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DELIVERABLE REPORT

WP2 MGT2 – Pilot scheme for the management of a distributed research infrastructure offering harmonised, interoperable and integrated services

D2.6
Harmonised nano-safety procedures

Due date
M36

This initiative has received funding from the EU's H2020 framework program for research and innovation under grant agreement n. 101007417, NFFA-Europe Pilot Project

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1 INTRODUCTION

This report is a deliverable of Task 2.6 dedicated to the harmonisation of nanosafety procedures as part of WP2 "Pilot scheme for the management of a distributed research infrastructure offering harmonised, interoperable and integrated services".

The primary motivation within the context of NEP for the investigation of nanosafety procedures is the practical consideration that, when providing users with access to the facilities operated by the NEP beneficiaries, the staff of those beneficiaries routinely have to handle nanomaterials provided by the users. And while the users may have some information about the materials that they are providing, e.g., from their work on producing or modifying those materials, in many cases NEP is asked to perform the types of analytical measurements (e.g., of particle sizes, morphology, or composition) that ultimately can be part of the basis for evaluating the potential hazards posed by the (nano)material in question. In other words, until the measurements requested by the users have been performed via access provided by NEP, information about the (nano)materials being handled may be limited.

The challenge of making decisions about the potential hazards posed by (nano)materials based on limited information, of course, is not unique to NEP but rather is encountered by other entities that routinely handle materials provided by third parties. This challenge is also related to the framework for evaluating the safety or potential hazards of nanomaterials that is under development in the European Union and worldwide, due to the proliferation of nanomaterials—both incidental and deliberately engineered—encountered in industry/commerce and environment.

Accordingly, the work in this task focused on collecting information and analysing resources that have been created by previous and ongoing dedicated nanosafety efforts by expert communities (both from NEP beneficiaries and external entities), rather than independently developing nanosafety procedures. The results from this task are considered in the context of NEP and interactions with the expert community, with conclusions and recommendations provided in the final section of this report.

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2 NANOMATERIALS TERMINOLOGY

2.1 Definition of a Nanomaterial

In the European Union, formal and systematic efforts on both the research and regulations related to nanomaterials have been closely connected with the process of developing the definition of a *nanomaterial*.

2.1.1 The 2011 EC Recommendation

In 2011, the European Commission (EC) introduced a proposed definition for the term *nanomaterial*.[1] specifically for regulatory use. That definition was based solely on the size of the constituent particles of a material.

> *'Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm – 100 nm.*

In the context of NEP activities, it is notable that the above definition does not mention composition or specific functional or hazardous properties or risk associated with the material in question.

2.1.2 Technical Review and Clarifications

To keep pace with the research and technological developments, the EC Recommendation included a provision to review the proposed definition: "The definition including descriptors should therefore be subject to a review by December 2014 to ensure that it corresponds to the needs."[1] Accordingly, the Joint Research Centre of the EC (JRC) produced a series of three scientific and technical reports to support the review of the definition of a *nanomaterial*. The first JRC report was a compilation of the collected feedback and data.[2] The second report provided an assessment of the information collected in the first report.[3]

Particularly important for charting the pathway for future research activities on nanomaterials were the insightful scientific and technical discussions in the third JRC report that provided recommendations on possible clarifications of the nanomaterial definition, with a view to facilitate the use and implementation of the definition.[4]

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[1] European Commission, Commission Recommendation of 18 October 2011 on the definition of nanomaterial, Official Journal of the European Union. 2011/696/EU:38-40, 2011

[2] H. Rauscher, G. Roebben, V. Amenta, A. Boix Sanfeliu, L. Calzolai, H. Emons, C. Gaillard, N. Gibson, T. Linsinger, A. Mech, L. Quiros Pesudo, K. Rasmussen, J. Riego Sintes, B. Sokull-Klüttgen, H. Stamm, Towards a review of the EC Recommendation for a definition of the term "nanomaterial" Part 1: Compilation of information concerning the experience with the definition, JRC Scientific and Policy Report, EUR 26567 EN, Eds. H. Rauscher, G. Roebben, 2014

[3] G. Roebben, H. Rauscher, V. Amenta, K. Aschberger, A. Boix Sanfeliu, L. Calzolai, H. Emons, C. Gaillard, N. Gibson, U. Holzwarth, R. Koeber, T. Linsinger, K. Rasmussen, B. Sokull-Klüttgen, H. Stamm, Towards a review of the EC Recommendation for a definition of the term "nanomaterial" Part 2: Assessment of collected information concerning the experience with the definition, JRC Scientific and Policy Report, EUR 26744 EN, Eds. G. Roebben, H. Rauscher, 2014

[4] H. Rauscher, G. Roebben, A. Boix Sanfeliu, H. Emons, N. Gibson, R. Koeber, T. Linsinger, K. Rasmussen, J. Riego Sintes, B. Sokull-Klüttgen, H. Stamm, Towards a review of the EC Recommendation for a definition of the term "nanomaterial" Part 3: Scientific-technical evaluation of options to clarify the definition and to

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2.1.3 The 2022 EC Recommendation

Following the extensive process of reviews and consultations, in 2022, the EC published a revised recommendation on the definition of nanomaterial.[5] The clarifications from this Recommendation most relevant for the materials handled by NEP providers are outlined below (emphasis added).

- The term nanomaterial should address materials consisting of **particles in solid state**, present on their own or bound as constituent parts of aggregates or agglomerates.
- The definition should **exclude** non-solid (i.e. liquid and gaseous) particles.
- **A single molecule**, including a macromolecule such as a protein that may be larger than 1 nm, **should not be considered as a particle**.
- The definition **should not cover large solid products or components**, even when they have an internal structure or a surface structure at the nanoscale, such as coatings, certain ceramic materials and complex nanocomponents, including nanoporous and nanocomposite materials.

2.1.4 Non-solid particles

The exclusion of non-solid particles from the definition is primarily related to the ambiguity of determining their sizes (or even boundaries), which is difficult to reconcile with the size-based definition. Accordingly, this exclusion does not imply that concerns, including nanosafety, are not applicable to non-solid particles. The focus on nanosafety evaluations for non-solid particles, however, tends to be on their behaviour in the context of the intended application, e.g., food or medicine (as highlighted below), rather than on their general handling.

Specifically, the European Food Safety Authority (EFSA) published the first guidance specific to nanomaterials in 2018, which included within the scope "[n]anoscale entities made of natural materials that have been deliberately produced to have nano-enabled/enhanced properties, or that have been modified for use in the development of other nanoscale materials, e.g. for encapsulating (bioactive) compounds" and "organic nanomaterial, such as encapsulates".[6] EFSA currently maintains a webpage dedicated to the topic of nanomaterials in food, which includes links to the guidance documents.[7]

Similarly to EFSA, the European Medicines Agency (EMA) maintains a dedicated webpage with links to scientific guidance on the evaluation of nanomedicines.[8] The European Nanomedicine Characterisation Laboratory (EUNCL) project was funded by the EC until 2019 and published systematic evaluation protocols, some of which are applicable to non-solid particles.[9]

2.1.5 Implications for Harmonization in NEP

The EC recommendation for the definition of a nanomaterial directly and indirectly affects a wide range of activities and projects related to nanosafety. The industrial and commercial use of

facilitate its implementation, JRC Scientific and Policy Report, EUR 27240 EN, Eds. H. Rauscher, G. Roebben, 2015

[5] European Commission, Commission Recommendation of 10 June 2022 on the definition of nanomaterial, Official Journal of the European Union. 2022/C 229/01:1-5, 2022

[6] A. Hardy, D. Benford, et al., Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health, EFSA Journal 16:5327, 2018; doi: 10.2903/j.efsa.2018.5327

[7] https://www.efsa.europa.eu/en/topics/topic/nanotechnology

[8] https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/multidisciplinary-guidelines/multidisciplinary-nanomedicines

[9] https://www.euncl.org/about-us/assay-cascade/

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nanomaterials in the EU is regulated by the European Chemicals Agency (ECHA) under the framework for Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). REACH terminology refers to nanomaterials (relying on the EC recommended definition) and a related concept of nanoforms; since 2020, explicit legal requirements under REACH apply for companies that manufacture or import nanoforms.[10]

A wide range of projects[11] developing nanosafety frameworks, tools, and guidelines has been, in part, motivated by the needs of the companies under REACH, therefore, many such projects focused on evaluation of solid particles. Accordingly, the harmonization activities in NEP focused on solid particles, to take advantage of the existing expertise in the nanosafety community.

The explicit exclusion from the 2022 definition of nanomaterials of macroscopic objects that may have nanoscale coatings, pores, or other features also helped to resolve the ambiguity (under the 2011 definition) of how to consider wafers or other macroscopic substrates with nanoscale films or other features: such objects are not considered in NEP in terms of applying nanosafety-specific handling protocols.

2.2 Descriptors for Nanomaterials

Closely related to the development of the definition of a nanomaterial are the efforts to harmonize the descriptors of nanomaterials. These efforts (past and ongoing) are motivated by the need to ensure compatibility among various entities collecting data for nanomaterials and creating tools that work with such data.

2.2.1 Terminology Harmonizer

A systematic effort on harmonizing the descriptors of nanomaterials has been carried out by several stakeholders in the nanosafety community since 2018.[12] The *Terminology Harmonizer* is described by its developers as "a software system which aids agreement upon term definitions towards the creation of harmonized ontologies" (**Figure 1**).

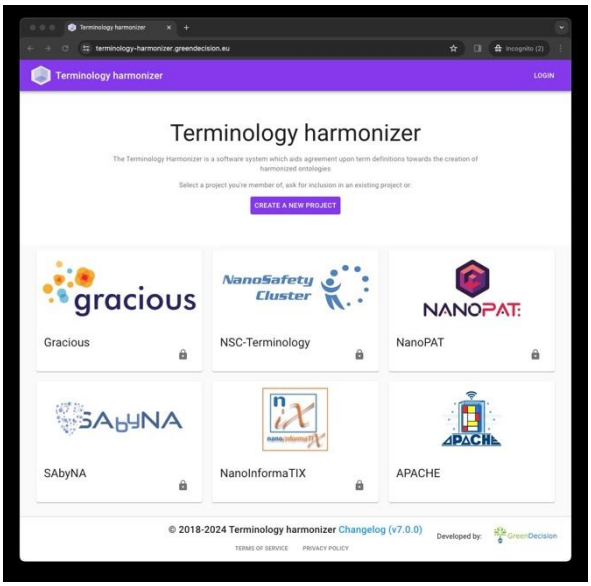

Figure 1 Terminology harmonizer platform (from terminology-harmonizer.greendecision.eu)

[10] https://echa.europa.eu/regulations/nanomaterials
[11] A. Falk, F. R. Cassee, E. Valsami-Jones, Safe-by-design and EU funded NanoSafety projects, Zenodo, 2020; doi: 10.5281/zenodo.4652587
[12] https://terminology-harmonizer.greendecision.eu/

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NEP received information about the harmonized descriptors for nanomaterials established by the terminology harmonizer community via a contact established with the *Gracious* project.[13] These harmonized descriptors (Table 1) have been established, in part, to be aligned with the REACH framework for nanomaterials (a practical example of the influence of REACH on activities of nanosafety projects that was mentioned in Section 2.1.5). The methods summarized in Table 1 reference standard operation procedures (SOPs) and standards developed by various stakeholders and projects in the metrology and nanosafety community.

TABLE 1 HARMONIZED DESCRIPTORS FOR NANOMATERIALS

Physicochemical property	Method
Aspect ratio (shape)	SEM or TEM (NanoDefine methodology, consistent with ECHA nanoforms)
Granulometry (constituent particle size)	SEM or TEM for dry samples (NanoDefine methodology, and NanoDefine SOP consistent with ECHA nanoforms) Centrifugal AC (NanoDefine SOP), DLS (Nouryon SOP), CLS, FFF or ES-DMA (Nouryon SOP) for liquid suspension; OECD TG in preparation
Specific surface area	BET, VSSA by gas adsorption, (ISO 9277:2010; Hackley and Stefaniak, 2013); OECD TG in preparation
Zeta potential	Zeta-potential with pH titration (generic): University of Vienna SOP Charge density (for silica): Nouryon SOP
Hydrophobicity (water contact angle)	otentially: sessile drop, water contact angle (SOP by KRÜSS Technical Note TN306e, C. Rulison, 1999) OECD TG in preparation (based on: Desmet et al 2017; Valsesia et al 2018)
Density	He-pycnometry DIN EN ISO 1183-3
Composition	Identify composition by XRF (Nouryon SOP), ICP-OES, ICP-MS (CEH SOP + Nouryon SOP) or XRD (JRC SOP) (applicable for inorganic materials) TGA (for organics): NRCWE SOP
Chemical nature of the surface	TGA-MS/IR, LC-MS (NRCWE SOP), XPS (JRC SOP)

[13] https://www.h2020gracious.eu/

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3 NEP SAMPLE AND SAFETY FORM

During the initial setup of the NEP activities, the main responsibility of Task 2.6 was to recommend the descriptors of nanomaterials to be listed on the NEP *Sample and Safety Form*. The objective was to establish a harmonized set of descriptors for internal use in NEP forms and platforms, while maintaining an alignment with external efforts on systematization of nanomaterials.

3.1 Recommendations on the Scope

Many of the NEP beneficiaries were aware of the 2011 EC Recommendation on the definition of a nanomaterial (Section 2.1.1), some of the beneficiaries participated in projects that were closely related to the metrology and other research activities supporting the development of the definition. This background knowledge also included awareness of the various ambiguities regarding the scope of the definition, e.g., the inclusion of soft particles or nanoscale films on macroscopic substrates.

Decisions on the scope of the nanomaterial definition, terminology, and ontology for the purposes of NEP activities and forms had to be made in 2021, i.e., before the release of the 2022 EC Recommendation on the definition of a nanomaterial (Section 2.1.3). Accordingly, the activity in Task 2.6 on following the process of technical reviews, discussions, and clarifications (Section 2.1.2) was critical for aligning the NEP framework with the future activities of the nanosafety community.

This methodology was successful, as important qualitative clarifications of the 2022 EC Recommendation have been correctly foreseen, such as the explicit focus on solid particles and exclusion from the scope of macroscopic objects having some nanoscale features.

3.2 Descriptors Adopted by NEP

An important part of the above strategy was the decision to align the considerations of nanosafety by NEP with those of the dedicated communities of experts. One practical aspect of this alignment was to adopt for the *Sample and Safety Form* the harmonized descriptors that have been selected by an expert community in the Terminology Harmonizer process (Section 2.2.1).

- Morphology: aspect ratio, particle size distribution, specific surface area
- Material: composition, surface chemistry, crystalline phase(s), density
- Properties in solution: zeta potential, hydrophobicity, water solubility
- Stability: thermal stability

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4 NANOSAFETY PROCEDURES

Following the successful methodology of addressing the selection of the harmonized descriptors for nanomaterials (Section 3.2), the first step in Task 2.6 in considering the nanosafety procedures has been to collect and organize the information that had been produced by preceding and ongoing systematic efforts.

4.1 Expert Group on Nanosafety

The NEP Expert Group (EG) on Nanosafety was initially established with four members, who have been selected, in part, to ensure continuity with previous NFFA activities on nanosafety. Of course, experience with nanosafety research and contacts with external expert communities were also important considerations.

- Dmitri Petrovykh, INL (Chair)
- Emmanuel Stratakis, FORTH
- Ennio Capria, ESRF
- Pascal Colpo, JRC

4.2 Internal NEP Resources

Personnel changes and other logistical complications (including the COVID-19 pandemic) meant that some efforts were required to maintain continuity of information and other resources from the previous NFFA work. In particular, the files from the January 2020 NFFA Nanosafety Workshop and from the preparation of the NFFA Nanosafety Report (2020) have been used to define the baseline for the NEP activities.


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Figure 2 The title page of the NFFA Nanosafety Report (2020)

Understanding of the substantial efforts and human resources (including the significant dedication of the time by the ESRF authors to producing the report, **Figure 2**) also suggested that within Task 2.6 it would be more appropriate to follow the advances in the field,[11] rather than to try and replicate the work previously carried out by NFFA.

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4.3 Nanosafety Evaluation for Specific Materials

The most direct pathway to establishing nanosafety procedures is to evaluate a specific nanomaterial, ideally via a combination of measurements, assays, and modelling. The prototypical example of this approach is the work involved in producing a REACH registration dossier for a nanomaterial (or nanoform). While this is an effective approach to nanosafety, the practical experience indicates that successfully completing a REACH registration dossier for a nanomaterial requires significant expertise, time, and resources, with multiple months of work and budgets in the range of 100k to 1M Euro being common. Therefore, this is not an approach that can be practically adopted by NEP providers for materials that NEP users submit for characterization.

An important variant of this approach relies on the data that are already available for specific nanomaterials to perform essentially a nanosafety meta-analysis.

4.3.1 DaNa Project

The *Da*ta and knowledge on *Na*nomaterials (DaNa[2.0]) project[14] is a good example of a systematic effort to produce easily comprehensible nanosafety and nanotoxicology information by collecting, evaluating, and presenting up-to-date research data. For each nanomaterial in the DaNa database (**Figure 3**), the record provides information of interest to non-expert audience and using descriptions that are understandable to non-experts. Each record also includes the supporting technical information, for those visitors who are looking for a more in-depth understanding of the specific nanomaterial and the reasoning behind the summary descriptions provided by the project.

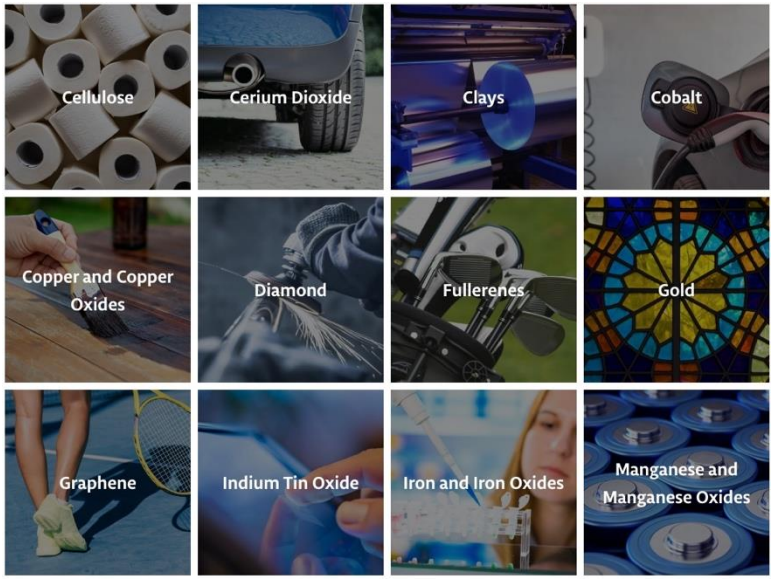

Figure 3 Several nanomaterials included in the *DaNa* database (from https://nanopartikel.info/en/knowledge/materials/)

The record for "Iron and Iron Oxides" provides a good example of the easy-to-understand overall conclusion about nanosafety of a nanomaterial: "In the day-to-day life the human body is only exposed to very small amounts of iron nanoparticles or iron oxide nanoparticles which are considered generally to be non-toxic."[15]

[14] https://nanopartikel.info/en/research/projects/dana-2-0/
[15] https://nanopartikel.info/en/knowledge/materials/iron-and-iron-oxides/

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The focus of the DaNa$^{2.0}$ project is on providing an unbiased evaluation of nanosafety based on high-quality data from the literature. Accordingly, the project assembled an interdisciplinary team of experts to analyse up-to-date resources in fields as diverse as human and environmental toxicology, biology, physics, chemistry, and pharmacy; a formal methodology for assessment of the quality of information obtained from each source also has been established.[16]

The DaNa$^{2.0}$ project is an excellent source of nanosafety information for the nanomaterials included in its database. The extensive research required to produce each record does limit the number of materials covered by the database (currently about 30). Another systematic limitation acknowledged by the project team is the funding, which the project acquires from government sources to maintain its objectivity and independence from commercial entities.[16]

Being based on a large body of published data also limits the practical relevance of this project for NEP activities, which often involve novel nanomaterials, rather than ones that have been extensively studied previously.

4.4 Read-Across Tools

It is generally acknowledged by the nanosafety community and regulators that the broad range and large number of novel nanomaterials will limit the applicability of directly evaluating individual nanomaterials to those of particular commercial and/or research importance. Accordingly, the more general strategy will need to rely on drawing conclusions about a new nanomaterial based on the existing data for different substances, conditions, and applications. Therefore, significant resources have been dedicated to the development of grouping and **read-across** frameworks that will enable such indirect evaluations of nanosafety for novel materials. The EU Observatory for Nanomaterials (EUON) systematically monitors these efforts.[17]

The efforts to develop grouping and read-across frameworks had significant influence on driving the harmonization activities in the nanosafety community, including the terminology harmonization mentioned earlier in this report (Section 2.2.1).

4.4.1 GRACIOUS Framework

GRACIOUS Framework is an excellent example of a framework for grouping and read-across of nanomaterials and nanoforms.[13] The name of the project GRACIOUS stands for Grouping, Read-Across, Characterisation and classificatiOn framework for regUlatory risk assessment of manufactured nanomaterials and Safer design of nano-enabled products.

Specifically, the GRACIOUS Framework provides a stepwise approach to making decisions about justifying the grouping, with each subsequent step requiring an increased amount and complexity of data (**Figure 4**, left). The concepts underlying this framework are summarized in a brief "nutshell" guidance document.[18] A more comprehensive guidance document (**Figure 4**, right) covers the individual steps in more detail and provides an overview of the grouping and read-across concepts and associated terminology.[19]

[16] H. F. Krug, N. Bohmer, D. Kühnel, C. Marquardt, K. Nau, C. Steinbach, The DaNa$^{2.0}$ Knowledge Base Nanomaterials—An Important Measure Accompanying Nanomaterials Development, Nanomaterials 8:204, 2018; doi: 10.3390/nano8040204
[17] https://euon.echa.europa.eu/safety
[18] N. Hunt, Guidance in a Nutshell: GRACIOUS Framework for grouping and read-across of nanomaterials and nanoforms (1.0), Zenodo, 2021; doi: 10.5281/zenodo.5534105
[19] N. Hunt, Guidance on the GRACIOUS Framework for grouping and read-across of nanomaterials and nanoforms (1.0). Zenodo, 2021. doi: 10.5281/zenodo.5534466

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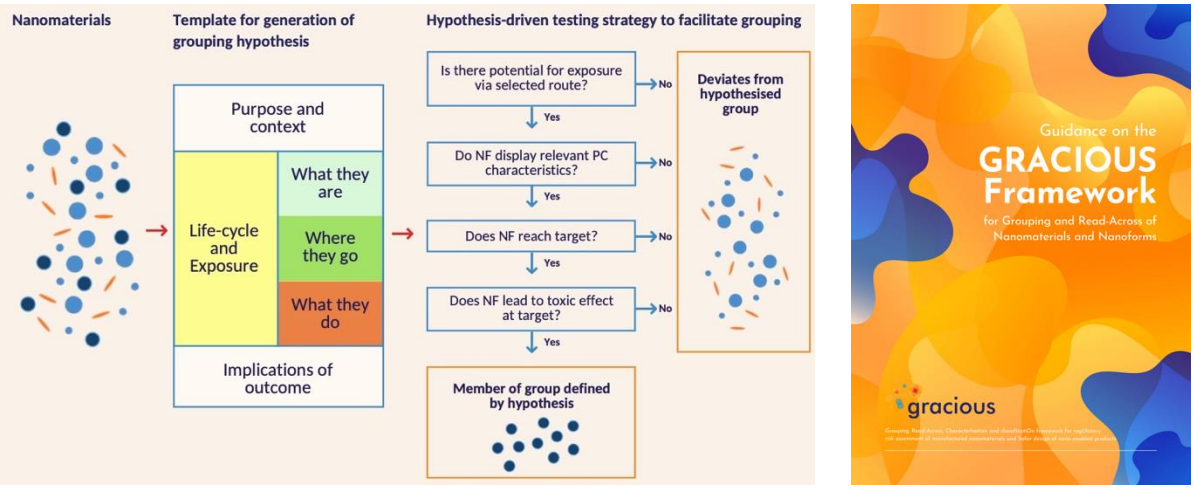

Figure 4 Left: Diagram that shows how the hypotheses are used to group nanoforms (NFs), adapted from Ref [18]. Right: title page of the full guidance document, Ref [19].

In the context of NEP activities, applying the GRACIOUS Framework to individual nanomaterials submitted by the users would be rather resource intensive, relative to the time allocated for individual measurements. As illustrative use cases in the guidance document[19] appropriately indicate, applying this framework typically can be justified when safety is considered in a long-term context rather than for a single measurement, e.g., when deciding if additional safety measures may be needed after adding a new nanomaterial or nanoform in a production environment.

4.4.2 Control-Banding Tools

Control banding is a strategy related to grouping and read-across, whereby it evaluates the hazards associated with a new or unknown nanomaterial based on semi-quantitative estimates of properties that are known to be important when considering nanosafety. Control banding is a simplified solution, as it can be applied, in principle, in absence of high-quality toxicological and exposure data.[20]

For example, Workplace Health and Safety Queensland has developed a Nanomaterial control banding tool worksheet,[21] to help with nanosafety risk management.[22] The worksheet guides the user in calculating the hazard severity and exposure probability scores based on known or estimated properties of the material (e.g., surface chemistry, particle diameter, mutagenicity, etc.) and the exposure scenarios (e.g., duration of typical handling of the material and the amounts used). The calculated scores can then be evaluated using a risk level (RL) matrix (**Figure 5**) which places the material in one of the four control bands:

RL1. General ventilation

RL2. Fume hoods or local exhaust ventilation

RL3. Containment

RL4. Seek specialist advice

[20] https://controlbanding.llnl.gov/
[21] Workplace Health and Safety Queensland, Nanotechnology control banding tool worksheet, PN10698 Version 2, 2015
[22] https://www.worksafe.qld.gov.au/safety-and-prevention/hazards/hazardous-exposures/nanotechnology/nanomaterial-control-banding-risk-assessment

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		Exposure probability			
HAZARD SEVERITY		Extremely unlikely (0-25)	Less likely (26-50)	Likely (51-75)	Probable (76-100)
	Very high (76-100)	RL 3	RL 3	RL 4	RL 4
	High (51-75)	RL 2	RL 2	RL 3	RL 4
	Medium (26-50)	RL 1	RL 1	RL 2	RL 3
	Low (0-25)	RL 1	RL 1	RL 1	RL 2

Figure 5 Risk level (RL) matrix as function of severity and probability, adapted from Ref [21].

This methodology is most helpful for materials for which many of the parameters used to calculate the scores are known, particularly when resulting scores correspond to the lowest (RL1) or highest (RL4) control bands, i.e., when minimal or special care is required.

For unknown nanomaterials, however, the worksheet assigns by default medium-high scores for each unknown parameter, which typically will result in recommendation of one of the intermediate control bands (RL2 or RL3). In other words, for the typical NEP context of infrequently handling small amounts of unknown nanomaterials, the default recommendation would be to use a fume hood or local exhaust ventilation, i.e., the typical "common sense" protective measures. Accordingly, this methodology offers limited additional information for the typical NEP context of nanosafety.

4.4.3 ECETOC Targeted Risk Assessment Tool

ECETOC is a community of experts from academia, governments, and industry that develops resources and tools focused on safety and sustainability,[23] among them the Targeted Risk Assessment (TRA) tool[24] that can be applied to nanomaterials. The ECETOC TRA tool is a sophisticated software platform (**Figure 6**) that is able to take advantage of existing nanosafety data and validated models to produce recommendations, including for nanomaterials with limited information about their properties.

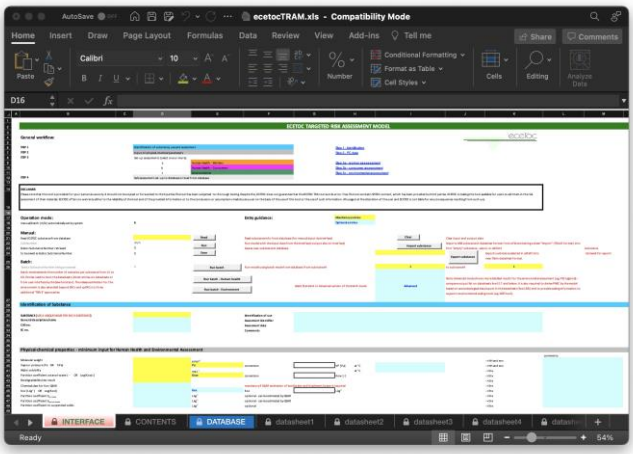

Figure 6 Screenshot of the ECETOC TRA tool.

[23] https://www.ecetoc.org/
[24] https://www.ecetoc.org/tools/tra-main/

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This TRA tool is recognized as reliable and effective by the expert community and regulators. For non-expert users, the software presents a steep learning curve and a high threshold of access to and knowledge about the required resources, including databases and models. Accordingly, it would be challenging to use in the context of NEP, as most NEP providers and even many research groups specializing in nanosafety or nanotoxicology do not have resident experts in using this software.

4.5 Current Advances and Outlook

In addition to the advances in the field of nanosafety, various aspects of nanosafety are becoming incorporated in new rapidly developing areas, such as Safe and Sustainable by Design (SSbD)[25] and Findable, Accessible, Interoperable, and Reusable (FAIR)[26] data (and metadata). All these advances highlight importance of design and modelling steps, which means that tools for evaluating nanosafety in a robust, user-friendly, and automated fashion are considered critical for the future of nanosafety research and practical evaluations.

4.5.1 nanoSAFE 2023

The 8th International Conference on Health and Safety Issues for a socially responsible approach to nanomaterials (nanoSAFE 2023)[27] that was organized in Grenoble, France (June 5–9, 2023) is an excellent example of the ongoing interactions among the different communities involved in nanosafety and its implications for other fields (**Figure 7**).

Figure 7 Participants of nanoSAFE 2023.

One of the important lessons learned to-date from the development of tools for nanosafety evaluation is that the original vision of creating tools that are user-friendly and accessible for non-expert casual users is more challenging than originally anticipated. Instead, the sophisticated current tools (some of which were briefly presented earlier in this section) are used by experts. Companies that need to perform nanosafety evaluations, e.g., for a REACH dossier, typically hire consultants who have the expertise with regulations and using the advanced tools. The important role of such consultants has been highlighted in panel discussions during the conference.

[25] https://research-and-innovation.ec.europa.eu/research-area/industrial-research-and-innovation/key-enabling-technologies/chemicals-and-advanced-materials/safe-and-sustainable-design_en
[26] https://www.go-fair.org/fair-principles/
[27] https://www.cea.fr/cea-tech/pns/nanosafe/en

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Several of the projects presented at the conference are working on developing nanosafety evaluation tools that are more accessible to non-expert users:

- NanoInformaTIX (https://www.nanoinformatix.eu/)
- SbD4Nano (https://www.sbd4nano.eu/)
- PARC (https://www.eu-parc.eu/)

All of the above projects (and many others) recognize the need for interoperability in terms of the data in existing databases and newly created from measurements or modelling. This aspect has been repeatedly discussed at the conference and is currently advancing in the broader context of FAIR (meta)data for nanomaterials.[28]

4.6 Advice from External Experts

Several experts from the nanosafety community have been contacted for discussions of the possible harmonized nanosafety procedures for NEP.

- Prof. Vicki Stone, Heriot-Watt University, Scotland
- Prof. Eugenia (Éva) Valsami-Jones, University of Birmingham, UK
- Dr. Blanca Suarez Merino, Nanotechnology Industries Association, Belgium
- Dr. Lya G. Soeteman-Hernández, National Institute for Public Health and the Environment (RIVM), the Netherlands
- Members of the Nanosafety Research Group at INL

The conclusions from these discussions regarding the available tools largely agree with the summary provided in Section 4.4. It is also notable that while various entities involved in characterization of nanomaterials face the uncertainty of handling these materials safely, no harmonized procedures have emerged with organized expert communities, e.g., among the members of the Nanosafety Cluster.

An additional challenge for NEP providers is that many nanosafety researchers work with assays and techniques that operate with nanomaterials in solution, whereby the most critical steps in terms of potential exposure are during the handling of any dry powders, while handling the solutions of nanomaterials is typically not dramatically different from the standard wet-bench safety procedures. In case of NEP, many of the techniques require dry samples, sometimes also placed inside vacuum chambers, conditions not commonly encountered within the nanosafety expert community. Likewise, the use of disposable laboratory plastics is typical when working with solutions of nanomaterials, thereby avoiding the potential issues with cross-contamination, whereas many of the instruments used by NEP providers operate with reusable, often complex, sample holders, for which effective cleaning procedures can be necessary.

[28] T. E. Exner, A. G. Papadiamantis, G. Melagraki, J. D. Amos, N. Bossa, G. P. Gakis, C. A. Charitidis, G. Cornelis, A. L. Costa, P. Doganis, L. Farcal, S. Friedrichs, I. Furxhi, F. C. Klaessig, V. Lobaskin, D. Maier, J. Rumble, H. Sarimveis, B. Suarez-Merino, S. Vázquez, M. R. Wiesner, A. Afantitis, I. Lynch, Metadata stewardship in nanosafety research: learning from the past, preparing for an "on-the-fly" FAIR future, Front. Phys. 11:1233879, 2023; doi: 10.3389/fphy.2023.1233879

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5 CONCLUSIONS AND OUTLOOK

The first objective of Task 2.6 was to recommend the harmonized descriptors for the *Sample and Safety Form* used by NEP. This objective was successfully achieved, with the scope and selection of the descriptors being aligned with the 2022 EC Recommendation and REACH, as described in Section 3.

Considering the harmonized nanosafety procedures, the conclusions from Task 2.6 are more equivocal. Having investigated external tools and resources, authoritative harmonized procedures that could be applied in the context of NEP have not been found. Accordingly, a harmonized procedure for taking into account specific properties of the nanomaterials handled by NEP is not possible within the scope of the resources available in the project.

Fortunately, there are strong indications (e.g., as described in Section 4.4.2) that the safety procedures already in place at NEP providers (Section 4.2) are largely appropriate for handling nanomaterials for which there is no *a priori* knowledge or indication of being significantly hazardous (e.g., radioactive or acutely toxic) and thus requiring non-standard protective measures.

The amounts of nanomaterials handled by NEP providers are typically very small, so handling them under a fume hood and with standard (for chemical safety) personal protective equipment is appropriate.

5.1 Future Actions

Established interactions with the nanosafety community will continue. Three specific topics of interest in the context of NEP are:

- Handling of powder samples
- Cleaning of reusable sample holders and instrument components
- Cooperation on providing data from NEP activities for standardized nanosafety databases

The tools for nanosafety evaluation will continue to be monitored for possible inclusion in the NEP workflow.

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