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

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Introduction

GRACIOUS

- EU-H2020 project lasting 3.5 years
- Started in January 2018
- Consortium of 23 partners
- Coordinator: Vicki Stone (v.stone@hw.ac.uk)

- Status
  - Done: Draft framework
    Overview terminology, EU legislation addressing NMs or NFs, existing approaches
  - Now: Input from stakeholders
  - Future: further research & Framework development

GRACIOUS Framework

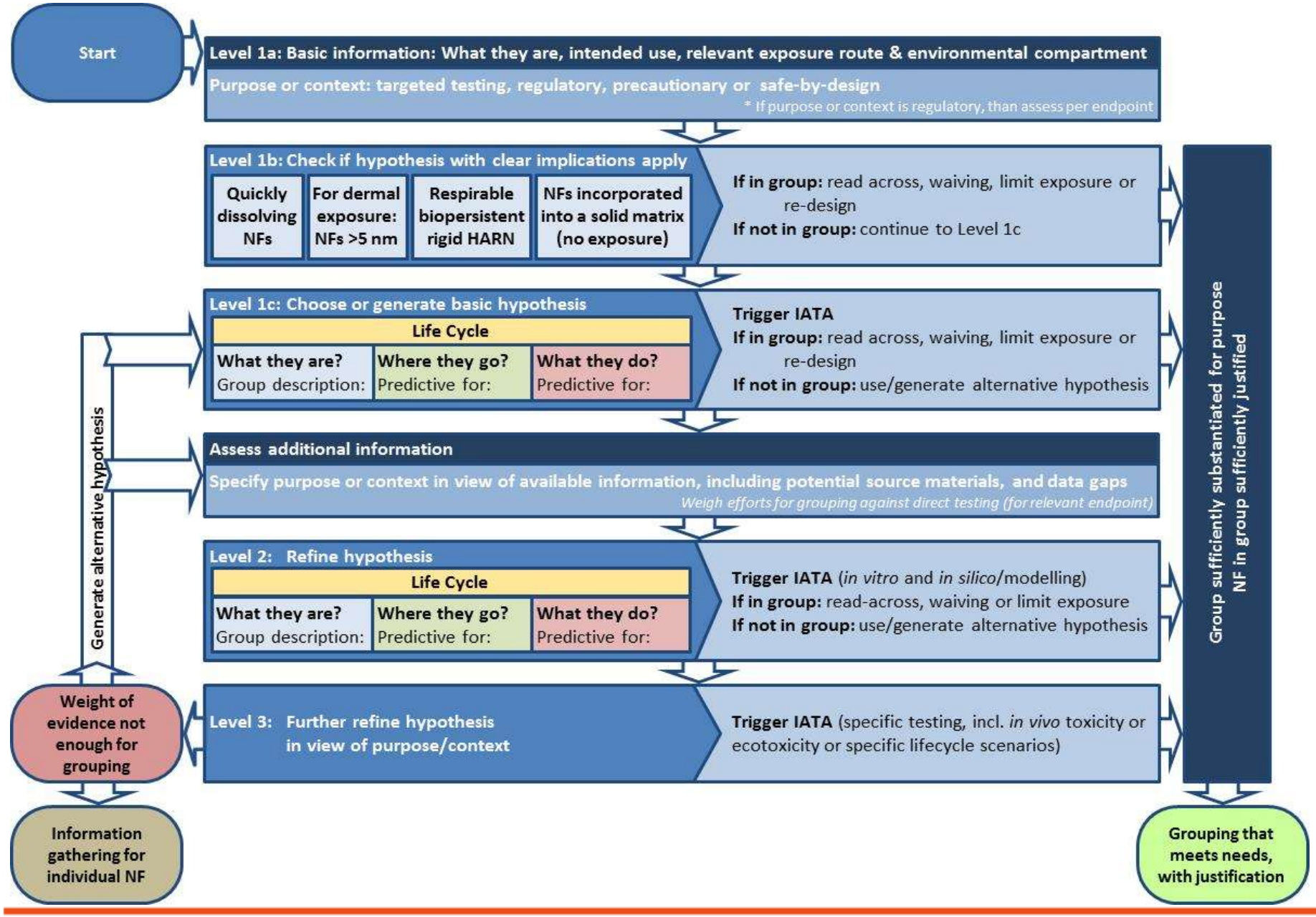
- **Aim GRACIOUS Framework:** support practical application of grouping of nanomaterials/nanoforms (NFs)

- Key aspects
  - Alignment to present EU legislation
  - Hypothesis driven

Potential use and application of grouping

- To facilitate targeted testing or targeted risk assessment
- To fill a data gap in a regulatory dossier
- To develop precautionary measures
- To steer safe innovation/safe-by-design

Introduction: Draft Framework

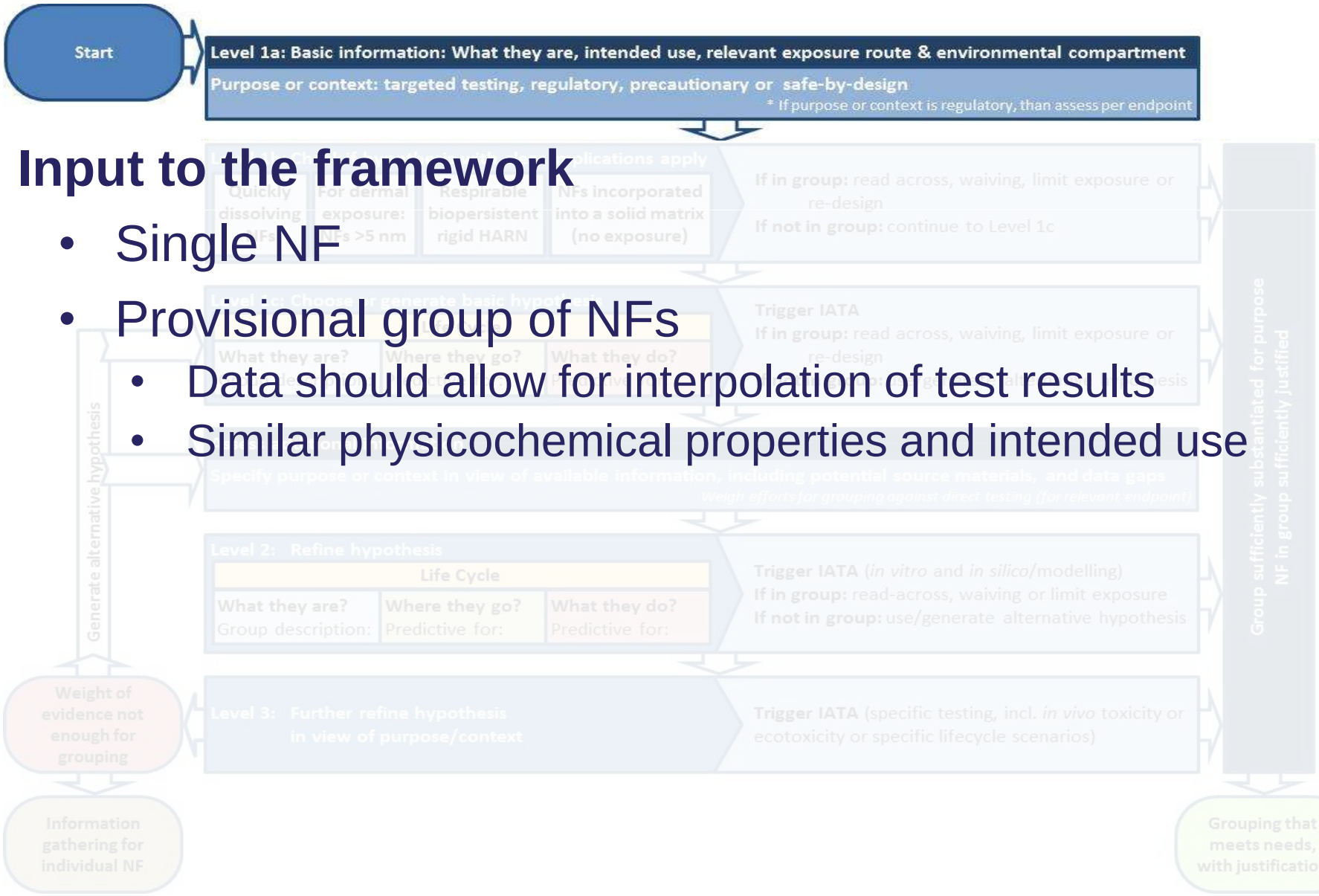


Hypothesis Driven

- A hypothesis is used that can underpin the grouping
- The implications of the grouping should be considered
- To progress to the next level the user needs **to test if the hypothesis applies and justify the use of the grouping**
- Testing will be guided via IATAs tailored to the hypothesis
- Data from the IATAs can be used to refine the hypothesis
- Goal: grouping decision with justification

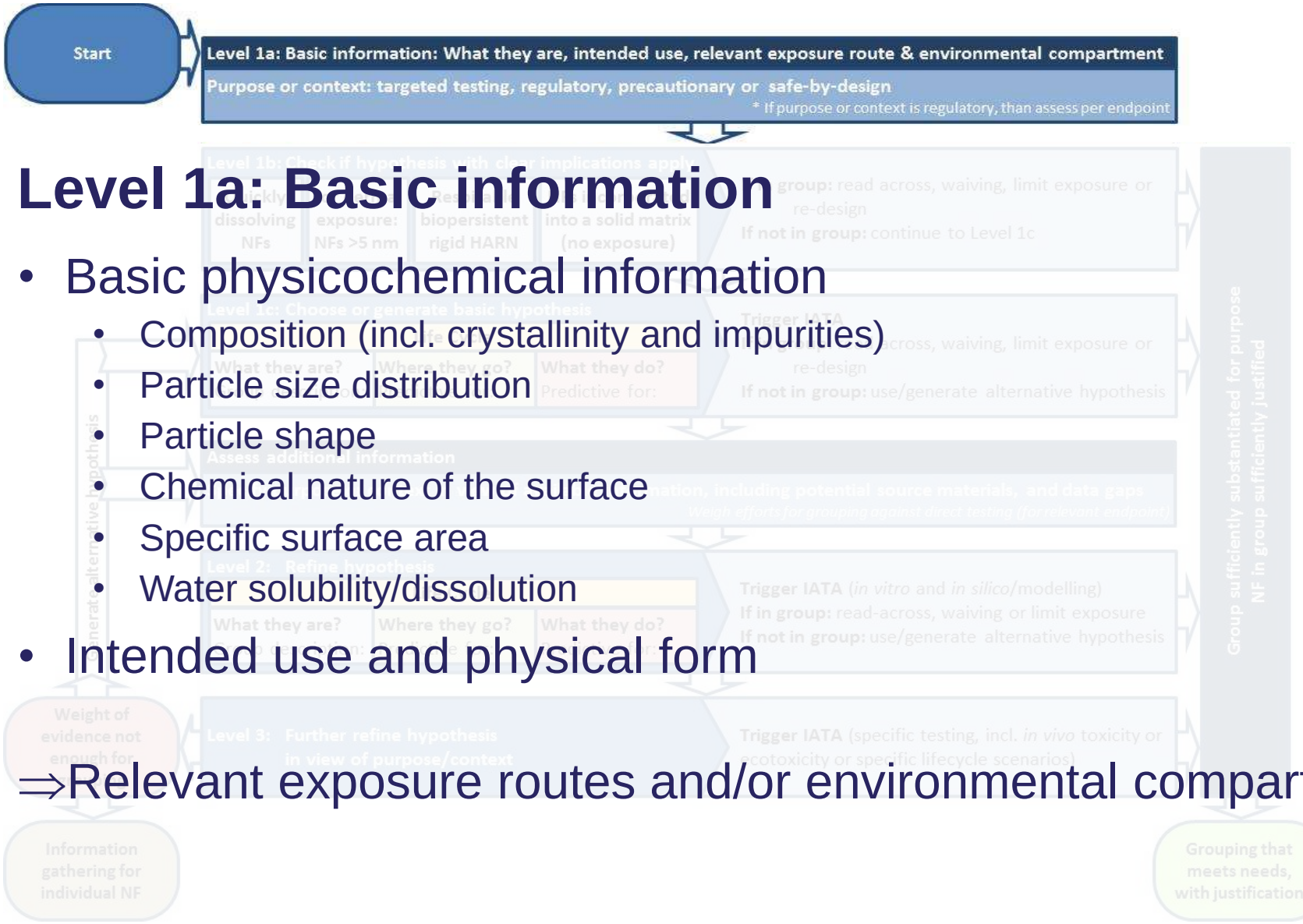
IATA = Integrated Approach to Testing and Assessment

Introduction: Draft Framework



Input to the framework

- Single NF
- Provisional group of NFs
  - Data should allow for interpolation of test results
  - Similar physicochemical properties and intended use



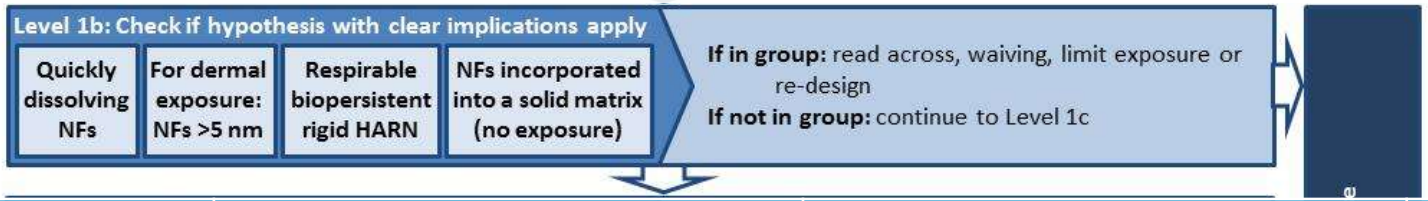
Level 1a: Basic information

- Basic physicochemical information
  - Composition (incl. crystallinity and impurities)
  - Particle size distribution
  - Particle shape
  - Chemical nature of the surface
  - Specific surface area
  - Water solubility/dissolution
- Intended use and physical form

⇒Relevant exposure routes and/or environmental compartments

Level 1b: Hypothesis with clear implications

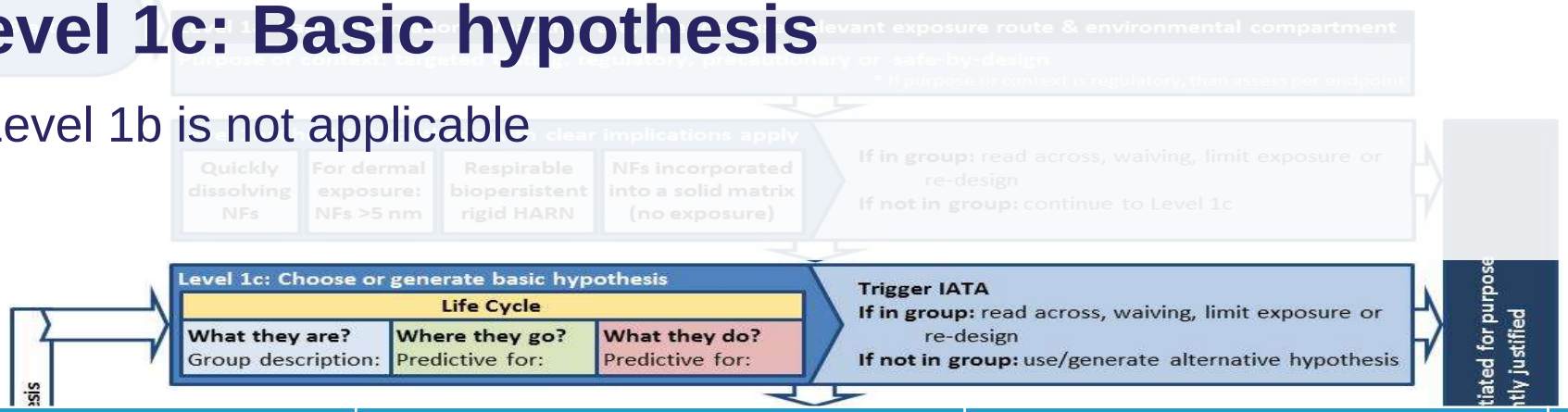
Groups that can relatively quickly be substantiated to meet the needs of the user



Group	Hypothesis	Potential implications	Relevant testing
DISS: Quickly dissolving NFs	Quick transformation to ions/ molecules => same fate, kinetic and tox. profile as soluble form	Regulatory: read-across to soluble form	Dissolution rate and transformation in water and relevant media.
Respirable HARN	Translocation, frustrated phagocytosis, mesothelioma	Precautionary/SbD: prevent/minimised exposure Regulatory: read-across to asbestos or other HARN	Dissolution in representative fluids
D5NM: NFs larger than 5 nm will not translocate across healthy skin	No translocation across healthy skin	Regulatory: waiving of endpoints related to systemic exposure	In vitro or ex vivo translocation studies.
SNEPs: NFs incorporated in solid matrix	No release as free NFs, depending on use/aging process	Precautionary/SbD: minimise exposure or adjust NEPs	Incorporation in matrix. Release under relevant conditions.

Level 1c: Basic hypothesis

If Level 1b is not applicable



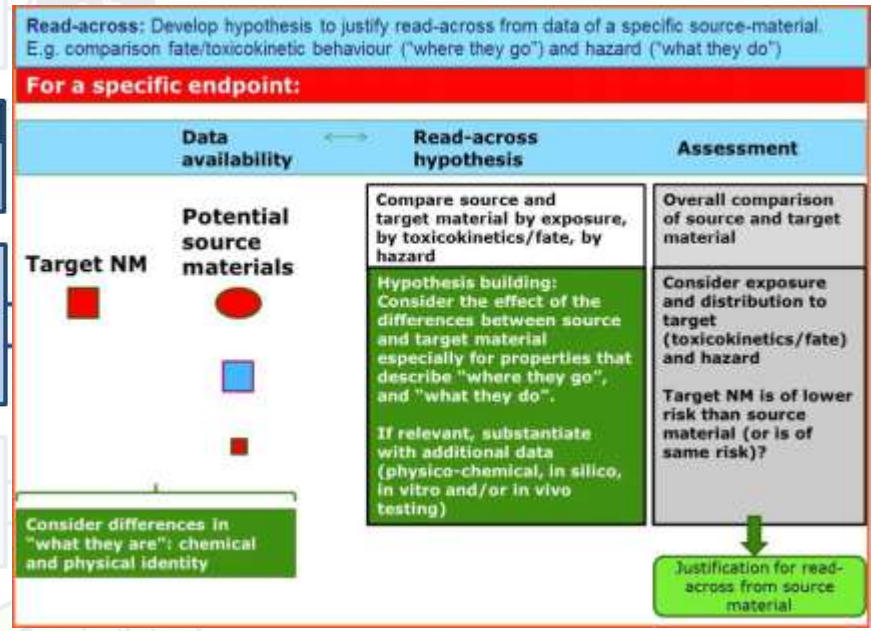
Group	Hypothesis	Potential implications	Relevant testing
NFs with low dissolution rate and chemical composition of low toxicity	May accumulate in humans and environment => increase likelihood for toxicity after chronic exposure.	Targeted testing: testing to address accumulation and long term toxicity. Regulatory: read-across to another poorly soluble low toxicity NF	Dissolution rate and transformation in water and relevant media. Reactivity.
NFs with low dissolution rate and specific toxicity	NF accumulate in humans and environment => increase likelihood for toxicity after chronic exposure + specific toxicity related to active nature	Targeted testing: testing to address active nature, accumulation and long term toxicity. Regulatory: read-across to another similarly active poorly soluble NFs.	Dissolution rate and transformation in water and relevant media. Reactivity. Mobility in soils.
Moderately dissolving NFs			
…			

Assess information + additional info (source materials)

- Specify purpose or context

Level 2: Generate refined hypothesis

- **Read-across** that can be used in a regulatory dossier
  - Assess for which endpoints
  - Develop hypothesis for read-across based on comparison to source-material
- Refine **grouping** hypothesis
- In vitro and in silico tests/tools.



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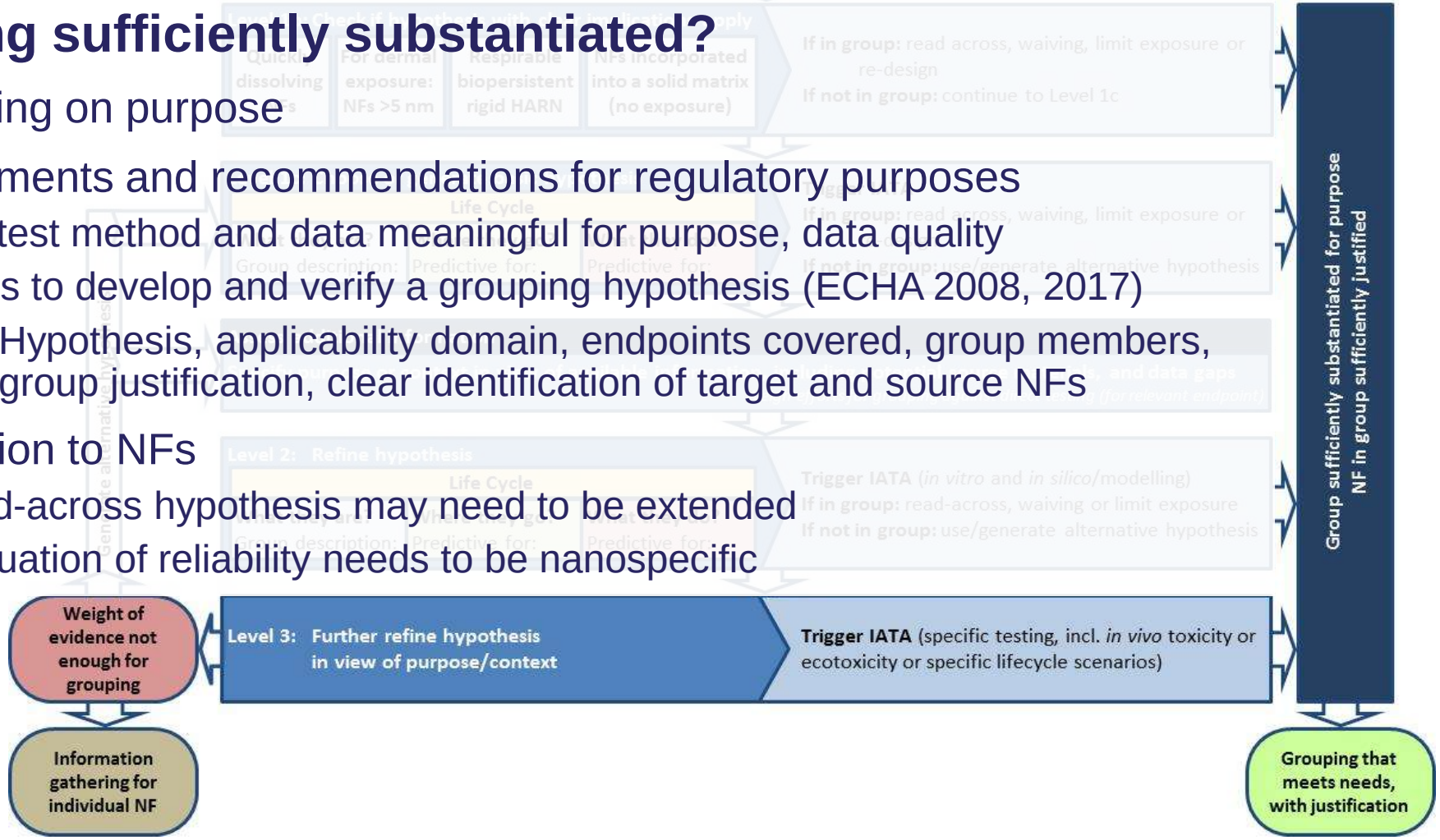
Level 3: further refine hypothesis

- May comprise in vivo testing

Grouping sufficiently substantiated?

- Depending on purpose
- Requirements and recommendations for regulatory purposes
  - e.g. test method and data meaningful for purpose, data quality
  - Steps to develop and verify a grouping hypothesis (ECHA 2008, 2017)
    - Hypothesis, applicability domain, endpoints covered, group members, group justification, clear identification of target and source NFs
- Application to NFs
  - Read-across hypothesis may need to be extended
  - Evaluation of reliability needs to be nanospecific



Next steps

- Input from stakeholders
- Assessment of scientific validity of (prioritised) hypotheses
  - NFs for which the hypothesis is applicable
- Development of IATA's for justification of grouping
  - Assessment suitability of tools, methods and protocols
  - Determination of quality criteria
  - For read-across: evaluate the ability of in vitro and in silico methods to correctly rank hazard as well as fate/toxicokinetic behaviour as compared to in vivo situation
- Further elaborate to assess when a grouping is sufficiently substantiated
- Incorporate in Framework
- Case studies

- 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
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- HWU: Vicki Stone, Teresa Fernandes

Thank you!

Outline Framework and Safe-by-Design