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ARTICLE

A methodology for the automatic evaluation of data quality and completeness of nanomaterials for risk assessment purposes

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ABSTRACT

This manuscript proposes a methodology to assess the completeness and quality of physicochemical and hazard datasets for risk assessment purposes. The approach is also specifically applicable to similarity assessment as a basis for grouping of (nanoforms of) chemical substances as well as for classification of the substances according to the Classification, Labeling and Packaging regulation. The unique goal of this approach is to assess data quality in such a way that all the steps are automatized, thus reducing reliance on expert judgment. The analysis starts from available (meta)-data as provided in the data entry templates developed by the NanoSafety community and used for import into the eNanoMapper database. The methodology is implemented in the templates as a traffic light system—the providers of the data can see in real time the completeness scores calculated by the system for their datasets in green, yellow, or red. This is an interactive feedback feature that is intended to provide an incentive for anyone inserting data into the database to deliver more complete and higher quality datasets. The users of the data can also see this information both in the data entry templates and on the database interface, which enables them to select better datasets for their assessments. The proposed methodology has been partially implemented in the eNanoMapper database and in a Weight of Evidence approach for the regulatory classification of nanomaterials. It was fully implemented in a publicly available online R tool.

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1. Introduction

Using high-quality data is essential for the robust and reliable risk assessment of chemical substances, including engineered nanomaterials (NMs) (Marchese Robinson et al. 2016). It is indeed fundamental for risk assessors to be aware of the quality of the datasets that they use and of the degree of completeness of the (meta)data in respect to the minimum regulatory requirements and the state-of-the-art scientific knowledge. The use of data with insufficient quality and/or of incomplete data may result in risk assessment outcomes, which are too uncertain to adequately support regulatory or risk management decision making. Using high-quality data is also essential for making scientifically justified decisions related to the grouping of substances as a basis for read-across of information for purposes ranging from safe-by-design to regulatory risk assessment and management (ECHA 2017a; Loosli et al. 2022). Specifically, using high-quality data for similarity assessment is as an important prerequisite for well-substantiated grouping decisions (Jeliazkova et al. 2022; Seleci et al. 2022; Tsiliki et al. 2022; Zabeo et al. 2022). Similarly, the classification of substances according to the Classification, Labeling and Packaging (CLP) regulation (European Parliament and Council 2008) requires robust physicochemical and (eco)toxicity datasets thoroughly assessed for their quality and completeness (ECHA 2017a).

The evaluation of data quality is not only required for risk assessment but also for underlying tasks such as predictive modeling of properties, (eco)toxicity (Basei et al. 2019; Furxhi et al. 2020a,

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2020b), toxicokinetics, toxicogenomics (Saarimäki et al. 2021), and exposure (Furxhi et al. 2021). Generic definitions for data completeness and data quality, which are now agreed upon by the nanosafety community, were provided by Marchese Robinson et al. (2016), namely: *data completeness* is a measure of the availability of the necessary, non-redundant (meta)data for a given entity, e.g. an NM or a set of NMs, while *data quality* is a measure of the potential usefulness, clarity and correctness of data and datasets.

Several approaches have been proposed to assess the quality (Klimisch et al. 1997; Card and Magnuson 2010; Lubinski et al. 2013; Hristozov et al. 2014; Moermond et al. 2016; Hartmann et al. 2017; Fernández-Cruz et al. 2018; Krug et al. 2018) and completeness (Comandella et al. 2020) of nanospecific datasets, many of which are based on the methodology proposed by Klimisch et al. in 1997 (Klimisch et al. 1997). However, none of those approaches is capable of automatically (i.e. programmatically) assessing data completeness/quality, as all of them almost exclusively rely on expert judgment. This makes them less suitable to be implemented into the current and emerging nanosafety databases (such as NanoSafety Data Interface https://search.data.enanomapper.net based on eNanoMapper database (Jeliazkova et al. 2021)) as well as into risk assessment and management software tools, such as SUNDS (Hristozov et al. 2018; Pizzol et al. 2019; Cazzagon et al. 2022), to enable seamless data quality and completeness analysis and communication.

To fill this gap, we propose a novel methodology to facilitate automated assessment of quality and completeness for sets of nanospecific physicochemical and (eco)toxicity (meta) data. The purpose of this approach is to support regulatory risk assessment, but it is also applicable to other related tasks such as similarity assessment and grouping, as well as to the classification of nanomaterials according to the CLP regulation (European Parliament and Council 2008). The goal of this approach is to define data quality and completeness scores and enable their computation in such a way that all the steps are automatized, thus reducing as much as possible the need of expert judgment. This is done starting from the GRACIOUS/NANoREG templates (Totaro et al. 2017; Gottardo et al. 2019) used to collect data in a structured way for input into the eNanoMapper database. The average of the computed scores for the templates comprising a dataset represent the overall quality and completeness scores for the particular dataset. Based on the calculated scores, a 'traffic light' indicator is assigned to each template/dataset: i.e. green, yellow or red. These colors can be displayed in real time both in the web browser when assessing the NanoSafety Data Interface and when downloading the results in the format of data reporting templates. This on one hand could serve as an incentive for data providers to insert more complete and higher quality data in the database, while on the other hand it can guide risk assessors in the selection of better datasets.

Our methodology has been partially implemented in the eNanoMapper database to enable real-time analysis of the completeness of each dataset that is included in it, as well as in a Weight of Evidence (WoE) approach for CLP classification of NMs (Basei et al. 2021). The methodology is also available as an online R tool (https://shinyapps.greendecision.eu/apps/gracious-data-quality), which was designed specifically to be interoperable with eNanoMapper as well as with other software tools, including decision support systems for risk assessment and management of NMs and other chemicals such as SUNDS (https://sunds.gd).

This article is structured as follows. In Section 2, the steps taken to develop the data completeness and quality assessment methodology are described. This includes (1) a literature review to identify other existing methods to learn from and the most relevant criteria to consider as a basis for our approach, and (2) results from a stakeholder workshop which was organized in June 2021 to discuss our methodology and collect constructive feedback from its potential users (>80 participants) on how to improve it. The results of the literature review are summarized in Section 3. The same section also describes in detail the proposed data completeness and quality assessment methodology and its implementation in the eNanoMapper database and as the online R tool. Moreover, the results of applying the methodology to a case study of silver nanoparticles (i.e., JRCNM03000a, NM-300K, Ag 16.7 nm) are presented. Finally, Section 4 discusses the strengths and limitations of the proposed approach and outlines the next steps for its further development and implementation.

2. Materials and methods

2.1. Literature review on existing data quality criteria

To develop this methodology, we first performed a literature review to identify the most suitable criteria to assess the quality and completeness of nanosafety (meta)data. Based on the review, we created an inventory of criteria as well as relevant tools and methodologies (*GRACIOUS deliverable 6.1: Requirements for data quality criteria, data sources, modelling tools and terminology* 2021) to operationalize those. This inventory was regularly updated in a period of 36 months to include any new approaches as they became available.

Then, we selected from the collected approaches the ones that address the criteria for evaluation of the quality of data to be used for safety assessment of chemicals (including nanomaterials), as defined in the European Chemical Agency's (ECHA) guidance on Information Requirements and Chemical Safety Assessment (IR&CSA) (ECHA 2011).

Such criteria are as follows:

- *Data completeness* refers to the degree to which all required (meta)data in a data set is available.
- *Data relevance* measures if a study was conducted using agreed (standard) protocols/procedures.
- *Data reliability* measures if a study was conducted in a reliable manner.
- *Data adequacy* defines the usefulness of the data for risk assessment purposes.

These approaches are reported in Section 3.1, and we used them as a basis to develop our methodology in co-creation with stakeholders from industry, regulation, and academia via a dedicated workshop (cf. Section 2.2). Our approach automatically (i.e. programmatically) assigns a score related to each of the four criteria starting from the available (meta)data (cf. Section 2.3), as it is described in detail in Section 3.2.

2.2. Workshop with stakeholders

On 28 of June 2021, a 'virtual' workshop[1] was organized in the frame of the EU H2020 Gov4Nano and GRACIOUS projects. The goal was to collect feedback from stakeholders on the robustness of the proposed approach for assessment of data quality and completeness. The discussion topics of the workshop ranged from the conceptual basis of the methodology, through its mathematical representation, to the specifics of its implementation in the GRACIOUS/NANoREG harmonized data reporting templates (cf. Section 2.3) and as part of the eNanoMapper database to enable real-time analysis of each dataset that is included in it.

The workshop was open to data experts and risk assessors from industry, regulation, and academia. More than 80 participants, mainly from Europe, attended the workshop. To collect stakeholders' feedback, 16 questions related to each aspect of the methodology were asked to the audience by using Slido.[2] These questions and the results of the workshop are reported in Section S1 of the Supplemental Information (SI). The results were used as starting point for improving and further refining our methodology.

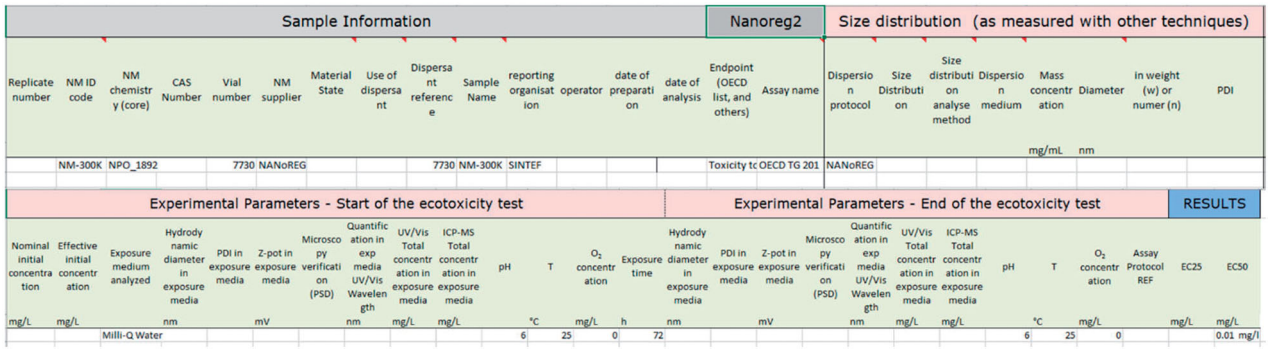
2.3. NANoREG data reporting templates

The methodology is based on the evaluation of quality and completeness of data included in the eNanoMapper database by means of the harmonized data reporting templates introduced by the NANoREG (Totaro et al. 2017) project and further advanced in the GRACIOUS project (Gottardo et al. 2019). These templates are in fact an extension of OECD[3] data reporting templates. An example of such a data entry template is presented in Figure 1.

The information provided in the data entry templates is submitted to the FAIRification workflow (Jeliazkova et al. 2021) developed for the eNanoMapper database during the data integration activities across several nanosafety projects and recently described in Kochev et al. (2020). Once in the eNanoMapper database, the data is available via an Application Programming Interface (API)[4] and can be exported or visualized in the eNanoMapper user interface as illustrated in Figure 2. In this example, the data on NM-101 include results from four ecotoxicity studies, 157 physicochemical experiments and 130 toxicological studies.

Specifically, the properties and (eco)toxicological results for the NMs are listed under the following tabs:

- *P-Chem,* which includes results related to physicochemical characterization.



Sample Information														Nanoreg2	Size distribution (as measured with other techniques)							
Replicate number	NM ID code	NM chemistry (core)	CAS Number	Vial number	NM supplier	Material State	Use of dispersant	Dispersant reference	Sample Name	reporting organisation	operator	date of preparation	date of analysis	Endpoint (OECD list, and others)	Assay name	Dispersion protocol	Size Distribution	Size distribution analyse method	Dispersion medium	Mass concentration	Diameter	in weight (w) or numer (n)	PDI
																				mg/mL	nm		
	NM-300K	NPO_1892		7730	NANoREG			7730	NM-300K	SINTEF				Toxicity to	OECD TG 201	NANoREG							

Experimental Parameters - Start of the ecotoxicity test														Experimental Parameters - End of the ecotoxicity test										RESULTS	
Nominal initial concentration	Effective initial concentration	Exposure medium analyzed	Hydrodynamic diameter in exposure media	PDI in exposure media	Z-pot in exposure media	Microscopy verification (PSD)	Quantification in exp media UV/Vis Wavelength	UV/Vis Total concentration in exposure media	ICP-MS Total concentration in exposure media	pH	T	O_2 concentration	Exposure time	Hydrodynamic diameter in exposure media	PDI in exposure media	Z-pot in exposure media	Microscopy verification (PSD)	Quantification in exp media UV/Vis Wavelength	UV/Vis Total concentration in exposure media	ICP-MS Total concentration in exposure media	pH	T	O_2 concentration	Assay Protocol REF	EC25	EC50
mg/L	mg/L		nm	mV		nm		mg/L	mg/L		°C	mg/L	h	nm	mV		nm		mg/L	mg/L		°C	mg/L		mg/L	mg/L
		Milli-Q Water								6	25	0	72								6	25	0			0.01 mg/l

Figure 1. Example of data reporting template for an ecotoxicological study, partially filled with information related to a specific study.

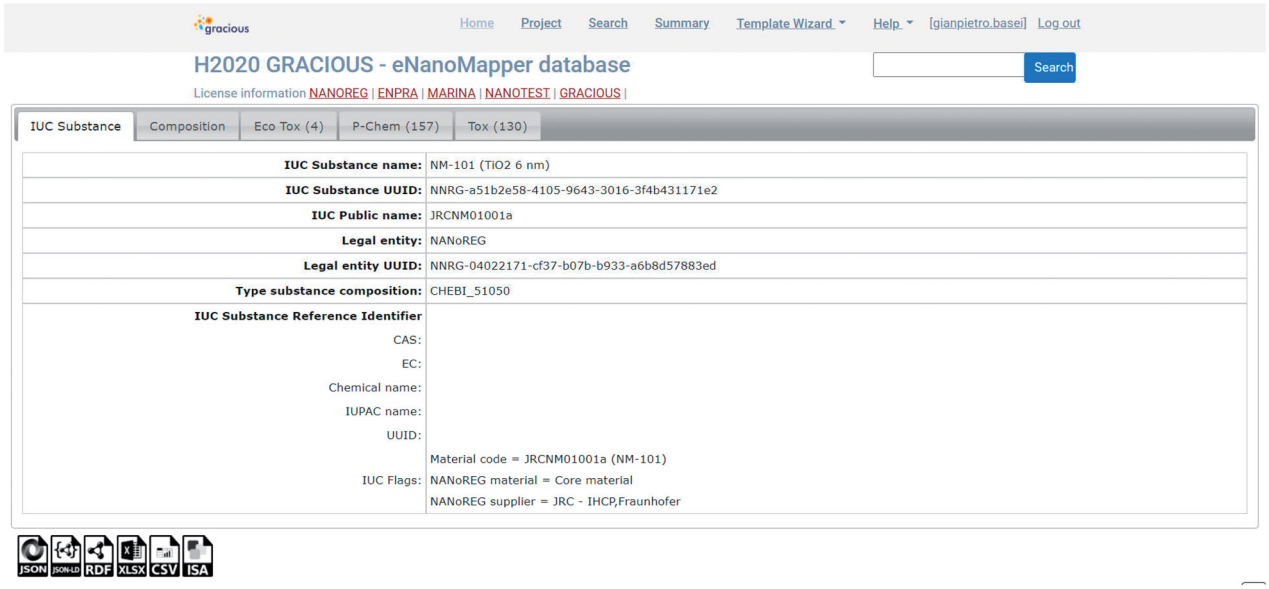


Figure 2. Details and studies for a particular material (here TiO_2) in the eNanoMapper database. For this particular NM, data related to ecotoxicological studies (4 studies), physicochemical studies (157 studies) and toxicological studies (130 studies) are available. Data is structured according to the eNanoMapper data model (Jeliazkova et al. 2015; Kochev et al. 2020).

- *Eco Tox*, related to the ecotoxicological characterization, including aquatic toxicity, toxicity to terrestrial and soil organisms, and toxicity to terrestrial plants.
- *Env Fate*, which includes studies related to environmental fate.
- *Tox*, which is related to results relevant to effects to human health, including (depending on the availability) human and animal data derived either *in vivo*, *in vitro*, or *in silico*.
- *Exposure*, which includes exposure estimates in occupational or consumer scenarios.

If there is no data available for a specific tab, that tab is omitted (in the example of Figure 2 these are Env Fate and Exposure).

2.4. Case studies to demonstrate the data quality assessment methodology

The methodology was tested using data from the GRACIOUS instance of the eNanoMapper database (Jeliazkova et al. 2015). This includes data generated in the following European projects: GRACIOUS, ENPRA, MARINA, NanoGRAVUR, NANoREG, NanoTest, and SANOWORK.[5] This data refers to three main categories: physicochemical endpoints, toxicological endpoints, and ecotoxicological endpoints. We extracted data from this database collecting a total of 81 860 entries[6] (17 810 of these related to physicochemical endpoints, 63 655 related to toxicological endpoints, and 395 related to ecotoxicological endpoints) on 323 nanoforms of different NMs.

To test the methodology, we selected from this collection as case study the nanoscale silver material JRCNM03000a (NM-300K, Ag 16.7 nm), and we limited the analysis to physicochemical and hazard data generated in the context of the NANoREG project (Dusinska et al. 2016, NANoREG 2016a, 2016b). The reason was that data coming from this project was publicly available at the time of the analysis. Furthermore, according to data availability we selected as endpoints 'Aquatic Toxicity' and 'Genotoxicity,' as described in S2 of the SI.

Duplicates were removed and partial duplicates (entries referring to the same measurement but providing complementary information about it) were combined generating one individual result per study. Erroneously reported information in the original data was corrected. Specifically, NM names were harmonized to be the same in all entries, and information inserted in wrong columns (i.e. parameters) was moved to the correct one. Empty columns, with the only exception of columns required by data reporting templates, were removed.

After this process, the dataset was narrowed down to a total of 9 aquatic toxicity and 44 genotoxicity studies available for the target material.

3. Results

3.1. Relevant approaches for assessing quality and completeness of nanosafety physicochemical and hazard datasets

The data quality assessment approach by Klimisch et al. (Klimisch et al. 1997) was originally developed as a response to the requirements of the EU Existing Substances Regulation (European Commission 1994), a predecessor of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) (European Commission 2006) regulation. Specifically, as part of the reporting requirements to industry, any hazard data for the substance was expected to be entered into its IUCLID (International Uniform Chemical Information Database) record (Alessandrelli and Polci 2011), together with an assessment of the relevance, reliability, and adequacy of the data. This approach to quality categorization has enabled substance IUCLID records to be structured in a manner that allows primary data and metadata to be displayed in a manner that is scientifically valid, repeatable, and consistent across substances (Money et al. 2013). Since then, the Klimisch methodology has been widely applied to assessing the quality of human and environmental toxicity data for chemical substances, and more recently, it inspired the introduction of approaches for quality assessment of nanospecific physicochemical and hazard datasets (cf. Table 1).

However, most of these approaches almost exclusively rely on expert judgment, which makes them unsuitable to be implemented as part of a methodology for the automatic assessment of data quality and completeness. For automatic assessment, the criteria need to be defined in such a way that quality and completeness can be directly inferred from the available metadata.

One approach for evaluation of completeness of physicochemical (meta)data that we considered a suitable basis to achieve automatization was proposed by Comandella et al. (2020). Therefore, we included this approach in our methodology and extended it to cover also human and environmental toxicology studies. This resulted in an approach that is capable of automatically assigning quality and completeness scores according to the four selected principal quality criteria (i.e. completeness, relevance, reliability, and adequacy). This methodology is described in Section 3.2.

3.2. Data quality and completeness assessment methodology

3.2.1. Data completeness assessment

Our approach evaluates data completeness for an (eco)toxicological study, with respect to the provided information related to both the physicochemical characterization and to the testing procedure and test conditions. This is an extension of the work of Comandella et al. (Comandella et alet al. 2020), who proposed the evaluation of (meta)data completeness considering 11 measured physicochemical properties: i.e. crystallinity, composition, particle size, surface chemistry, particle shape, specific surface area, surface charge, surface hydrophobicity, dustiness, water solubility and density. This data is either required by REACH for nanoform identification or are recommended by ECHA as a

Table 1. State-of-the-art criteria for evaluating data quality and completeness.

Criteria \ Ref	Completeness	Reliability	Relevance	Adequacy	Additional criteria
(Klimisch et al. 1997)	NA	Four categories ('Reliable without restrictions,' 'Reliable with restrictions,' 'Not reliable,' and 'Not assignable) based on 12 criteria for acute studies and 14 for chronic studies.	Covers the extent to which data and tests are appropriate for risk assessment.	Defines the usefulness of data for risk assessment purposes.	NA
(Card and Magnuson 2010)	List of 10 key physicochemical properties adequately characterizing NMs in human toxicity studies. Results in a score 0-10.	Base of ToxRTool. Generic questions related to 1) Test substance identification; 2) Test system characterization; 3) Study design description; 4) Study results documentation and 5) Plausibility design and results.	NA	NA	NA
(Lubinski et al. 2013)	NA	Based on Klimisch criteria, focused on quality for QSAR models	NA	NA	Usefulness of the data for developing computational models: The Klimisch criteria have been expanded and revised to take into account the specific nature of nanomaterials, which differs from bulk compounds in terms of size, shape, and surface properties, etc. (related to 'quality'). In addition, the dataset size is considered as a fundamental criterion for assessing usefulness for computational modeling.
(Hristozov et al. 2014) (ENPRA/ MARINA/SUN)	NA	As in Klimisch et al. (Klimisch et al. 1997).	NA	The two main types of toxicological studies (i.e. *in vivo* and *in vitro*) are considered and weighted differently, moreover such studies are subdivided by means of the route of exposure.	Statistical power: statistical significance and sample size. Toxicological significance: relevance of the dose used in the test system.
(Moermond et al. 2016)	NA	Concerns the intrinsic scientific quality of the study, regardless of the purpose for which it is assessed. It is determined by an assessment of the design, performance, and analysis of the experiment. Four categories: reliable without restrictions (R1), reliable with restrictions (R2), not reliable (R3), and not assignable (R4). Based on 20 criteria related to Test setup, test compound, test organism, exposure conditions, statistical design, and biological response.	Relevance depends on the purpose of the assessment and concerns the way the study will be used for a specific purpose. 4 relevance categories: relevant without restrictions (C1), relevant with restrictions (C2), not relevant (C3), and not assignable (C4). Based on 13 criteria related to biological relevance and exposure relevance.	NA	NA

(*continued*)

Table 1. Continued.

Criteria \ Ref	Completeness	Reliability	Relevance	Adequacy	Additional criteria
(Hartmann et al. 2017)	NA	Reliability categorization of nanomaterial ecotoxicity based on 1) the appropriateness of the study design for the purpose of nanomaterial testing, 2) documentation provided on the study design, 3) data on nanomaterial properties and d) nanomaterial characterization in the test system and during the test. Revised version of Moermond et al. (Moermond et al. 2016), specific for NMs, where each criterion has different weights (1, low importance, to 3, critical importance)	Revised version of the criteria defined by Moermond et al. (Moermond et al. 2016), with nano-specific guidance on certain criteria. Not weighted, as opposed to reliability.	NA	NA
(Fernández-Cruz et al. 2018) (GUIDEnano)	Substance characterization score, based on a modified version of the work proposed by Card & Magnusson (Card and Magnuson 2010).	Based on a Modified version of the ToxRTool, reducing as much as possible the need of expert judgment. Applies for in-vivo and invitro data (Human Health) as well as ecotoxicological data. Questions are divided in three groups: test organism characterization, study design description and results documentation.	NA	NA	NA
(Krug et al. 2018) (DANA/ NanoGRAVUR)	Minimum information checklist: criteria adopted in DANA database to evaluate scientific literature before inserting it in the knowledge base. It consists of a set of minimum information that must or might be provided (related to Physicochemical properties, sample preparation, testing parameters and other general aspects, i.e. if data evaluation/ statistics are provided or whether a SOP was used). Also related to data reliability.	NA	NA	NA	NA
(Comandella et al. 2020)	Based on 11 physicochemical properties and 30 associated experimental techniques, a Completeness Score (CS) is computed for each entry of a template related to a study as the number of items reported divided by the number of	NA	NA	NA	NA

(*continued*)

Table 1. Continued.

Criteria \ Ref	Completeness	Reliability	Relevance	Adequacy	Additional criteria
	items required. This then is averaged for each material to compute the CS for 'a template' and may be further generalized to compute a CS for a query.				
(Basei et al. 2021) (partial implementation of the methodology described in this paper).	Same as Comandella et al. (Comandella et al. 2020), extended to also consider (eco)toxicological data reporting templates	Based on ToxRTool/ NanoCRED tool outcomes.	Based on the relevance of the adopted protocol with respect to the endpoint (protocols suggested by ECHA CLP guidance or IR&CSA guidance are prioritized)	*In vivo* data is considered more reliable than data obtained *in vitro* or *in silico*.	NA

NA = Not assessed, or not directly assessed.

basis for grouping (Comandella et al. 2020). In addition, we propose to evaluate in the same way the completeness of reported (meta)data for human and environmental toxicology endpoints, thus covering completeness of information related to the testing procedure (e.g. reference to the Standard Operating Procedure, the tested endpoint, the assay name, etc.) and test conditions (e.g. the adopted dispersion protocol and medium, the concentration, details on the cell lines and culture conditions, etc.).

Specifically, the Completeness Score (CS) of the data in a data reporting template is defined as the number of items (parameters) *reported* in a data entry template (cf. Section 2.3) divided by the number of items (parameters) *required* by the templates related to the eleven physicochemical properties.

Mathematically, given the set of required templates for physicochemical endpoints, the Completeness Score of the *i*th template in the set ($CS_{template_i}$) is computed as follows:

$$\mathrm{CS}_{template_i} = \frac{\text{number of items available}}{\text{number of items required by template}} \quad (1)$$

Equation (1) may be adapted according to user's needs, for instance associating different weights to each parameter of each template, thus obtaining a weighted CS. Furthermore, it is possible to compute the CS as an average of completeness, as defined by Equation (1), of each individual section of the templates (cf. Figure 1). The latter is indeed the default approach proposed when downloading templates from the eNanoMapper database (cf. Section 3.4.1). The user can in principle also evaluate the CS associated with the individual template sections.

After computing the CS of each physicochemical template, CSs of physicochemical templates may be averaged, obtaining an overall completeness score of the physicochemical characterization, i.e. $CS_{physchem}$:

$$CS_{physchem} = \frac{\sum_{i=1}^{i=11} CS_{template_i}}{11} \quad (2)$$

This score could be further averaged with the CS related to the information about the (eco)toxicological data reported in the associated template (i.e. CS_{ecotox}), which is computed similarly to the completeness score of physicochemical templates (Equation (1)),

thus obtaining an overall CS for a particular study:

$$CS = \frac{CS_{physchem} + CS_{ecotox}}{2} \quad (3)$$

Finally, the completeness of the whole dataset could be computed by averaging the overall CSs of the collected studies.

3.2.2. Data relevance assessment

Data relevance evaluates whether the NM has been tested against the appropriate species and route of exposure, and if appropriate doses/concentrations have been tested and critical parameters influencing the endpoint have been adequately considered (ECHA 2011). In our methodology, this is assessed in such a way to ensure that the (eco)toxicity study is conducted using experimental protocols (standards) (with respect to the endpoint of interest) that are appropriate for risk assessment purposes. Four categories were defined for data relevance:

- **Category 1**: data derived by means of internationally recognized and agreed protocols and standard guidelines, such as the Organization for Economic Co-operation and Development Test Guidelines TGs (OECD TGs) or Good Laboratory Practices/International Organization for Standardization Test Conditions (GLP/ISO TCs).
- **Category 2**: data derived using nanospecific validated protocols, and protocols that are candidates to become standard guidelines or 'standard guidelines with modifications.'
- **Category 3**: data for which the protocol is not included in categories 1 and 2, including nanospecific protocols which are not yet validated (e.g. scientific studies in general).
- **Category 4**: data for which the adopted protocol is not reported in the original source.

Our methodology assesses relevance by automatically comparing the experimental protocol used to derive the data against a pre-defined list of protocols for each endpoint of interest, to which either Category 1 or 2 was already assigned. This list of protocols is reported in S3 of the SI and it covers all recommended protocols for each endpoint from the ECHA's guidance on IR&CSA (ECHA 2017b, 2017c).

3.2.3. Data reliability assessment

Following the works of Card and Magnuson (2010) and Fernández-Cruz et al. (2018), reliability assessment of toxicological data is performed by means of the ToxRTool (Schneider et al. 2009), which is an excel spreadsheet with an easy user interface. ToxRTool extends the approach originally proposed by Klimisch et al. (1997) by including nanospecific considerations and highlighting the importance of physicochemical characterization.

Similarly to the Klimisch et al. (1997) approach, based on information provided by the user this tool assigns data to the following categories (Schneider et al. 2009):

- **Category 1**: *Reliable without restriction*: Studies or data from the literature or reports which were carried out or generated according to generally valid and/or internationally accepted testing guidelines or in which the test parameters documented are based on a specific (national) testing guideline or in which all parameters described are closely related/comparable to a guideline method.
- **Category 2**: *Reliable with restrictions*: Studies or data from the literature, reports in which the test parameters documented do not totally comply with the specific testing guideline but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.
- **Category 3**: *Not reliable*: Studies or data from the literature/reports in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g. non-physiological pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment.

It does not assign to Category 4 ('Not assignable'), as this assignment should be made by direct consideration of the user.

Table 2. Comparison of the criteria for assessing reliability of *in vivo* data by means of the ToxRTool (Schneider et al. 2009) and corresponding mapping on the criteria adopted by the methodology for data quality and completeness.

	ToxRTool criteria (*in vivo* data)	Mapping in other criteria included in the data quality and completeness methodology
Criteria Group I: Test substance identification	**1. Identification of the test substance**	Substance names and CAS (Chemicals Abstract Source) number are included in every template. Composition is one of the 11 parameters considered when computing the CS for physicochemical characterization.
	2. Information on the purity	This information is included in the template *Surface Chemistry*.
	3. Information on the source/origin of the substance	Information on NM supplier is included in each data reporting template.
	4. Information on the nature and/or *indispensable* (for the test) physicochemical properties, such as particle size, physical state, and pH.	Key physicochemical properties are covered by the 11 parameters considered when computing the CS for physicochemical characterization.
Criteria Group II: Test organism characterization	**5. Information on the test species**	This information is included in toxicological templates.
	6. Information on the sex of the test organism	This information is included in toxicological templates
	7. Information on the strain of test animals	This information is included in toxicological templates.
	8. Information on age/body weight at the start of the study	This information is included in toxicological templates.
	9. Information on housing/feeding conditions (for dose–response studies only)	This information is included in dose–response toxicological templates.
Criteria group III: Study design description	**10. Information on the administration route**	This information is included in toxicological templates, and implicitly derivable from the adopted protocol.
	11. Information on doses administered or concentration in application media	This information is included in toxicological templates, and implicitly derivable from the adopted protocol.
	12. Information on frequency and duration of exposure, as well as time-points of observation	This information is included in toxicological templates, and implicitly derivable from the adopted protocol.
	13. Are negative/positive controls included?	This information is included in toxicological templates, and implicitly derivable from the adopted protocol.
	14. Information on the number of animals per group	This information is included in in toxicological templates.
	15. Details on the administration scheme	This information is implicitly derivable from the adopted protocol.
	16. Were achieved concentrations analytically verified, or was the stability of the test substance ensured or made plausible? (Inhalation and repeated dose toxicity only)	This information is only partially included in toxicological templates.
Criteria group IV: Study results documentation	17. Information on the study endpoint and method of determination.	This information is included in toxicological templates.
	18. Is the description of results for all endpoints investigated transparently and complete?	This information is directly related to the completeness of toxicological templates.
	19. Information/documentation on the statistical methods applied for data analysis	This information is implicitly derivable from the *results* Section of toxicological templates.
Criteria group V: Plausibility of study design and results	**20. Information of the study design appropriateness for obtaining the substance-specific data**	This information is directly related to the completeness of toxicological templates, and to the relevance of the adopted protocol.
	21. Are the quantitative study results reliable?	This information requires expert judgment, thus is only indirectly related to completeness and relevance.

Parameters highlighted in bold are considered essential to be categorized at least in Category 2 by the ToxRTool.

Similarly, for ecotoxicological data, an adapted version of the ToxRTool is enabled by the NanoCRED tool (Moermond et al. 2016; Hartmann et al. 2017), which allows assigning data to the same categories, based on filling an excel spreadsheet similar to the ToxRTool and drawing conclusions on reliability of the data by means of expert judgment.

The main drawback of the ToxRTool and NanoCRED is the requirement of expert knowledge to decide whether a study is reliable or not. Moreover, unlike the methodology for computing the CS score, the ToxRTool and the NanoCRED tool cannot be automatically filled and thus it is not possible to automate the process of evaluating reliability directly on data reporting templates.

However, as illustrated in Table 2 for *in vivo* endpoints and in Table 3 for *in vitro* endpoints, we found that most of the requirements of the ToxRTool are already considered when evaluating completeness (cf. Section 3.2.1) and relevance (cf. Section 3.2.2). Similar considerations were made for NanoCRED tool (to assess reliability of ecotoxicity data), as reported in Table 4.

The findings summarized in Table 2, Table 3, and Table 4 suggest that if data is sufficiently complete and the adopted protocol is relevant for the task with respect to the endpoint of interest, it is also sufficiently reliable.

Consequently, to reduce the need of expert judgment and thus enable the methodology to be fully

Table 3. Comparison of the criteria for assessing reliability of *in vitro* data by means of the ToxRTool (Schneider et al. 2009) and corresponding mapping on the criteria adopted by the methodology for Data Quality and Completeness.

	ToxRTool criteria (*in vitro* data)	Mapping in other criteria included in the data quality and completeness methodology
	Criteria Group I - Test substance identification: criteria 1-4 are the same as Table 2.	Considerations for criteria 1-4 are the same as Table 2.
Criteria Group II: Test system characterization	5. Description of the test system	This information is included in toxicological templates, and directly related to the adopted protocol (relevance).
	6. Information on source/origin of the test system	This information is included in toxicological templates.
	7. Information on test system properties, conditions of cultivation and maintenance	This information is included in toxicological templates and related to the adopted protocol (relevance).
Criteria group III: Study design description	8. Information on the method of administration	This information is included in the toxicological template, and implicitly derivable from the adopted protocol.
	9. Information on doses administered or concentration in application media	This information is included in toxicological templates, and implicitly derivable from the adopted protocol.
	10. Information on frequency and duration of exposure, as well as time-points of observation	This information is included in toxicological templates, and implicitly derivable from the adopted protocol.
	11. Are negative controls included?	This information is included in toxicological templates, and implicitly derivable from the adopted protocol.
	12. Are positive controls included?	This information is included in toxicological templates, and implicitly derivable from the adopted protocol.
	13. Are the number of replicates provided?	This information is included in toxicological templates.
	Criteria group IV - Study result: criteria 14-16 are the same as criteria 17-19 in Table 2.	Considerations for criteria 14-16 are similar to the considerations for criteria 17-19 in Table 2.
	Criteria group V - Plausibility of study design and results: criteria 17-18 are the same as criteria 19-20 in Table 2.	Considerations for criteria 17-18 are similar to the considerations for criteria 19-20 in Table 2.

Parameters highlighted in bold are considered essential to be categorized at least in Category 2 by the ToxRTool.

automatable, in this methodology, data reliability is considered implicitly assessed while evaluating and scoring completeness and relevance, as having a high (low) CS and high (low) relevance of the adopted protocol with respect to the endpoint of interest, also implies high (low) data reliability. This was further supported by a case study reported in Section S4 of the SI.

3.2.4. Data adequacy assessment

Adequacy defines the usefulness of data for the purposes of the analysis. Three main types of studies were selected to define this criterion, namely *in vivo, in vitro* and *in silico*.

According to the 3R principle (replacement, reduction, refinement of *in vivo* tests for a more ethical use of animals in testing and research), *in vitro* and *in silico* data—depending on the predictivity for effects *in vivo*—should be used as an alternative to test data on laboratory animals (ECHA 2011, 2017b, 2017c). However, especially when adopting a WoE approach (EFSA Scientific Committee et al. 2017), higher weight is usually associated to the most reliable test for risk assessment purposes (i.e. *in vivo)*, while lower weights are associated to *in vitro* and *in silico* studies.

Therefore, since the adequacy criterion is tailored to assess tasks related to risk assessment purposes only, analogously to what described in Section 3.2.2 we automatized the assessment of data adequacy by associating to the adopted protocol a data adequacy score, which relates to the nature of the test (i.e. *in vivo, in vitro* or *in silico*).

This is consistent with other approaches, like for instance the one proposed by Hristozov et al. (2014), where authors additionally considered the exposure route in evaluating adequacy, and the one proposed by Basei et al. (2021).

3.2.5. 'Traffic lights' methodology for data quality assessment

The proposed, fully automatable methodology, consists in the following steps:

- Computation of score for each of the criteria (i.e. completeness, relevance, and adequacy; reliability is implicitly integrated in completeness and relevance scores, cf. Section 3.2.3)
- Aggregation of scores into a final data quality and completeness score for a specific dataset, by computing the arithmetic mean of the computed scores
- Highlight of data quality and completeness (on the database interface, in the data reporting templates or in risk assessment software tools)

Table 4. Comparison of the criteria for assessing reliability of ecotoxicological data by means of the NanoCRED evaluation method for reliability (Moermond et al. 2016; Hartmann et al. 2017), and corresponding mapping on the criteria adopted by the methodology for data quality and completeness.

	NanoCRED criteria (ecotoxicological data)	Mapping in other criteria included in the data quality and completeness methodology
Criteria Group I: General information	1. Information on the (modified) guideline method used	This information is included in ecotoxicological templates and is directly related to the relevance criteria.
	2. Is the test performed under good laboratory practices conditions?	This information is indirectly related to the relevance criteria.
	3. Information on the validity criteria (e.g., control survival, growth)	This information is indirectly related to the relevance criteria and partially included in parameters of ecotoxicological templates.
	4. Information on the test controls (e.g., negative/positive controls, solvent)	This information is directly related to the relevance criteria and included in parameters of ecotoxicological templates.
Criteria Group II: Test compound	5. Information on the substance (CAS number or substance name)	This information is included in both psychochemical and ecotoxicological templates.
	6. Information on the purity of the substance	This information is included in the template *Surface Chemistry*.
	7. If a formulation is used or there are impurities, is an environmental effect known for such impurities/formulation? Is the amount known?	This information is partially included in templates *Surface Chemistry* and in information on the *Composition*.
Criteria group III: Study test organism	8. Information on test organism	This information is included in toxicological templates, and implicitly derivable from the adopted protocol.
	9. Are the test organisms from a trustworthy source and acclimatized to test conditions? Have the organisms not been pre-exposed to test compound or other unintended stressors?	This information is implicitly derivable from the adopted protocol. Information on the provider is included in ecotoxicological templates.
Criteria group IV: Exposure conditions	10. Information on the appropriateness of the experimental system (whether it takes into consideration physicochemical properties of the NM)	This information is strongly based on expert judgment; however, the physicochemical characterization is highly considered in the CS computation, and this information in principle is related to the relevance of the adopted protocol.
	11. Information on the test system and on the test conditions (including the stability of such conditions during the experiment)	This information is included in ecotoxicological templates.
	12. Information on the exposure concentration with respect to water solubility, as well as on the solvent used	This information is included in ecotoxicological templates.
	13. Information on the spacing between exposure concentrations	This information is directly related to the adopted test protocol (data relevance).
	14. Information on exposure duration	This information is directly related to the adopted test protocol (data relevance) and included in ecotoxicological templates.
	15. Information on the chemical analyses adopted to verify concentrations during the study	This information is partially included in ecotoxicological templates, and implicitly related to the test protocol (data relevance).
	16. Information on the appropriateness of biomass loading of organisms in the test system	This information is implicitly related to the adopted test protocol (data relevance).
Criteria group V: Statistical design and biological response	17. Information on the number of replicates, for the test and positive/negative controls	This information is implicitly related to the adopted test protocol (data relevance) and partially included in ecotoxicological templates.
	18. Information on the statistical methods used	Partially accounted in the *results* Section of ecotoxicological templates.
	19. Information on the existence of a dose–response relationship and on the statistical significance of the response	Partially accounted in the *results* Section of ecotoxicological templates.
	20. Information on the amount of data available to check the correctness of calculations on endpoints.	Partially accounted in the *results* Section of ecotoxicological templates, and directly related to the adopted test protocol (data relevance).

based on the computed scores using either 'traffic lights' or continuous scales.

The computation of scores for the defined criteria is proposed in Table 5.

A good physicochemical characterization is not only essential for grouping, read-across, and similarity assessment of nanomaterials (Stone et al. 2020; Jeliazkova et al. 2022), but it is also a prerequisite for any safety assessment of nanomaterials (OECD 2012), and required for fulfilling regulatory obligations (EFSA Scientific Committee et al. 2021; ECHA 2022). For this reason, in addition to the scoring system presented in Table 5, this methodology requires a minimum CS of the physicochemical characterization (i.e. $CS_{physchem}$) for data to be of overall 'high quality.' We suggest here 0.5 as minimum value for $CS_{physchem}$, or in other words at least half of the metadata included in physicochemical templates must be provided for data to be of

Table 5. Proposed setup for the selected criteria.

Criteria	Description	Score
Completeness	Data completeness is assessed following the methodology proposed by Comandella et al. (Comandella et al. 2020), extended in order to evaluate also completeness of (eco)toxicological templates. The CS is computed as described in Section 3.2.1. The final CS is the average of the CSs of physicochemical templates and the CS of the (eco)toxicological template. A possible improvement consists of providing weights to the parameters of each template, assigning higher weighs to parameters that are considered more important by the user, and/or computing the CS on each section of the template, weighing the score for each section, and then averaging the scores (cf. Section 3.2.1).	Corresponds to the final CS (i.e. the average of the CS related to physicochemical templates, and the CS related to (eco)toxicological template).
Relevance	Data is considered relevant to the task if they are derived using internationally recognized protocols and methods, as described in Section 3.2.2. This step was automatized by providing a list of protocols for the first two categories with respect to each endpoint of interests.	Category 1 (data derived following standard guidelines): 1 Category 2 (data derived following nanospecific guidelines, guidelines with modifications, or protocols that are candidate to become guidelines): 0.7 Category 3 (data derived following protocols that are not considered in Category 1 or Category 2): 0.1 Category 4 (data for which the adopted protocol is not reported): Data should be considered of insufficient quality
Adequacy	Data adequacy is evaluated based on the fact that in general *in vivo* data (Category 1) is considered to be more appropriate than *in vitro* (Category 2) and *in silico* (Category 3) data for risk assessment from a regulatory perspective, as described in Section 3.2.4. This was again automized by associating an adequacy score to the reported protocol.	Category 1 (*in vivo*): 1 Category 2 (*in vitro*): 0.6 Category 3 (*in silico*): 0.3

overall 'high quality.' For certain purposes, it might be appropriate to define an even higher threshold as minimum value for $CS_{physchem}$. Assessors may well conclude on the need for relatively high minimum $CS_{physchem}$ of datasets to be useful for regulatory safety assessment, and on 'insufficient quality' of the entire dataset if $CS_{physchem}$ is below such a threshold, the value of which could be agreed on by experts.

Thus, after assessing the weights, and computing the arithmetic mean of the resulting scores, the last step involves to set-up thresholds to the quality score, in order to highlight data with a 'traffic light.' We propose the following default thresholds:

- Overall score > 0.7 and $CS_{physchem} > 0.5$: 'green light,' data is of high quality.
- $0.3 <$ overall score $< = 0.7$, or $CS_{physchem} <= 0.5$ and overall score $>= 0.3$: 'yellow light,' data is of sufficient quality, but needs further consideration to be used for the specific task.
- Otherwise: 'red light,' data is of insufficient quality.

Alternatively, it is possible to display the data quality and completeness score using a continuous scale from 0 to 1, thus resulting in a gradient from red (i.e. data of insufficient quality) to green (i.e. data of high quality), keeping in mind that a sufficient physicochemical characterization is a prerequisite for high data quality.

The proposed methodology is fully automatable, allowing to highlight data quality directly on the user interface of the eNanoMapper (or any other) database, on external tools and/or in the data reporting templates when uploading/downloading data from the database.

3.3. Demonstration in case studies

3.3.1. Aquatic toxicity

To demonstrate the robustness of the proposed data quality assessment methodology, we applied it to a publicly available dataset obtained from the eNanoMapper database. The dataset involves the nanoscale silver material JRCNM03000a (NM-300K, Ag 16.7) (cf. Section 2.4). The results of the application are reported in Table 6 and are downloadable within the developed online R tool (cf. Section 3.4.2).

It is worth noting that all the computed CSs of (meta)data were low. These low scores are due to the lack of reported information on many physicochemical parameters. Indeed, information on surface area, surface hydrophobicity, dustiness, and density were not available in any of the collected studies, and moreover CSs related to (meta)data

Table 6. Results of applying the methodology to publicly available data in eNanoMapper related to JRCNM03000a (NM-300K, Ag 16.7 nm). Overall completeness and quality scores for the studies are highlighted in bold. The traffic light indicator (last row of the table) highlights both the 'traffic light' and the corresponding meaning (i.e., 'green light' for data of high quality, 'yellow light' for data of sufficient quality, and 'red light' for data of insufficient quality).

NM	JRCNM03000a (NM-300K, Ag 16.7 nm)								
Reference	NANoREG D4.12 (NANoREG 2016a)								
Endpoint	LC50	EC50				LC10	EC20	EC10	
Endpoint value (mg/L)	[4.57, 22.22]	[0.71, 0.83]	[0.006, 9.4]	0.01	[4.68, 9.82]	[2.68, 15.65]	[0.52, 0.63]	[0.001, 2.35]	[1.78, 8.26]
Test method	OECD TG 203	OECD TG 202	OECD TG 201	OECD TG 201	OECD TG 201	OECD TG 203	OECD TG 202	OECD TG 201	OECD TG 201
Relevance	1	1	1	1	1	1	1	1	1
Adequacy	1	1	1	1	1	1	1	1	1
Completeness ($CS_{physchem}$)	0.35 (0.30)	0.36 (0.30)	0.35 (0.30)	0.24 (0.30)	0.28 (0.24)	0.35 (0.30)	0.36 (0.30)	0.35 (0.30)	0.28 (0.24)
Overall score	**0.78**	**0.79**	**0.78**	**0.78**	**0.76**	**0.78**	**0.79**	**0.78**	**0.76**
Traffic light indicator	Data is of sufficient quality[a]	Data is of sufficient quality[a]	Data is of sufficient quality[a]	Data is of sufficient quality[a]	Data is of sufficient quality[a]	Data is of sufficient quality[a]	Data is of sufficient quality[a]	Data is of sufficient quality[a]	Data is of sufficient quality[a]

[a]Even though the overall score is greater than 0.7, data is of sufficient (not high) quality because the CS related to the physicochemical characterization is below the threshold of 0.5 (i.e. it is not sufficiently characterized).

associated to particle size and surface charge templates were always below 0.32, resulting in an overall CS for physicochemical templates not greater than 0.30 for all studies. Similar considerations apply concerning ecotoxicological templates: indeed, most of the (meta)data required by the templates was not available.

For this reason, the overall quality of the collected data cannot be higher than 'sufficient for risk assessment purposes,' because even though data was obtained from *in vivo* tests on either fish, algae, and cyanobacteria, and derived from tests following OECD TGs, the physicochemical characterization was not sufficiently reported.

3.3.2. Genotoxicity (in vitro)

A relatively high number of studies (44 studies) concerning genotoxicity (*in vitro*) of JRCNM03000a (NM-300K, Ag 16.7 nm) were available in eNanoMapper, for this reason in this section aggregate values are reported, while the full analysis is available within the developed online R tool (cf. Section 3.4.2).

In Figure 3, aggregate CSs related to physicochemical characterization are reported. Scores have been classified using the thresholds defined in Section 2.3 for the traffic light system into four categories, namely: 'no data' if no data was available, 'incomplete data' if the CS was lower than 0.3, 'sufficiently complete data' if the CS was between 0.3 and 0.7, and 'highly complete data' if the CS was greater than 0.7.

Specifically, no data were available related to the characterization of surface area, surface hydrophobicity, dustiness, and density, and for a subset of data, no data were available related to crystallinity. As a result, the final CS related to physicochemical characterization was low for all the available data (ranging from 0.24 to 0.30), and for this reason even though the CS associated to toxicological templates was relatively high (ranging from 0.61 to 0.77), the final CS resulted to be in the range [0.45, 0.50], as summarized in Figure 4.

After averaging the overall CS with the scores related to relevance (all data was relevant to the task, Category 1, since it came from standard tests and procedures) and adequacy (all data was derived *in vitro*), the computed overall data quality and completeness scores ranged in [0.68, 0.70], but since the CS related to the physicochemical characterization was below 0.5 for all the data (i.e. it was not sufficiently characterized), all studies resulted to be of sufficient quality, as displayed in Figure 5.

3.4. Implementation of the methodology in data reporting templates and software

3.4.1. Implementation in templates and the eNanoMapper database

Data completeness and reliability assessment is already implemented in the development version of eNanoMapper database, by providing the completeness score directly in the templates for inserting and retrieving data (Gottardo et al. 2019), as displayed in Figure 6.

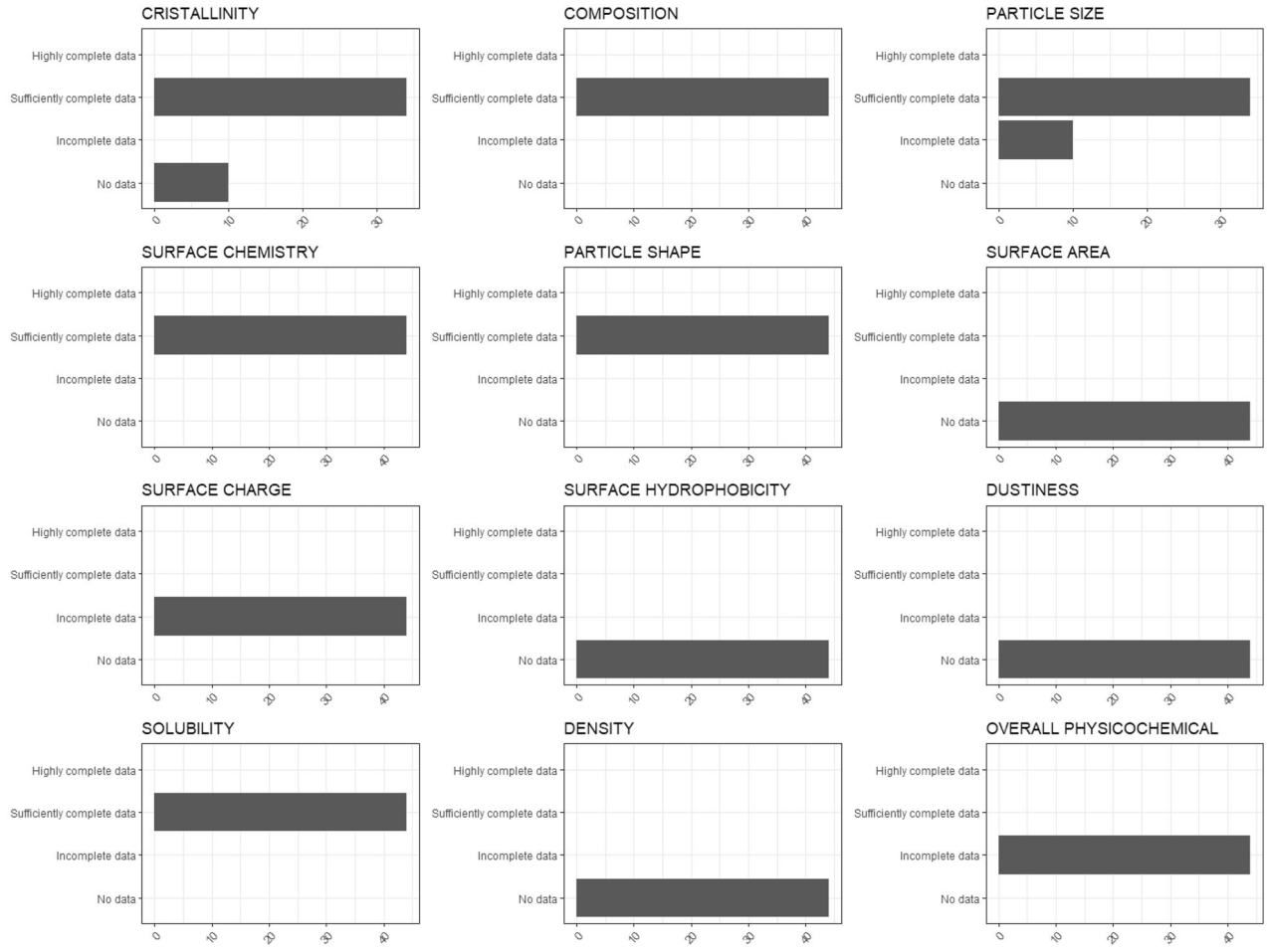


Figure 3. Aggregate CSs related to physicochemical characterization of the selected data for the second case study (i.e. genotoxicity in vitro). Scores have been classified using the thresholds defined in Section 3.2.5 for the traffic light system into four categories (i.e. 'No data,' 'Incomplete data,' 'Sufficiently complete data,' and 'Highly complete data').

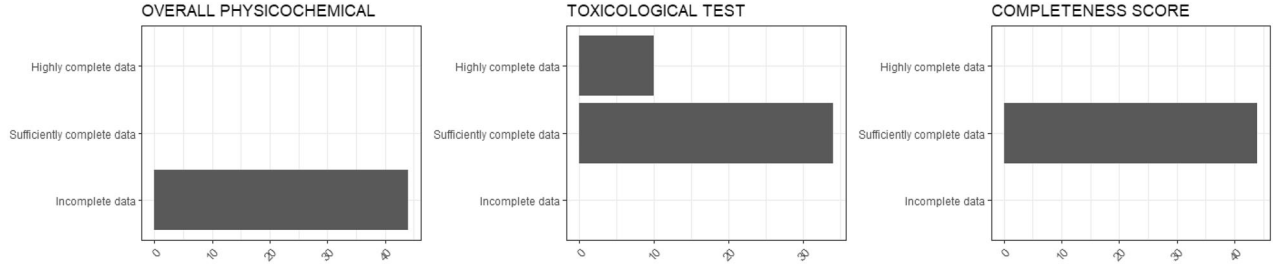


Figure 4. Aggregate CSs related to the overall physicochemical characterization, the toxicological test, and the overall CS for physicochemical data of the selected data for the second case study (i.e. genotoxicity in vitro). Scores have been classified using the thresholds defined in Section 3.2.5 for the traffic light system into three categories (i.e. 'Incomplete data,' 'Sufficiently complete data,' and 'Highly complete data').

Similarly, the step of data relevance evaluation is already implemented in the database, as a predefined list of protocols and Standard Operating Procedures (SOPs) for each template is already available, as displayed in Figure 7. Thus, it is sufficient to associate each of the SOPs to one of the four data relevance categories to automatize the computation of relevance scores. Similarly, an adequacy score can be associated to each SOP as it is of course already known if it is an *in vivo* or an *in vitro* test.

3.4.2. An online R tool implementing the methodology

In addition to the initial implementation in the eNanoMapper database, the methodology was implemented as an online R tool (https://shinyapps.

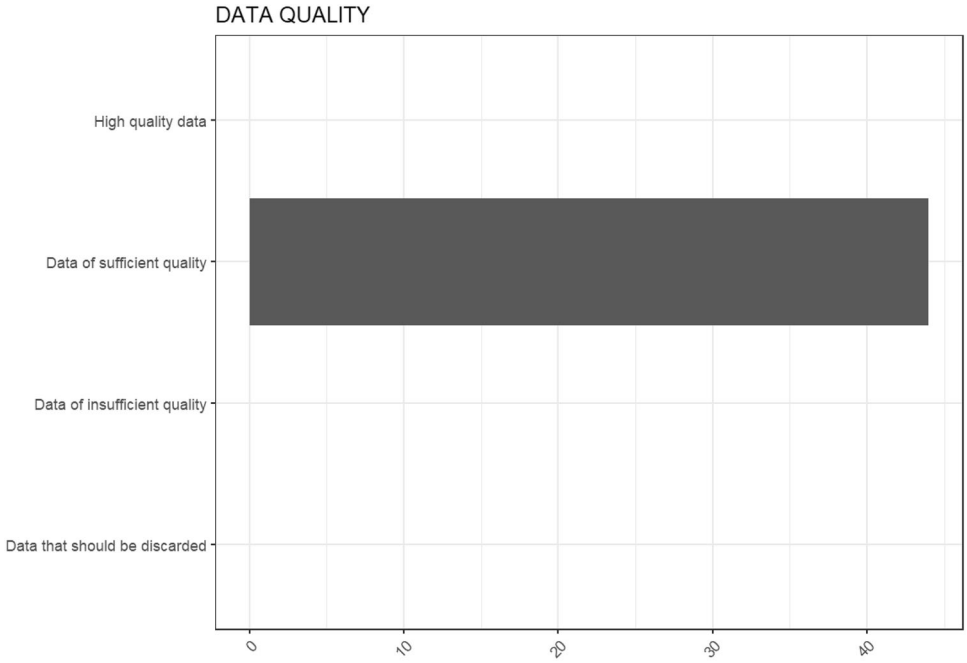


Figure 5. Results of the evaluation of data quality and completeness for genotoxicity. Two studies resulted to be of high quality, while 42 studies resulted to be of sufficient quality.

greendecision.eu/apps/gracious-data-quality), which in the current version only displays the results of the computed scores in a user friendly way and categorizes data according to (user inserted) thresholds as being 'data is of high quality,' 'data of sufficient quality,' 'data of insufficient quality,' and 'data that should be discarded.'

The next version of the tool will be made interoperable with the eNanoMapper database through the eNanoMapper APIs, so that it can automatically compute completeness, relevance, and adequacy scores while querying the database. In detail, the user will be able to directly query eNanoMapper data (by means of a user interface built upon the eNanoMapper APIs), then quality and completeness scores will be automatically computed following the methodology described in Section 3.2 according to the specified weights, and finally results will be displayed in the tool as highlighted in Figure 8.

The tool can be made interoperable also with other databases (note that correspondence between the data models and the NANoREG/GRACIOUS templates and fields need to be established) as well as with relevant software tools such as the SUNDS decision support system for risk assessment and management of NMs. Screenshot of the current version of the tool is provided in Figure 8. The tool and an example of its integration in a relevant decision support system (i.e. SUNDS) are described in more detail in the SI.

4. Discussion

In this article, we propose a methodology to automatically assess the quality of physicochemical and hazard data for risk assessment purposes based on established criteria (i.e. completeness, relevance, reliability, and adequacy). The assessment starts from the available (meta)data as provided in the harmonized NANoREG/GRACIOUS templates for data entry into the eNanoMapper database. The methodology was tested in a case study using publicly available physicochemical and (eco)toxicity (i.e. aquatic toxicity and genotoxicity) data on the nanoscale silver material JRCNM03000a (NM-300K, Ag 16.7 nm). To enable easy implementation of the methodology in databases and software tools, an online R tool was developed. The methodology was also partially implemented in the eNanoMapper database and was adopted as part of a WoE approach for classification of NMs according to the CLP regulatory requirements (Basei et al. 2021).

The main novelty of this methodology is that in addition to (meta)data completeness, the assessment of data quality can be automated, thus reducing the reliance on expert judgment. This is

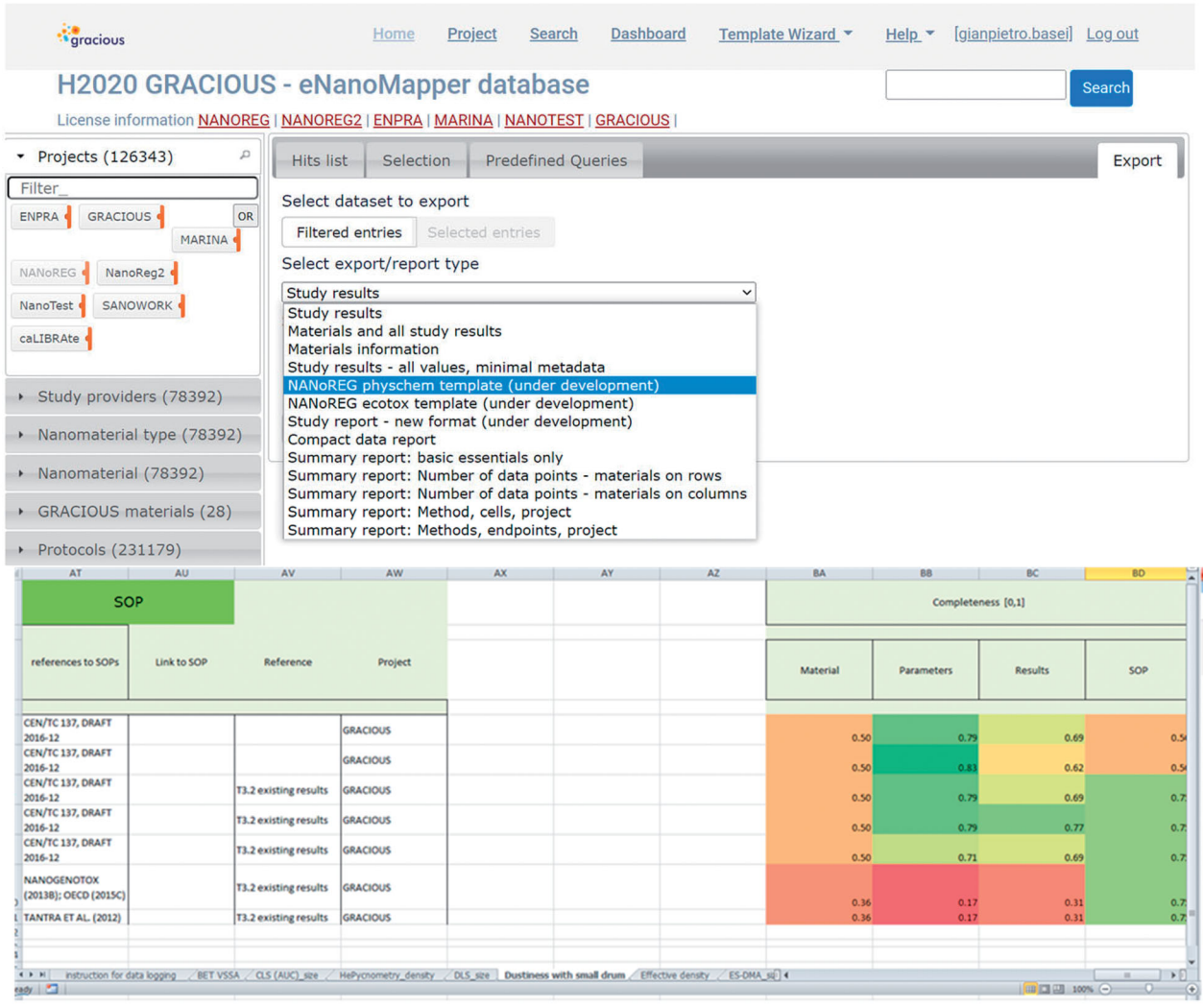


Figure 6. Implementation of the data completeness and reliability criteria in the development version of eNanoMapper. When downloading information selecting as format 'NANoREG template,' completeness is computed, and the completeness score is highlighted using an heatmap from red (0, data fully incomplete) to green (1, data fully complete). The numbers between parentheses in the left menu of eNanoMapper represent the total number of data points associated to each category, after application of filters. The number of substances, instead, is shown on the top of the main window.

extremely useful for implementing the approach in data reporting templates (Totaro et al. 2017; Gottardo et al. 2019), databases, and software-based risk assessment tools.

It is important to highlight, however, that even though this methodology was developed with the aim of being automatable, expert judgment is always important in risk assessment, and although the results of our methodology are helpful to guide risk assessors in the selection of more complete and higher quality datasets, in many cases, a follow-up analysis by experts may be required.

Specifically, the assumption made in Section 3.2.3, namely, to consider *reliability* implicitly assessed when evaluating *completeness* and *relevance,* may trigger additional analysis by some assessors. Indeed, we made this assumption to reduce the need of expert judgment and to provide a fully automatable methodology, but some risk assessors may decide for a more in-depth assessment of data reliability, which would then require the use of expert judgment.

Moreover, while our methodology works with defined weights and thresholds, some experts may have a different idea of which criteria may be more important than others in specific cases. To address this, our methodology is flexible enough to allow these experts to change the weights and thresholds according to their opinion. For example, although our case study analysis of JRCNM03000a datasets

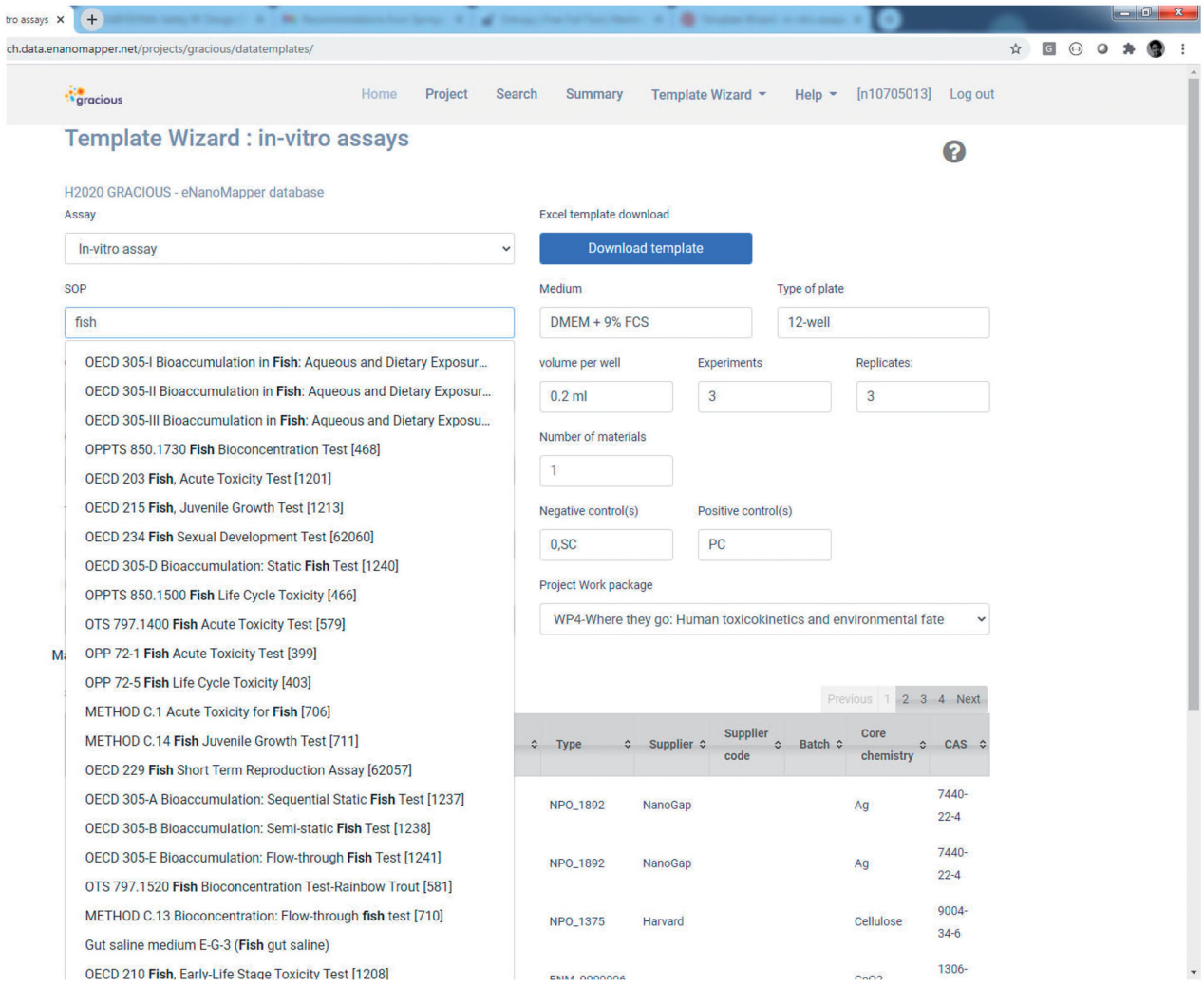


Figure 7. A list of Standard Operating Procedures is already provided in the eNanoMapper database when selecting a reporting template.

concluded that the data is of 'sufficient quality,' some experts may consider the same data being of 'insufficient quality' because information on several physicochemical parameters was not available. In this case, these experts would still be able to use our approach by changing weights and thresholds, but this would of course require their expert judgment. Nevertheless, it is worth noting that data of low or insufficient quality may still be useful when used together with data of higher quality, e.g. in a WoE approach (ECHA 2011; Basei et al. 2021).

Involvement of a pool of domain experts is envisaged to further define aspects of the methodology such as the weighting schemes. These weights, however, can be adapted by the final users according to their needs, for instance by weighting more the parameters, which are related to data reliability assessment done by means of the ToxRTool/NanoCRED tool (i.e. the parameters highlighted in Table 2, Table 3, and Table 4). Similarly, when evaluating endpoints for which no *in vivo* data is available (or are not needed as in a safe-by-design assessment scenario for example), assessors may decide to give an adequacy score of 1 to data derived *in vitro* or may decide to give a score greater that the one proposed in this article (i.e. 0.6) to such data, emphasizing the need to reduce animal testing in compliance with the 3R principles.

This methodology is tailored to risk assessment purposes and particularly to evaluate quality of (eco)toxicological data. Indeed, the evaluation of data quality for exposure is not covered by the approach described in this article, and further work is needed to evaluate quality for dose–response

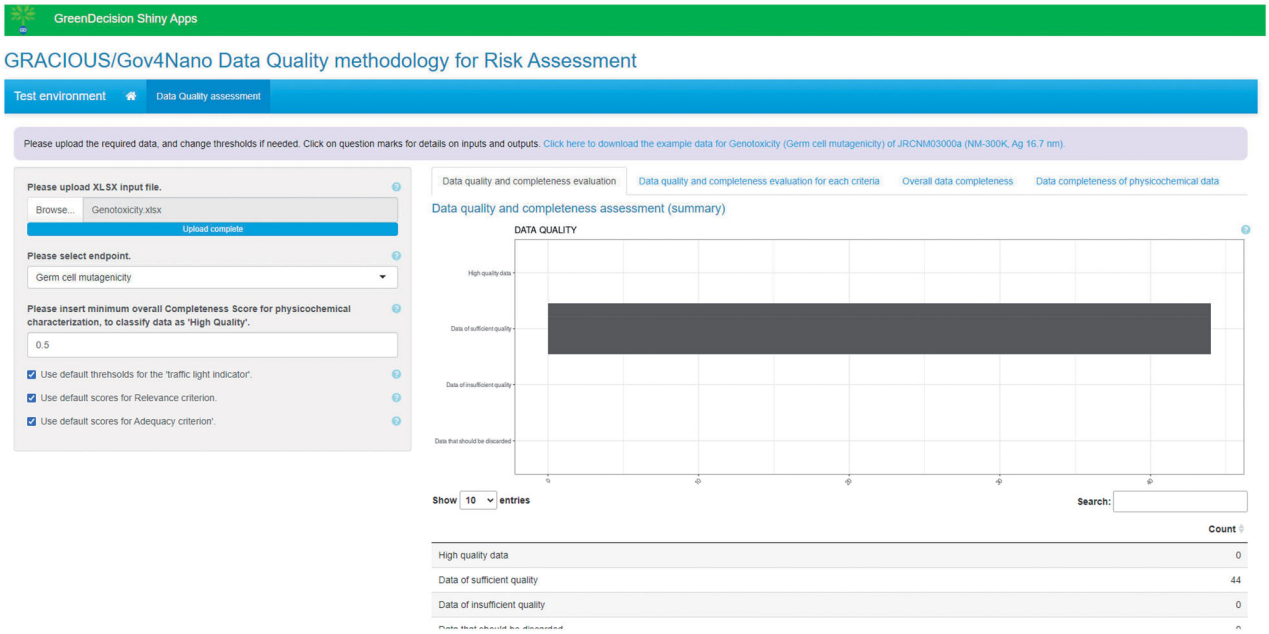


Figure 8. Screenshot of the initial version of a tool implementing the data quality assessment methodology. The results of the case study related to genotoxicity *in vitro* (cf. Section 3.3.2) are displayed. Currently, the tool computes data quality and completeness scores starting from the selected endpoint, the CSs of physicochemical parameters, and the classification into data reliability and adequacy categories, and then displays aggregate information on data quality and completeness of the dataset. In future versions, it will be able to directly query the eNanoMapper database.

data based on additional criteria such as biological relevance and statistical significance. Moreover, this methodology does not focus on the quality of physicochemical data but considers the completeness of the available physicochemical (meta)data associated to (eco)toxicological tests. A further limitation of the approach described in this article is that Adverse Outcome Pathways (AOPs) are not considered in the current version.

The proposed methodology could also serve as a starting point for other domains (e.g. modeling) or as a reference for creating methodologies for physicochemical and exposure data, after adapting the selected evaluation criteria or adding additional criteria. For instance, in case of modeling, also the statistical significance (Hristozov et al. 2014) and the size of the dataset (Lubinski et al. 2013) could be selected as potential assessment criteria or as a basis to redefine the adequacy criterion, since publicly available data in databases for building computational models is known to be more sparse with respect to other domains (Basei et al. 2019; Furxhi et al. 2020a, 2020b). Similarly, for evaluating data quality related to exposure or physicochemical data, this methodology needs to be modified by redefining the assessment criteria.

Finally, it is worth noting that adopting automatic methodologies like the one proposed in this manuscript allows to perform the analysis at 'real time.' Hence, one can monitor the degree of completeness and quality over time for a specific query or even for the whole data in a database, which helps to ensure that the degree of quality and completeness of new (or updated) data is sufficiently addressed by data providers.

Indeed, we are confident that adopting (automatic) methodologies like the one proposed in this manuscript, will not only help the final user (e.g. the risk assessor or the modeler) to evaluate the quality and completeness of data, but their implementation in data reporting templates and databases can also serve as a strong incentive for data providers to deliver more complete datasets of higher quality.

5. Conclusions

This article describes a methodology to automatically assess quality and completeness of nanosafety data for risk assessment purposes. The methodology is tailored to physicochemical and hazard (meta)data, but with appropriate criteria it can be

re-configured to support also modeling or exposure assessment. Therefore, in combination with expert knowledge, this methodology can be applied as a powerful data analytical tool in different contexts. To enable practical application of the proposed methodology, it was implemented as an online R tool, which can be attached to both databases and risk assessment software tools. The approach was also implemented in a WoE approach to classify NMs according to CLP regulatory requirements (Basei et al. 2021), and it was implemented as a 'traffic lights' system in the NANoREG/GRACIOUS data reporting templates exported from eNanoMapper database. The latter enables data providers to see in real time how their datasets perform in terms of completeness and quality. The users of the data can also see this information both in the data entry templates and on the database interface, which enables them to select better datasets for analyses ranging from similarity assessment and grouping to classification and regulatory risk assessment.

Notes

1. See https://www.h2020gracious.eu/event/assessing_quality_and_completeness_of_nanosafety_data_for_risk_assessment_purposes.
2. See https://www.slido.com.
3. See https://www.oecd.org/ehs/templates/.
4. See https://api.ideaconsult.net/.
5. Information on the mentioned projects may be found at the following web pages: https://www.h2020gracious.eu/ (GRACIOUS); http:// http://www.enpra.eu/ (ENPRA); https://cordis.europa.eu/project/id/263215 (MARINA); https://cordis.europa.eu/project/id/310584 (NANoREG); https://nanopartikel.info/en/research/projects/nanogravur/ (NanoGRAVUR); http:// http://www.nanotest-fp7.eu/ (NANOTEST); https://cordis.europa.eu/project/id/280716/ (SANOWORK).
6. An entry of raw data is a single data element resulting from a query, expressing information on one specific quantity (or value) determined in an experiment using a specific measurement technique. For instance, a dose–response curve of five elements resulting from a single study consists of five entries. Data was retrieved from the eNanoMapper database in August 2021.

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