Grouping, Read-Across and ClassIficatiOn framework for regUlatory risk assessment of manufactured nanomaterials and Safer design of nano-enabled products

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About Gracious

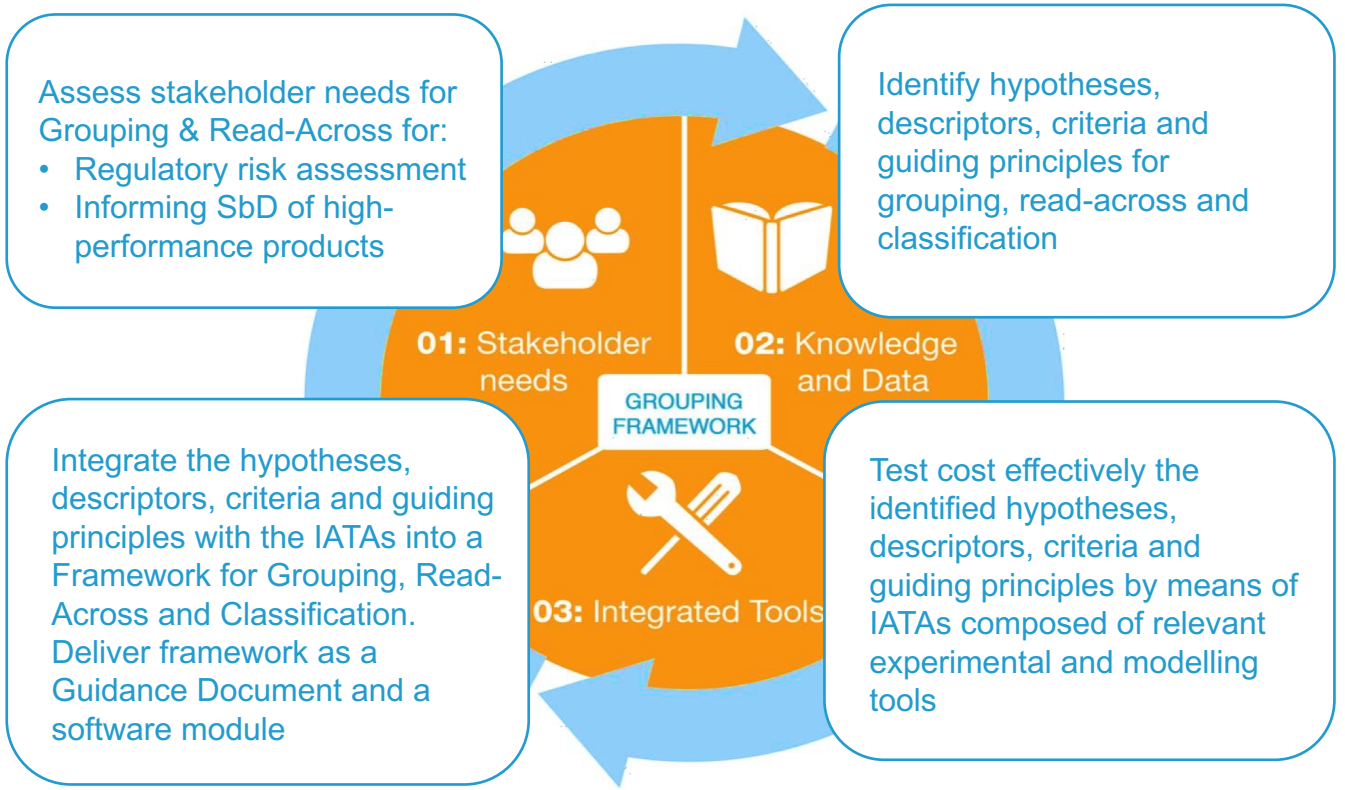
Development of a highly innovative science-based framework that supports the assessment of risk posed by the ever increasing array of nanomaterials on the market and under development.

The framework will streamline the process for assessing risk by logically grouping nanomaterials.

Grouping will allow extrapolation between (read-across) nanomaterials, materials and substances, and reducing the need to assess exposure to and toxicity on a case by case basis.

Objectives

- O1: Integrate key stakeholder needs with state-of-the-art thinking on grouping and read-across of nanomaterials (NMs)/nanoforms (NFs) in order to design, develop and refine a sustainable Framework
- O2: Develop knowledge and generate data as the basis to derive hypotheses, criteria and guiding principles for grouping, leading to classification and read-across, as building blocks for the GRACIOUS Framework
- O3: Refine and integrate tools to build the GRACIOUS Framework, Guidance Document and software module



Expected Results

The Framework and its Integrated Approaches to Testing and Assessment (IATAs) will be delivered as:

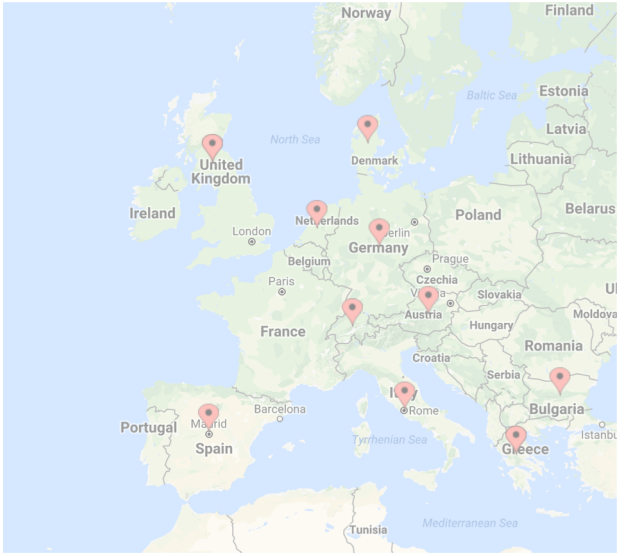
- An E-tool fit-for-purpose for various key stakeholders (regulatory and industrial)
- A Guiding Background Document

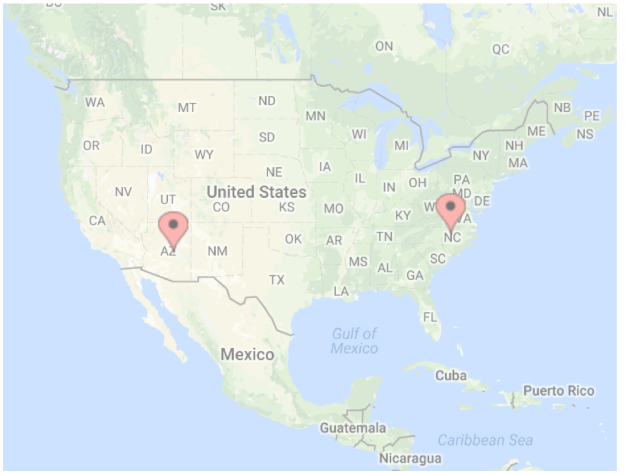
Both the E-tool and the guiding background document will be designed for practical application to:

- Help industries and regulators assess environmental and human health risks of existing NMs/NFs cost-effectively
- Facilitate business decisions concerned with developing new nano-enabled products (NEPs)
- To inform Safety-by-Design practices

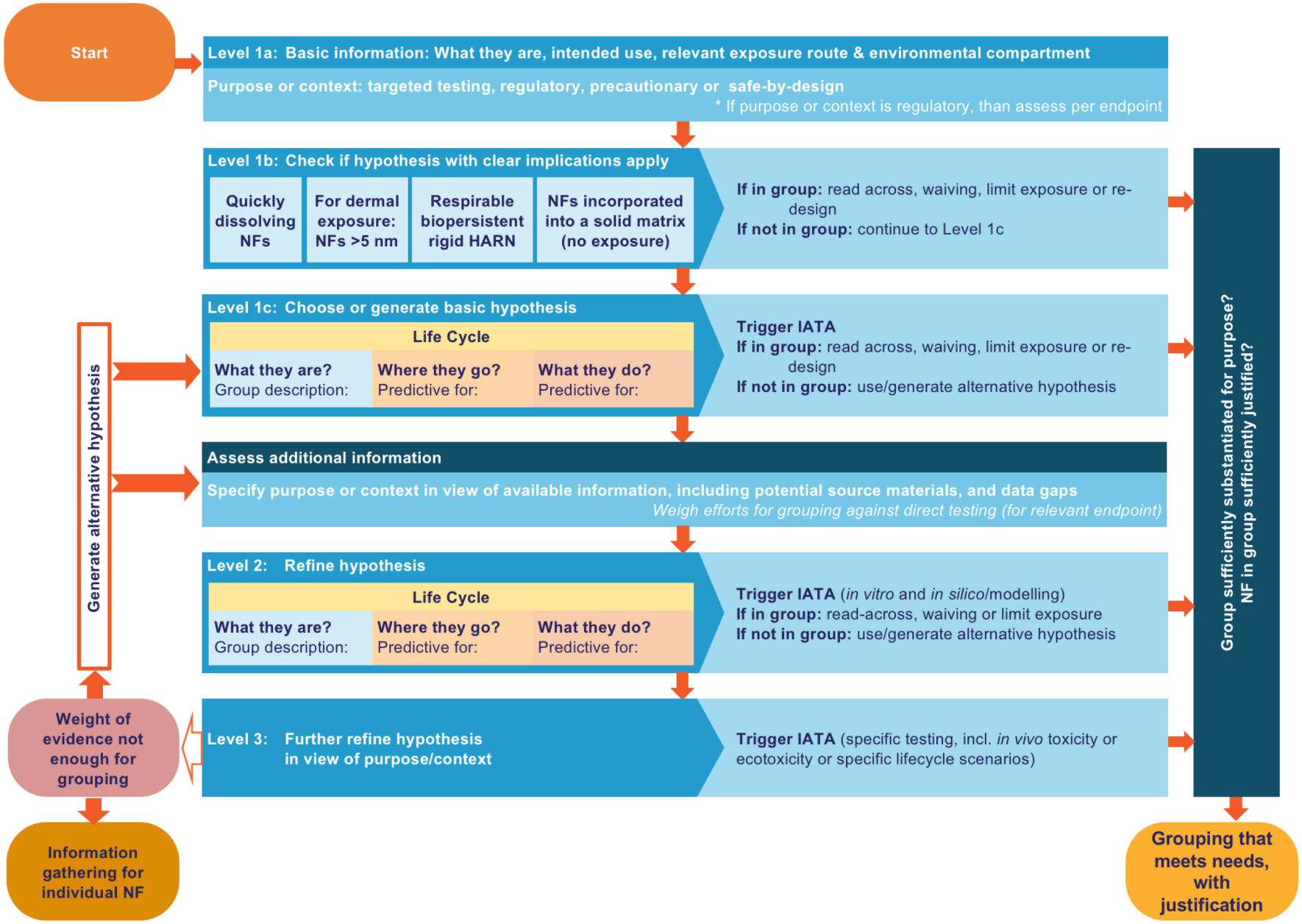
The GRACIOUS Consortium

Number	Organisation	Country
1 Coordinator	Heriot-Watt University (HWU)	**UK**
2	BASF SE (BASF SE)	**DE**
3	Green Decision (GD)	**IT**
4	Institute of Occupational Medicine (IOM)	**UK**
5	European Research Services (ERS)	**DE**
6	Yordas Group (Yordas)	**UK**
7	National Research Centre for the Working Environment (NRCWE)	**DK**
8	German Federal Institute for Risk Assessment (BfR)	**DE**
9	Natural Environment Research Council (NERC)	**UK**
10	University of Vienna (UNIVIE)	**AT**
11	Italian Institute of Technology (IIT)	**IT**
12	National Institute for Public Health and the Environment (RIVM)	**NL**
13	Eidgenoessische Technische Hochschule Zuerich (ETH Zurich)	**CH**
14	Leitat Technological Centre (LEITAT)	**ES**
15	Akzo Nobel Pulp and Performance Chemicals (AKZO)	**SE**
16	Ideaconsult (IDEA)	**BG**
17	JRC-Joint Research Centre-European Commission (JRC)	**IT**
18	Unilever (Unilever)	**UK**
19	ThinkWorks (ThinkWorks)	**NL**
20	Arizona State University (ASU)	**US**
21	Duke University (DUKE)	**US**
22	Athens Research and Innovation Center (ATHENA)	**EL**
23	Swiss Federal Laboratories for Materials Science and Technology (EMPA)	**CH**





Grouping Framework Design



Hypothesis Driven

- Each tier is based upon a hypothesis that could underpin the grouping of NMs together
- To progress to the next tier the user needs to test the hypothesis
- Testing will be guided via IATAs tailored to the hypothesis
- Data from the IATAs will allow the hypothesis to be refined
- Successive rounds of hypothesis refinement will generate a Grouping Decision with Justification

Integrated Approaches to Testing and Assessment

- The GRACIOUS Framework will involve four IATAs:

i) "Lifecycle: Human exposure and environmental release",

ii) "What they are: physicochemical identity",

iii) "Where they go: Environmental fate, uptake and toxicokinetics"

iv) "What they do: human and environmental toxicity"

NB IATAs were previously known as Intelligent Testing Strategies ITSs

HARN - ITS testing options (WP5)

Tier 1
- What they are
  - Rigidity

Tier 2
- What they are, Where they go
  - Dissolution *in vitro*
- What they do
  - Macrophage frustrated phagocytosis, ROS, cytokine

Tier 3
- Where they go
  - Biopersistence *in vivo*
  - Translocation into lung and pleura
  - Systemic translocation
- What they do
  - Inflammation
  - Fibrosis
  - Lung granuloma
  - Mesothelial inflammation
  - Mesothelial granuloma
  - Tumour

NM – ITS testing options
- Tier 1 What they are
- Tier 2 What they are, Where they go, What they do *in vitro*
- Tier 3 Where they go, What they do *in vivo*

See Arts et al. 2015 Regulatory Toxicology and Pharmacology 71 S1-S27

Solute – ITS testing options
- REACH and other regulations.
- What they are: Depending on intended use, check transformation (speciation to another particulate species)
- Consider interaction between solute and NM/HARN

Tiers and Stage-Gate

Problem framing

- Objectives of the analysis and associated information requirements
- Data quality evaluation (e.g. adequacy, relevance, reliability)

Tier 1

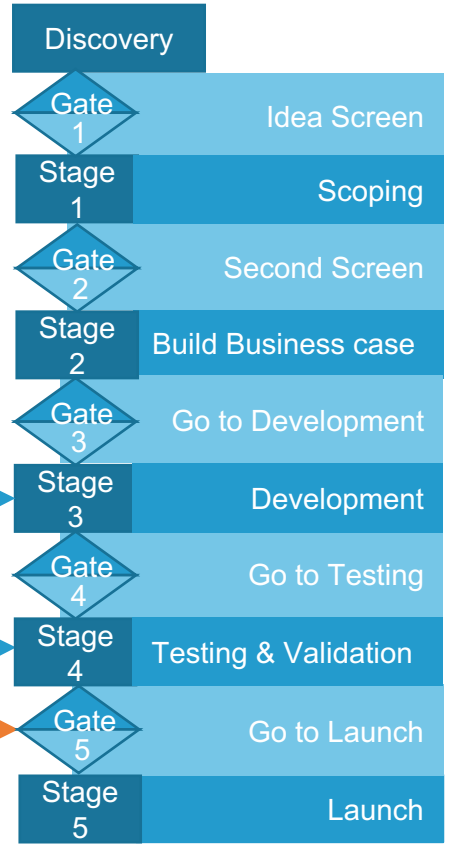
- What they are: Physicochemical identity and attribution to nanoforms (**characterisation of pristine NMs)**
- Intended use and relevant exposure routes and environmental compartments

Tier 2

- Identification and description of exposure scenarios (**screening tools**)
- Where they go: Environmental fate, uptake and toxicokinetics (***in silico*, *in vitro* models**)
- What they do: Human and environmental toxicity (***in silico*, *in vitro* models**)

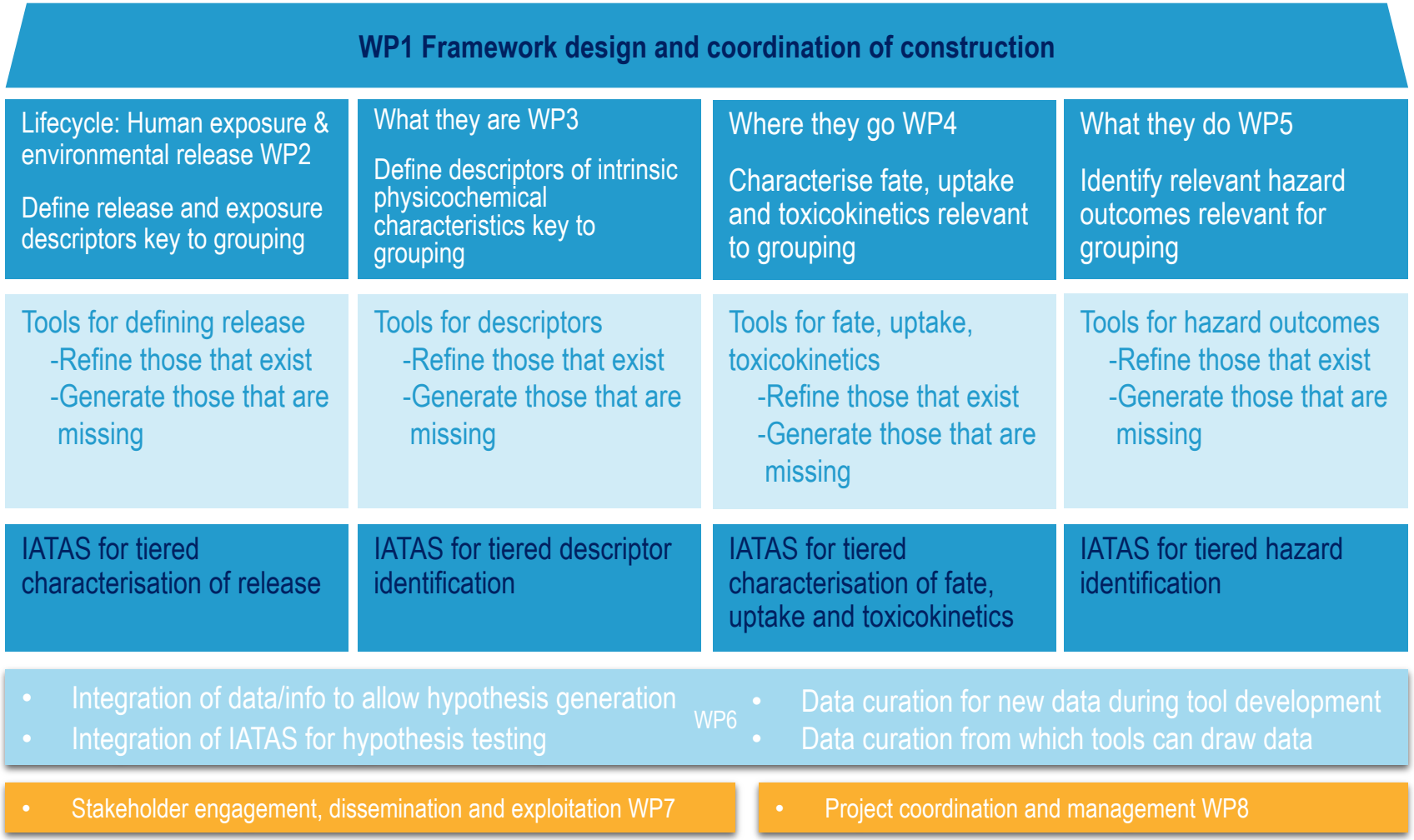
Tier 3

- Quantification of release/exposure (high-tier exposure models, monitoring)
- Where they go: Environmental fate, uptake and toxicokinetics (***in vivo* experiments, characterisation of NEP fragments in complex media**)
- What they do: Human and environmental toxicity (***in vivo* experiments**)



Stage-Gate stages

Construction Process



Thank you!

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