Draft GRACIOUS framework for grouping and read-across of nanomaterials for regulatory risk assessment and safe-by-design

Executive Summary - For consultation

Partners

RIVM: Agnes Oomen, Eric Bleeker, Susan Dekkers, Hedwig Braakhuis, Willie Peijnenburg

Green Decision: Lara Lamon, Danail Hristozov

JRC: Stefania Gottardo, Hubert Rauscher, Kirsten Rasmussen, Paula Jantunen, Laia Quiros Pesudo

BASF: Wendel Wohlleben, Robert Landsiedel

IdeaConsult: Nina Jeliazkova

Leitat: Socorro Vázquez-Campos

BfR: Andrea Haase

Yordas: Neil Hunt

IOM: Araceli Sánchez Jiménez

HWU: Vicki Stone, Teresa Fernandes

Please return your comments to: f.murphy@hw.ac.uk and s.stoycheva@yordasgroup.com

Key points

The GRACIOUS Framework aims to support practical application of grouping of nanomaterials/nanoforms[1] for risk assessment and decision making. This includes the ability to read across from data rich substances to similar nanoforms for which information is lacking.

The use of grouping and read-across will reduce the need for testing and facilitate the risk assessment of each new nanoform.

The Framework is designed to be useful to various stakeholders, particularly regulators and industry.

The Framework supports the development of 'hypotheses' that outline why specific nanomaterials/nanoforms can be grouped. This takes into account the purpose or context of the user (targeted testing, regulatory, precautionary or safe-by-design).

The grouping hypotheses are scientifically based and comprise information that relates to what the nanoforms are (physicochemical characteristics), where they go (fate and kinetics in the environment and in organisms), and what they do (hazard) at different life cycle stages of the nanoforms, including within nano-enabled products.

The Framework provides basic information as a starting point, leading into tailored Integrated Approach to Testing and Assessment (IATA)[2] which are designed to test and refine the initial grouping hypotheses.

The information generated is used to assess if the grouping or read-across is sufficiently justified for the intended purpose.

The Framework also facilitates a safe-by-design approach by alignment with the Stage-Gate innovation process.

Finally, this document describes the first Draft version of the GRACIOUS framework, to which stakeholders are invited to comment via either:

- Completion of a questionnaire
- Comments written on the document
- E-mail.

Deadline for comments is 03/09/18.

Please return your comments to: f.murphy@hw.ac.uk and s.stoycheva@yordasgroup.com

The Draft Framework description will be updated to incorporate stakeholder feedback and published in spring 2019.

The Framework description will be used to build a practical open-access Framework for grouping and read-across that will be available in 2021 both as a guidance document and as modular software.

[1] 'nanoform' is the term used in this document (see text box on page 3 for explanation)

[2] IATA is preferred over the earlier used term ITS, as IATA is nowadays more commonly used in a regulatory context (REACH, OECD) and it is considered that the term IATA better describes the intended purpose in that it includes a combination of different types of testing as well as assessment approaches.

Introduction

Manufacturing and functionalising materials at the nanoscale leads to a whole array of nanoforms (NFs) (see text box[3]), varying not only in chemical composition, but also in e.g. size, morphology and surface characteristics. Apart from expected benefits, distinctive properties of NFs may also affect environmental and human health. However, testing every unique NF for their potential adverse effects would be resource demanding. More efficient ways to obtain risk information are therefore needed, which could be achieved by grouping similar NFs (and non-nanoforms). In doing so, grouping can serve several purposes:

Nanomaterials (NMs) and nanoforms (NFs)

A nanomaterial is defined only by its size according to the EC Recommendation 2011/696/EU (EU, 2011). Under REACH, a nanoform is a form of a substance, which fulfils the EC recommended definition of nanomaterial (EU, 2018). In addition to size, nanoforms are characterised by shape and surface chemistry (EU, 2018). These properties may be described by ranges of values with clear boundaries. Different nanoforms may or may not show different exposure, fate/toxicokinetic behaviour and toxicity. As the draft GRACIOUS framework for grouping and read-across of nanomaterials is developed for the purposes of regulatory risk assessment and safe-by-design, the term nanoform is used in the remainder of the manuscript. The terminology is further explained in Chapter **Error! Reference source not found.** and

- **To facilitate targeted testing or targeted risk assessment.** Existing and generated information about a material can be used to inform understanding of potential exposure, fate, kinetic behaviour or a specific hazard, for the purposes of risk assessment. The knowledge can also be used in identifying and targeting specific issues that influence risk assessment of NFs (e.g. in a substance evaluation in REACH), where factors such as human inhalation risks or hazards for the aquatic environment can be focused upon.
- **To fill a data gap in a regulatory dossier.** Regulatory dossiers on a chemical may provide the requested information to regulators by grouping chemicals based on similarity and by applying read-across. Read-across can be conducted from NFs (or non-nanoforms) with appropriate justification, to NFs for which information is lacking.
- **To develop precautionary measures.** Based on the known information on exposure, fate, kinetic behaviour or hazard of similar materials, precautionary measures can be taken for a material for which that information is not available, e.g. by reducing or preventing exposure.
- **To steer safe innovation/safe-by-design.** For a new material under development, information available on similar materials can provide an indication of potential issues relating to exposure, fate, kinetic behaviour, or hazard. This information can steer safe innovation/safe-by-design in order to reduce or prevent such risks.

For more detail see section 1.1 of the full Draft GRACIOUS framework document.

[3] These definitions may be revisited for a next version of the GRACIOUS Framework to ensure alignment with regulatory developments.

Aim of the GRACIOUS Framework

The GRACIOUS Framework aims to support practical grouping of NFs for risk assessment and risk decision making, meeting the needs of stakeholders such as regulators and industry. The GRACIOUS Framework will support the user to identify or generate the evidence to justify specific groupings of NFs and related read-across cases. By targeting data acquisition more effectively, application of the Framework will reduce the testing burden of a case-by-case assessment. The GRACIOUS Framework thereby aims to improve the efficiency of information gathering for NF risk assessment. In addition, it will support decision making for safe innovation/safe-by-design of nano-enabled products (NEPs).

The Framework will be delivered as a guiding Background Document and as software modules. In order to ensure sustainability, the Framework will be open for easy integration of new knowledge, as well as modular and sufficiently flexible to accommodate new insights.

For more detail see section 1.2 of the full Draft GRACIOUS Framework document.

GRACIOUS Framework overview

The GRACIOUS Framework (Figure 1) integrates state-of-the-art scientific and industrial thinking (e.g. the DF4NanoGrouping approach by Arts et al. (2015) and regulatory requirements (e.g. ECHA, 2017) to make a tiered Framework allowing the users to make decisions with a level of detail that is sufficiently flexible to adapt to their needs.

The groups generated by the GRACIOUS Framework are driven by scientific hypotheses. These hypotheses relate combinations of physicochemical, fate and kinetics, and hazard endpoints that are relevant for the use of grouping and read-across in risk assessment and decision making.

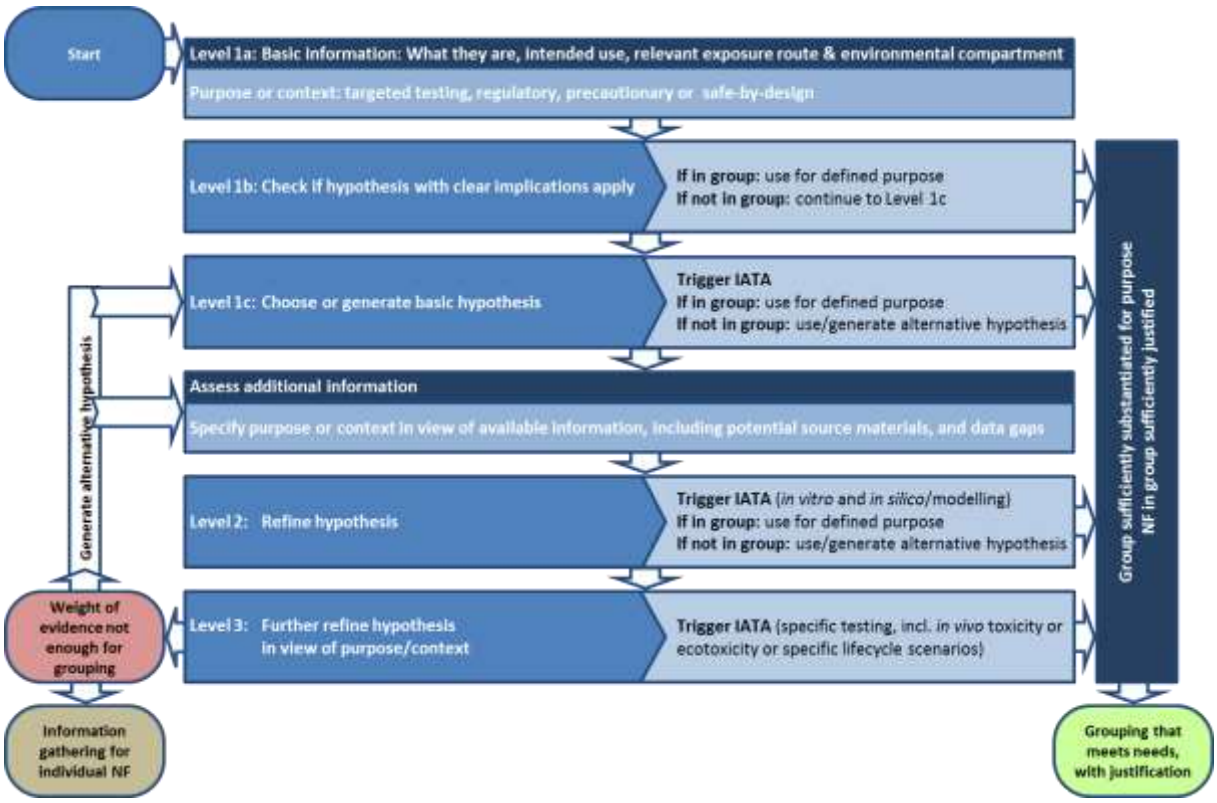

Figure 1 Structure of the Draft GRACIOUS Framework.

In Level 1a, basic information (e.g. physicochemical data) is gathered for a (group of) NF(s), which combined with the purpose of grouping, is used to quickly screen the applicability of several well-justified hypotheses (see table 1). The justification of these hypotheses is derived from a strong scientific evidence base[4]. This evidence base means that these hypotheses have clear implications (Level 1b) for human health or the environment. The Framework guides the identification or gathering of information (e.g. physicochemical characteristics) needed to confirm whether a NF fits into one of the well-justified hypotheses.

However, if none of these well-justified hypotheses apply, a basic (or new) hypothesis is developed (Level 1c), which triggers identification of relevant existing information and an IATA to fill data gaps. The IATAs incorporate a range of information relevant for risk assessment, namely: (i) "uses in the lifecycle that lead to environmental release and human exposure", (ii) "what they are: physicochemical identity", (iii) "where they go: environmental fate, uptake and toxicokinetics", and iv) "what they do: human and environmental toxicity". The IATAs prioritise robust modelling and *in vitro* tests at the early levels in order to promote the reduction, refinement and replacement of animal testing.

Based on the results of the IATA, the user will identify whether the NF(s) fall within the group, and whether the grouping are sufficiently substantiated for the original grouping purpose. If the grouping is not sufficiently justified, further refinement and testing in Level 3 IATAs, using more advanced *in vitro* and/or *in vivo* studies, can be performed. Again the Framework will aid the user to determine if the grouping is sufficiently substantiated. If the group is not sufficiently substantiated, the Framework will guide the user to assess an alternative hypothesis or determine whether the grouping needs can be further specified and refined.

Table 1 The groups defined by well-justified hypotheses

Group	Abbreviation	Potential implications/consequences
Quickly dissolving NFs	DISS	*Regulatory:* Read-across to the ionic or molecular form may be possible (to be further developed in next Level).
Dermal exposure to NFs larger than 5 nm	D5NM	*Regulatory:* Waiving of endpoints related to systemic exposure.
Respirable biopersistent rigid High Aspect Ratio Nanomaterials	HARN	*Precautionary approaches or safe-by-design:* Minimise exposure, or modify the NF/NEP to reduce hazard. *Targeted testing:* Testing to assess concerns. *Regulatory:* Read-across to asbestos or another rigid HARN (to be further developed in next Level) may be possible.
NFs incorporated into a Solid matrix Nano-Enabled Product	SNEP	*Precautionary approaches or safe-by-design:* Control-banding, minimise exposure or adjustment of NEP. *Targeted testing:* Testing to assess concerns.

[4] The scientific basis for the justification of these hypotheses is being assessed in GRACIOUS.

Using the Framework for Safe-by-Design

Grouping and read-across can be used in all stages of the innovation process (Figure 2). In the first two stages of the *Stage-Gate* Idea-to-Launch process, existing knowledge can be used to select a NF for which read-across from another (data rich) NF seems feasible. The Level 1b and 1c hypotheses can facilitate in the selection of the NFs, and inform decisions to either "*Go on"* or reconsider building a business case (stage 2), in development of NFs (stage 3) or in their testing and validation (stage 4). The Level 2 refined hypotheses are probably most helpful in development (stage 3) and testing and validation (stage 4) stages of the innovation process. The further refined hypothesis in Level 3 will be most helpful in weighing the health and environmental risks against other criteria, when conducting the decision to launch (stage 5).

For more detail see section 3.3 of the full Draft GRACIOUS Framework document.

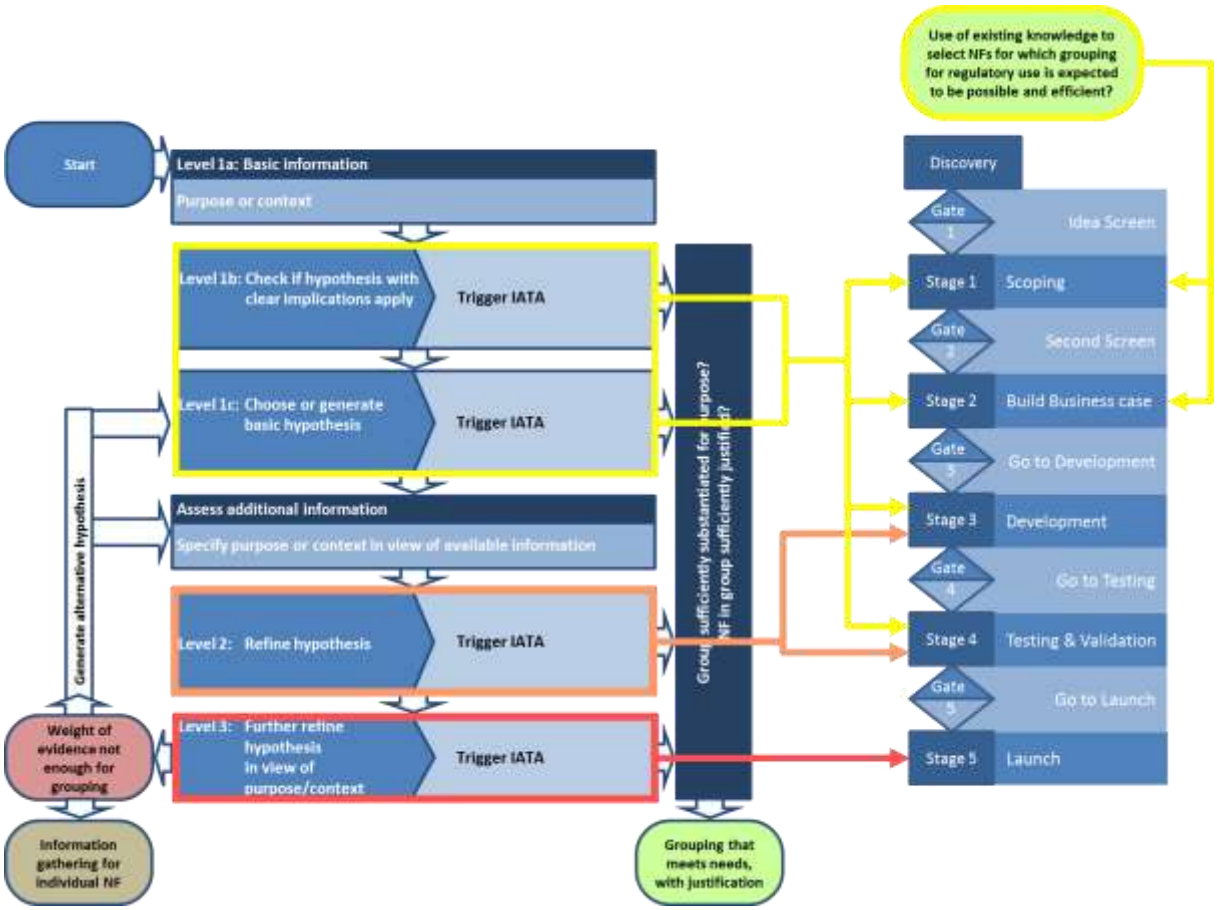

Figure 2 Outline for the relationship between the GRACIOUS Framework and Safe-by-Design via the Stage-Gate innovation process. The yellow, orange and red boxes indicate which Level of the Framework is most helpful in the different Stages of the Stage-Gate Idea-to-Launch process.

More detailed can be found in the *full Draft GRACIOUS Framework document* as follows:

- Background on existing approaches *section 2.2.*
- How existing approaches feed into the GRACIOUS Framework design *section 3.1.*
- Elaboration of the different parts of the Draft Framework *Chapter 4.*
- Terminology used throughout the Framework *section 2.1 and Appendix A.*
- The hypotheses *section 4.3 and Table 5*.
- Hypothesis justification section 5.3
- Use of existing tools and building IATAs Chapter 6

We need your input

The Draft GRACIOUS Framework is now open for discussion with stakeholders, with the intention to adapt it according to the received feedback. Stakeholders are invited to comment via:

- Completion of a questionnaire
- Comments written on the document
- E-mail.

Please return your comments to: f.murphy@hw.ac.uk and s.stoycheva@yordasgroup.com

The Draft Framework description will be updated to incorporate stakeholder feedback and published in spring 2019. The Framework description will be used to build a practical open-access GRACIOUS Framework for grouping and read-across that will be available in 2021.

References

Arts JHE, Hadi M, Irfan M-A, Keene AM, Kreiling R, Lyon D, Maier M, Michel K, Petry T, Sauer UG, Warheit D, Wiench K, Wohlleben W and Landsiedel R, 2015. A decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping). Regul. Toxicol. Pharmacol. 71: S1–S27.

ECHA, 2017. Appendix R.6-1 for nanomaterials applicable to the Guidance on QSARs and Grouping of Chemicals. Guidance on information requirements and chemical safety assessment. Version 1.0, European Chemicals Agency (ECHA), Helsinki, Finland. Available at https://echa.europa.eu/documents/10162/23036412/appendix_r6_nanomaterials_en.pdf.

EU, 2018. Commission Regulation (EU) …/… of XXX amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annexes I, III,VI, VII, VIII, IX, X, XI, and XII to address nanoforms of substances. Available at http://ec.europa.eu/transparency/regcomitology/index.cfm?do=search.documentdetail&Dos_ID=15915&DS_ID=56122&Version=2.