 and 0.96.

Two exposure assessing T&M, i.e. SimpleBox4Nano, NanoDUFLOW Model, were not graded for this pillar, as their focus is on environmental fate for which several parameters like photoreaction, heteroaggregation, sulfidation etc., are highly relevant which can only be considered within an environmental fate dedicated module. The Completeness pillar is also not well-suited for conceptual T&M, like MARINA framework, due to which it was also not graded.

In terms of 5 modules (Figure 4), both NanoSafer CB and LRI Ambit 2 score highest (0.77) among human risk assessment T&M; ECETOC TRA has the highest score (0.55) among exposure assessment T&M; LICARA NanoScan scores higher (0.92) among the two T&M for socio-economic impact assessment as well as for environmental impact assessment (1). LRI Ambit 2 is the only remaining T&M (other than MARINA Framework) which belongs to environmental risk assessment module and scores 0.73. This illustrates that only a few of these T&M (with scores >0.7) have the potential to fulfill the new REACH regulatory requirements or high compatibility with the ECHA requirements for the risk or socio-economic assessment (SEA), wherever applicable. The details on calculated scores for each T&M in each module are shown in the Supplementary Information (Table S6).

3.3 Overall TRAAC score per T&M

The overall TRAAC score is also shown for each T&M in Figure 3, in which LICARA scores highest overall TRAAC score of 0.78 and MARINA framework scores lowest overall TRAAC score of 0.44. None of the studied T&M show a perfect or excellent TRAAC performance. The three best performing T&M, i.e. LICARA, ECETOC TRA and PM, show a ‘good’ performance (overall TRAAC score >0.7). The remaining 11 T&M show ‘average’ TRAAC performance with none of the T&M showing ‘poor’ performance.

3.4 In-depth analysis of LICARA nanoSCAN

The obtained scores for each criterion in each of the 5 pillars for the best performing tool, i.e. LICARA, are shown in Figure 5 (a) to (e). The scores shown in Figure 5 (a) indicate clear details about the tool developers, their contacts and public availability of the tool description for an easy understanding, which make the tool highly transparent (maximum score of 1 for T.1 to T.3). However, the output limitation boundaries of the tool are difficult for the user to identify (thus medium score of 0.5 to T.4) due to which a transparency score of 0.86 is attributed to the tool.

In terms of reliability (Figure 5 (b)), the factors like the availability of performance test of the tool (for some specific modules, e.g. worker and consumer risk assessment), scientific peer reviewed publication on the tool (van Harmelen et al. 2016) and collaborative effort towards the tool development during EU FP7 LICARA project make the tool to score highest (i.e. 1) for R.1, R.2 and R.6 criteria. On the contrary, the non-applicability of the quality of the data used during tool’s development and absence of user variability and tool’s uncertainty analysis make the tool to score lowest (i.e. 0.1) for R.3 to R.5 criteria and thus a low reliability score of 0.49 (lowest among all 5 pillars). LICARA nanoSCAN is accompanied by a basic conceptual guidance material (Som et al. 2014) and to operate the tool, some knowledge/expertise of the product and its life cycle processes are needed. These two factors make the tool to score 0.5 for A.1 and A.2 criteria (Figure 5 (c)). Apart from them, the tool and its guidance material are available in only one language (i.e. English) and it’s not liable for any license which make the tool score lowest (i.e. 0.1) for A.3 and A.4 criteria. In the contrast, the tool has been regularly cited in several publications, accessible via a

website and fairly easy and straightforward to use because of its modular structure. These positive attributes make the tool to score highest (i.e. 1) for the rest of the criteria and thus result in an accessibility score of 0.74.

The nanospecifity and full life cycle approach within the LICARA nanoSCAN tool makes it applicable for the analysis of MNMs and nanoproducts over all life cycle stages and for all routes of exposure. Consequently, it scores highest (i.e. 1) for P.1 to P.3 criteria (Figure 5 (d)). The semi-quantitative risk and benefit output scores of the tool, however, lower down the P.4 criterion score to 0.5. There are certain default values attributed for the unknown tool's input parameters due to which it is capable to work even when there are knowledge gaps. It is quick to use and has been further developed recently to fix certain architectural issues and extend beyond nanomaterials. These positive attributes help the tool to score highest for the P.5 to P.7 criteria. The tool scores poorly (i.e. 0.1) for the last criterion, P.8, because it does not provide any advice on relevant risk management measures to lower down the risk levels. Due to these factors, an applicability score of 0.88 is assigned to the LICARA nanoSCAN.

For the socio-economic impact assessment purpose, LICARA nanoSCAN tool scores high (1) for all criteria within Completeness pillar (Figure 5 (e)), except for C.3.6 (availability and suitability of alternative substances), thus attributing a high completeness score of 0.96. When assessed for environmental impact assessment, LICARA nanoSCAN scores perfect 1 (see Figure 4).

Based on these results, the LICARA nanoSCAN clearly needs some improvements in its reliability (criteria R.3 to R.5) and, to some extent, in its accessibility (mainly criteria A.1 and A.2) to perform better for the respective pillars and have better readiness for regulatory acceptance and wider stakeholder use.

4. Discussion

4.1 Designing TRAAC

The TRAAC framework, as developed in the current study, was designed as a structured approach to identify the potential readiness of T&M for the assessment of MNMs with respect to regulatory acceptance and stakeholder needs. As a proof of concept, the framework was tested with 14 selected T&M, providing insight into the usability of the framework. In addition, this exercise provided explorative insights into the strengths and weaknesses of these 14 investigated T&M by the use of this framework.

The TRAAC framework addresses the aspect of regulatory acceptance of T&Ms and methods through its 5 pillars on the basis of three elements: (i) regulatory compliance (compliance with the law, which is embodied by the Completeness pillar), (ii) trends in regulation (e.g. transparency, multi-stakeholder approaches), and (iii) values upheld by the regulatory institutions and stakeholders (e.g. veracity of data/scientific method, output correctness, open-access, and re-usability of knowledge). All five pillars of the framework are currently considered equally important for regulatory acceptance and usability, although that might not always be the case with T&M developers who may deem one pillar more critical than others (e.g. reliability compared to transparency).

4.2 T&M scoring

While scoring the T&M, it was observed that the T&M with the highest rankings achieved in general a good balance between the five pillars. However, the results showed that the most of the nano-specific T&M score consistently low for the reliability pillar particularly because of the lack of their validation studies and uncertainty analysis compared to the T&M used under REACH for conventional chemicals which are all checked on reliability (e.g. ECETOC TRA, Stoffenmanager and ART) (Kupczewska-dobecka et al.,2011; Delmaar et al., 2013; Hesse et al., 2015; Lamb et al., 2015; Riedmann et al., 2015; Jung et al., 2016; Marquart et al., 2017; van Tongeren et al., 2017; Franken et al., 2020). This aspect will likely change though with the advent of the recently accomplished OECD initiative on the assessment of T&M accessibility, sensitivity and performance in regard to nano-specific environmental, consumer and occupational exposure assessment (OECD 2021), indicating a possible shift from development of new T&M, towards validation of existing T&M for their nano-specificity.

In the context of the Completeness pillar, low scores of most of the T&M was observed in each module. The performance further lowers down in the case of 'human exposure assessment' module. The reason for such a low performance can be attributed to the fact that these T&M are limited to particular exposure routes (e.g. inhalation, dermal, oral) and, therefore, their input and output information are relevant to only those exposure routes. The criteria within the Completeness pillar, on the other hand, are constituted in such a way that they are relevant to any exposure route in accordance with the regulatory requirements. The criteria, thus, inadvertently lower down the individual Completeness scores of T&M. Consequently, for these T&M to score higher, they have to improve their applicability to multiple exposure routes (criterion P.2 in Applicability pillar).

The TRAAC framework is intended to be easy to use when grading a variety of T&M. However, a certain degree of knowledge on the T&M is needed to apply it. Some literature search is also required to assess some of the criteria (e.g. investigate for available validation studies, available guidance documents and publications with regards to the T&M), which was found to be occasionally time consuming and the information was scattered over different sources. Therefore, the intended target users of this framework are regulators or industrial users of existing T&M who are interested in assessing the regulatory readiness of a certain T&M or T&M developers who can specifically investigate where their T&M might improve upon in future updates.

From the experiences of previous EU projects (e.g. NANoREG2, caLIBRAte), it has been observed that the qualitative T&Ms which require less data and are considered quicker to operate are preferred by the stakeholders, particularly SMEs, over more complicated (and often quantitative) ones because the latter can require data inputs which are often unknown. The general lack or low availability of the data/information on human or environmental impact of rapidly innovated MNMs basically accentuates this constraint. Although the qualitative T&M serve their purpose of risk screening in especially the early stages of innovation value chain, and can help users set "red-flags" based on possible health risks, or lack of benefits, they provide the output with higher uncertainty than the quantitative ones which are more to be used along the later stages of innovation value chain when more data/information is known. Shandilya et al. 2020b and Soeteman-Hernandez et al. 2019a recommend the use of certain T&M type based on the stage within the innovation value chain: the higher the stage level within the innovation process, more quantitative the T&M is to be used and relied upon.

Within the Reliability and Accessibility pillars, there are two respective criteria named as Uncertainty analysis (criterion R.5) and Quantitative output (criterion P.4) which give higher scores to the quantitative T&M (e.g. FNN-BBN) than to the qualitative ones (e.g. PM), which in the perspective of legislative frameworks is logical considering quantitative input is required in the product registration dossiers. On the other hand, the Accessibility and Applicability pillars consider respective criteria named as User-friendliness (criterion A.7) and Time and cost efficiency (criterion P.6) for which qualitative T&M score higher over quantitative ones. Thus, at the end, any undue advantage over the T&M type (qualitative or quantitative) balances out and the TRAAC framework allows for an unbiased assessment.

4.3 Strengths, limitations and future perspectives

This study investigates how available T&M can be assessed for their regulatory and wider use readiness in a structured manner and as objectively as possible. This is especially important in the field of nanomaterial science as the field progresses quickly and numerous T&M are continuously developed and introduced while regulators and industries have difficulty in selecting the most appropriate T&M for their use. The vast majority of the criteria proposed within the TRAAC framework is based on a literature search of (i) existing regulatory frameworks, (ii) stakeholders needs in regards to MNMs governance and (iii) T&M for the assessment of MNMs for their human and environmental risk as well as socio-economic impacts. This ensures that the needs brought forward by the TRAAC framework for the further development of the T&M for improving their potential for regulatory acceptance and downstream use are supported and grounded in literature as well as supported by the current vision of the stakeholders' needs. This helps in imparting regulatory preparedness, as underlined within Safe Innovation Approach (Soeteman-Hernández et al. 2019b) and constitutes the main strength of the TRAAC framework.

In addition, the entire framework, its pillars, criteria and its weights have been reviewed by experts in the field of nano risk assessment which led to some reconsiderations and improvements of certain criteria descriptions and weighting of the relevance of these criteria. Different pillars and modules in the TRAAC framework allows for a flexible structure of the framework which can be customized depending on the needs of its user. This also includes the customization of the allotted weights and scores to the criteria within each pillar.

Moreover, the results of the case study on 14 T&M showed that the overall results provided by the TRAAC framework seem to correlate well with the results obtained in previous reviews of the existing T&M which considered T&M assessment with regards to stakeholder needs and available regulations (Franken et al., 2020; Sorensen et al., 2019; Isigonis et al., 2019; Trump et al., 2017). These review studies also considered some of the top performing T&M in the TRAAC framework, e.g. LICARA NanoScan, NanoSafer CB and Stoffenmanager nano, as promising options for supporting risk governance for MNMs.

The TRAAC framework also has the potential to be useful for T&M developers themselves, as it allows for them to identify the strengths and weaknesses of their T&M, identify areas of concern and future opportunities for improvement of their T&M.

While several strengths were identified, some limitations must be considered as well. With regards to the reliability assessment, the framework currently assesses it through several criteria, but occasionally it is sufficient to simply indicate that certain information with regards to a T&M is known. For example, a T&M receives a score of 1 when the uncertainty around the T&M results is known and reported. However, the current framework does not state what level of uncertainty is acceptable for regulatory acceptance. Similarly, it is stated that a T&M needs to be validated preferably with data, but the framework does not set conditions to when a T&M can be considered validated. The framework, thus, can be refined and updated in the future in this particular context. In addition, the framework can further include a thorough assessment of the scientific quality of the T&M, which will require the results of the performance testing or validation study and establishing proper metrics to measure the performance of a T&M (OECD 2021). With regards to the Completeness pillar, it was developed using REACH as an example. Further developments in the pillar can address other regulatory frameworks as well, like the CLP 1272/2008 or the cosmetics regulation (EC 1223/2009).

Currently, the TRAAC framework has been designed to evaluate only T&M. In the future, the use of the framework is planned to be further extended to consider data, information and knowledge readiness level (i.e. KaRL) for an efficient risk governance. This effort is currently being undertaken within the framework of EU NMBP-13 NANORIGO project. This will include the data stored as resource and managed according to formal data resource management concepts, principles, and techniques.

5. Conclusion

By developing a multi-faceted and multi-criteria approach, founded upon an extensive literature search and the current regulatory requirements for MNMs, the TRAAC framework proved to be a useful tool to evaluate T&M for the safe innovation or safe-by-design of MNMs against five pillars: Transparency, Reliability, Accessibility, Applicability, and Completeness. The framework aimed to achieve three goals: (i) investigate whether the results from T&M are ready to be accepted in regulatory context and widespread use by the stakeholders, (ii) increase the trust and confidence of the stakeholders in the T&M, and (iii) demonstrate the use of the framework and the interpretation of its results by assessing several existing T&M. The concept and the structure of the TRAAC framework were found to be overall adequate to evaluate the selected list of the 14 T&M in the context of framework's aims.

Declarations

Acknowledgement

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Figures

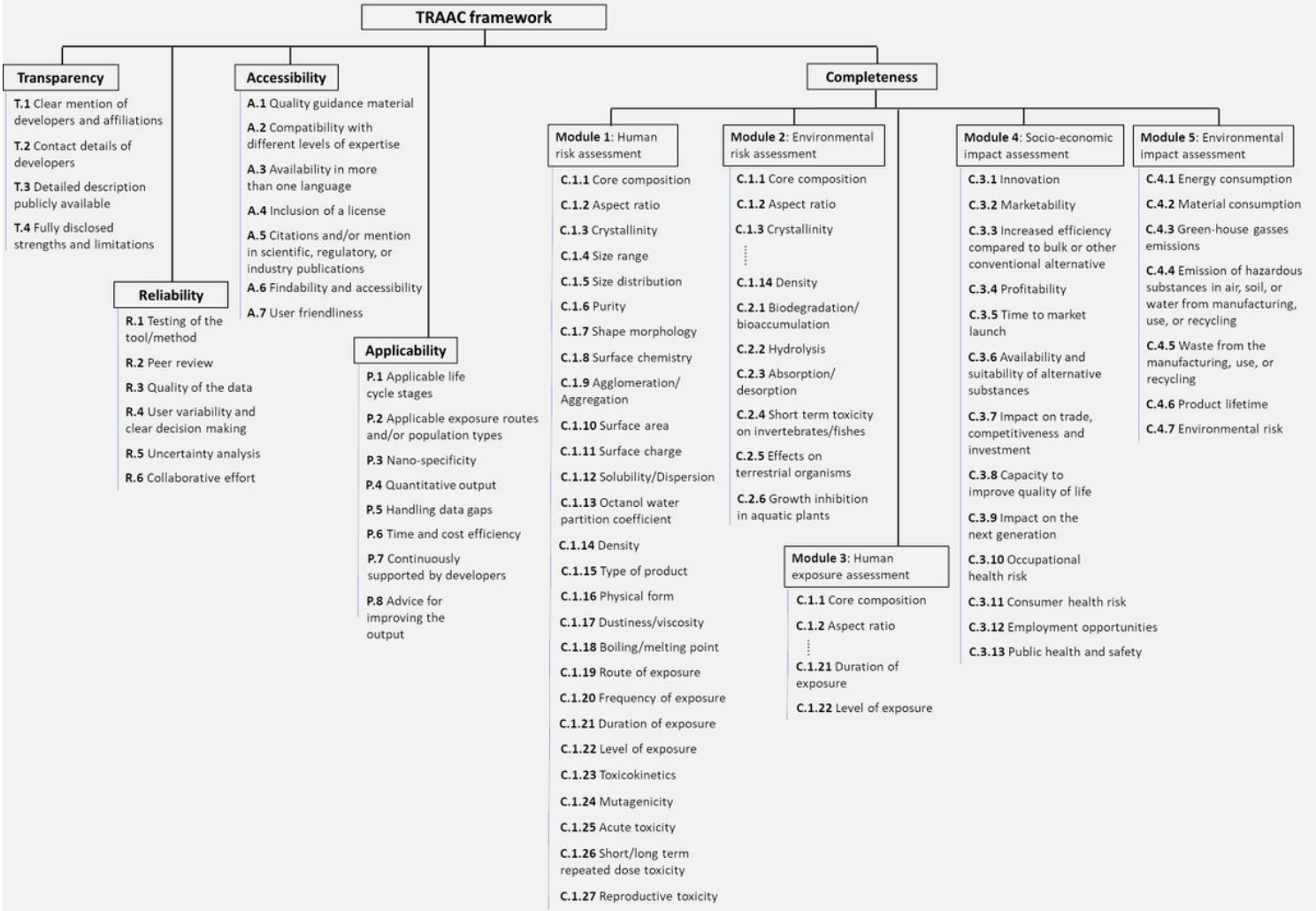

Figure 1

Overview of the TRAAC framework: five pillars of the framework, i.e. Transparency, Reliability, Accessibility, Applicability and Completeness, and their respective constituting criteria; five modules within the Completeness pillar are also shown with the parameters/criteria for the completeness evaluation within each module.

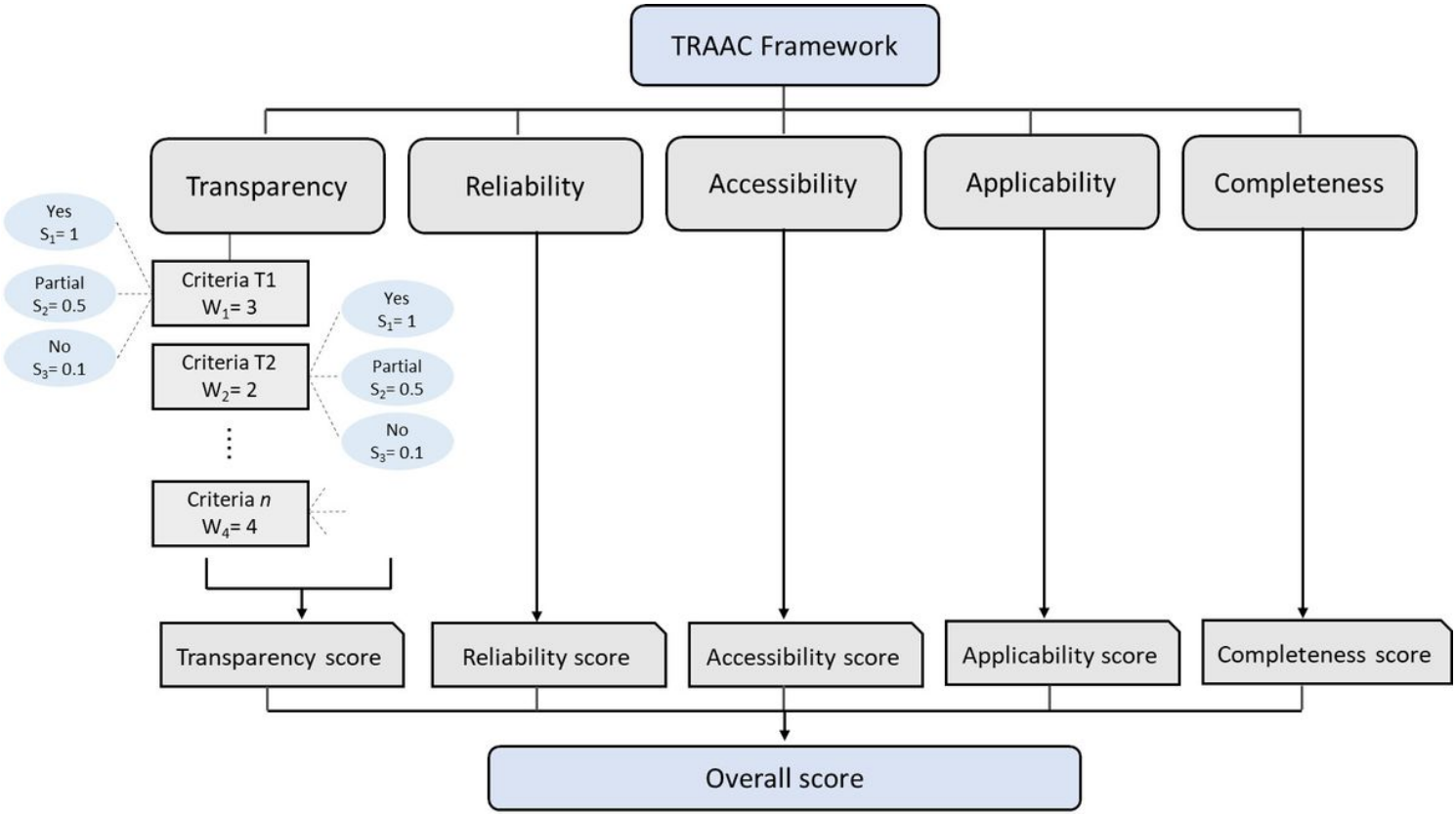

Figure 2

Scoring system in TRAAC framework

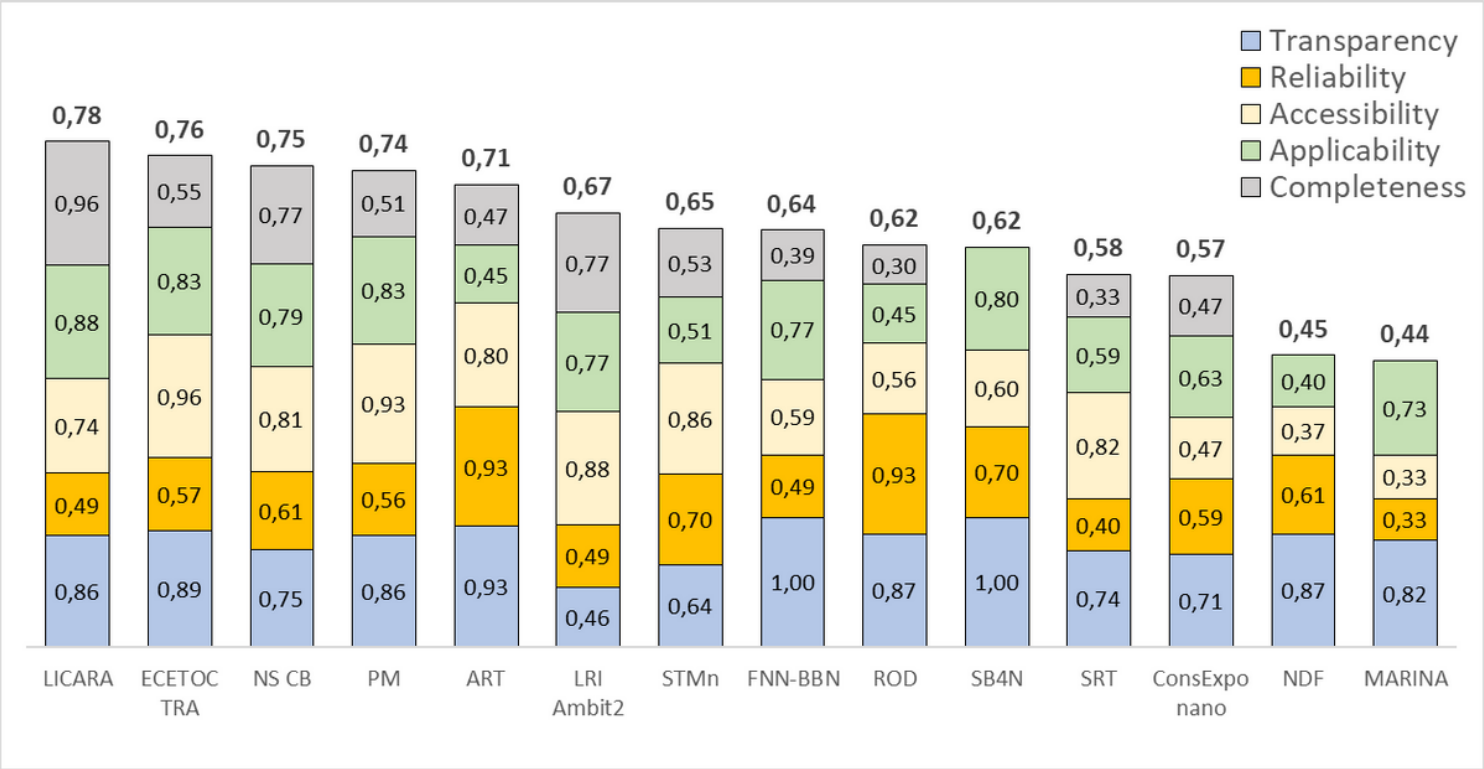

Figure 3

Overall scores for the TRAAC framework. From left to right: LICARA NanoScan (LICARA), ECETOC-TRA, Precautionary Matrix for synthetic nanomaterials (PM), Stoffenmanager Nano (STMn), Nanosafer Control Banding (NS CB), Advanced REACH Tool (ART), LRI Ambit-2, Future Nano Needs Bayesian Belief Network (FNN-BBN), RiskofDerm (ROD), SimpleBox4Nano (SB4N), ConsExpo nano, The NewHoRRIzonSocial Readiness Thinking Tool (SRT), NanoDUFLOW (NDF) and

the MARINA Framework (MARINA). For each T&M, score per pillar is shown in the pillar dedicated colour band and overall score (all pillars combined) is shown at the top of each bar.

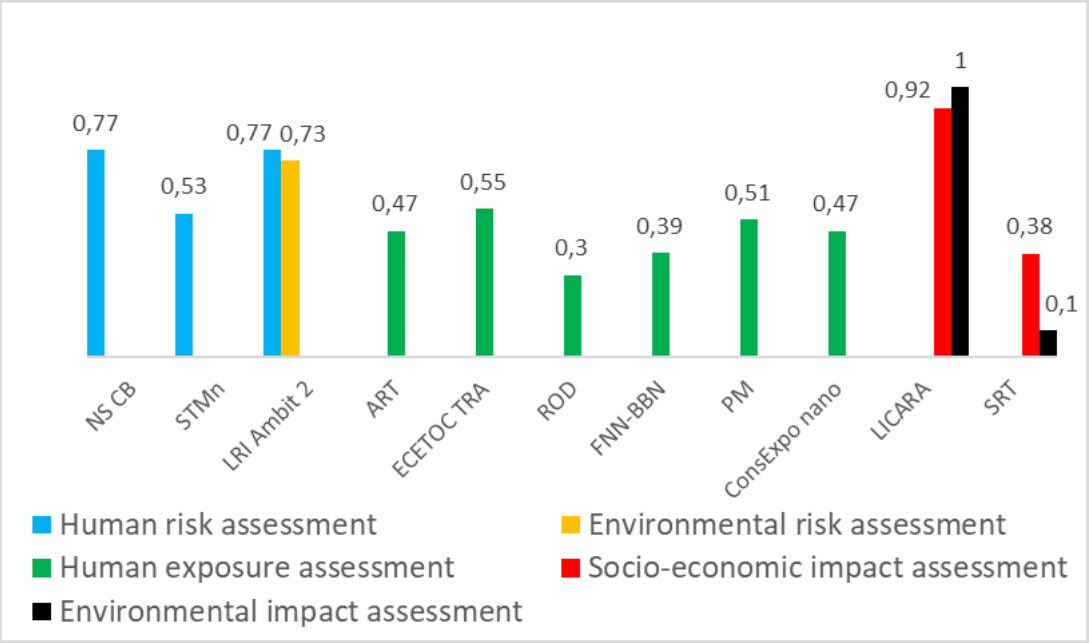

Figure 4

Scores for each module in the Completeness pillar. From left to right: Nanosafer Control Banding (NS CB), Stoffenmanager Nano (STMn), LRI Ambit-2, LICARA NanoScan (LICARA), The NewHoRRIzonSocial Readiness Thinking Tool (SRT). Score for each T&M is shown over the module dedicated colour bars.

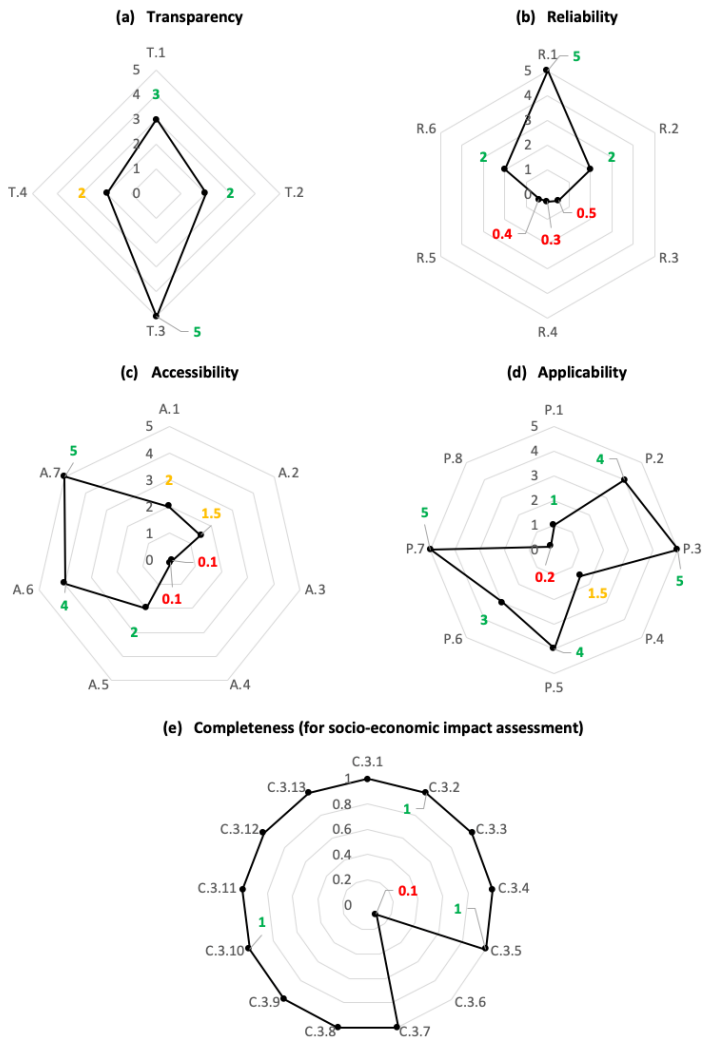

Figure 5

LICARA nanoSCAN scores for **(a)** Transparency pillar **(b)** Reliability pillar **(c)** Accessibility pillar **(d)** Applicability pillar **(e)** completeness pillar (for socio-economic impact assessment) of the TRAAC framework; highest scored criteria (i.e. 1) are shown in green font colour, medium scored criteria (i.e. 0.5) are shown in orange font colour (wherever applicable) and lowest scored criteria (i.e. 0.1) are shown in red font colour; axis values and criteria codes are shown in black font colour.

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