Electronic Supplementary Information

for

How should the completeness and quality of curated nanomaterial data be evaluated?

Contents

Section S1. Overview of survey respondents and their corresponding data resources

Table S1 summarises the respondents to the NDCI data completeness and quality survey and matches them to the corresponding nanomaterial data resources, as reviewed in the current work, with which they are involved. Table S2 provides an overview of those data resources, including the time period for which they existed prior to completion of the NDCI data completeness and quality survey in 2015.

The corresponding, original survey responses may be found in the additional supporting information file: NDCI_Completeness_Quality_Article_Additional_SI.zip. (The liaisons for the DaNa Knowledge Base and the Nanoparticle Information Library provided their input via direct correspondence.) It should also be noted that additional information and clarifications were kindly provided by the noted liaisons during subsequent correspondence.

The original survey responses were provided in January - February 2015, and the information provided regarding the data resources was current as of the time of writing.

The findings and conclusions in this work are those of the authors and do not necessarily represent the views of their respective organisations or funding bodies. The information and opinions provided in this publication by members of the caNanoLab team are solely attributable to the caNanoLab team and none of the content of this publication necessarily reflects the views or policies of the National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Table S1 Respondents to the Nanomaterial Data Curation Initiative (NDCI) data completeness and quality survey and their corresponding nanomaterial data resources

Liaisons	Contact details	Data Resource
caNanoLab team	Sharon Gaheen (gaheens@mail.nih.gov)	caNanoLab[1]
Dr. Christoph Steinbach	Dr. Steinbach (steinbach@dechema.de)	DaNa Knowledge Base[2]
Dr. Clarissa Marquardt	Dr. Marquardt (clarissa.marquardt@kit.edu)	
Dr. Christine Ogilve Hendren	Dr. Hendren (christine.hendren@duke.edu)	Center for the Environmental Implications of NanoTechnology (CEINT) NanoInformatics Knowledge Commons (CEINT NIKC)[3]
Dr. Sandra Karcher	Dr. Karcher (sck@andrew.cmu.edu)	
Dr. Willie Peijnenburg	Dr. Peijnenburg (willie.peijnenburg@rivm.nl)	NanoNext Database on the Environmental Fate and Effects of Nanomaterials – developed by the National Institute for Public Health and the Environment in the Netherlands (RIVM)
Dr. Hubert Rauscher	Dr. Rauscher (Hubert.RAUSCHER@ec.europa.eu)	European Commission (EC) Joint Research Centre (JRC) NANOhub Database[4]
Hanne Vriens	Hanne Vriens (hanne.vriens@med.kuleuven.be)	MOD-ENP-TOX Datasets[5]
Dr. Peter Hoet	Dr. Hoet (peter.hoet@med.kuleuven.be)	
Dr. Iseult Lynch	Dr. Lynch (i.lynch@bham.ac.uk)	NanoMILE Knowledgebase[6]
		ModNanoTox Datasets[7]
Dr. Mark D. Hoover	Dr. Hoover (mhoover1@cdc.gov)	Nanoparticle Information Library (NIL)[8]
Dr. Stacey L. Harper	Dr. Harper (harpers@science.oregonstate.edu)	

Table S2 Summary of data resources for which liaisons responded to the Nanomaterial Data Curation Initiative (NDCI) data completeness and quality survey

Data Resource	Public?	Type of Nanomaterial Data	Type of Resource	Purpose	Resource start date
caNanoLab[1]	Yes	Chemical composition, physicochemical, in vitro, ex vivo and in vivo characterisation data; intended function (e.g. "therapeutic" or "imaging")	Searchable, online database	caNanoLab has the "ultimate goal of accelerating the translation of nanotechnology-based cancer therapeutics, diagnostics, and imaging agents to the clinic"[9]	2006
DaNa Knowledge Base[2]	Yes	Free text summaries of "material properties", "exposure", "uptake" and "behaviour" of different nanomaterial classes (e.g. Gold, Carbon Nanotubes) with different intended applications	Searchable, online database	Providing quality-approved, scientifically sound and easy to understand information on the current status of nanosafety research for interested laymen, stakeholders and scientists.	2006
Center for the Environmental Implications of NanoTechnology (CEINT) NanoInformatics Knowledge Commons (CEINT NIKC)[3]	No[a] - intended for use by Center and contributing data partners	Literature curated and *de novo* experimental data from various material characterization processes, exposure studies, and toxicity studies; estimated fate and transport parameters	Searchable database with customized visualization apps	Storage, sharing, interrogation and visualisation of data in support of modeling and forecasting nanomaterial behavior and effects in complex systems	2012
NanoNext Database on the Environmental Fate and Effects of Nanomaterials – developed by the National Institute for Public Health and the Environment in the Netherlands (RIVM)	Anticipated	Toxicity endpoint data with respect to selected aquatic organisms and physicochemical characterisation data	The final format is currently to be determined; data were collected using Excel	To support toxicologists who work with (metal based) nanoparticles	2014
European Commission (EC) Joint Research Centre (JRC) NANOhub Database[4]	No[b]	Physicochemical, toxicity, ecotoxicity, fate and transport data as specified in the OECD Harmonised Templates and required for safety assessment according to REACH	Online IUCLID5.6 database	To support data exchange between nanomaterials research projects	2008

		legislation			
MOD-ENP-TOX Datasets[5]	Anticipated	Physicochemical and *in vitro* toxicity data (viability, apoptosis/necrosis, genotoxicity, oxidative stress and pro-inflammation) for amorphous silica nanoparticles extracted from the literature	ISA-TAB-Nano	To support predictive modelling of nanoparticle hazard	2013
NanoMILE Knowledgebase[6]	Anticipated	Physicochemical characterisation (under different conditions), high content *in vitro* and *in vivo* plus human exposure toxicity data	Searchable, online database of linked nanomaterial physicochemical, screening, toxicology and "omics" data	Visualisation, modelling and sharing of data: more specifically, the interrogation of the interrelationships between biological impacts and the physicochemical properties of aged, environmentally transformed and pristine nanomaterials is facilitated.	2013
ModNanoTox Datasets[7]	Anticipated[c]	Physicochemical and *in vitro and in vivo* ecotoxicity data (such as mortality data, including LC_{50} values, uptake, retention, growth inhibition and genotoxicity data amongst other endpoints) for silver and titania nanoparticles in multiple aquatic species (fish, daphnia, microalgae, bacteria, worms) extracted from the literature	In-house format initially, mapped onto ISA-TAB files using the ISA-Tools software,[10,11] and subsequently using a parser which will be made available as a webtool.	To support predictive modelling of nanoparticle hazard in aquatic species	2011
Nanoparticle Information Library (NIL)	Yes	Nanomaterial composition; method of production; particle size, surface area, and morphology (included scanning, transmission, or other electron micrographic images); demonstrated or intended applications	Searchable, online database	A prototype database to help occupational health professionals, industrial users, worker groups, and researchers organize and share information on nanomaterials	2004

		of the nanomaterials; availability for research or commercial applications; associated or relevant publications; links to health and safety information; and points of contact for additional details or partnering			

a. Portions of CEINT NIKC data are shared via export to public repositories e.g. Nanomaterial Registry.
b. Subsets of the JRC NANOhub data will be made publicly available in agreement with the data owners.[12]
c. The ModNanoTox datasets will be added to FigShare[13] and submitted for publication in the journal "Scientific Data" in the near future; interested readers may contact Dr. Iseult Lynch for further information (I.Lynch@bham.ac.uk).

Section S2. Summary of the schemes employed by these data resources to evaluate data completeness and quality

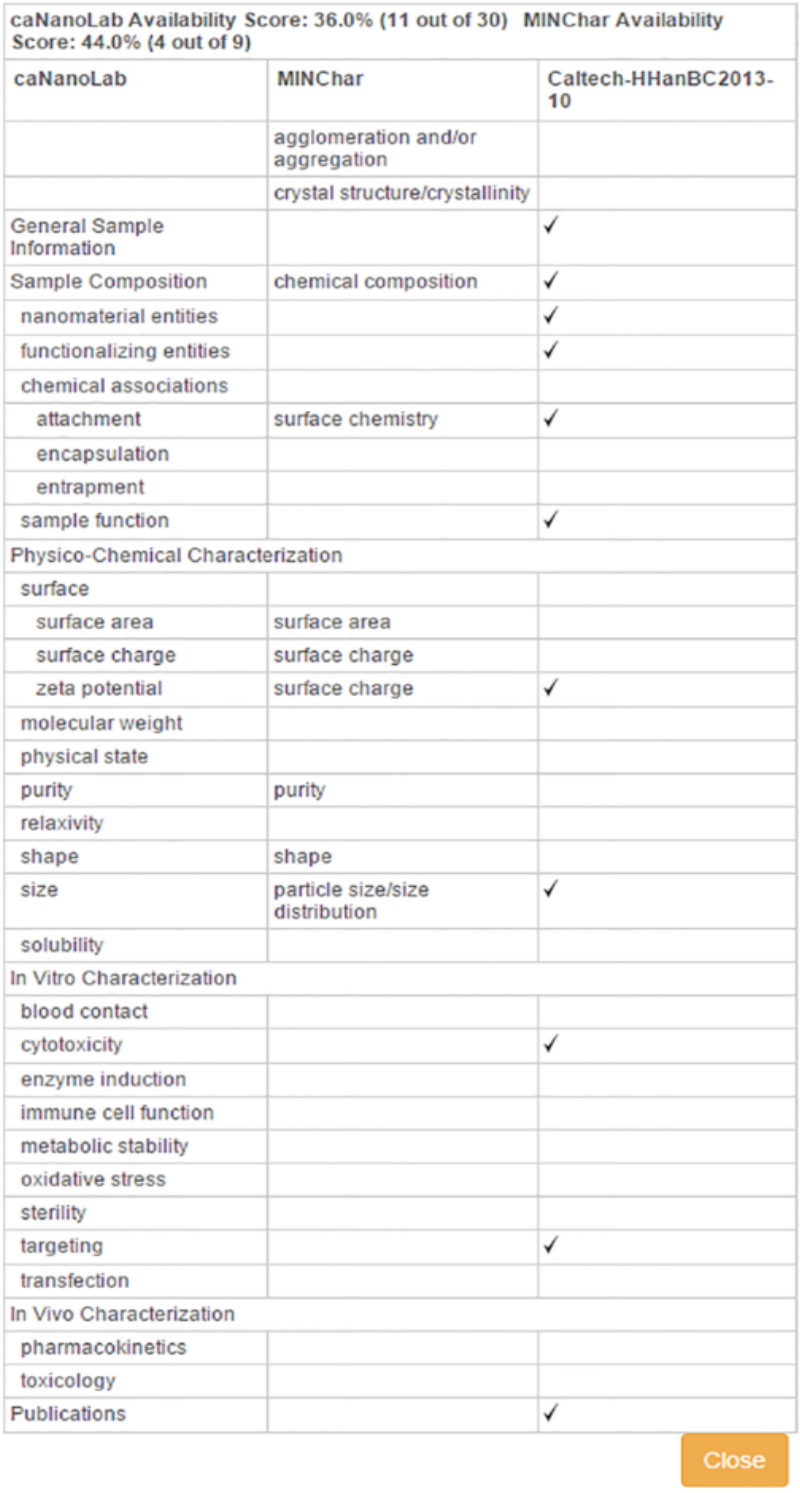
caNanoLab

The following explanation is based upon the cited references[1,9,14,15] as well as additional information provided by the caNanoLab team.

All nanomaterial sample records in caNanoLab are assigned two data completeness scores (termed "data availability metrics").[9] Both scores are calculated as the percentage of a list of different kinds of characterisation properties for which corresponding data are available for that nanomaterial sample record. The two lists of characterisation data types correspond to the Minimum Information for Nanomaterial Characterization (MINChar) Initiative Parameters List,[16] for which the kinds of characterisation properties include "chemical composition" and "particle size/size distribution", as well as a more extensive list created for the purposes of caNanoLab which not only considers a greater number of physicochemical characteristics (e.g. "relaxivity") but also biological characterisation data types as well (e.g. the availability of "cytotoxicity" data). An example of how these scores are assigned for a given nanomaterial sample record in caNanoLab is provided in Figure S1.

caNanoLab completeness criteria are also used when selecting primary literature references to be curated.[14]

Regarding data quality assessment, this concept is not formally defined within caNanoLab. However, data quality is considered to correspond to the accuracy of individual data points and associated metadata e.g. have transcription and/or interpretation errors been made when curating a publication or are data points entered otherwise erroneous? The rigorous data curation workflow employed by caNanoLab includes following up on potential problems with the primary data providers e.g. the authors of curated publications.



caNanoLab Availability Score: 36.0% (11 out of 30) MINChar Availability Score: 44.0% (4 out of 9)

caNanoLab	MINChar	Caltech-HHanBC2013-10
	agglomeration and/or aggregation	
	crystal structure/crystallinity	
General Sample Information		✓
Sample Composition	chemical composition	✓
nanomaterial entities		✓
functionalizing entities		✓
chemical associations		
attachment	surface chemistry	✓
encapsulation		
entrapment		
sample function		✓
Physico-Chemical Characterization		
surface		
surface area	surface area	
surface charge	surface charge	
zeta potential	surface charge	✓
molecular weight		
physical state		
purity	purity	
relaxivity		
shape	shape	
size	particle size/size distribution	✓
solubility		
In Vitro Characterization		
blood contact		
cytotoxicity		✓
enzyme induction		
immune cell function		
metabolic stability		
oxidative stress		
sterility		
targeting		✓
transfection		
In Vivo Characterization		
pharmacokinetics		
toxicology		
Publications		✓

Close

Figure S1 An illustration of the assignment of "availability" scores for a sample record in caNanoLab, reproduced with permission from Morris et al.[9] The first column corresponds to the caNanoLab data recommendations, for which many terms are defined in the caNanoLab glossary,[17] and the middle column corresponds to the MINChar recommendations.[16]

DaNa Knowledge Base

The following explanation is based upon the cited references as well as additional information provided by Dr. Clarissa Marquardt and Dr. Christoph Steinbach.

The information summaries for different kinds of engineered nanomaterials in the DaNa Knowledge Base are derived from peer-reviewed literature.[2,18,19] A "Literature Criteria Checklist",[20,21] which was recently revised,[21] is used for the evaluation of the publications used to derive these summaries. N.B. The following description refers to the latest version of this checklist. This "Literature Criteria Checklist" specifies 12 assessment criteria which "must" (see below) be fulfilled for the nanomaterials studied in a given publication. In addition, a set of nine desirable criteria which "might" (meaning "should") be fulfilled are also evaluated. These criteria are concerned with the availability of different kinds of physicochemical characterisation data (e.g. the name - or CAS number - along with the form of delivery and chemical composition, including the purity and contaminants as well as size and surface chemistry "must" have been provided), details regarding the biological evaluations (e.g. positive and negative controls which are appropriate for the specific endpoint and assay, including checks for nanomaterial interference,[22–31] "must" have been used), along with other kinds of metadata designed to assess the validity of the (biological) results (e.g. appropriate data evaluation, including *enough* replicates/repetitions of the assays, "must" have been used). In addition, adherence to standardised protocols is preferred - all else being equal.

The information specified as part of these criteria might be considered an implicit definition of data completeness, with the criteria which "must" be fulfilled implicitly defining a "minimum information checklist" (**Key concept 2** described in Table 2 of the main text). However, the quality evaluation inherent in this checklist (i.e. studies are evaluated according to a binary 'in/out' quality score), clearly goes beyond consideration of the available (meta)data i.e. the expert evaluators are expected to consider, for example, not merely whether positive and negative controls were used for biological evaluation, but whether or not these controls were appropriate to gain conclusive (e.g. free from artefacts) results for the chosen assay. N.B. At the present, the DaNa team considers adherence to standardised protocols (e.g. OECD guidelines) to be useful insofar as this facilitates comparability of different studies and, hence, integration of their findings into self-consistent conclusions. However, they do not necessarily consider this to be directly related to nanomaterial data quality. In their opinion, adherence to standardised test guidelines will become a definitive quality criterion for nanosafety data once the scientific community has finalised international standards with regards to reference materials and testing protocols that all organisations aiming to generate data for risk assessment (e.g. in a regulatory context) should adhere to.

Since this checklist is applied by nanoscience experts, the checklist criteria (including the so-called "must") criteria, are not rigidly adhered to i.e. the decision to reject or accept a publication is guided by the checklists but, for example, failure to (fully) comply with one "must" criterion might be considered acceptable on a case-by-case basis.

CEINT NanoInformatics Knowledge Commons (CEINT NIKC)

The following explanation is based upon the cited references[3,32,33] as well as additional information provided by Dr. Christine Ogilvie Hendren and Dr. Sandra Karcher.

For the purpose of selecting suitable publications for literature curation, "minimum information criteria" were developed which emphasised the critical importance of the test media in which characterisation was performed being thoroughly described.[34,35] Publications not meeting these criteria are not prioritised for investing the necessary effort to curate. Beyond this, data completeness may be evaluated based upon querying the degree to which key fields are populated in the database and these key fields are defined on a case-by-case basis, related to the intended use of the data.

The CEINT NIKC resource is being developed (in terms of structure, associated visualization tools, and selected data) with the purpose of supporting data interrogation in pursuit of specific research questions. Because of this, slight changes to the structure and additional fields are being added iteratively according to the needs of various researchers with which the Data Integration Team (DIT) engages. Furthermore, the level of detail necessary to curate into the NIKC depends on the queries and visualizations the data are intended to support. As the database and toolset grows, the DIT anticipates defining relative levels of

data completeness for use in establishing a linkage between the detail level of curation and the use case for which a specific dataset was targeted for curation. CEINT is in the process of formalising the development of a method to quantify quality.

NanoNext Database on the Environmental Fate and Effects of Nanomaterials (RIVM)

The following explanation is based upon the cited references as well as additional information provided by Dr. Willie Peijnenburg.

The criteria used to select data, extracted from various ecotoxicity studies, into this database are described in Chen et al.[36] (The work carried out within Chen et al. refers to the ecotoxicity subset of the NanoNext database.) This database includes a large number of pre-defined fields designed to capture various kinds of characterisation data and experimental metadata i.e. characterisation technique and test conditions. The degree to which these fields were populated *might* be considered a measure of data completeness although it was stressed (Dr. Willie Peijnenburg) that additional important data might be generated by "novel" methods or for "new" endpoints in the future.

An important finding which was obtained when populating this database from the available studies was that there were a large number of blank entries. Indeed, the difficulty of obtaining a high degree of data completeness, according to the predefined database fields, meant that the application of strict inclusion criteria for the studies was not considered appropriate.

JRC NANOhub Database

The following explanation is based upon the cited references as well as additional information provided by Dr. Hubert Rauscher. The European Commission's Joint Research Centre (JRC) NANOhub database ,[4] which should not be confused with the online computational resource nanoHUB,[37] does not employ any formalised definitions or set of assessment criteria for data completeness or quality.

The JRC NANOhub database[4] stores data in IUCLID5.6 format according to the OECD Harmonised Templates (OHTs), which include a variety of fields for different kinds of (meta)data.[38–41] The OECD in its "Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme"[42] lists reporting elements that should be considered when addressing the endpoints for the first part of the testing programme. A number of those elements were transformed into nanomaterial-specific OHTs and have been implemented in the IUCLID5.6 version of the NANOhub database. This guidance has been developed to ensure consistency between the various tests to be carried out on specific sponsored manufactured nanimaterials and the datasets developed.

Therefore, one *might* argue that this database *implicitly* defines a set of "minimum information" criteria (**Key concept 2** described in Table 2 of the main text) for the safety testing of manufactured nanomaterials. However, it is important to note that not all fields in these templates would be deemed necessary to complete for all purposes i.e. the templates should not be interpreted as defining "OECD data requirements".[40]

MOD-ENP-TOX Datasets

The following explanation is based upon information provided by Hanne Vriens and Dr. Peter Hoet. Further details are provided in the MOD-ENP-TOX deliverable report D1.3, which is available on request from Hanne Vriens (hanne.vriens@med.kuleuven.be) and Dr. Peter Hoet (peter.hoet@med.kuleuven.be).

The MOD-ENP-TOX FP7 E.U. project[5] developed "minimum information criteria" for excluding publications from those used to derive their literature curated datasets. Papers which failed to provide information regarding composition, shape, crystallinity and primary size of the nanomaterials were excluded prior to data extraction.

In addition, this project developed three data quality scoring schemes to assess the reliability (see Table S5, literature definition 3.4)[43] of the data, taking into account data completeness (see Table 1 in the main text), including in terms of information related to the suitability of the experimental techniques (methodology) used. Specifically, a separate scoring scheme was associated with the nanomaterial, the toxicity assay or the biological system.

Scoring of the data and methodology associated with the nanomaterial took account of the degree of characterisation (including the availability of information regarding characteristics such as size, shape, crystallinity, surface area, endotoxin contamination and contamination with metal impurities)[28,44] and whether or not the measurement device / method was specified to assess these characteristics. Partial consideration was given to whether or not characterisation of certain physicochemical characteristics (PCCs) was carried out under biologically relevant conditions:[45] one of the characteristics considered was "Agglomeration/aggregation in test medium". These points were aggregated to yield an overall reliability score for a given nanomaterial.

For scoring of a given toxicity assay or biological system, points were added based upon compliance with certain criteria. Each criterion was treated as a "yes" (one point) or "no" (zero points) question. The toxicity assay scoring scheme took account of considerations such as whether or not interference of the nanomaterial with the assay was considered.[22–31] Statements indicating that the results may have been affected by assay interference or that the results were not expected to be affected by assay interference were considered equally valid to determine that "yes, they did consider assay interference". The biological system scoring scheme took account of considerations such as whether or not the origin of the cells (e.g. the cell line)[46] and the density of the cells[47] (e.g. confluence percentage)[48] at the start of the exposure period was known.

NanoMILE Knowledgebase

The following explanation is based upon the cited references and information provided by Dr. Iseult Lynch. The NanoMILE project,[49] established under the 7th Framework Programme (FP7) of the European Union (E.U.), approach to data completeness and quality is presented in NanoMILE deliverable report D9.1 (available on request from Dr. Lynch, I.Lynch@bham.ac.uk) and is described in detail in a publication currently in preparation.

The purpose of the NanoMILE Knowledge Base (KB) is to share data and results about nanoparticle physicochemical characterisation, ageing and interactions with /impacts on living systems and the environment (from high content screening, *in vitro* and *in vivo* toxicology and ecotoxicology studies including "omics" data) in an integrated and collated manner to facilitate QNAR[50] development, within the NanoMILE project and externally with NanoMILE cooperation partners. Hence, each individual nanoparticle has an entry in the database, and all associated data are linked to that entry, including where nanoparticles are artificially "environmentally aged" in order to be able to interrogate the relationships between initial physicochemical properties to aged properties and impacts. For aspects such as the metabolomics and proteomics data, where data standards are already emerging (e.g. MIAME[51–53] for expression data , MIAPE for proteomics,[54] and mzQuantML for mass spectrometry data)[55] the NanoMILE knowledge base adheres to these. All nanoparticles are characterised in-house according to an agreed set of "minimum characterisation criteria" which includes time and concentration resolved characterisation in the relevant exposure and *in vitro/in vivo* test media (i.e., those tested within NanoMILE). The characterisation information is considered to be "complete" according to current best practice. For biological assays and "omics" assessments, best practice guidelines are adhered to including assessment of nanoparticle interference[28,30,56,57] with the assay, as well as reporting the origin of the cells (e.g. the cell line,[46] the passage number) and the density of the cells[47] (e.g. confluence percentage)[48] at the start of the exposure period etc.

For datasets imported into the project (e.g. for initial QNAR development), data completeness and quality are assessed using the criteria described below for ModNanoTox data.

ModNanoTox Datasets

The following explanation is based upon information provided by Dr. Iseult Lynch, with full details included in ModNanoTox deliverable report D7.4 (available on request from Dr. Lynch, I.Lynch@bham.ac.uk).

The ModNanoTox FP7 E.U. project[7] developed quality assessment criteria based upon assessing the completeness of the available physicochemical data, for the nanomaterials for which ecotoxicity data were reported in a publication considered for curation, and the associated metadata (such as experimental techniques and key experimental conditions such as the light regime for TiO_2 studies) in terms of "minimum information" criteria (see Table 2 in the main text), as well as taking into account the appropriateness of the manner in which certain physicochemical characteristics were determined. It is important to note that the manner in which physicochemical data completeness and quality were evaluated in this project was intended to be nanoparticle type specific i.e. different physicochemical parameters and different experimental parameters were recognised as being important for different kinds of nanoparticles based upon their chemical composition and other physicochemical attributes such as crystal phase. For example, crystal phase is an important parameter for TiO_2 nanoparticles (which can exist as three district polymorphs as well as mixed phases, thus requiring characterisation of which phase/phases are present in a specific material) and the light exposure regime is important experimental metadata for these nanoparticles as the anatase polymorph, in particular, is known to be photoactive.[58–61] However, other nanomaterials may require different characterisation: crystal phase is not considered relevant for CeO_2, whilst redox state is considered relevant for CeO_2 but not TiO_2.[62] Figure S2 provides a schematic overview of the ModNanoTox quality assessment criteria, as applied to TiO_2 nanoparticles.

As shown in Figure S2, for TiO_2 nanoparticles, the project developed "quality control criteria" for excluding publications, from those for which data were extracted, during a "quality control" (QC) evaluation stage. This QC stage comprised two steps: an "initial screen" and a "secondary screening" step. Papers which used commercial particles and failed to perform in-house characterisation were deemed to have failed the "initial screen". During the "secondary screening" step, whether or not the crystal phase was determined was considered as well as whether or not the light regime was documented: papers for which these (meta)data were not provided were also not curated to derive the ModNanoTox datasets.

A set of criteria were developed with which to rank the extent and appropriateness of nanoparticle characterisation in each study which passed the QC stage, leading to a "quality score" for each study. Thus, each study that passed the initial QC stage was then scored for the completeness of particle characterisation. Here, it is important to reiterate that this scoring is specific for each particle chemistry (or crystal phase), as not all physicochemical parameters are relevant for all particles. Studies were evaluated against a matrix of physicochemical parameters as determined by specific methodologies and characterisation under relevant exposure conditions and over relevant timescales (shown schematically in Figure S2), giving a characterisation score for each, which is included as a field in the database. This score gives the database user an indication of the confidence they should have in the study carried out on a single nanoparticle from a characterisation perspective.

Initial Screen:

A) Particle source	
Commercial	0
Prepared in house	1

B) Extent of particle characterisation	
Nominal values used, no in house characterisation	0
In house characterisation	1

Any studies with a combined score of 0 will not pass this initial screen will be added to a 'reserve list', for subsequent analysis if necessary

Secondary Screening:

Crystalline phase determined (XRD/TEM/AFM)	0-2
Light regime described (photoperiod / wavelength / intensity)	0-2

As anatase, one of the three crystalline forms of TiO_2, is photoactive it is a **prerequisite** for inclusion in the database that the study determines the crystalline phase of the nanoparticle using appropriate methods and describes the light regime as extensively as possible.

Subsequent Ranking:

C) TiO_2 specific characterisation assessment criteria				
Parameter	Appropriate Techniques	Pristine Particles	*In situ*	Over exposure duration
Size	TEM/AFM/NTA	0-2	0-2	0-2
Morphology	TEM	0-2	0-2	0-2
Crystalline Phase	XRD / TEM / AFM	0-2	2	
Surface Properties	XPS / SEM-EDX	0-2	0-2	0-2
Aggregation	DLS/SEM /TEM	0-2	0-2	0-2

Papers that pass the initial and secondary screens will be ranked for the extent of characterisation of each of the five parameters given in the table above as follows:
0 = no characterisation; 1 = limited or qualitative characterisation; 2 = extensive quantitative characterisation, sufficient for statistical analysis
e.g. a paper that fully characterises all five parameters for the pristine particles, but performs no *in situ* characterisation, and no characterisation over the exposure duration would have a score of 10 (5x2). A 'perfect' study would be awarded a score of 28 (full characterisation of the pristine particles, the particles *in situ* and over the course of the experiment).

Figure S2 Protocol for ranking studies of TiO_2 engineered nanoparticles for inclusion in the ModNanoTox datasets. N.B. In addition to characterisation of the pristine nanoparticles, ModNanoTox characterisation criteria also take account of whether the particles have been characterised in the relevant exposure media ("in situ") and over the relevant exposure time period used in the corresponding biological assay ("over exposure duration"), as shown in this figure.

The Nanoparticle Information Library (NIL)

The following explanation is based upon the cited references,[8,63,64] as well as additional information provided by Dr. Mark D. Hoover.

The Nanoparticle Information Library (NIL)[8,63,64] was established in 2004 by the National Institute for Occupational Safety and Health (NIOSH) and its national and international partners as part of the NIOSH Nanotechnology Research Program.[65] The NIL is a prototype searchable database of nanoparticle properties and associated health and safety information designed to help occupational health professionals, industrial users, worker groups, and researchers organise and share information on nanomaterials, including their health and safety-associated properties. NIOSH released the NIL web resource in draft form for public review and feedback. The current hosting, administration, and maintenance of the NIL web resource is being conducted by Oregon State University (OSU) in conjunction with its program to characterize nanomaterials and to create a Nanomaterial-Biological Interactions (NBI) Knowledgebase.[66]

To illustrate how information can be organized for many types of nanomaterials, the NIL staff populated the database with entries corresponding to representative nanomaterials for which there are peer-reviewed, public literature publications. Priority was given to publications having as complete as possible data related to the following information: nanomaterial composition; method of production; particle size, surface area, and morphology (included scanning, transmission, or other electron micrographic images); demonstrated or intended applications of the nanomaterials; availability for research or commercial applications; associated or relevant publications; links to health and safety information; and points of contact for additional details or partnering.

For each nanomaterial entry, members of the NIL staff contacted the corresponding author of the associated publication or publications to confirm how the available information would be transferred into the format of the NIL. The NIL process for assessing data quality focused on whether the experimental methods used in each study were documented in the associated publications.

The NIL provides links to other resources, including the NIOSH Pocket Guide to Chemical Hazards (a source of general industrial hygiene information on several hundred chemicals/classes of material for workers, employers, and occupational health professionals)[67] and the Registry of Toxic Effects of Chemical Substances (a compendium of chemical and toxicity data extracted by NIOSH researchers from the public scientific literature).[68]

At the time that the NIL was initiated, little work had been done on organised ontologies and there was no clear understanding on how the data customers, creators, curators, and analysts would ultimately need to interact to compile and make use of the data. The NIL added significant value to the nanoscience community by serving as an early example for much of the work that has followed, including work to build other data bases, to map a community-based approach to informatics and data sharing,[69] confirm and clearly communicate critical terminology concepts and context,[70] and develop and apply an informatics-based framework and process for decision-making.[71]

Figure S3 provides a snapshot of how information is displayed on the NIL webpage.

Figure S3 Example of the online Nanoparticle Information Library homepage at http://www.nanoparticlelibrary.net.

Section S3. Explicit or implicit definitions of data completeness and quality presented in the relevant scientific literature

As explained in section 2 of the main text, various definitions of data completeness and quality, as well as the related concept of a minimum information checklist, are presented in the literature and used by different researchers or research initiatives. These somewhat different definitions were synthesised into the broad and flexible definitions presented in Tables 1, 2 and 3 in the main text. These broad and flexible definitions were used when reviewing existing work, as reported in the literature and in response to the NDCI data completeness and quality survey, which was summarised under sections 3 – 5 of the main text and section S2 of the current Electronic Supplementary Information file.

The explicit and implicit definitions presented in the published literature are provided in Tables S3, S4 and S5.

Table S3 Data completeness: some definitions presented in the relevant scientific literature

Literature definition no.	Reference	Definition	Comment
1.1	Hendren et al.[72]	"Completeness is a measure of the raw data, assays, processed data, or derived data…" [Questions might include] "What are different ways data completeness could be defined, and are these completeness criteria shaped of the goals for the data being curated?"	The Nanomaterial Data Curation Initiative (NDCI) framing paper
1.2	Batini et al.[73]	"the degree to which a given data collection includes data describing the corresponding set of real-world objects"	Literature review. Computer science (data storage) focus. Their definition is a synthesis of earlier definitions in the computer science literature. Completeness viewed as one dimension of data quality. Metadata viewed as a distinct issue to data completeness.
1.3	Fu et al.[74]	"data completeness …. indicates that the required data are well recorded without missing values. A complete data source covers adequate data in both depth and breadth to meet the defined business information demand"	Literature review. Predictive toxicology focus. Completeness viewed as one dimension of data quality. Metadata viewed as a distinct issue to data completeness.
1.4	Klimisch et al.[43]	No specific definition is provided. However, the importance of "complete documentation" or a "complete report" - documenting the test compound, experimental systems, conditions and protocols - for evaluating toxicology data is stressed.	Key paper on data quality in the context of regulatory toxicology. Hazard and risk assessment focus; completeness implicitly viewed as critical to data quality assessment.
1.5	Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) report[75]	No specific definition is provided. However, the "completeness and detail of reporting and referencing" is implicitly considered in terms of the degree to which "details of the methodology and results obtained are provided".	Focused on risk assessment to support regulatory decisions; completeness viewed as critical to data quality assessment.
1.6	European Chemicals Agency (ECHA) guidance[76]	"The completeness of the information refers to the conclusion on the comparison between the available information and the information that is required"	Guidance is provided regarding compliance with legislative information requirements for chemical safety assessment.

Table S4 Minimum information checklist:[a] some definitions presented in the relevant scientific literature

Literature definition no.	Reference	Definition	Comment
2.1	Thomas et al.[77]	"minimum information standards (data reporting guidelines) …. are guidelines that specify the minimum level of information that must be represented and shared about a method, protocol, or material in publications, reports or in databases".	Literature review. Nanoinformatics focus; "minimum information standards" are considered necessary to ensure data quality and completeness.
2.2	Taylor et al.[78]	No specific definition is provided. However, "minimum information guidelines" or "minimum information checklists" are implicitly defined as a "regularized set of the available metadata", for which researchers should "strive for compliance in their own publication".	Literature review. Experimental reporting for biological and biomedical investigations focus; metadata considered in terms of the "biological and methodological contexts"

a. Minimum information checklists might otherwise be referred to as minimum information standards, minimum information criteria, minimum information guidelines or data reporting guidelines etc.

Table S5 Data quality: some definitions presented in the relevant scientific literature

Literature definition no.	Reference	Definition	Comment
3.1	Hendren et al.[72]	No specific definition is provided, as the authors intended this as a focal area for exploration within the NDCI series of manuscripts. Nonetheless, it is noted that "High quality data could still be sparse or 'incomplete'" and that "data quality" includes "issues such as precision, error, and sufficiency of meta-data for reproducibility". The authors also note the possibility that there might be "differences when evaluating data quality captured from a database versus from the primary literature".	The Nanomaterial Data Curation Initiative (NDCI) framing paper
3.2	Batini et al.[73]	Data quality may be considered in terms of "a basic set of data quality dimensions, including accuracy, completeness, consistency, and timeliness …. referred either to the extension of data — to data values, or to their intension— to their schema".	Literature review. Computer science, data storage focus. Discrepancies in the computer science literature regarding precise definitions of these terms are noted.
3.3	Fu et al.[74]	Data quality "refers to its fitness for serving its purpose in a given context". In the context of predictive toxicology, this may be considered in terms of "data storage sense (e.g. accuracy, completeness and integrity)" or "in a toxicological sense (e.g. the quality of experimental results)".	Literature review. Predictive toxicology focus. The provision of metadata is considered important to enable the quality of experimental results to be *judged* by a domain expert.
3.4	Klimisch et al.[43]	Data quality, or the quality of a corresponding test report or publication, is defined in terms of "their **reliability**, **relevance**, and **adequacy**". -**Reliability** means "inherent quality" and is related to the "clarity and plausibility of the findings". - **Relevance** means whether or not the data are "appropriate for a particular hazard identification or risk characterization". - **Adequacy** means "usefulness of data for risk assessment purposes" and is a function of reliability and relevance.	Key paper on data quality in the context of regulatory toxicology. Hazard and risk assessment focus.
3.5	Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) report[75]	In this report, the quality of "a set of data (e.g. a publication)" is considered a function of its "**reliability**" and "**validity**". - **Reliability** means whether or not "findings were reproducible between experiments" and this is considered, in part, to depend upon the "completeness and detail of reporting and referencing". - **Validity** implicitly refers to the "suitability of the experimental design and the application of the methods and models". - **Relevance** is considered to be entirely independent of quality.	Focused on risk assessment to support regulatory decisions. Note the somewhat different definitions used for these terms vs. definition 3.4 (Klimisch et al.).[43]
3.6	ISO/IEC Guide 98-3:2008[79]	In this report, the "quality of a result of a measurement" is considered to be evaluated and expressed in terms of	Report from the International Standards Organisation. Focused on

		its “uncertainty”, which is viewed as a “quantifiable attribute”.	quantitative measurements of physical quantities.
3.7	Chirico et al.[80]	In this publication, “high quality” data refers to data which “are well-defined … in terms of the chemical system studied, property measured, numerical data reported, and the uncertainty in those reported values”.	Focused on evaluating the quality of thermophysical and thermochemical data.

Section S4. Detailed explanations of the recommendations presented in section 6 of the main text

Terminology recommendations

6.1.1 Specific definitions of completeness and quality are recommended to the nanoscience community.

The definitions introduced in section 6.1.1 of the main text are repeated below, along with accompanying detailed notes which clarify their meaning. N.B. The notes regarding repeatability, reproducibility, error and uncertainty were informed by consultation of NIST guidelines regarding measurement uncertainty, but are not perfectly consistent with these guidelines.[81] These guidelines[81] adopted certain ISO accepted definitions of repeatability, reproducibility, error which are broadly in keeping with ISO recommendations provided elsewhere.[79,82,83] Specific, internationally agreed, definitions of these terms, for quantitative measurements, can be found in various ISO documents.[81–83] However, the current notes consider these concepts in a broader sense.

Data completeness. This is a measure of the extent to which the data and metadata which serve to address a specific need are, in principle, available.

Note 1: Here, "address a specific need" refers to answering a specific question. This could entail testing a specific research hypothesis. In an industrial context, this could entail deciding whether the development of a product or project should be continued. In a regulatory setting, this could entail deciding whether to grant regulatory approval for a specific product in a specific context.

Note 2: Hence, an assessment of the relevance of the data for answering a specific question is related to data completeness. Irrelevant data cannot be counted when assessing data completeness. Likewise, the degree to which relevance can be assessed is contingent upon the availability of metadata.

Note 3: The qualifier "in principle" refers to the fact that, even if values are available for all required data and metadata, they may still be of insufficient quality (e.g. due to high uncertainty in those values) to address the specific need in practice.

Note 4: In contrast to data quality, the concept of data completeness is applicable to both a single datum, in terms of its associated metadata, or a collection of data.

Data quality. This is a measure of the degree to which a single datum or finding is clear and the extent to which it, and its associated metadata, can be considered correct.

Note 1: A datum or finding might be quantitative or qualitative.

Note 2: A "finding" might be a conclusion derived from analysis of a set of raw or processed data and the "metadata" associated with that finding might include these data. Hence, multiple findings might be derived from the same underlying data and these might be of varying quality.

Note 3: The extent to which a datum or finding can be "considered correct" will be a function of quantifiable error and uncertainty contributions, as well as qualitative issues, such as the extent to which it can be trusted. Uncertainty and trust are both related to the degree of repeatability and reproducibility. Trust may also be related to issues such as provenance and compliance with quality assurance protocols, GLP etc.[84] Quantifiable errors may arise due to artefacts in the data and a qualitative finding drawn from the data may not be trusted unless the potential for artefacts to have affected the finding has been excluded.[85] Hence, checks for artefacts might be considered criticial metadata for quality assessment.

Note 4: The extent to which a datum or finding is "clear" refers to the degree to which it is precisely defined. This will be a function of uncertainty estimates and other metadata which define exactly what information a datum or finding conveys. This can be considered in both a qualitative (e.g. "this uniquely identified nanomaterial is associated with this biological property under these conditions") and quantitative sense (e.g. "the true LC_{50} value lies within this range with a confidence of 95%").

Note 5: The quality of a curated datum or finding is a function of the quality of the originally reported datum or finding and additional issues related to curation. The quality of the originally reported datum or finding is dependent upon issues such as the extent to which this is experimentally reproducible and experimental sources of error. Issues related to curation include the probability of transcription errors and whether the available metadata include links back to the original data source (e.g. publication). Links back to the original data source allow for greater trust in the curated data to be established.

Note 6: Repeatability is a quantitative or qualitative measure of the extent to which a given scientist working under, ostensibly, the exact same conditions in the same laboratory can exactly repeat the result within a short period of time. This will be dependent upon random experimental errors.

Note 7: Reproducibility is a quantitative or qualitative measure of the extent to which the datum or finding can exactly be reproduced by a different scientist, possibly in a different laboratory. The degree of reproducibility will depend upon the availability of the corresponding experimental metadata. Likewise, the degree to which a given datum or finding can be said to have been reproduced will be contingent upon the degree to which the nature of this datum or finding is clear. Consequently, the degree to which the datum or finding can be said to have been reproduced will depend upon the availability of the experimental metadata.

Note 8: An error is the known deviation of a given item of (meta)data (or finding) from its true result. Sources of error may be random or systematic. This may be considered in a quantitative (e.g. "this LC_{50} has an error of +0.1 log units") or qualitative (e.g. "this nanomaterial identifier is incorrect") sense.

Note 9: Uncertainty is a measure of the degree to which the true result is unknown as a result of (possibly unknown) random or systematic sources of error. The total uncertainty may comprise different quantitative and qualitative uncertainty components.[81]

Note 10: Quality is associated with a specific datum or finding, not a dataset or publication. Nonetheless, if most data in a dataset are of high quality for a given endpoint, one may talk (loosely) of a "high quality dataset".

Note 11: Format compliance of a dataset is not considered a data quality issue. However, validation software developed to assess data quality as well as completeness may also check format compliance or be dependent upon receiving data in a standard format, e.g. ISA-TAB-Nano.

Note 12: Data quality should not be considered a function of the purpose for which the data are used. Hence, the relevance of the data for a specific purpose should not be considered related to their quality. (This is in contrast to some definitions of data quality,[43] *presented in Table S5, which informed the broad and flexible definition in Table 3.) Nonetheless, the degree of data quality required may depend upon the specific purpose for which the data are used. For example, the cost of making an incorrect decision based upon unclear or incorrect data may be scenario specific. Hence, higher quality data may be required for some purposes than others.*

Relationship of data quality to completeness. The quality of a specific datum or finding is partly dependent upon the completeness of the, readily available, associated metadata. This is true to the extent that these metadata are required to clarify the meaning of the datum or finding (e.g. to assess exactly which nanomaterial is causing which effect under which conditions), enable the reproducibility of the datum or finding and assess the degree to which the datum or finding is trustworthy, repeatable, of low uncertainty and low error. The completeness of the metadata also allows the extent to which the data are relevant for answering a specific question to be assessed. However, the quality of a given datum or finding is not dependent upon its relevance for answering a specific question. N.B. What is meant by metadata (as opposed to data) will be context specific. For example, physicochemical data are metadata for a biological datum associated with a given nanomaterial. The raw data associated with processed data may also be considered part of the metadata required to verify that data are reproducible.

Additional considerations related to data quality but not completeness. The quality of a given datum or finding also depends upon its level of reproducibility and repeatability, as well as the level of trust, uncertainty and error associated with the value of that datum (or finding) and its corresponding metadata. (See the data quality definition notes 3,6,7,8 and 9.) For example, if a specific datum, or its associated metadata, has been incorrectly transcribed into a database, that datum may be considered of lower quality. As another example, a higher standard deviation associated with a quantitative experimental result means that result is of lower quality.

Additional considerations related to data completeness but not quality. Data completeness, but not quality, also depends upon the extent to which sufficient data points are available in order to answer a specific question. For example, data for multiple biological endpoints or at multiple time points might be required to answer some questions e.g. the sustainability of different biological responses in response to nanomaterial exposure.[86] However, the number of time points or the number of biological endpoints assessed does not affect the quality of the individual data points. As another example, the availability of biological data obtained under experimental conditions which are relevant to assessing risk to human health should be considered related to data completeness rather than quality. This is a departure from some definitions of data quality (see Table S5),[43] which were incorporated into the broad and flexible definition (Table 3) used to assess prior work.

Key recommendations regarding specific (meta)data

6.2.2.1 For many physicochemical properties, in-house determination, including under biologically relevant exposure conditions, is recommended.

It is important to measure physicochemical data "in-house", rather than relying on nominal/vendor supplied data. In addition, for biological studies, it is typically of value to measure many of these properties under biologically relevant exposure conditions rather than, or in addition to, under pristine conditions. Indeed, in-house physicochemical characterisation under biologically relevant conditions has previously been recommended.[45]

From a data curation standpoint, it is important to ensure that the necessary metadata are curated to enable end-users of a data collection to determine whether physicochemical data comply with these recommendations. For example, the media used for agglomerate size determination and biological testing should be curated. The ISA-TAB-Nano specification facilitates this.[87–89]

It should be noted that a variety of caveats are applicable to the recommendation that, when carrying out biological assays, physicochemical properties should be measured under biologically relevant exposure conditions. Firstly, not all physicochemical properties are equally dependent upon experimental conditions. For example, primary particle size and shape, as opposed to the size and shape of any agglomerates, can be expected to be less dependent upon the suspension medium composition. (However, in principle, even primary particle size and shape might change over time under certain conditions, as is discussed in section 5.3 of the main text. Hence, capturing corresponding media and, as per recommendation 6.2.2.2, temporal metadata may still be important.)

Secondly, physicochemical characterisation under pristine conditions might be sufficient in order to achieve certain aims. This could be the case even for properties which depend strongly upon experimental conditions e.g. media. For example, physicochemical characterisation under pristine conditions might be sufficient if the aim (see section 5.7 of the main text) was simply to determine whether a given nanomaterial could cause an effect under a given set of conditions. (However, even under this scenario, detailed recording of the necessary experimental conditions and corresponding temporal metadata, as per recommendation 6.2.2.2, would still be important.) In contrast, if the aim was to determine the specific, changed identity and properties of the nanomaterial responsible for the effect, physicochemical characterisation under pristine conditions would not be sufficient. This latter aim would likely need to be achieved if the ultimate goal was mechanistic insight and/or generalisation from the data (e.g. modelling).[35]

Thirdly, some medium dependent properties may no longer correspond to their values measured in the assay exposure medium, following cellular uptake and transport to the site of biological action. For example, the nanoparticle "corona" may determine cellular uptake but get degraded within lysosomes before triggering toxicological endpoints.[90,91] Hence, one can argue that physicochemical characterisation in various media, *in addition to* the exposure medium used in the assay, is important. This argument is reinforced by the work of Liu et al., [92] who developed models for cellular association. They used a non-linear modelling technique to relate this endpoint to descriptors obtained from measurements of nanomaterial properties. They obtained a better model if zeta potential measured "as synthesized" was selected as a descriptor, in combination with properties measured under biologically relevant exposure conditions, instead of zeta potential measured with serum.

Finally, even if certain properties are dependent upon experimental conditions, their measurements obtained under pristine conditions might still be related in a suitably complicated, non-linear fashion to biological activity obtained under different conditions. A suitable non-linear modelling technique may be able to discern these complicated relationships. However, capturing complicated non-linear relationships and obtaining mechanistic interpretation may be challenging in practice if measurements are *only* performed under pristine conditions. Indeed, even with a non-linear modelling approach, Liu et al. indicated that their best model for cellular uptake was obtained using a combination of properties measured "as synthesized" and under biologically relevant conditions.[92] Hence, physicochemical characterisation under biologically relevant conditions is still recommended.

6.2.2.2 Temporal metadata are particularly important to capture.

The dynamic nature of nanomaterials (see section 5.3 of the main text) means that corresponding temporal metadata need to be captured for all physicochemical and biological characterisation measurements. These metadata should include time differences between

different measurements, along with corresponding storage and processing (e.g. sonication) history.[93,94] Other temporal metadata may also be important to capture.[94] Indeed, unless physicochemical data were obtained within a "sufficiently short" time period of biological assessment, the data for a biological study might not be complete, regardless of the medium used for physicochemical characterisation. (Here, a "sufficiently short" time period would be dependent upon the storage and processing history as well as the specific nanomaterial.) This would arguably be the case if the exact nanomaterial identity and properties responsible for biological effects were required for mechanistic insight or generalisation from the data. Correspondingly, nanomaterial data curators need to ensure that temporal metadata are captured in a suitably standard way. This could entail building upon the "instance of characterization" (IOC) approach employed by the Nanomaterial Registry[95,96] and/or via careful consideration of how best to capture temporal metadata using ISA-TAB-Nano.[87–89]

6.2.2.3 (Meta)data allowing for assessment of possible artefacts are required.

Recent reviews and primary research articles which presented clear guidelines for identifying and avoiding possible artefacts (e.g. assay interference)[28,30,56,57] should inform specific (meta)data requirements to address this issue. From a nanomaterial curation perspective, basic metadata could include whether assay interference was "considered", although it would be better to document whether the possibility of assay interference affecting the results had been "avoided". However, a simple "yes/no" metadata scheme could require a rather subjective judgement. This could also be very time consuming for curators if this went beyond documenting the conclusions of the experimentalists. It would arguably be better to explicitly determine which (meta)data need to be curated in order for this judgement to be made after curation. (The literature analysis of Ong et al.[57] might serve as a starting point.) However, this is an active area of research. New insights and corresponding recommendations are likely to be introduced in the literature for the foreseeable future.

6.2.2.4 (Meta)data related to experimental errors and uncertainty are required.

Experimental error and uncertainty estimates should be considered a key aspect of data quality. (See data quality definition notes 3, 4, 8 and 9 in the detailed discussion of recommendation 6.1.1.) Here, the focus is on documenting numerical estimates of error or uncertainty which may arise from (a) random or (b) systematic sources of error.[81]

a. For example, uncertainty associated with a single, quantitative measurement arising from random sources of error may be expressed in terms of the standard deviation.[81,97] The corresponding uncertainty associated with an estimate of the true value obtained from repeated measurements, in terms of the arithmetic mean, may be expressed in terms of the standard error of the mean.[98] Because the terms "error" or "uncertainty" are insufficiently precise, the exact nature of the experimental "uncertainty" should be documented, in keeping with recommendation 6.2.2.7. For example, the terms "standard deviation" and "standard error of the mean" should be documented. Furthermore, information about the number of replicates used to derive a given "uncertainty" estimate should also be provided. For example, this would enable a standard deviation to be converted into a standard error of the mean or vice-versa.

b. One systematic source of error is artefacts (e.g. assay interference)[28,30,56,57] in biological studies. Another example is errors due to inadequately calibrated biological assay systems or physicochemical measurement systems. In general, biological assay systems need to be validated using appropriate controls.[27,44,47] Biological assay systems and physicochemical measurement systems might be calibrated using appropriate nanoscale reference materials, if these exist for the specific measurements of interest.[44] In either case, documenting the controls, or reference materials, their corresponding measurements and their reference values is important. (The reference values are the values expected if the biological assay system was responding as expected or the physicochemical measurement system was properly calibrated.)

N.B. Random sources of variability in biological results may also be monitored using appropriate controls, which also need to be documented appropriately.[29]

6.2.2.5 Data identifying (biologically significant) impurities are important.

Biologically significant impurities could include endotoxin, metals and residual dispersion medium/solvent.[28] However, if the aim (see section 5.7 of the main text) of a particular user of the curated data is simply to determine whether a specific nanomaterial could cause a specific effect under a given set of experimental circumstances and point in time, it may not be essential to document the impurities - or any other characteristics of the nanomaterial. This would arguably be the case if the nanomaterial sourced for testing is sufficiently well identified via manufacturer supplied IDs (see recommendation 6.2.2.6). Nonetheless, if mechanistic insight and generalisation from the data (e.g. modelling) were desired, documenting biologically significant impurities would be critical.

6.2.2.6 Various manufacturer supplied IDs should be recorded.

If the originally sourced nanomaterial used in two different investigations can be identified as the same, it might be possible to treat them as the same dataset/database record (e.g. a single ISA-TAB-Nano Material file).[99] This would mean characterisation data reported in both investigations could be linked together. Hence, the same characterisation data may not need to be regenerated. (Indeed, one might consider the two investigations to really correspond to a single investigation on the same nanomaterial.)[89] The information required to determine whether the same nanomaterial had been sourced for two different investigations would arguably include the "batch identifier" - otherwise known as a "lot number" or "manufacturer lot identifier".[45,99,100] This probable requirement reflects the potentially significant batch-to-batch variability associated with some nanomaterial synthesis procedures.[45,101,102]

However, if only the trade name is available, the two nanomaterials (as originally sourced) might still be considered the same, if metadata regarding the synthesis procedure were available and these suggested limited batch-to-batch variability.[45,101,102] (The ISA-TAB-Nano Material file includes predefined fields for recording the material synthesis and manufacturer lot identifier.)[99] In this case, it would arguably not be advisable to merge the same originally sourced nanomaterial sample records into a single record (e.g. create a single ISA-TAB-Nano Material file)[99] in the first instance. However, they might reasonably be treated as identical during computational analysis.

In all cases, supposing that two originally sourced nanomaterials were essentially identical would arguably require temporal metadata (see recommendation 6.2.2.2), even if their manufacturer lot identifiers were same. This temporal metadata would include their corresponding storage and processing history and the period elapsed between synthesis and the start of experimentation.[94] These temporal metadata would arguably be required to judge whether two nanomaterials judged to be (essentially) identical at the point of synthesis, based on manufacturer supplied IDs, were still identical at the start of two different investigations.

6.2.2.7 Sufficient metadata should be provided to precisely identify any measured data.

For example, the specific kind of "average size" parameter obtained from dynamic light scattering or laser diffraction should be reported.[103–105] More generally, the precise nature of statistical quantities, including "uncertainty" estimates[81] (recommendation 6.2.2.4), should be documented. From a data curation and nanoinformatics standpoint, these important metadata can be documented precisely using the ISA-TAB-Nano framework.[87–89] Likewise, standardised use of statistical terminology could be promoted via linking curated terms to terms from the STATistics Ontology (STATO).[106] (However, as of version 1.2 of the ISA-TAB-Nano specification, there was no accepted way of linking statistical terms to terms from ontologies within ISA-TAB-Nano.)[89] Definitions of statistical terms might also be retrieved from standards bodies such as ISO or ASTM International.[107–109] Indeed, publicly available ontologies might be improved via citing definitions established by these organisations. A related challenge concerns the need for metadata terms which are sufficiently precise to differentiate statistical quantities related to repeat measurements from statistical quantities related to nanomaterial polydispersity.

6.2.2.8 Provenance metadata are essential.

For curated data, this should certainly include links back to the original publication(s) from which the data were curated if this is applicable. Otherwise, if data were extracted from another data resource rather than (directly) curated from a (set of) publication(s), links should be provided back to the original data resource. These metadata enable possible transcription errors to be checked against the original source(s) and allow for greater trust in the data.

6.2.2.9 Data regarding the surface composition and structure/morphology are important.

The importance of surface composition and the corresponding structure/morphology has received

considerable attention in the recent literature. In spite of this, only one of the 18 lists of "priority" properties reviewed by Stefaniak *et al.* considered "surface morphology/structure".[44] For inorganic nanoparticles, the surface composition and structure/morphology may arise due to a ligand shell/layer. For example, "stripe-like domains" may arise from mixed ligand shells formed at the surface of gold nanoparticles.[85] (The existence of this phenomenon was recently debated in the literature).[85,110–112] Surface composition and morphology/structure may affect various physiochemical properties,[113,114] adsorption of additional molecules from the atmosphere or biological media[115–117] and biological modes of action.[118] Understanding and/or modelling of biological effects or (see recommendation 6.4.4) the outcome of "functional assays" (e.g. dissolution behaviour)[35,114] may, therefore, require detailed characterisation of the composition and arrangement of surface ligands/functional groups. Similarly, unless manufacturer identifiers and corresponding temporal metadata were sufficient (see recommendation 6.2.2.6), determination of whether two nanomaterials were equivalent, or effectively equivalent,[119] could also require detailed characterisation of surface composition and structure/morphology. Detailed characterisation of surface composition and/or structure/morphology may be carried out using a variety of different experimental techniques.[85,120,121]

Computational recommendations

6.3.1 Computational tools for assessment of completeness and quality should be developed.

Suppose it was possible to define a prescriptive, algorithmic approach to completeness and quality assessment and to structure all of the necessary (meta)data in a standardised fashion. If this was possible, one could envisage completeness and quality scores being calculated in an entirely automated fashion via parsing structured datasets. For example, one might imagine datasets derived via populating the ISA-TAB-Nano templates envisaged in recommendation 6.3.2 being parsed to calculate completeness and quality scores. This could entail calculating a data completeness score based on the proportion of (an end-user specified subset of) populated fields in a set of ISA-TAB-Nano files. Likewise, data quality scores might be calculated for individual data points via considering the degree to which associated metadata fields were populated and the specific entries in certain fields. For instance, the value of an Investigation file "Comment [GLP]"[89,122] entry, denoting whether a set of studies complied with Good Laboratory Practice,[43,47,84] could be taken into account for the quality scores. However, fully automated assignment of completeness and quality scores is not possible if (i) the (meta)data are not sufficiently structured and standardised (e.g. if they are recorded using free text) and (ii) assessment of these issues, especially quality assessment, relies upon expert judgement. In principle, it should be possible to minimise the extent to which issue (i) remains the case for curated, electronic datasets, as opposed to data reported in journal articles or study reports. However, challenges still exist with standardised reporting of (meta)data for some circumstances.[89] Even if issue (ii) is unavoidable, computational tools to improve the transparency and consistency with which the quality of nanomaterial data are assessed might still be developed. These tools might function as per the ToxRTool,[123,124] or the extension of this tool recently proposed by Yang et al.[125]
Beyond the issue of "scoring" nanomaterial data, the development of tools to support assessment of the metadata completeness and error checking (part of quality assessment) of nanomaterial experimental data submitted for publication should be considered. A possible source of inspiration for such an initiative would be the tools described by Chirico et al.[80] for assessment of thermophysical and thermochemical experimental (meta)data documented in articles prepared for publication.

6.3.2 Standard templates for data exchange should be developed based upon the ISA-TAB-Nano specification.

The ISA-TAB-Nano specification,[87–89] a derivative of the ISA-TAB specification,[10,126,127,127,128] has been proposed as a standardised means of exchanging nanomaterial (meta)data. The ISA-TAB-Nano specification is based on four interlinked, spreadsheet-like (tab-delimited) file types (Investigation, Study, Assay and Material), with so-called "external" files, containing additional data, linked to the standardised file types. ISA-TAB-Nano is a designated ASTM International standard.[129] At the time of writing, version 1.2 was the latest version and discussions regarding a possible extension (version 1.3) were ongoing. The most up to date information regarding the specification can be found on the official wiki.[88]
Whilst it significantly supports standardised reporting, the generic specification does not address exactly which (meta)data should be recorded and there was still some ambiguity regarding exactly how best to record certain kinds of (meta)data at the time of writing.[89] Hence, the development of standardised templates based on the ISA-

TAB-Nano specification would be very valuable. This would facilitate the standardised exchange of sufficiently complete and high quality nanomaterial (meta)data. It is possible that different sets of templates might be agreed upon by different user communities working with different kinds of data or with different objectives.

Here, it is worth noting that the ISA-TAB-Nano developers already provide generic templates.[130] They also provide examples of how to capture a variety of experimental (meta)data for different nanomaterials,[131] different kinds of studies[132] and assays.[133] In addition, work within the NanoPUZZLES[134] and MOD-ENP-TOX[5] projects has developed ISA-TAB-Nano templates to be used for curating (meta)data from the nanotoxicology literature. Both the NanoPUZZLES and MOD-ENP-TOX projects recently made their templates publicly available.[122,135,136]

The caNanoLab team[1,9,14,15] has also drafted a proposal regarding ISA-TAB-Nano templates, for consideration by the wider nanoscience community, which they propose should be based upon a list of data types for specific, enumerated nanomaterial assays.

One further source of inspiration for globally accepted ISA-TAB-Nano templates, to be used in the context of safety evaluation of nanomaterials, could be the OECD Harmonised Templates (OHTs).[38–41] (The OHTs are discussed in the context of describing the JRC NANOhub database[4] in section S2 of the Electronic Supplementary Information.)

The eNanoMapper project enables OHT files to be imported into their database and is developing tools to enable export to ISA-TAB-Nano.[41] The development of tools allowing for data collected using ISA-TAB-Nano templates to be exported into the OHT based format would also be valuable. Harmonisation of datasets prepared using ISA-TAB-Nano templates with the OHTs would increase the likelihood of those templates gaining acceptance for regulatory purposes.

6.3.3 Nanomaterial data resources providing completeness and quality scores should allow end-users to customise these based upon their own requirements.

Obtaining complete consensus regarding (meta)data requirements for nanomaterial data is likely to be a significant challenge. This is likely to be the case even within specific sub-disciplines (e.g. nanomedicine and nanotoxicology), or amongst specific groups of stakeholders (e.g. regulators and nano-QSAR modellers). Furthermore, it will be appropriate to refine these requirements in line with improved scientific understanding and the specific (meta)data required may be contingent upon the questions posed of the data. (See section 5.7 of the main text and the detailed discussion of recommendation 6.1.1 in this Electronic Supplementary Information file as well as Figure 1 in the main text.) Hence, it would be highly advantageous if any system for scoring nanomaterial data in terms of completeness or quality could be customised by end-users depending upon their own judgements regarding the importance of specific (meta)data and the specific questions posed of the data. (Existing scoring systems which might be adapted along these lines include the "data availability metrics" developed by caNanoLab[1,9,14,15] or the "compliance levels" developed by the Nanomaterial Registry.)[95,137–139] In addition, building this degree of flexibility into the scoring system could also allow scores to be adjusted in light of new scientific evidence e.g. regarding the toxicological significance of particular physicochemical characteristics. If they were available, the non-default settings specified for any customised scores would need to be made transparent.

Strategic recommendations

6.4.1 Proposals for minimum information and data quality requirements could be informed via expert consensus, building upon existing proposals.

One suitable approach to refining minimum information guidelines would be for groups of experts in (particular areas of) nanoscience to hold further discussions to agree upon a consensus set of recommendations. This approach would also be appropriate for agreeing upon additional schemes for assessing the quality of nanomaterial data. For example, a workshop might be convened in a similar fashion to the workshop held in 2008 which established the MINChar Initiative Parameters List.[16]

To avoid duplication of effort, this kind of initiative should build upon previously proposed recommendations for minimum information requirements and data quality assessment in the nanoscience area, such as those discussed in section 3 of the main text. Furthermore, the quality assessment schemes and lists of minimum information requirements developed in mature fields (see section 4 of the main text) could also be worth consulting. This would be the case insofar as they refer to experimental (meta)data which are relevant to, certain sub-disciplines of, nanoscience. To the greatest extent possible, sub-discipline specific initiatives (e.g. development of requirements for nanotoxicology vs. nanomedicine) should aim to co-ordinate their efforts to

exploit possible synergies and avoid further duplication of effort. When evaluating such schemes and developing new proposals, it will be necessary to take into account the challenges and recommendations regarding terminology and specific (meta)data requirements presented in sections 5, 6.1 and 6.2.2 of the main text. The detailed discussion of these recommendations (6.1.1 and 6.2.2.1-6.2.2.8) can be found in the current Electronic Supplementary Information file.

Finally, since various organisations are already addressing (aspects) of these issues, these expert discussions should arguably be linked to their ongoing initiatives. Relevant organisations include the OECD and the CODATA/VAMAS Joint Working Group on the Description of Nanomaterials. Recommendation 6.5.1 further addresses how working with these, and other, organisations may be advantageous.

6.4.2 Proposals for minimum information and data quality requirements could be informed via targeted experimental studies.

For example, based on the "cause-and-effects analysis" approach described by Rosslein et al.,[29] it should be possible to enumerate the experimental variables which most significantly affect the outcome obtained in a particular biological assay. This should support identification of the most important experimental metadata which need to be complete in order to ensure high reproducibility and, hence, ensure high quality data (see the detailed discussion of recommendation 6.1.1). Here, it should be acknowledged that "[cause-and-effects analysis] does not provide quantitative information on the nominal variability in these cause factors and the size of the effect these factors have on the test result".[29] Nonetheless, it does allow for the systematic enumeration of potentially important experimental variables.[29] In turn, this might be employed to design targeted experiments in which certain variables were systematically varied to assess which contributed most to the variability in the observed assay readout.

With regards to assessing which physicochemical characterisation parameters are most related to a given assay readout, this requires the synthesis of systematically varied nanomaterial libraries.[140] However, actually discerning the effects of changing a single physicochemical parameter is challenging. This is partly due to the challenges associated with nanomaterial synthesis[45,101,102] and partly due to the interrelatedness in different physicochemical properties (see recommendation 6.4.4 below).

6.4.3 Proposals for minimum information requirements could be informed via data mining.

Statistical and machine learning approaches could be used to examine the contribution of the variability of different (meta)data to the variability in selected (biological) endpoints. For instance, an analysis of the most important descriptors in a nano-QSAR study might identify the experimental variables most responsible for the variation in the modelled endpoint. (This supposes the descriptors corresponded to either physicochemical parameters or experimental conditions.) This would support the refinement of minimum information checklists and, hence, promote evaluation of data completeness and quality. Examples of this kind of analysis already exist in the nano-QSAR literature. For instance, Liu et al.[92] recently carried out this kind of analysis. They developed nano-QSAR models of cellular association between gold nanoparticles and A549 cells. They further examined the relative contributions of descriptors related to a set of various physicochemical measurements (such as zeta potential) and those characterising the composition of the protein corona[140] towards the model predictions. These authors[92] also emphasised the importance of selecting the most appropriate informatics approach for correctly discerning the relative contributions of different nanoparticle properties towards biological activity. Another recent example of this kind of analysis was presented in Harper et al.,[141] who analysed data from the Nanomaterial Biological Interactions (NBI) Knowledgebase.[66] Their analysis suggested that the toxicological impact of nanoparticles towards embryonic zebrafish might be more strongly correlated with variations in surface chemistry rather than core composition.[141]

The preceding examples were relevant to identification of physicochemical characterisation requirements. Modelling of biological data obtained under diverse experimental conditions could enable identification of the experimental conditions which are most important to report. For example, Horev-Azaria et al.[142] recently developed a decision tree model for the impact of cobalt ferrite nanoparticles on cellular viability obtained under a variety of different experimental conditions. They were able to rank the various experimental conditions (concentration, cell type, time of exposure) according to their relative contributions towards the variability in biological impact.

It is worth noting that recommendations 6.4.1, 6.4.2 and 6.4.3 are by no means mutually exclusive. Expert consensus recommendations for minimum information requirements may inform those (meta)data which are

captured by experimentalists and data curators. In turn, targeted experimental studies could be designed to investigate the effects of systematically varying one or more of the proposed items of (meta)data. Finally, the quantitative significance of varying those (meta)data, for specific endpoints, could be discerned using informatics approaches. In turn, these combined experimental/informatics studies could then feed back into refined expert consensus proposals regarding minimum information requirements. However, as well as data mining of new experimental studies designed to better identify the most important (meta)data, data mining of existing datasets and databases (as per the nano-QSAR studies discussed above) may also yield new insights.

6.4.4 To reduce redundancy in physicochemical characterisation requirements, further modelling (or experimental) efforts targeting the interrelatedness of different physicochemical characteristics are required.

The interrelatedness in nanomaterial physicochemical properties[50] means that, in principle, extensive lists of "essential" properties[44] may call for excessive characterisation that is both a burden for experimentalists and curators. In principle, it might be possible to identify non-redundant physicochemical properties to reduce the minimum information requirements. One possibility is that certain physicochemical properties might be (reasonably) well predicted based upon other experimental data or, even, theoretical calculations. Insofar as this is the case, this could reduce the minimum information requirements. To some extent, this possibility has already been explored. For example, work carried out within the ModNanoTox project[7] examined effects of hydration and ligands on silver nanoparticle dissolution as a function of the cluster/particle size and the dominant crystal faces. (See the survey responses in the Electronic Supplementary Information for further details.) Another example is the recent work by Mikolajczyk et al.,[143] who suggested zeta potential could be reasonably well predicted using a nano-QSPR based on particle size obtained from TEM images and a parameter calculated using quantum chemistry. (They indicated that this latter parameter could be calculated using crystallographic information corresponding to basic nanoparticle chemical composition information. This would not necessarily correspond to crystallographic analysis of the nanoparticles.) If, as shown elsewhere,[91] zeta potential correlates well with biological activity, models for zeta potential *might* reduce the importance of determining this property experimentally. However, two important caveats should be noted here. Firstly, it is questionable whether a given nano-QSPR will ever be sufficiently predictive to make experimental determination of certain properties unnecessary. Secondly, it is questionable whether models developed for key physicochemical properties, using data obtained under a given set of conditions, could be applied to waive measurement requirements for those properties under (even slightly) different conditions.[143] (This is because key properties related to biological effects and nanomaterial fate, such as zeta potential and dissolution, may be highly dependent upon experimental conditions.)[35,91,143] Nonetheless, further exploration of this issue is arguably a valuable avenue for further research. Regarding the issue of the dependency of properties on experimental conditions, this may require nano-QSPR models to be recalibrated, or at least revalidated, using experimental data obtained under the relevant conditions.[143] One possibility might be to focus upon trying to predict the outputs of what Hendren et al. term "functional assays", such as "dissolution rate".[35]

One final point worth noting here is that it would only be valuable to make predictions for "functional assays" if making those predictions was more cost effective than simply performing the "functional assays" directly. For example, suppose generating those predictions required other data to be generated which would otherwise not be generated. In this scenario, it would only make sense to generate predictions if (1) they were sufficiently reliable and (2) generating those other data was more cost effective than simply performing the "functional assay".

Institutional and community level recommendations

6.5.1 Work to develop and promote acceptance of minimum information checklists, data quality assessment schemes and related resources should be carried out in collaboration with suitable organisations with a global reach.

As indicated in earlier recommendations, there is a need for harmonised work towards development and common acceptance of minimum reporting guidelines, data quality assessment schemes and related resources. (Related resources which would support evaluation of the completeness and quality of curated nanomaterial data include community accepted ISA-TAB-Nano templates, as

per recommendation 6.3.2.) These will support evaluation of (curated) data completeness and quality within (different areas of) the nanoscience community. It is necessary to develop standards that are widely accepted as well as avoid duplication of effort and potential inconsistencies. This requires that these be developed in as collaborative a manner as possible, engaging as many relevant global stakeholders as possible.[144] Organisations that exist on an ongoing basis, which may or may not have dedicated funding, and have experience in supporting the development and acceptance of standards, ideally within the nanoscience area, should be engaged with to support this work.

Insofar as is practical, initiatives should be undertaken under the aegis of and/or in collaboration with organisations with global - rather than national or regional - scope. Depending upon the organisation concerned, this may limit the pace at which developments take place. However, it does increase the probability that duplication of effort would be avoided and that any proposals would be accepted by the nanoscience community (or appropriate sub-communities) worldwide. The possibility of developing sub-community specific resources, in a co-ordinated fashion where overlap exists in terms of completeness and quality requirements, should also be considered. Here, "sub-community specific resources" refers to resources which are appropriate to the needs of specific data scenarios (e.g. types of nanomaterials) and stakeholder objectives (e.g. regulatory decision making). Possible organisations which could support these kinds of initiatives include the following: the OECD, the BioSharing initiative, ELIXIR, the CODATA/VAMAS Joint Working Group on the Description of Nanomaterials and the U.S. National Cancer Institute (NCI) National Cancer Informatics Program (NCIP) Nanotechnology Working Group (Nano WG). This list is meant to be illustrative, rather than exhaustive.

The OECD has considerable experience of developing internationally accepted guidelines and guidance documents relating to chemical safety assessment.[25] It has initiated the development of guidelines and guidance documents suitable for nanomaterial safety assessment.[145] (One important example is the "Guidance Manual for the Testing of Manufactured Nanomaterials: OECD Sponsorship Programme"[42] discussed in section 3.1 of the main text.) Furthermore, these activities are supported by the nanotechnology industry.[146]

The BioSharing initiative[144,147–149] was established in 2010, building upon the earlier work of the MIBBI project.[52,78] It facilitates the identification and dissemination of data standards, such as reporting guidelines, via its website. Furthermore, it engages with researchers, funding agencies and publishers to promote the development and acceptance of data standards in the life, biomedical and environmental sciences.

ELIXIR,[150] a Special Project of the European Molecular Biology Laboratory (EMBL), is a distributed infrastructure for life science information, comprising a central hub and member state nodes. ELIXIR aims to orchestrate the collection, quality control and archiving of large amounts of biological data produced by life science experiments. Proposals to establish a nanosafety community / platform within ELIXIR were understood to be under development at the time of writing.

The CODATA/VAMAS Joint Working Group on the Description of Nanomaterials[151] comprises an internationally and scientifically diverse set of scientists from a wide variety of different disciplines involved in developing and exploiting nanomaterials. They have recently developed a proposal[151] for a "Uniform Description System for Materials on the Nanoscale".

The Nano WG[152] was established in 2008 as a researcher led organisation to support computational and informatics approaches to nanotechnology research, with a particular focus on nanomedicine. The working group is actively contributed to by participants from academia, industry and government, both within the U.S. as well as internationally. The Nano WG led work on the development of the NanoParticle Ontology (NPO),[153] ISA-TAB-Nano[87,88] as well the Nanomaterial Data Curation Initiative (NDCI)[72] within which the current article was written.

Indeed, the caNanoLab team (active contributors to the Nano WG)[1,9,14,15] indicated, in their response to the current NDCI survey, that the Nano WG should lead work on the development of community accepted templates for recording nanomaterial (meta)data in ISA-TAB-Nano. It is possible that collaboration with the newly established Center for Expanded Data Annotation and Retrieval (CEDAR) would also support such an initiative. CEDAR recognises the challenges associated with promoting acceptance of minimum information guidelines for experimental metadata. It is dedicated to developing resources, such as (autocompleting) metadata sharing templates, which would facilitate their widespread use in the biomedical domain.[154,155] Within the specific area of regulatory nanosafety, co-ordination with the OECD, to ensure harmonisation with their OHTs,[38–41] could also be valuable when developing globally accepted ISA-TAB-Nano templates.

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