The GRACIOUS Framework

For Grouping and Read-Across of Nanoforms

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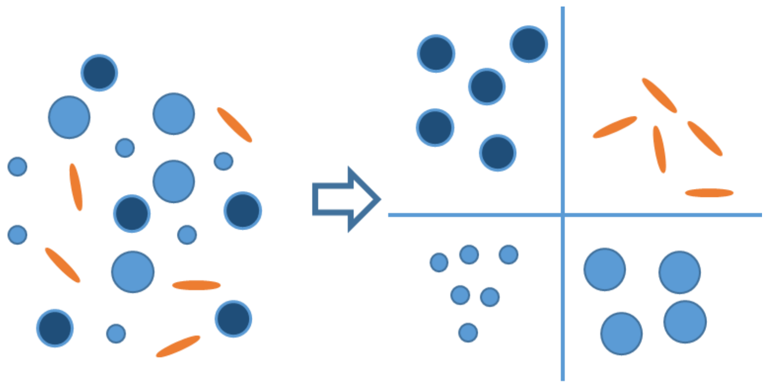
Project no. 760840

Presentation structure

- An overview of the GRACIOUS Framework
- Examples grouping hypotheses
- Example Integrated Approaches to Testing and Assessment
- Similarity
- Database links
- Quality
- Blueprint

Project Aim

Generate a Framework to enable practical application of grouping, and subsequent read-across of nanomaterials (NMs)/nanoforms (NFs).



"Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group" (REACH, Annex XI, 1.5).

GRACIOUS framework

Framework Design Process

EXISTING KNOWLEDGE

ECHA guidance on grouping and read-across

NanoReg2

NanoGruvar

DF4Nanogrouping

MARINA

GRACIOUS DRAFT FRAMEWORK

STAKEHOLDER ENGAGEMENT

- One-to-one interviews
- Open online consultation (30 responses)
- Stakeholder engagement platform
- GRACIOUS / NanoReg2 stakeholder event @OECD, Paris

GRACIOUS FRAMEWORK DESIGN

STAKEHOLDER FEEDBACK

- One-to-one interviews
- Open online consultation
- Stakeholder testing via case studies

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OECD NanoReg2 GRACIOUS workshop Sept 2018

Stakeholder engagement

- EU policy makers
  - E.g. EC
- EU regulatory bodies
  - E.g. ECHA, EFSA, JRC
- European national government bodies
  - E.g. RIVM, NRCWE, BfR
- Non-EU regulatory bodies
  - E.g. US EPA, Health Canada
- Industry bodies
  - E.g. NIA, ECETOC and BIAC
- Industry
  - E.g. BASF, Black Diamond
- Consultants
  - E.g. Yordas, Blue Frog

Thank you

GRACIOUS Framework paper

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ELSEVIER

A framework for grouping and read-across of nanomaterials-supporting innovation and risk assessment

Check for updates

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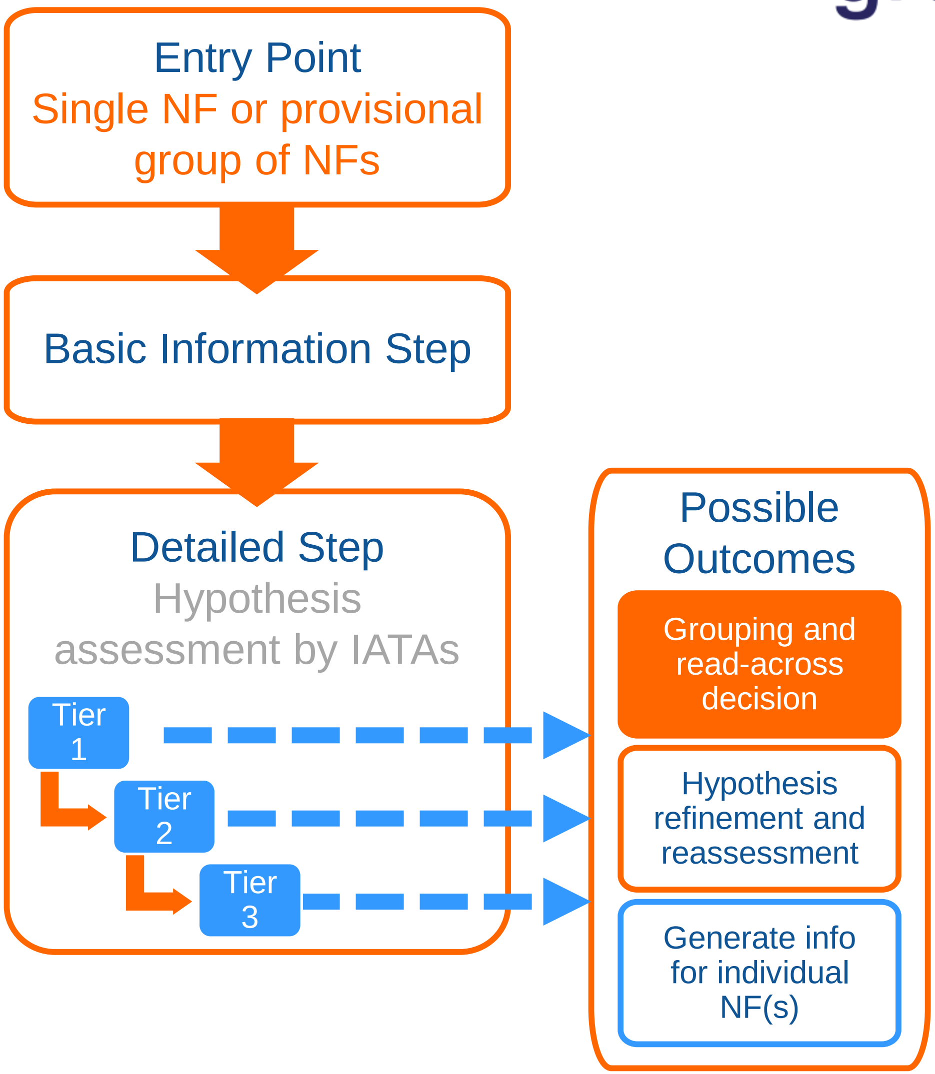
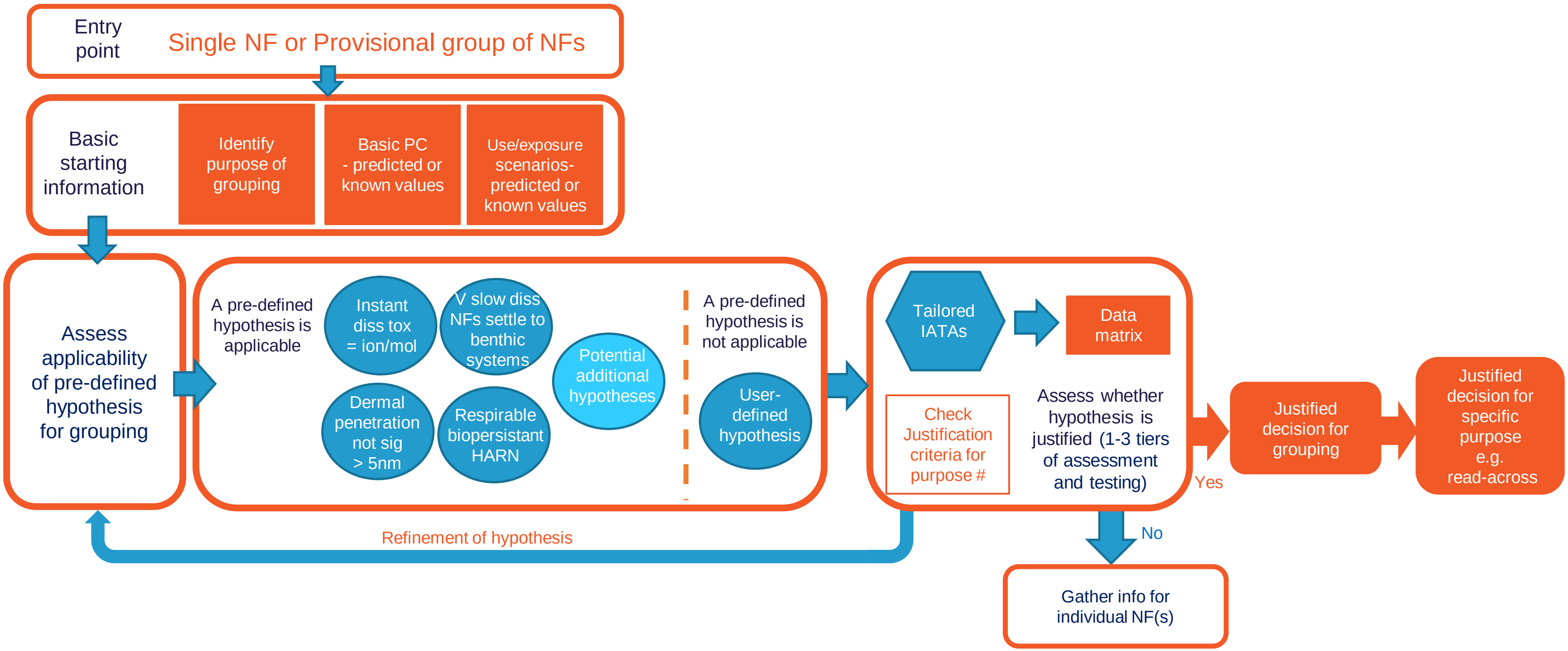
Simple form


Entry Point
Single NF or provisional group of NFs
Basic Information Step
Detailed Step
Hypothesis assessment by IATAs
Tier 1
Tier 2
Tier 3
Possible Outcomes
Grouping and read-across decision
Hypothesis refinement and reassessment
Generate info for individual NF(s)

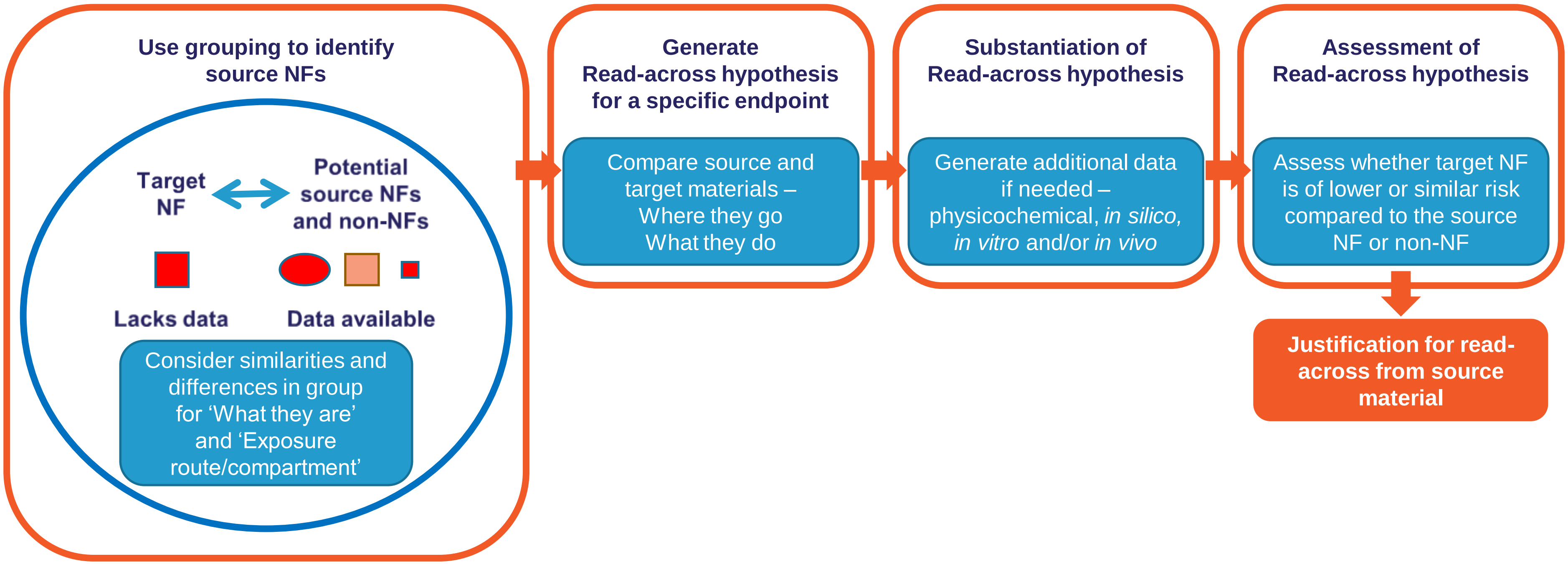
GRACIOUS Framework

Detailed form



Justification criteria are purpose specific. i.e. less stringent for SbD than for RA or legislation

Using the Framework for Read-Across



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Using the Framework for Innovation

- During innovation, safe(r)-by-design approaches help to avoid expensive, time consuming, unexpected problems with new nano-enabled products
- Grouping and Read-across can be used during the innovation process
  - E.g. aid prioritization of lower hazard candidate NFs while ensuring product functionality

Freerangestock.com

GRACIOUS Framework

Getting started

Entry point — Single NF or Provisional group of NFs

Basic starting information

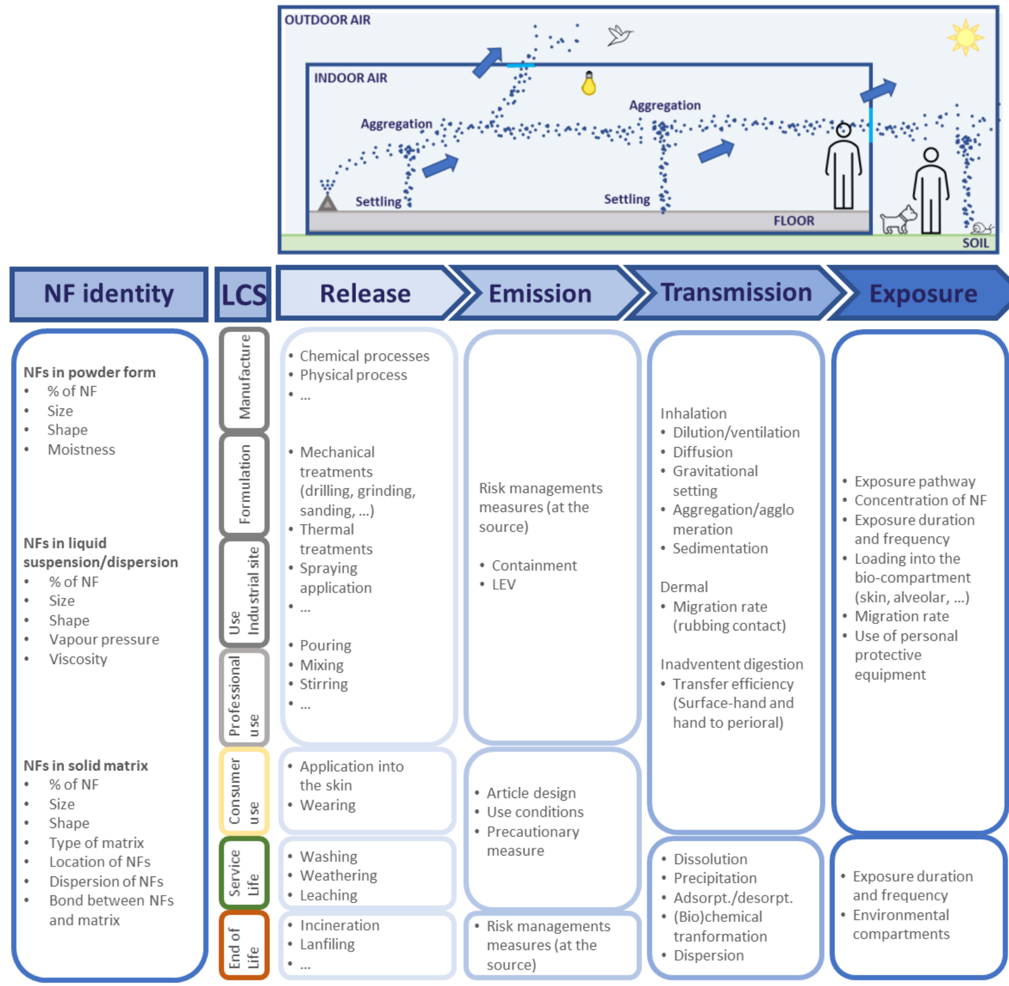
- Identify purpose of grouping
  - SbD
  - Precautionary
  - Tailored testing
  - Regulatory
- Basic PC - predicted or known values
  - Particle size
  - Shape
  - Composition
  - Surface chem
- Use/exposure scenarios- predicted or known values
  - Informs route of exposure + environmental compartment

ECHA guidance on registration of NFs, 2019

Along Nano-enabled produce life cycle

Steps to integrate release & exposure:

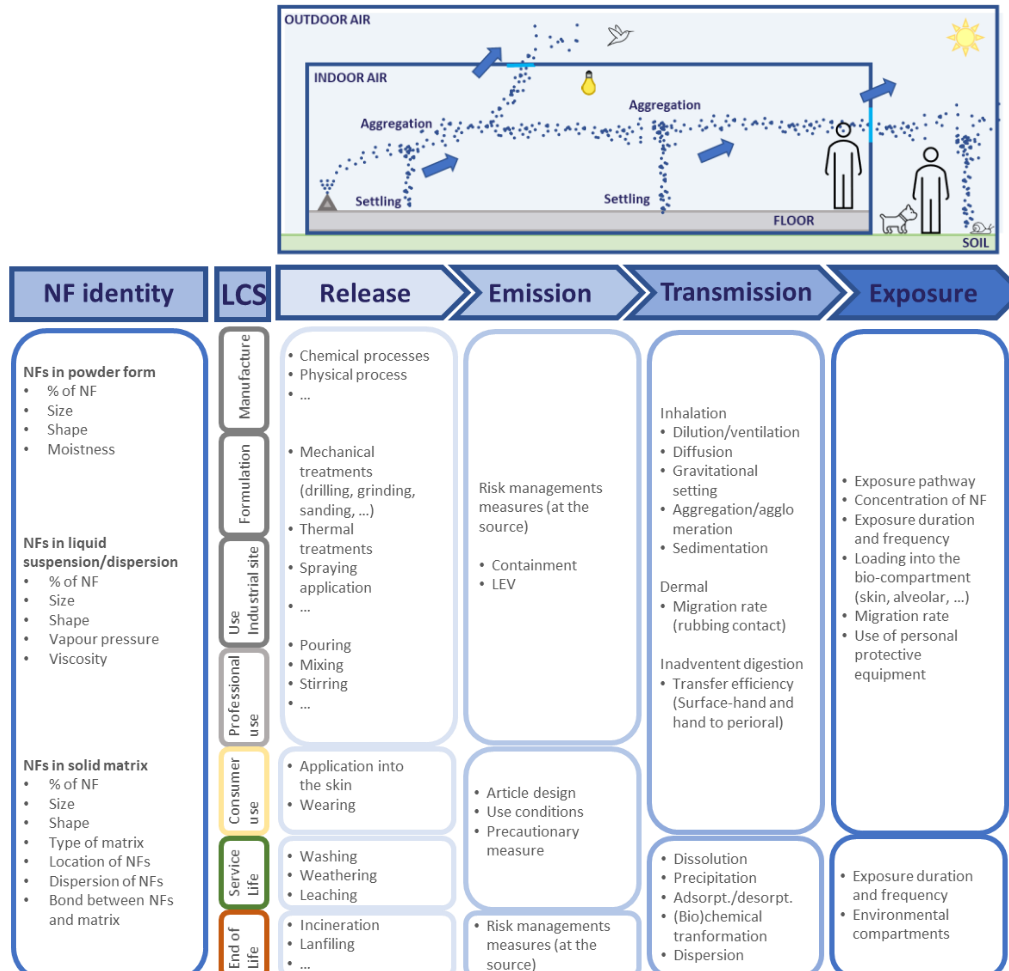
- Select key elements to describe release & exposure
- Identify main determinants of release & exposure
- Generate grouping hypothesis based on release & exposure
- Provide Integrated Approaches to Testing and Assessment of these hypotheses



Along Nano-enabled produce life cycle

Release & exposure components identified in the basic step:

- Likelihood of release & exposure
- Physicochemical form of NF during release & exposure
- Environmental compartments affected
- Exposed populations
- Exposure routes



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Hypothesis template

- The basic information triggers a hypothesis
- There are many ways to word and formulate a hypothesis
- To provide guidance to the user GRACIOUS has developed a Hypothesis Template

Purpose and context	
Life Cycle	**What they are?**
	Where they go?
	What they do?

Posters Topic 4 Risk assessment, risk management and risk governance

ID 1076 - A Template for Hypothesis Generation to Facilitate Grouping and read-Across of Nanomaterials and Support Risk decision-Making

Hypothesis template

The Framework guides users to pre-defined hypotheses if appropriate.

- Often encompass both fate and hazard
- Based upon the literature and available data
  - 17 for human hazard
  - 23 for environmental hazard

If no predefined hypotheses are appropriate, the Framework guides generation of a user-defined hypothesis.

Example Hypotheses - Human

Respirable NFs showing quick dissolution: Following inhalation both NFs and constituent ions or molecules may contribute to toxicity, but there is no concern for accumulation. Toxicity (also) depends on the location of the ionic or molecular release.

NFs with a very slow dissolution rate: Following oral exposure NFs will maintain nanospecific activity that may drive translocation across the GIT wall, subsequent biopersistence in the body and systemic toxicity in secondary organs.

NFs with constituent substance(s) or degradation products classified for dermal irritation or sensitization: Dermal exposure to the NFs may result in dermal irritation or sensitization.

Grouping is hypothesis driven

Example Hypotheses - Environment

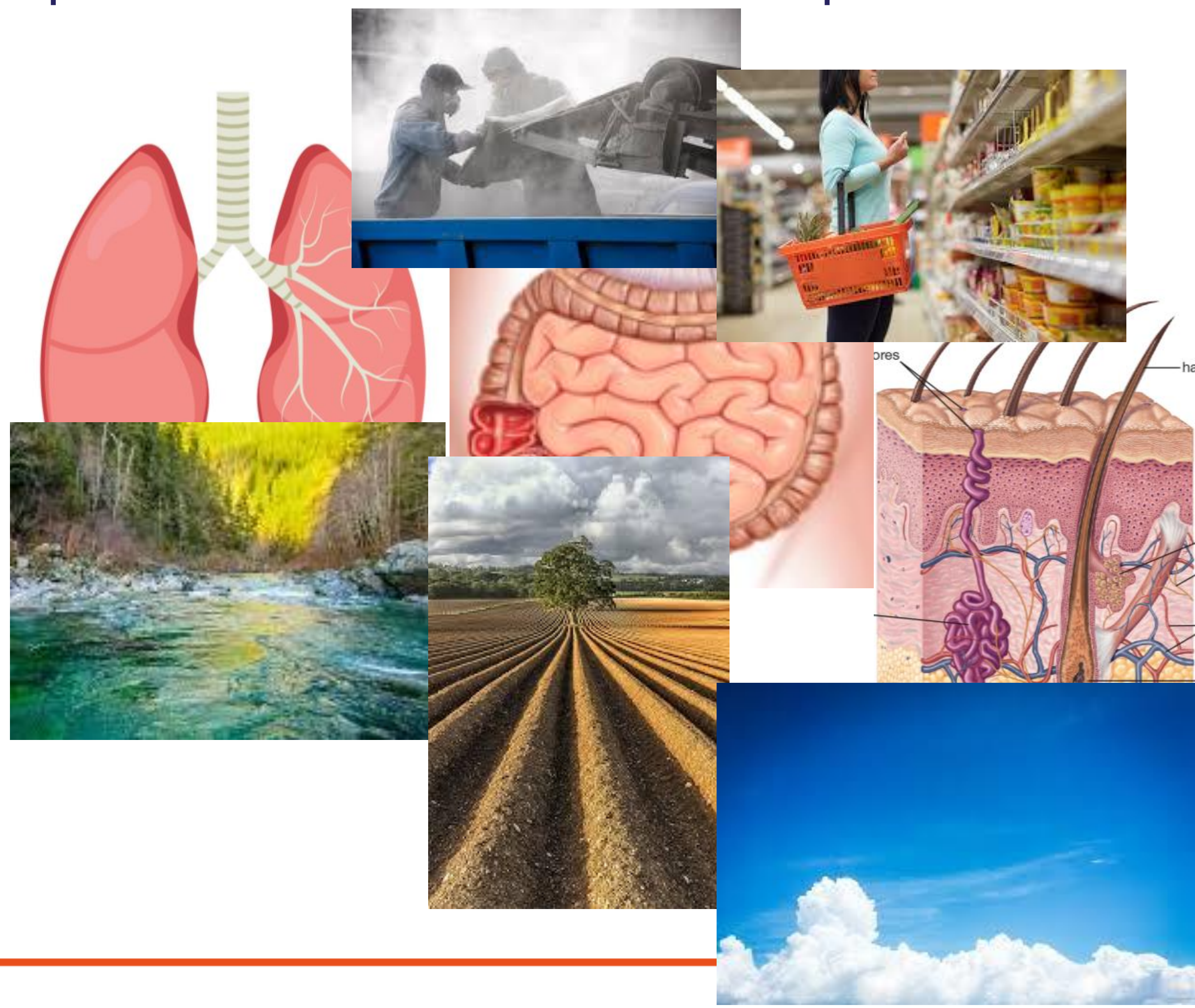
NFs with a quick dissolution rate in environmentally relevant aquatic media: Following aqueous exposure lethal and sub-lethal toxicity to representative aquatic species is driven by the fate and toxicity characteristics of the dissolution products.

NFs with a chemical coating that is lost from the NF surface following exposure in soil compartment can be grouped: Fate and toxicity of the exposure relevant NF can be considered similar to a non-coated analogous NF in soil compartment

Bioavailable NFs with a very slow dissolution rate in sediment can be grouped: Following sediment exposure, NFs in this group will maintain nano-specific activity and can cause lethal and sub-lethal toxicity to representative benthic species.

Pre-defined hypothesis

- Span different exposure scenarios and hence exposure routes
    - Inhalation
    - Ingestion
    - Dermal
    - Air
    - Aqueous
    - Sediment
    - Soil



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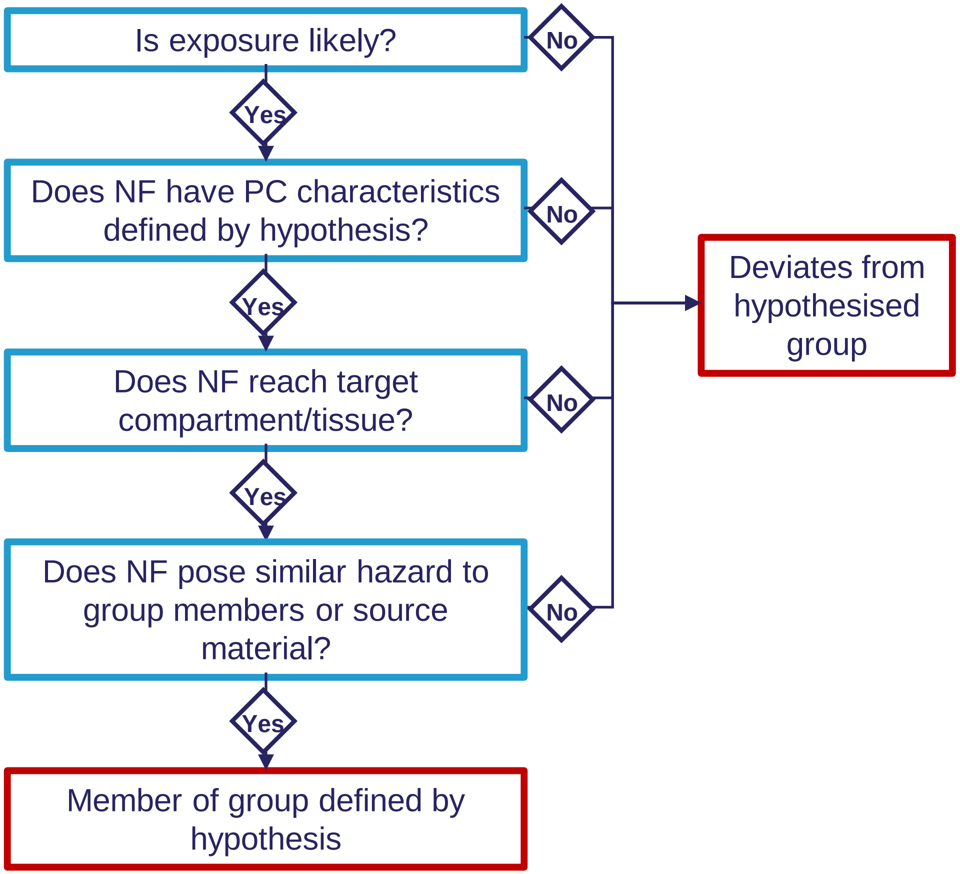
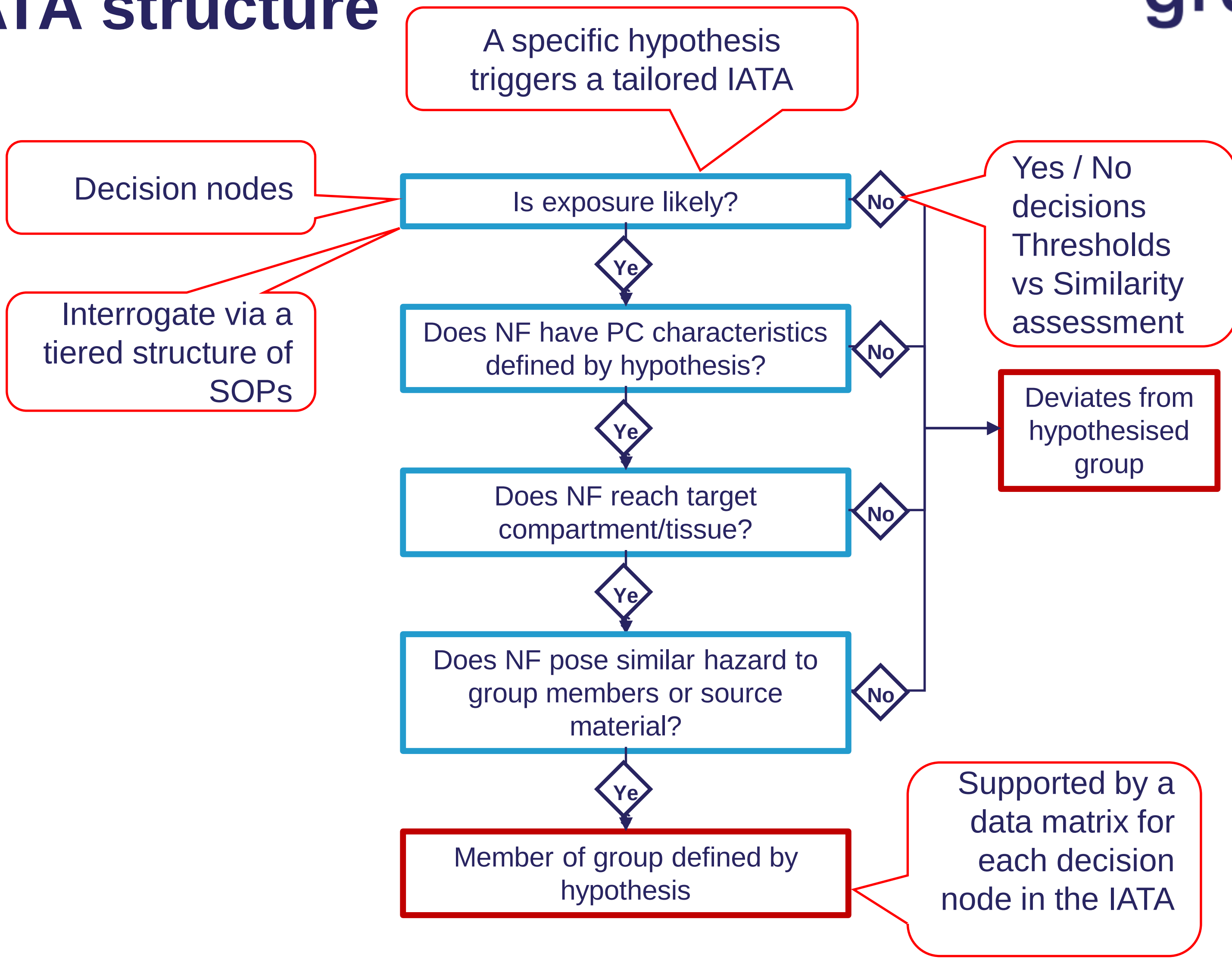
Integrated Approaches to Testing and Assessment

IATA Decision Tree Format

- Aligns with OECD recommendations (OECD 2017)
- Decision Nodes are measurable with defined criteria to ensure a clear 'yes' or 'no' answer
- Identify points of departure where you may deviate from, and therefore reject, the grouping hypothesis
- Combines and integrates all relevant existing evidence and guides the targeted generation of new data, where required, to support evidence-based grouping.

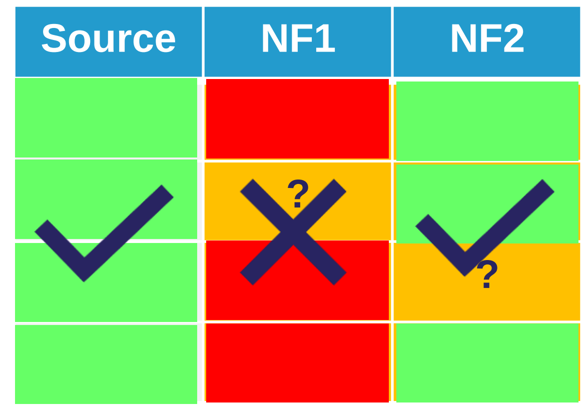


IATA structure



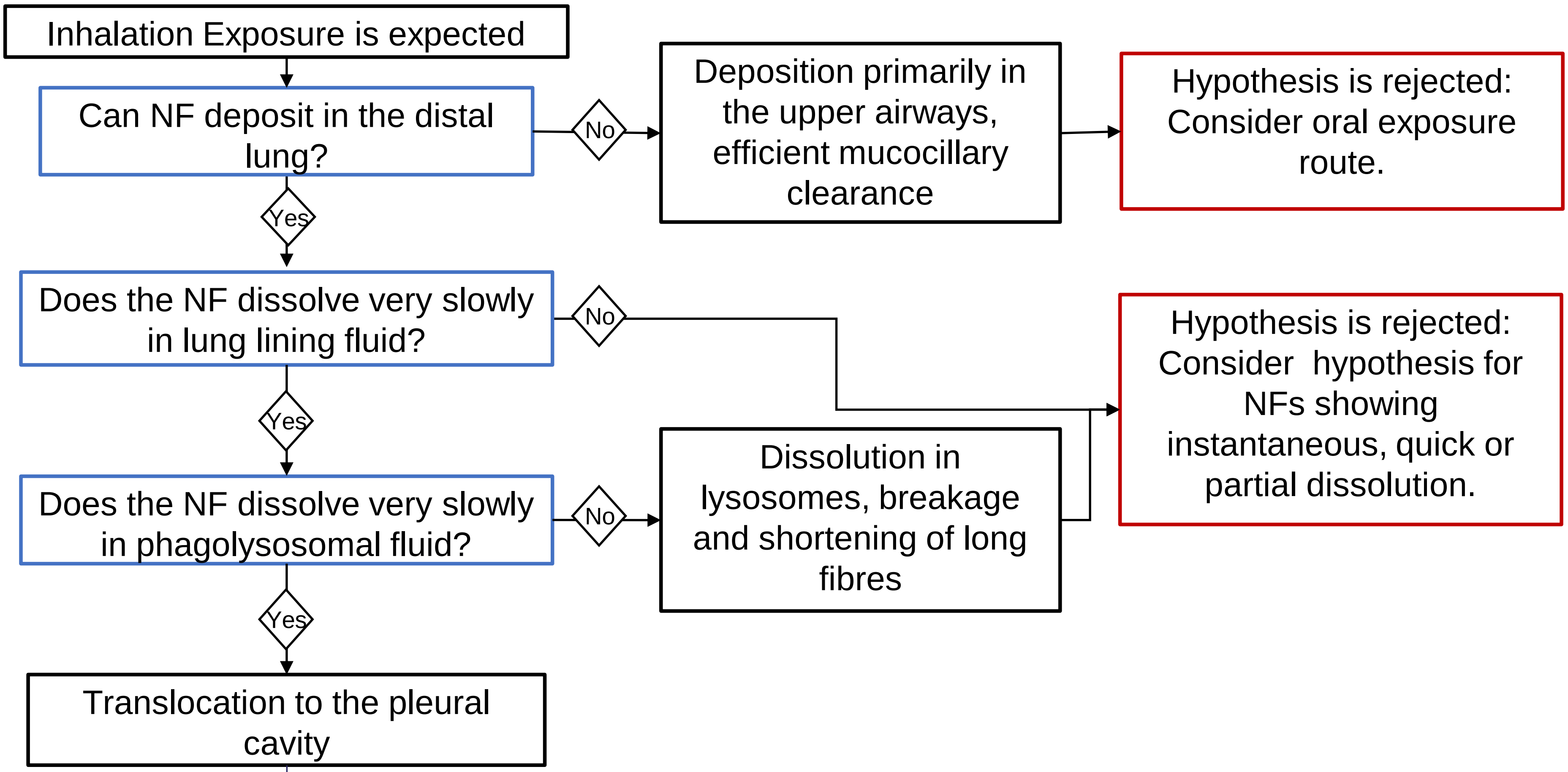
Data Matrix

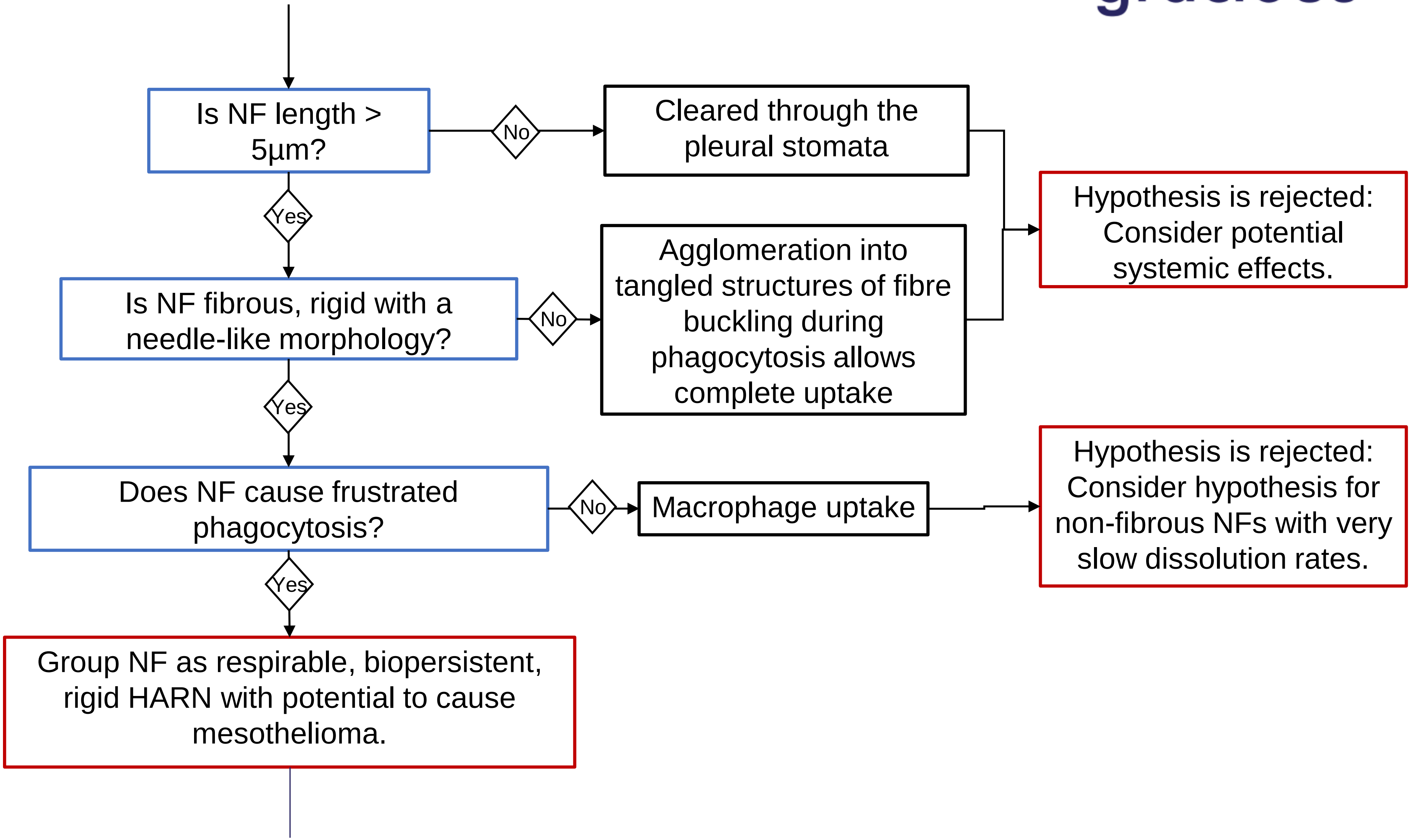
- The IATA provides the evidence needed to test the hypothesis
- Data is compiled into a data matrix which includes assessment of similarity for all endpoints

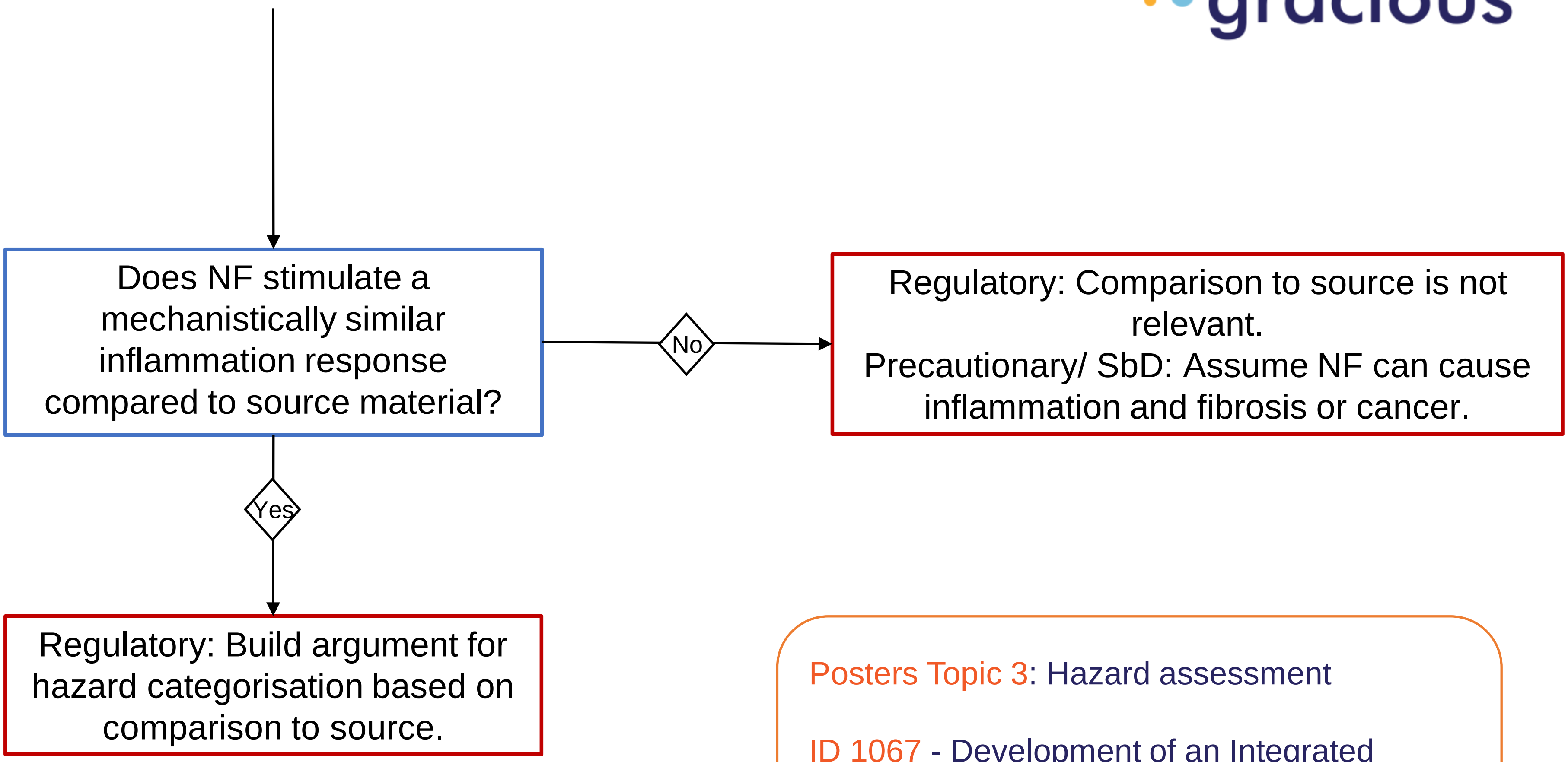


Respirable, biopersistent, rigid HARN:

Following inhalation exposure and translocation of HARN to the pleura, mesothelioma development can occur.




Is NF length > 5µm?
No
Cleared through the pleural stomata
Yes
Is NF fibrous, rigid with a needle-like morphology?
No
Agglomeration into tangled structures of fibre buckling during phagocytosis allows complete uptake
Hypothesis is rejected: Consider potential systemic effects.
Yes
Does NF cause frustrated phagocytosis?
No
Macrophage uptake
Hypothesis is rejected: Consider hypothesis for non-fibrous NFs with very slow dissolution rates.
Yes
Group NF as respirable, biopersistent, rigid HARN with potential to cause mesothelioma.

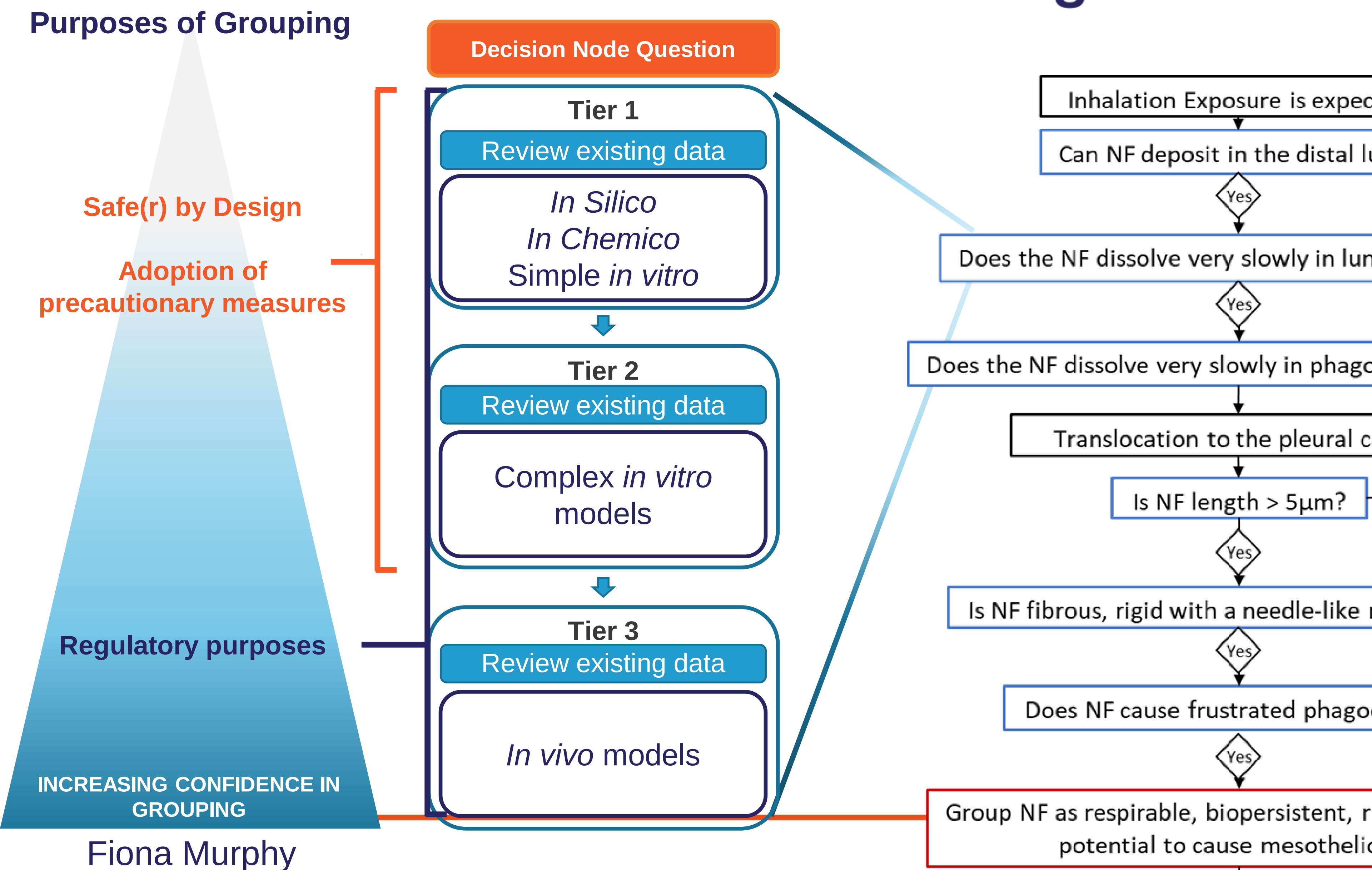


Posters Topic 3: Hazard assessment

ID 1067 - Development of an Integrated Approach to Testing and Assessment for Grouping High Aspect Ratio Nanomaterials Within the EU Project Gracious

Fiona Murphy

Tiered testing strategy



Fiona Murphy

Tailored Testing

Building a tiered testing strategy

Decision Node 1 Question	Decision Node 2 Question	Decision Node 3 Question	Decision Node 4 Question
Tier 1 Review existing data *In Silico* *In Chemico* Simple *in vitro* *Acute ecotox*	**Tier 1** Review existing data *In Silico* *In Chemico* Simple *in vitro* *Acute ecotox*	**Tier 1** Review existing data *In Silico* *In Chemico* Simple *in vitro* *Acute ecotox*	**Tier 1** Review existing data *In Silico* *In Chemico* Simple *in vitro* *Acute ecotox*
Tier 2 Review existing data Complex *in vitro* models Chronic ecotox	**Tier 2** Review existing data Complex *in vitro* models Chronic ecotox	**Tier 2** Review existing data Complex *in vitro* models Chronic ecotox	**Tier 2** Review existing data Complex *in vitro* models Chronic ecotox
Tier 3 Review existing data *In vivo* models Mesocosym	**Tier 3** Review existing data *In vivo* models Mesocosym	**Tier 3** Review existing data *In vivo* models Mesocosym	**Tier 3** Review existing data *In vivo* models Mesocosym

Tiered Testing Strategy

HARN

Can NF deposit in the distal lung?	Does the NF dissolve very slowly in lung lining fluid?	Does the NF dissolve very slowly in lysosomal fluid?	Is NF length >5µm?	Is the NF fibrous, rigid with needle-like morphology?	Does the NF cause frustrated phagocytosis?	Does NF stimulate a similar inflammation response to source material?
Tier 1						
Review existing data sets						
Estimation of D_{ae} from NF size measurements by TEM/SEM and density measurement	Batch dissolution test in lung lining fluid (pH 7.4) or Dissolution in continuous flow system in lung lining fluid (pH 7.4)	Batch dissolution test in lysosomal fluid (pH 4.5) or Dissolution in continuous flow system in lysosomal fluid (pH4.5)	NF size measurements by TEM/SEM	Measure diameter of NF by TEM	Inflammasome activation: • IL-1β release • CathepsinB activity and /or release • Lysosomal Disruption	Inflammation potency: *in vitro* testing using cell lines Acute Endpoints: • Cytotoxicty • Cytokine release
Tier 2						
Review existing data sets						
Measurement of MMAD by cascade impactor from an airborne dispersion of the material Lung deposition modelling: • Multiple Particle Path Deposition Model • FIBROS		Durability in cellular systems	NF size measurements by TEM/SEM from an airborne dispersion of the material	Measurement of flexural rigidity by dynamic scanning electron microscopy	*In vitro* granuloma formation	*In vitro* incubation with co-culture models of macrophages and mesothelial cells or 3D microtissue models Acute Endpoints: · Cytokine release Chronic: · Granuloma formation
Tier 3						
Review existing data sets						
		Lung burden measurement after *in vivo* instillation or inhalation studies		'Biologically stiff' NF determined experimentally by morphological assessment and size measurements after *in vitro* incubation with macrophages.		Intraperitoneal/ Intrapleural instillation: Acute Endpoint: • inflammation, Chronic: • Fibrotic lesion • Mesothelioma

Where they go

What they do

Review existing data

Tier 1

Batch dissolution test in lysosomal fluid (pH 4.5)
or
Dissolution in continuous flow system in lysosomal fluid (pH4.5)

Review existing data

Tier 2

Durability in cellular systems

Review existing data

Tier 3

Lung burden measurement after *in vivo* instillation or inhalation studies

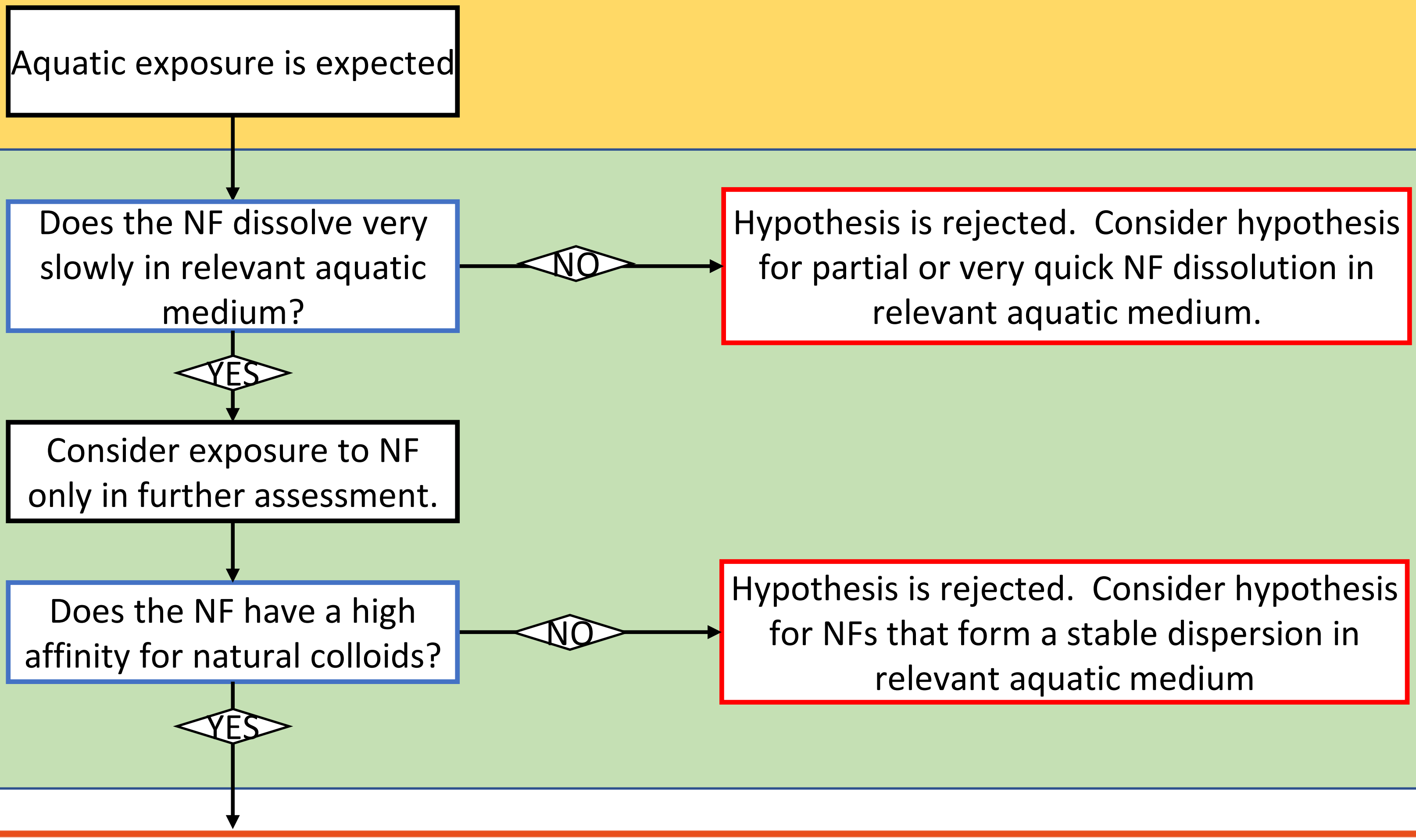
Persistent and unstable NFs in aquatic compartment:

Following aquatic exposure, NF are deposited to sediments where lethal and sub-lethal toxicity to sediment species can occur.

Purpose: Targeted testing, regulatory **Context:** Aquatic environments	
Input from life cycle Release to aquatic environment	**What they are?** NFs with a slow/partial dissolution rate that have a high affinity for natural colloids in aquatic compartments.
	Where they go? Removed from the aquatic compartment and deposited to sediment compartments (via sedimentation).
	What they do? Persist in sediment compartments resulting in lethal and sub-lethal toxicity to representative sediment species.

Persistent and unstable NFs in aquatic compartment:

Following aquatic exposure, NF are deposited to sediments where lethal and sub-lethal toxicity to sediment species can occur.



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Do NFs remain unchanged in dispersion without chemical transformation into “new” NFs?

NO

Hypothesis is rejected: Characterise/model the transformation process(es) and assess the “new” NFs.

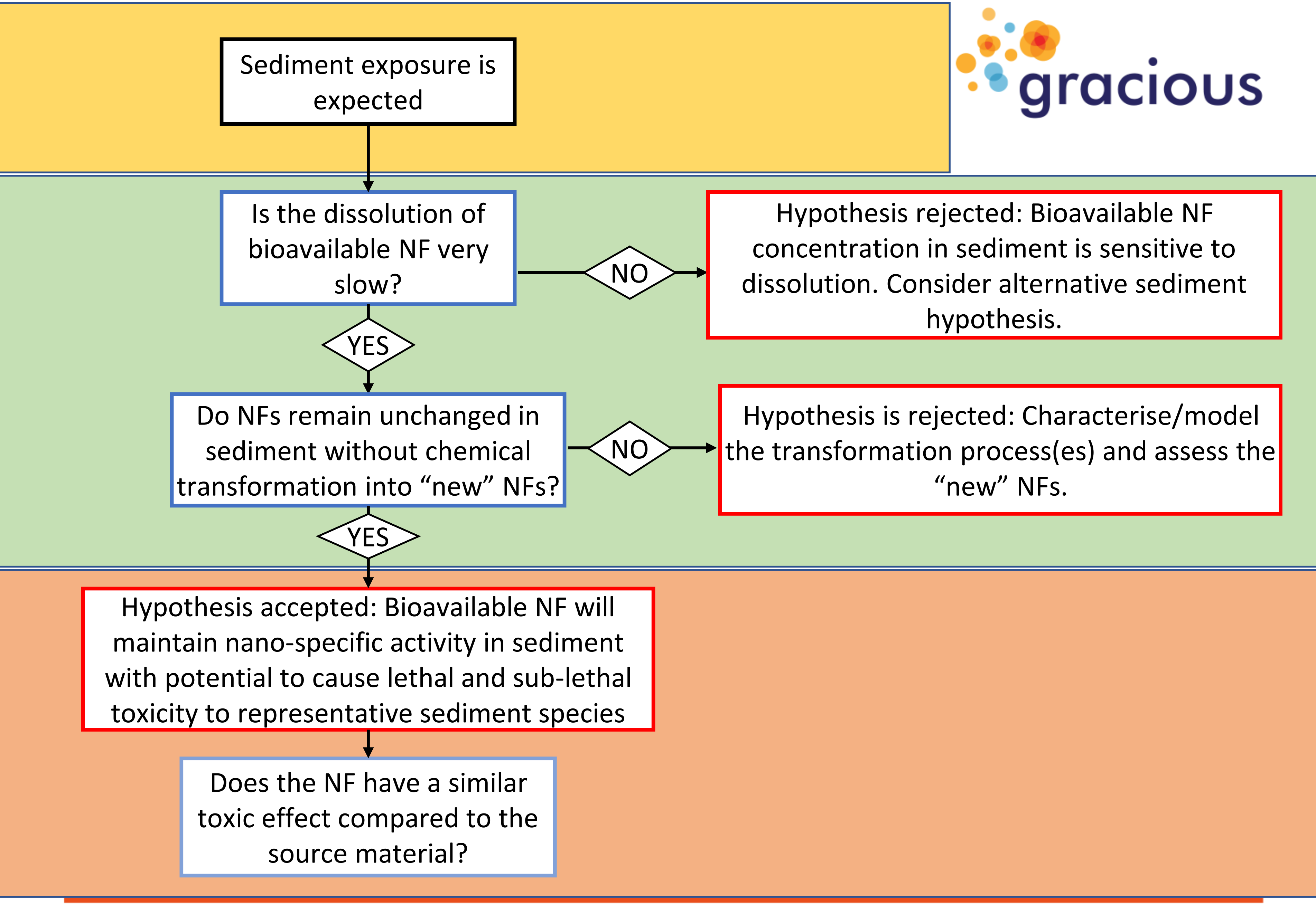
YES

Hypothesis is accepted: NF in this group will be removed from the aquatic compartment. Consider sediment-specific hypotheses in further assessment.

CONTEXT SWITCH

Persistant bioavailable NFs: Following sediment exposure, NFs will maintain nano-specific activity and can cause lethal and sub-lethal toxicity to representative sediment species.

Sediment exposure is expected


Sediment exposure is expected
Is the dissolution of bioavailable NF very slow?
NO
Hypothesis rejected: Bioavailable NF concentration in sediment is sensitive to dissolution. Consider alternative sediment hypothesis.
YES
Do NFs remain unchanged in sediment without chemical transformation into “new” NFs?
NO
Hypothesis is rejected: Characterise/model the transformation process(es) and assess the “new” NFs.
YES
Hypothesis accepted: Bioavailable NF will maintain nano-specific activity in sediment with potential to cause lethal and sub-lethal toxicity to representative sediment species
Does the NF have a similar toxic effect compared to the source material?

Tiered Testing Strategy

Tier 1

Review existing data

Acute sediment toxicity assays
e.g. *Vibrio fischeri* microtox assay, *Caenorhabditis elegans* sediment toxicity assay.

https://www.zmescience.com/medicine/scientists-increase-worms-lifespan-by-500/

Tier 2

Review existing data

Chronic single-species sediment toxicity tests
e.g. *Lumbriculus variegatus, Chironomus riparius* OECD TG

https://blogs.uef.fi/ecotox/2016/06/27/hands-on-research-with-chironomus-riparius/

Tier 3

Review existing data

Chronic single-species assays w/aged NF.
Microcosm/mesocosm

https://www.fera.co.uk/chemical-regulation/ecotoxicology/mesocosm-studies

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Approaches to similarity

- There are several methods being developed to assess similarity
- Similarity by bandings (fixed)
  - E.g. OECD TG318 proposes banding of dispersion stability
    - <10% | 10 to 50% | 50 to 90% | >90%
  - Fixed/bandings require clear thresholds which are difficult to justify
  - Fixed thresholds lead to problems with cases that lie close to the threshold/cut-off.
- Similarity by relative difference (floating)
  - E.g. to be in Group B, ROS production by NFs must be within a 5-fold range of each other (or a target NF) according to protocol x.x.1
  - Reduce issues associated with NFs that are close to a threshold/cut-off
  - Requires consideration of what dissimilarity is acceptable between NFs to allow them to be grouped

Approaches to similarity

- The GRACIOUS Framework generates a data matrix containing several relevant endpoints
  - A similarity assessment needs to be generated across all NFs per endpoint/assay
- To facilitate a similarity assessment even a single property often requires data reduction
  - A size distribution → D50 median size;
  - dose-response → BMD20 or EC50 or …
- "Acceptable dissimilarity" must consider:
  - measurement accuracy
  - biological relevance of dissimilarity
  - dose metrics
    - E.g. Surface area vs Mass
- Calibration of a case study tier 1 data with existing tier 3 data is required

Similarity historical example

Biologically relevant x-fold differences: fiber biodissolution

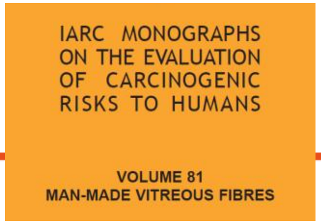
Table 65. Lung biopersistence, in-vitro dissolution and pathogenicity of selected fibres from inhalation studies in rats

Fibre		Biopersistence: fibres > 20 µm in length; lung clearance rates				In-vitro dissolution (k_{dis}) at pH 7.4 (pH 4.5)*	Pathogenicity (chronic inhalation)		
		Slower pool (T½)	WT½ (days)	90% clearance (T_{90}, days)	Reference		Lung fibrosis	Thoracic tumours	Reference
Amosite	Asbestos	1160	418	2095	Hesterberg *et al.* (1998a)	< 1	+	+	McConnell *et al.* (1999)
Crocidolite[d]	Asbestos	0	817	2770	Hesterberg *et al.* (1996a)	< 1	+	+	McConnell *et al.* (1994)
MMVF32	E Glass wool	179	79	371	Hesterberg *et al.* (1998a)	9 (7)	+	+	Davis *et al.* (1996a)
RCF1a[a]	Refractory ceramic fibre	88	55	227	Hesterberg *et al.* (1998a)	3	+	+	Mast *et al.* (1995a,b)
MMVF33	475 Glass wool	155	49	240	Hesterberg *et al.* (1998a)	12 (13)	+	+/–[b]	Davis *et al.* (1996a); McConnell *et al.* (1999)
MMVF21	Rock (stone) wool (96)	613	91	206	Hesterberg *et al.* (1996a)	20 (72)	+	–	McConnell *et al.* (1994)
MMVF21	Rock (stone) wool (98)	95	67	264	Hesterberg *et al.* (1998a)				
MMVF10[d]	901 Glass wool (96)	0	37	123	Hesterberg *et al.* (1996a)	300 (329)	–	–	Hesterberg *et al.* (1993)
MMVF10.1[c]	901 Glass wool	30	14.5	69	Hesterberg *et al.* (2002)		–	–	McConnell *et al.* (1999)

As Kdis increases from 13 to 329 (25-fold) the pathogenicity becomes qualitatively different.

Pathogenicity is moderately different at k=72 (5-fold)

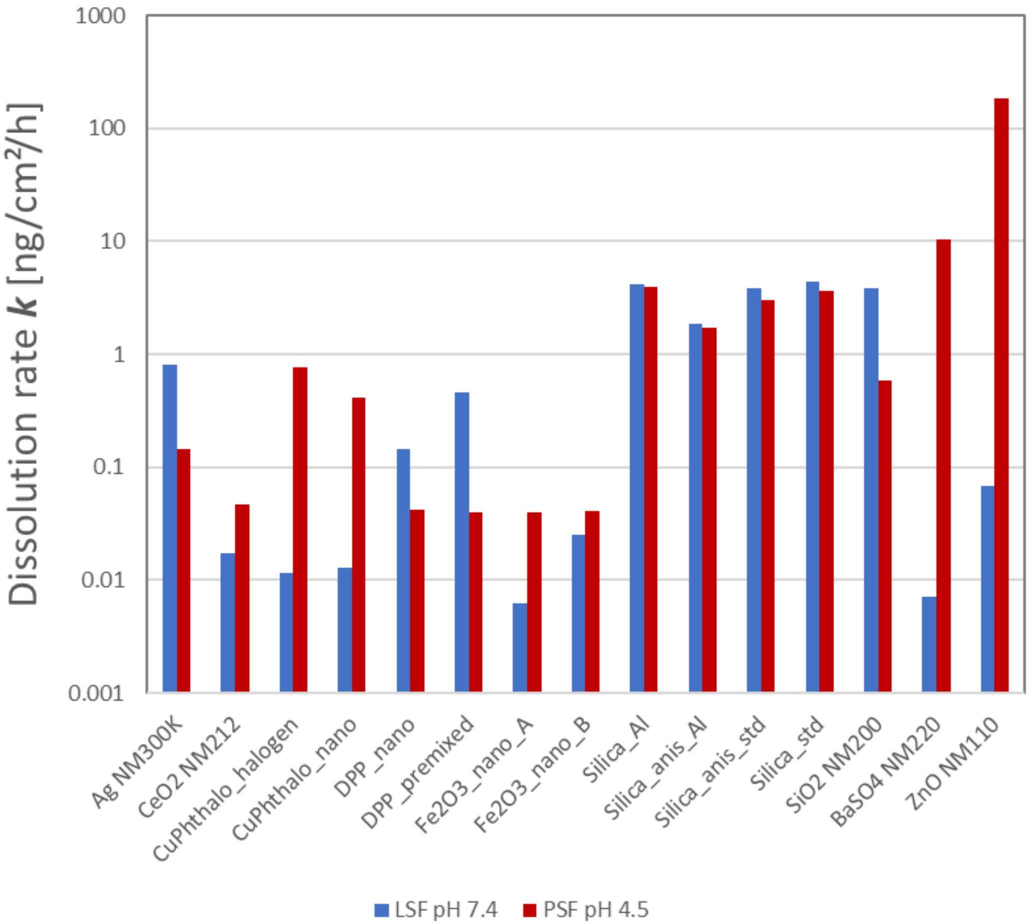
If values are > 5-fold different, then the values are not similar (close to a biological threshold of HARN effects).



Similarity Case Study

Biologically relevant x-fold differences: NF biodissolution

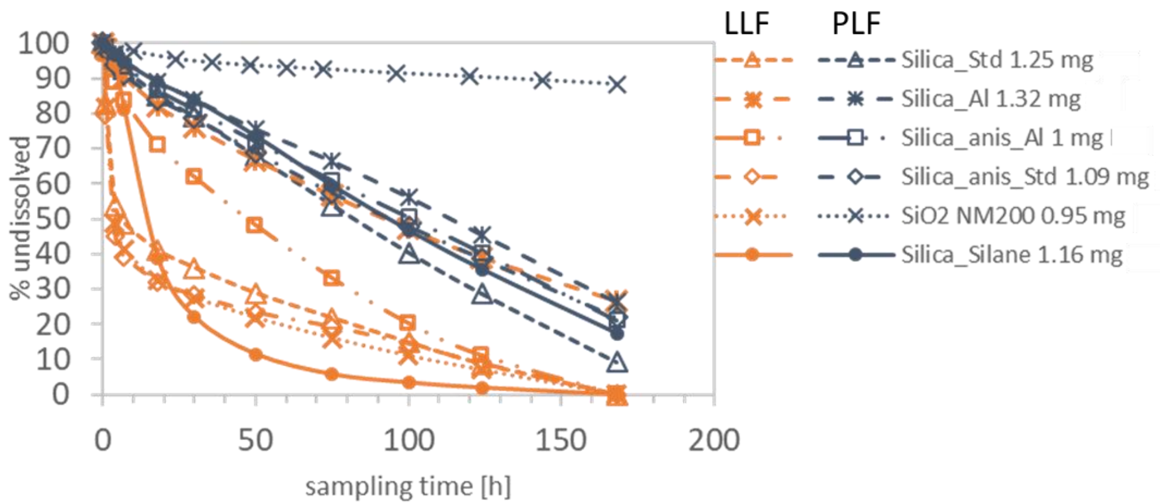
- Assess dissolution in
  - lung lining simulant fluid (LSF) pH7.4
  - Phagolysosomal simulant fluid (PSF) pH4.5
- Tested 17 NFs of silica, organic and inorganic pigments
- Benchmarked against
  - **TiO_2 - very slow** dissolution rate
  - **$BaSO_4$ - partial** dissolution
  - **ZnO - quick** dissolution.
- Assessed dissimilarity of dissolution halftime.



Similarity Case Study

Biologically relevant x-fold differences: NF biodissolution

- Dissolution divides the colloidal silica NFs into
  - group with Al-doping
  - group w/o Al doping.
  - NM200 remains separate
- Shape & silane treatment less important!



half time	Silica_std	Silica_anis_std	Silica_Al	Silica_anis_Al	Silica_silane	SiO2 NM200
	LSF pH 7.4					
Silica_std		1.96	7.28	5.78	1.26	8.29
Silica_anis_std	1.16		3.72	2.95	1.55	4.24
Silica_Al	1.07	1.08		1.26	5.78	1.14
Silica_anis_Al	1.03	1.13	1.04		4.59	1.44
Silica_silane	1.08	1.26	1.16	1.12		8.29
SiO2 NM200	9.03	7.76	8.41	8.74	9.77	
	PSF pH 4.5					

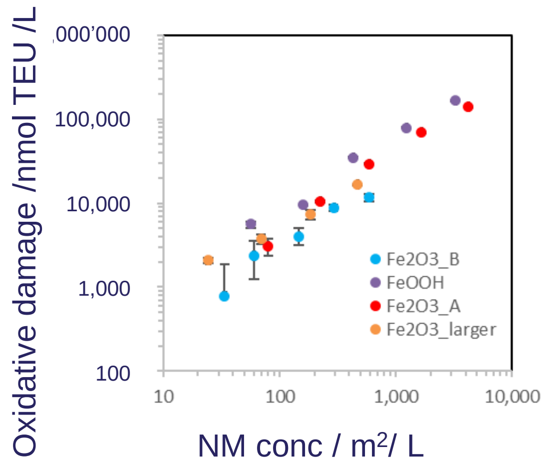
similar dissimilar

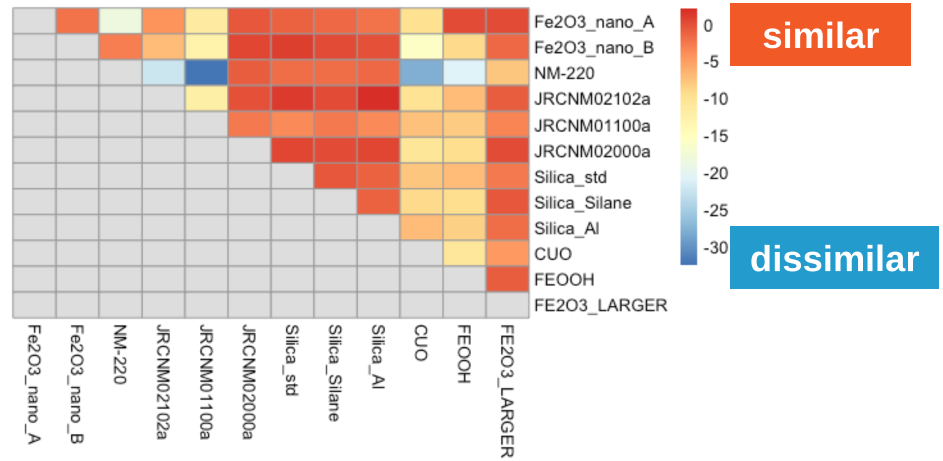
J. Keller

Pairwise similarity matrix

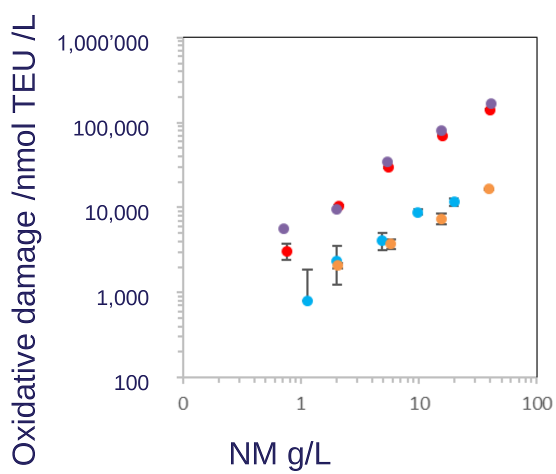
Case study: FRAS assay

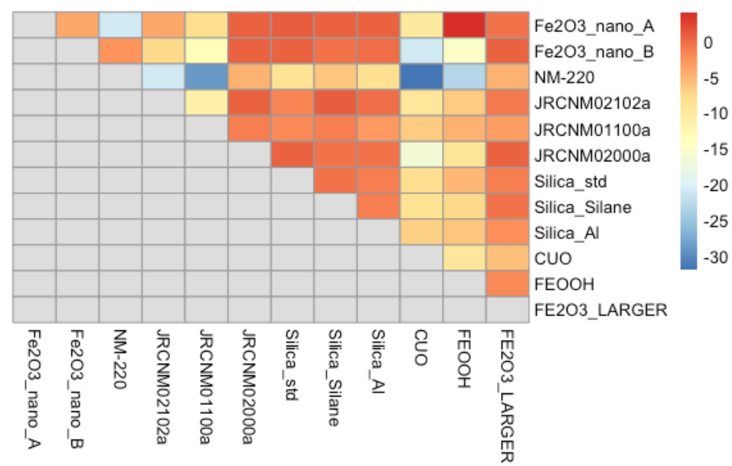
Surface dose





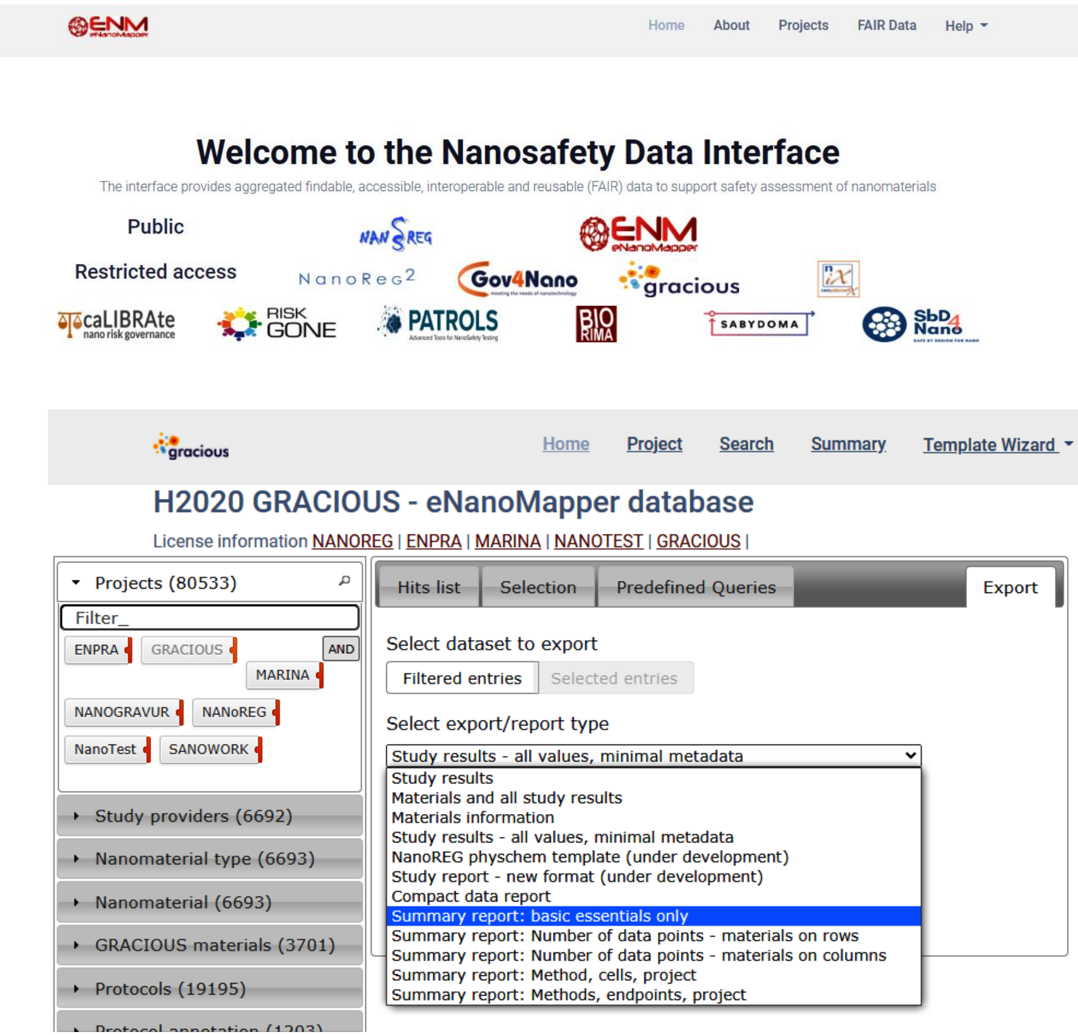
Mass dose





GRACIOUS eNanoMapper

Using existing and new data



Data to support GRACIOUS Framework

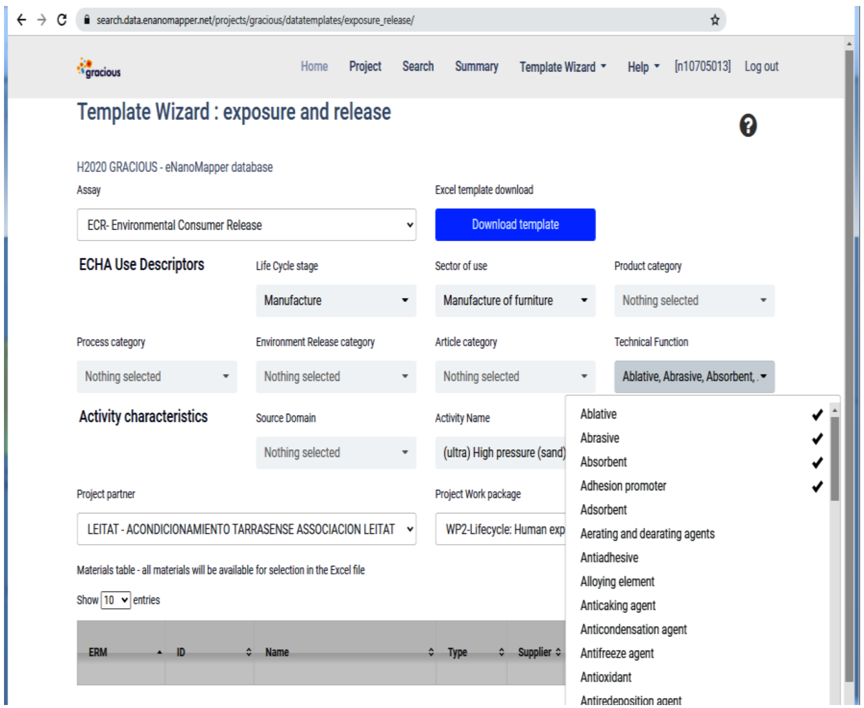
- Phys-chem
- Cell viability, oxidative stress, reactivity
- Harmonized templates and terminology
- Nanomaterial similarity
- Range of output formats
- All data is used by the blueprint test environment

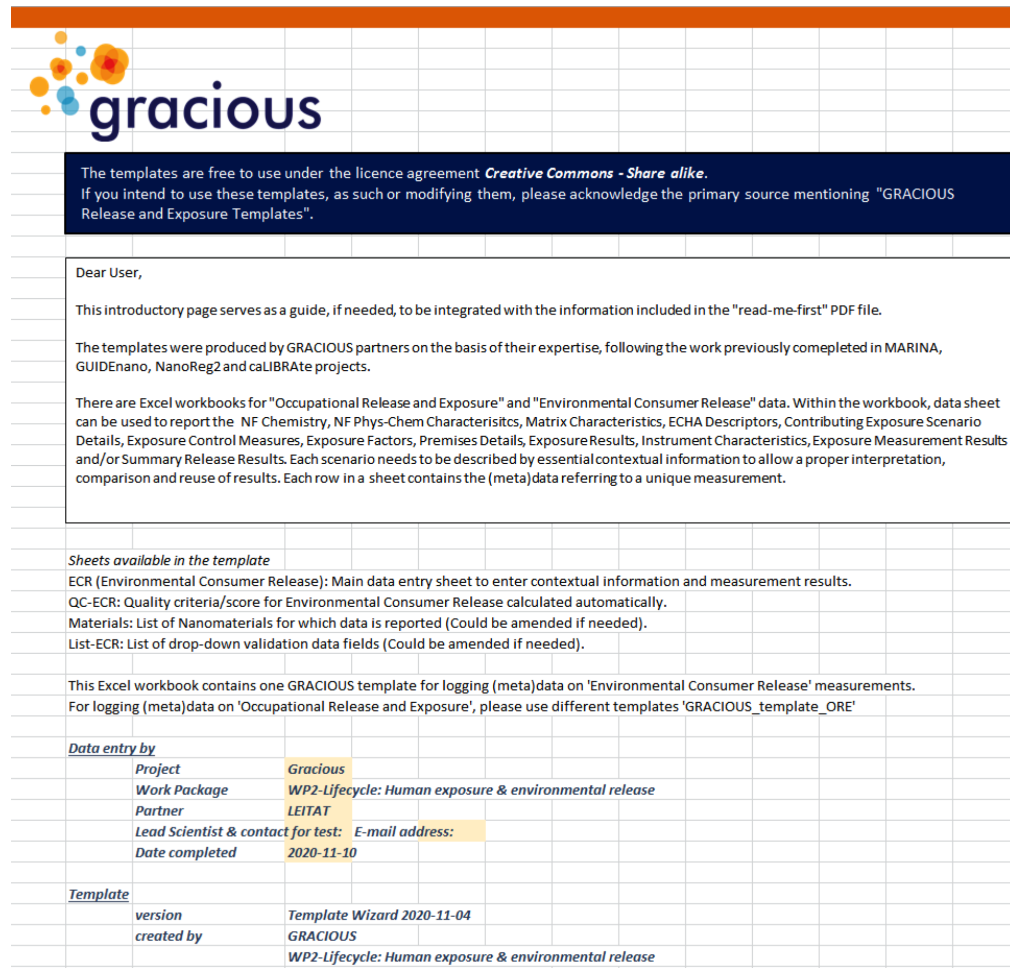
https://search.data.enanomapper.net/projects/gracious

Nina Jeliazkova

Release and exposure

Templates with quality scores




gracious

The templates are free to use under the licence agreement ***Creative Commons - Share alike***.
If you intend to use these templates, as such or modifying them, please acknowledge the primary source mentioning "GRACIOUS Release and Exposure Templates".

Dear User,

This introductory page serves as a guide, if needed, to be integrated with the information included in the "read-me-first" PDF file.

The templates were produced by GRACIOUS partners on the basis of their expertise, following the work previously comepleted in MARINA, GUIDEnano, NanoReg2 and caLIBRAte projects.

There are Excel workbooks for "Occupational Release and Exposure" and "Environmental Consumer Release" data. Within the workbook, data sheet can be used to report the NF Chemistry, NF Phys-Chem Characterisitcs, Matrix Characteristics, ECHA Descriptors, Contributing Exposure Scenario Details, Exposure Control Measures, Exposure Factors, Premises Details, Exposure Results, Instrument Characteristics, Exposure Measurement Results and/or Summary Release Results. Each scenario needs to be described by essential contextual information to allow a proper interpretation, comparison and reuse of results. Each row in a sheet contains the (meta)data referring to a unique measurement.

Sheets available in the template
ECR (Environmental Consumer Release): Main data entry sheet to enter contextual information and measurement results.
QC-ECR: Quality criteria/score for Environmental Consumer Release calculated automatically.
Materials: List of Nanomaterials for which data is reported (Could be amended if needed).
List-ECR: List of drop-down validation data fields (Could be amended if needed).

This Excel workbook contains one GRACIOUS template for logging (meta)data on 'Environmental Consumer Release' measurements.
For logging (meta)data on 'Occupational Release and Exposure', please use different templates 'GRACIOUS_template_ORE'

Data entry by

Project	*Gracious*	
Work Package	*WP2-Lifecycle: Human exposure & environmental release*	
Partner	*LEITAT*	
Lead Scientist & contact for test:	*E-mail address:*	
Date completed	*2020-11-10*	

Template

version	*Template Wizard 2020-11-04*
created by	*GRACIOUS*
	WP2-Lifecycle: Human exposure & environmental release

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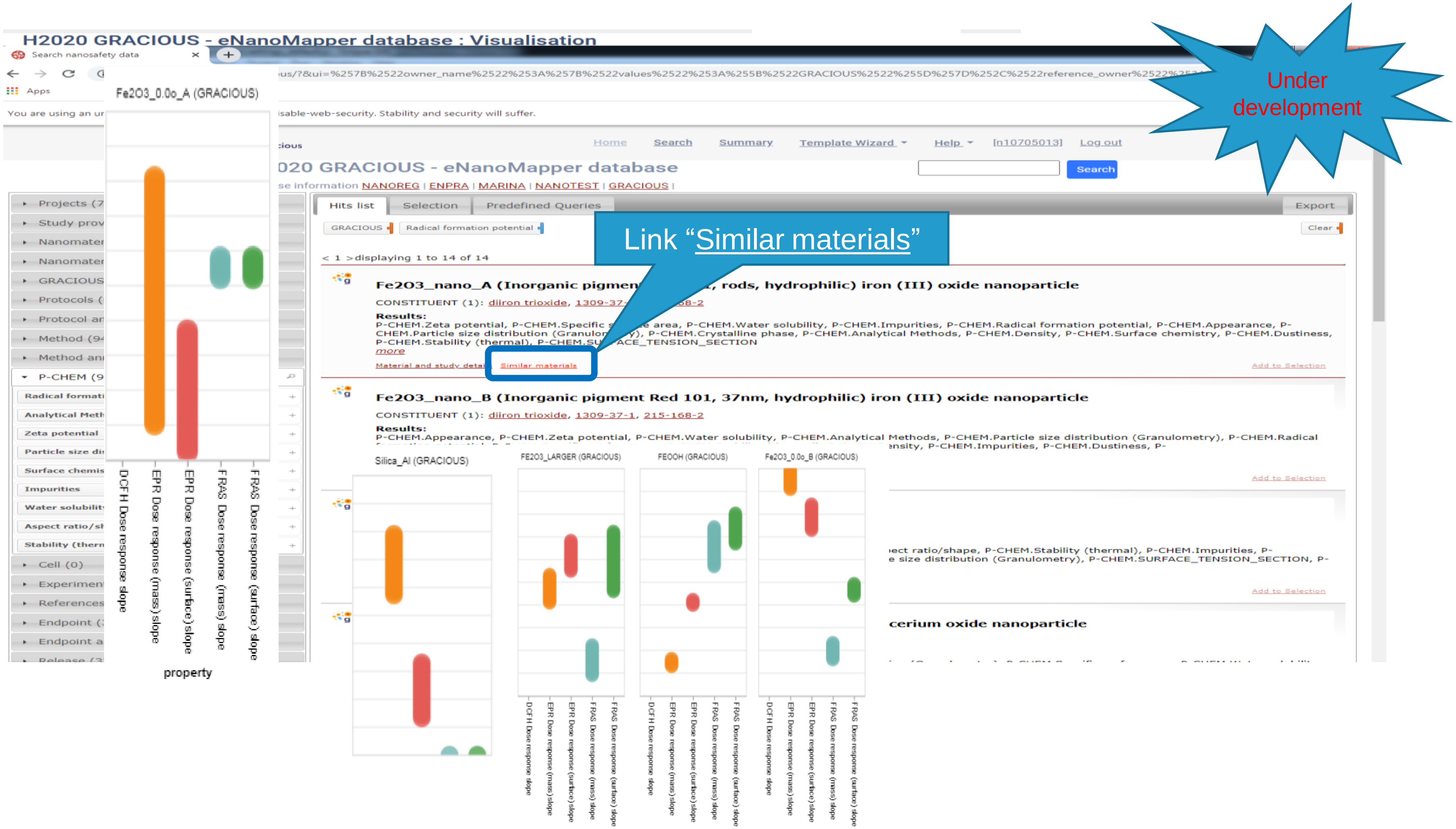
Exploratory multidimensional similarity analysis

Data similarity - eNanoMapper



Nina Jeliazkova

Presentation structure

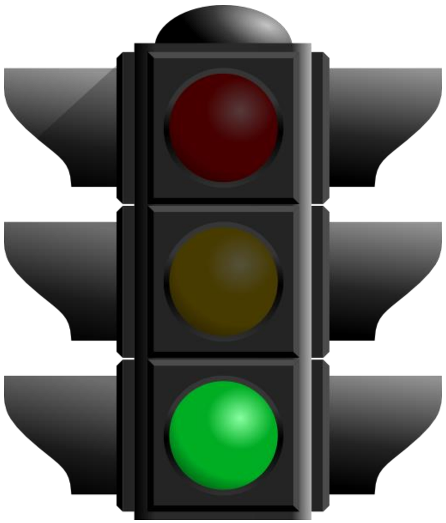
- An overview of the GRACIOUS Framework
- Examples grouping hypotheses
- Example Integrated Approaches to Testing and Assessment
- Similarity
- Database links
- Quality
- Blueprint

Data quality assessment methodology

Developed methodology to assess data quality aimed at reducing as much as possible the need of expert judgment.

The methodology takes into account the following criteria:

- **data completeness**;
- **data reliability**;
- **data relevance**;
- **data adequacy**.
- Scores are calculated for each of these criteria and those are aggregated into a **quality score** and a **completeness score**.



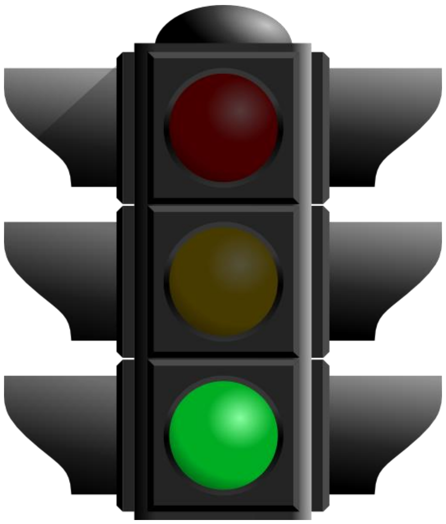
Data quality assessment methodology

The last step involves the assignment of final data quality and completeness scores to a traffic light system.

Green – data high quality

Yellow – data is sufficient quality, but needs further consideration to be used for a specific task

Red – data is of insufficient quality.



The whole process can be automised.

Data quality is highlighted on eNanoMapper user interface and/or in templates when uploading/downloading data from the database.

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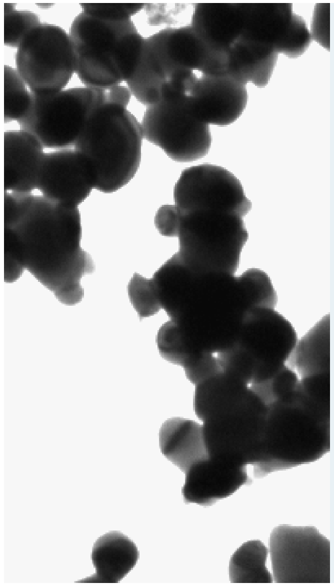


gracious blueprint 0.1

This tool is used to test the gracious framework and blueprint.

Learn more »

Getting started

To use this tool and get started you will need an account.

Ask for an account »

If you already have an account please:

Login »

Project

This tool is used within the GRACIOUS project funded from the European Union´s H2020 Framework Programme under grant agreement №760840

GRACIOUS project »

Development

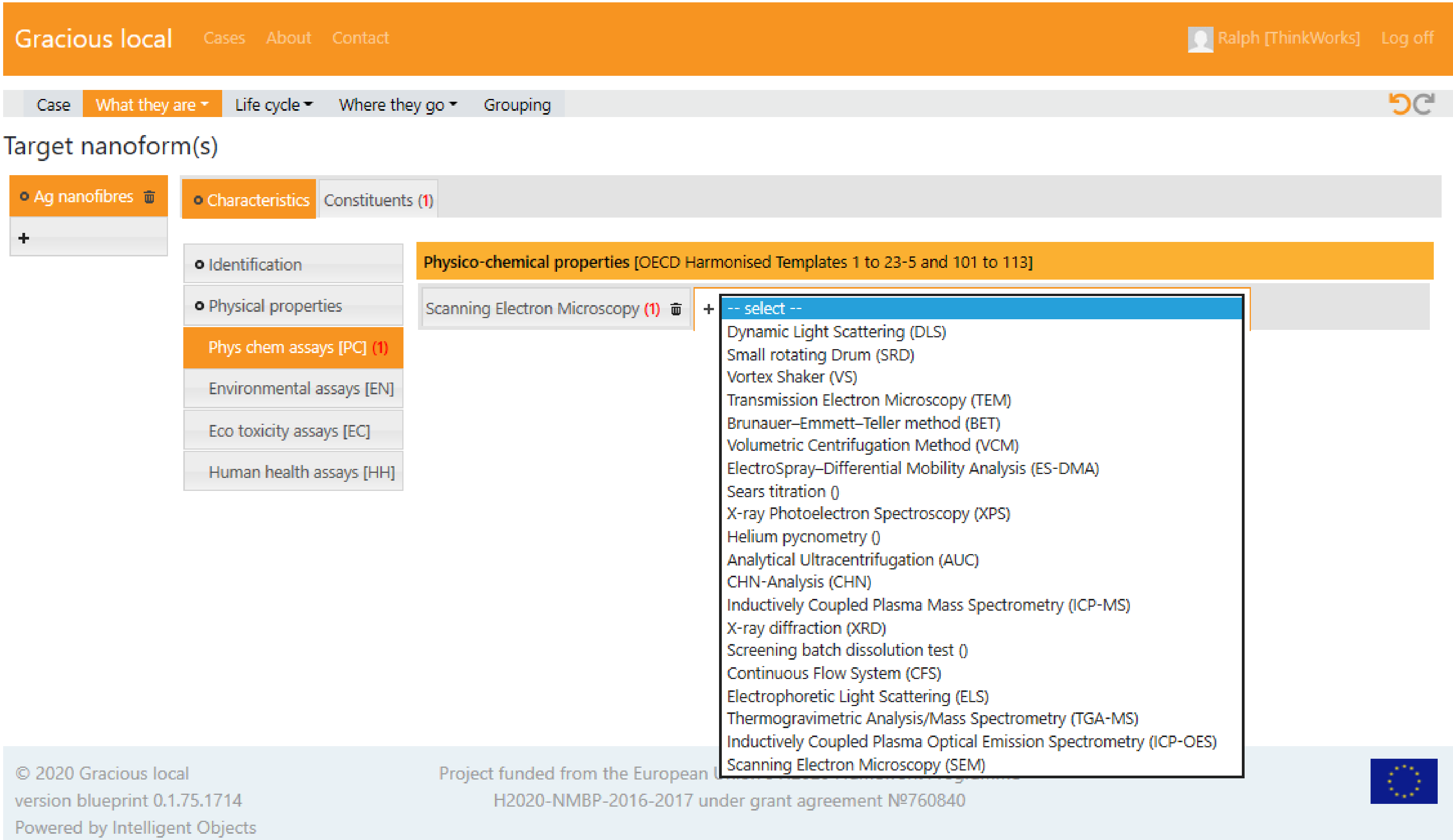
This tool is developed using ThinkWorks Intelligent Objects engine.

ThinkWorks »

version blueprint 0.1.75.1714
Powered by Intelligent Objects

Project funded from the European Union´s H2020 Framework Programme
H2020-NMBP-2016-2017 under grant agreement №760840

Ralph Vanhauten


Gracious local
Cases
About
Contact
Ralph [ThinkWorks]
Log off
Case
What they are
Life cycle
Where they go
Grouping
Target nanoform(s)
Ag nanofibres
Characteristics
Constituents (1)
Identification
Physical properties
Phys chem assays [PC] (1)
Environmental assays [EN]
Eco toxicity assays [EC]
Human health assays [HH]
Physico-chemical properties [OECD Harmonised Templates 1 to 23-5 and 101 to 113]
Scanning Electron Microscopy (1)
-- select --
Dynamic Light Scattering (DLS)
Small rotating Drum (SRD)
Vortex Shaker (VS)
Transmission Electron Microscopy (TEM)
Brunauer–Emmett–Teller method (BET)
Volumetric Centrifugation Method (VCM)
ElectroSpray–Differential Mobility Analysis (ES-DMA)
Sears titration ()
X-ray Photoelectron Spectroscopy (XPS)
Helium pycnometry ()
Analytical Ultracentrifugation (AUC)
CHN-Analysis (CHN)
Inductively Coupled Plasma Mass Spectrometry (ICP-MS)
X-ray diffraction (XRD)
Screening batch dissolution test ()
Continuous Flow System (CFS)
Electrophoretic Light Scattering (ELS)
Thermogravimetric Analysis/Mass Spectrometry (TGA-MS)
Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES)
Scanning Electron Microscopy (SEM)
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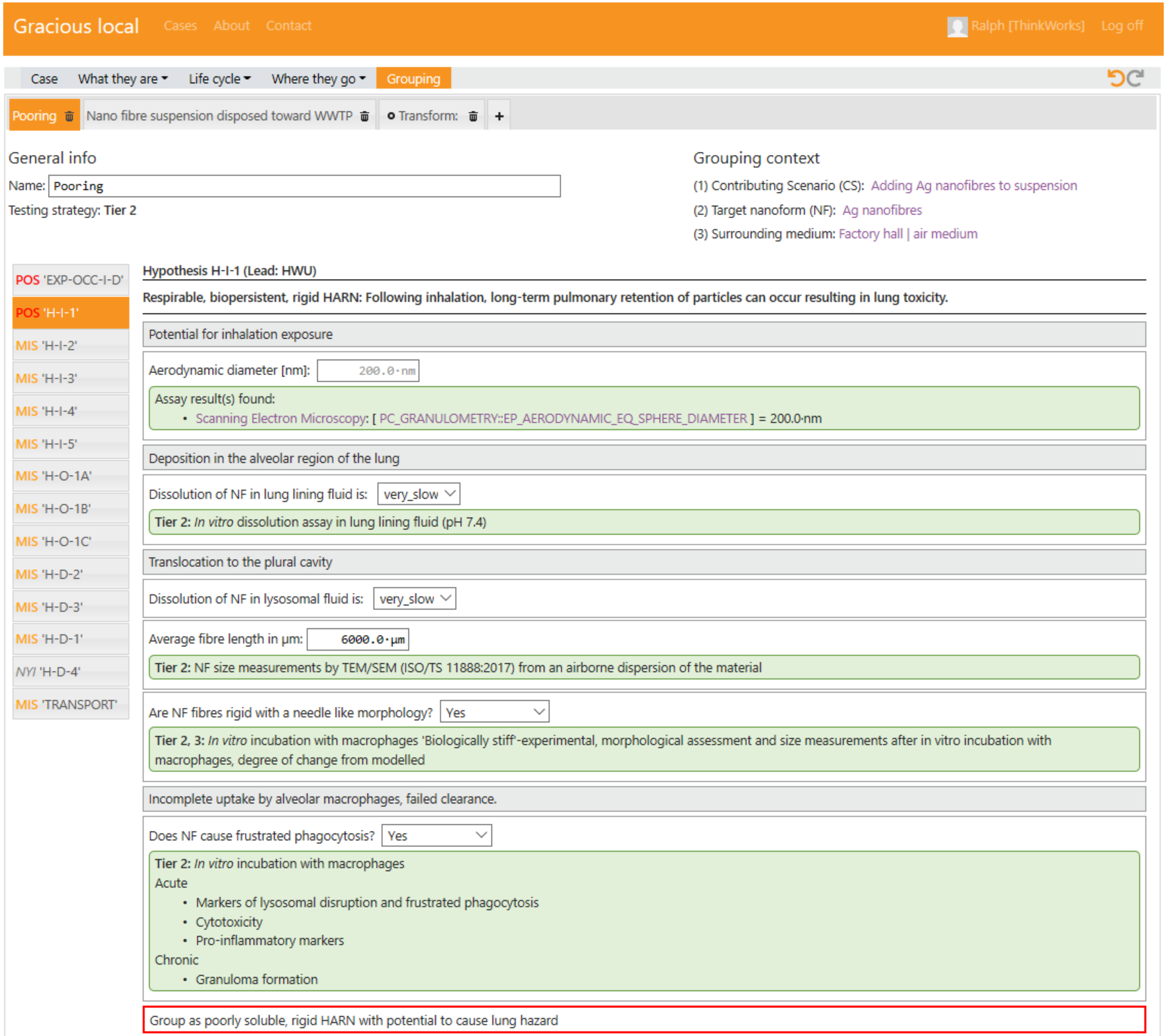


Ralph Vanhauten

Current status

- Hypotheses
  - Pre-defined list complete
  - User-defined template complete
- IATAs
  - Human complete
  - Environment complete

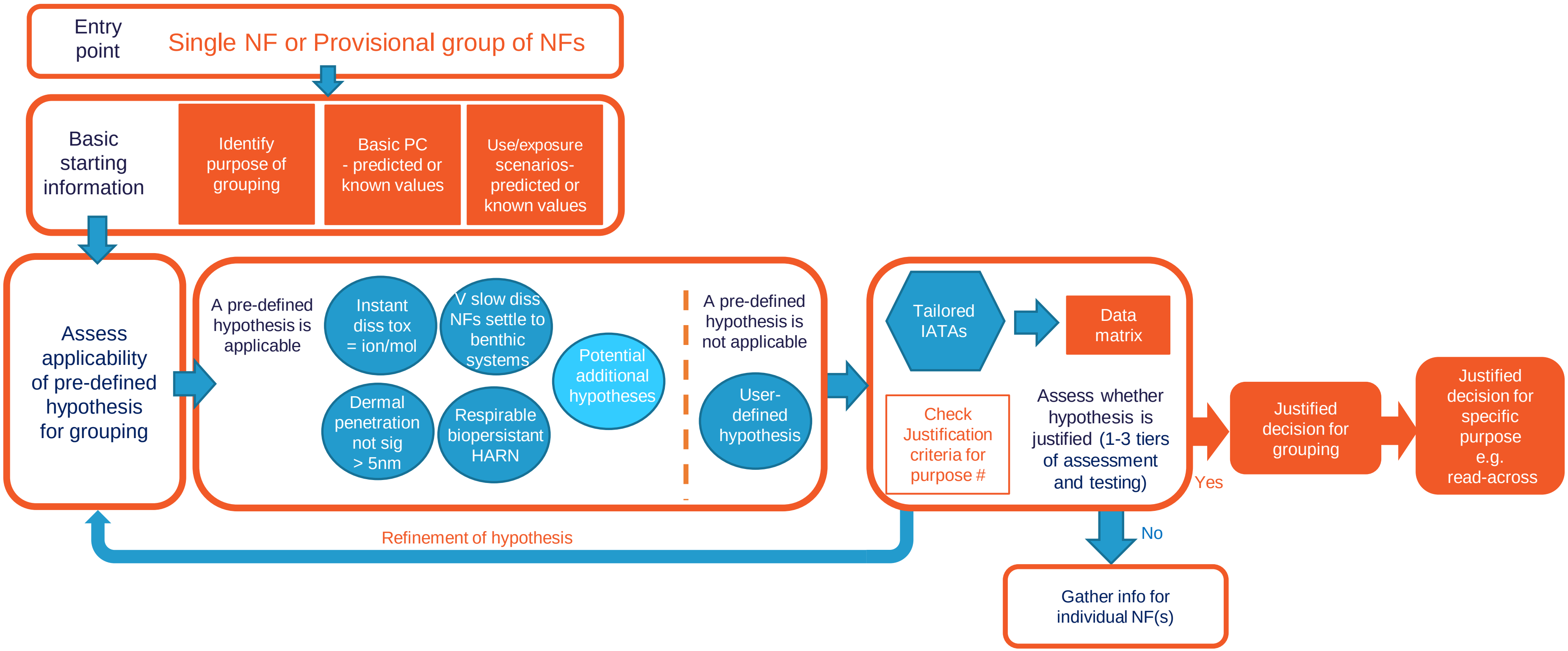
- Blueprint of software
  - Machine readable and open access
  - Integrates hypotheses, IATAs and data sources
  - Software undergoing internal testing

- Similarity methodology
- Quality criteria incorporation
- Blueprint and Framework testing
- Guidance document editing

There is still time to get involved in testing the GRACIOUS IATAs and Framework using your own case studies

GRACIOUS Framework

Detailed form



Justification criteria are purpose specific. i.e. less stringent for SbD than for RA or legislation

Thank you!

We look forward to hearing your ideas

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www.h2020gracious.eu