

GRACIOUS Hypotheses and IATAs

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Start

Level 1a: Basic information: What they are, intended use, relevant exposure route & environmental compartment

Purpose or context: targeted testing, regulatory, precautionary or safe-by-design

* If purpose or context is regulatory, than assess per endpoint



Level 1b: Check if hypothesis with clear implications apply

Quickly dissolving NFs

For dermal exposure: NFs >5 nm

Respirable biopersistent rigid HARN

NFs incorporated into a solid matrix

If in group: read across, waiving, limit exposure or re-

If not in group: continue to Level 1c

Level 1c: Choose or generate basic hypothesis

Life Cycle

What they are?
Group description:

Where they go?
Predictive for:

What they do? Predictive for:

Trigger IATA

If in group: read across, waiving, limit exposure or re-

If not in group: use/generate alternative hypothesis

Assess additional information

Specify purpose or context in view of available information, including potential source materials, and data gaps

Weigh efforts for grouping against direct testing (for relevant endpoint

Level 2: Refine hypothesis

Life Cycle

What they are?
Group description:

Where they go? Predictive for:

What they do?
Predictive for:

Trigger IATA (*in vitro* and *in silico*/modelling) **If in group:** read-across, waiving or limit exposure **If not in group:** use/generate alternative hypothesis

Level 3: Further refine hypothesis in view of purpose/context

Trigger IATA (specific testing, incl. *in vivo* toxicity or ecotoxicity or specific lifecycle scenarios)

Draft Framework

Presented by Agnes Oomen

Final version to be delivered 2021

Grouping that meets needs, with justification

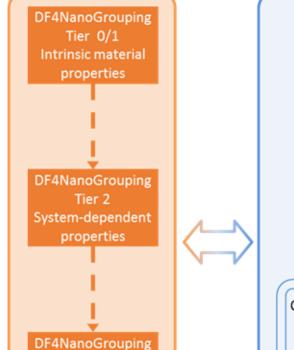
Group sufficiently substantiated for purpose? NF in group sufficiently justified?

Weight of evidence not enough for grouping

Generate alternative hypothesis

Information gathering for individual NF

Generating the First Draft



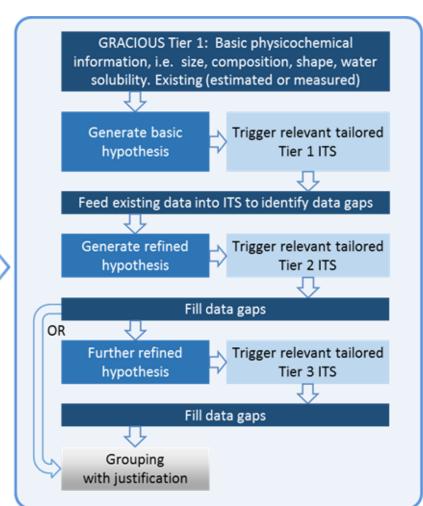
Tier 3

Biopersistence,

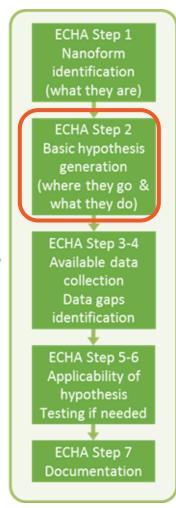
uptake, and biodistribution

Cellular and apical

toxic effects







ECHA
require a
hypothesis
driven
approach

ECHA Guidance on Grouping





Appendix R.6-1 for nanomaterials applicable to the Guidance on OSARs and Grouping of Chemicals

Version 1.0 May 2017

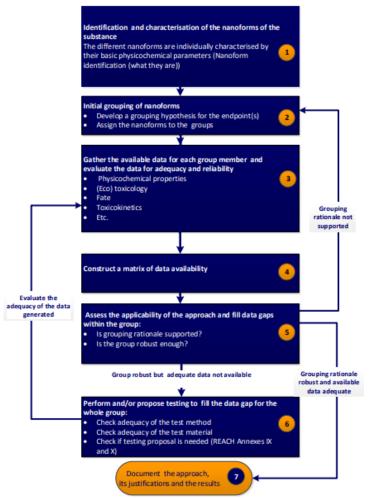


- Follows updated OECD 2014 Guidance on **Grouping of Chemicals**
- States that general concepts on grouping of chemicals are applicable to nanomaterials
- Describes a stepwise approach in which nanoforms are grouped
- Outlines the general principles to gather and combine information on:
 - physicochemical properties,
 - toxicokinetic
 - (eco)toxicological behaviour
 - expert judgement



ECHA Guidance on Grouping





"By seeking similarities in physicochemical properties, toxicokinetic behaviour and fate, and (eco)toxicological behaviour between different nanoforms,

mainly using physicochemical parameters and/or in vitro screening methods,

it may be possible to develop a robust scientific explanation, which supports the assumption of similar hazard properties within a defined group of nanoforms"

https://echa.europa.eu/documents/10162/23036412/appendix_r6_nanomaterials_en.pdf

Grouping Framework Design Identification and characterisation of the nanoforms of the **ECHA Guidance on Grouping –** substance The different nanoforms are individually characterised by hypothesis driven their basic physicochemical parameters (Nanoform identification (what they are)) Initial grouping of nanoforms Develop a grouping hypothesis for the endpoint(s) Assign the nanoforms to the groups Develop a grouping hypothesis for the endpoint(s) Gather the available data for each group member and evaluate the data for adequacy and reliability Physicochemical properties 3 (Eco) toxicology Fate: Toxicokinetics Grouping Etc. rationale not supported Construct a matrix of data availability

pluste the

GRACIOUS framework - Hypothesis Driven



There are many ways to word and formulate a

To provide guidance to the user GRACIOUS has

developed a Hypothesis Template

Purpose: Precautionary, Targeted testing, Regulatory, Safety by Design

Context: Occupational, Consumer, Environmental

Input from life cycle (WP2)

- Physical form when being handled (powder, suspension/liquid/ embedded in solid matrix, ...)
- Stability (agglomeration, solubility...)
- Exposure form (quasi-spherical, elongated, plate, pure, attached to a particle, embedded in a matrix, ionic form)
- Intended use, specific process (occupational)
- Environmental compartment where they are released (workplace atmosphere, outdoors atmosphere, water, soil as waste)
- · Population exposed
- Exposure route
- Exposure dose. This can be unfolded in several tiers:
- Qualitative; unlikely, negligible, likely
- Quantitative; short/peak exposure, long-term exposure

Potential implications:

if in group:

if not in group:

What they are? (WP3)

Physicochemical identity

Where they go? (WP4)

Environmental fate, uptake and toxicokinetics

What they do? (WP5)

Human and environmental toxicity

Purpose

hypothesis

- Precautionary
- Targeted testing
- Regulatory
- Safety by design
- Context
 - Occupational
 - Consumer
 - Environmental

GRACIOUS framework - Hypothesis Driven



Purpose: Precautionary, Targeted testing, Regulatory, Safety by Design

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What they do? (WP5)

luman and environmental toxicity

• Input from life cycle

- Physical form where handled (e.g. powder)
- Stability (e.g. agglomeration, solubility)
- Exposure form (e.g. spherical, elongated, plate)
- Intended use
- Environmental compartment to which released
- Population exposed
- Exposure route
- Exposure dose

GRACIOUS framework - Hypothesis Driven



Purpose: Precautionary, Targeted testing, Regulatory, Safety by Design

Context: Occupational, Consumer, Environmental

Input from life cycle (WP2)

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- What they are?
 - Physicochemical identity
- Where they go?
 - Environmental fate, uptake and toxicokinetics
- What they do?
 - Human and environmental toxicity

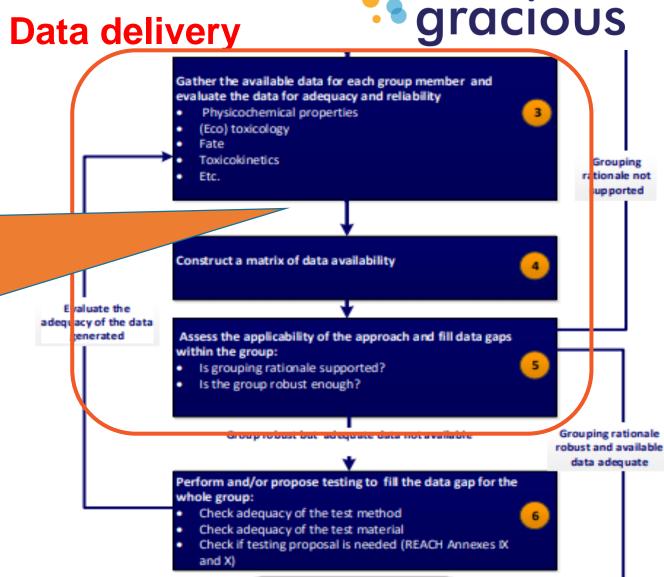
ECHA Guidance on Grouping – Data delivery

Gather available data

- Physicochemical
- (Eco) toxicological
- Fate
- Toxicokinetics etc

Construct a matrix of data availability

Assess the applicability of the approach Fill data gaps within the group



ECHA Guidance on Grouping – Data delivery

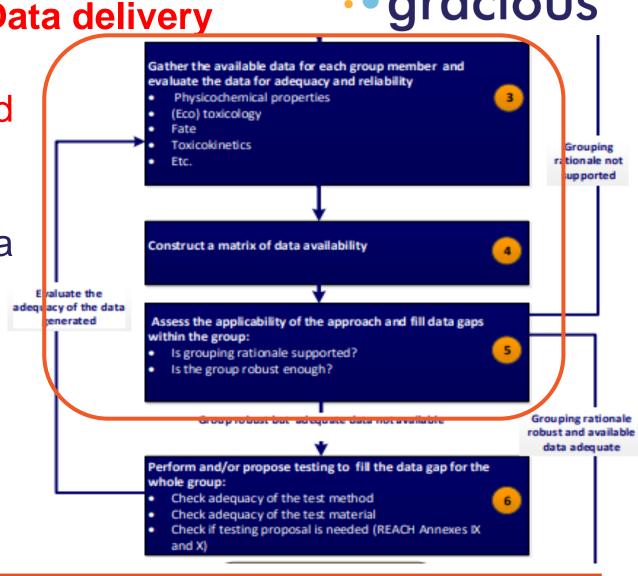
 GRACIOUS will develop Integrated Approaches to Testing and Assessment in order to

Identify and utilise the existing data

Identify essential data gaps

Strategically fill data gaps

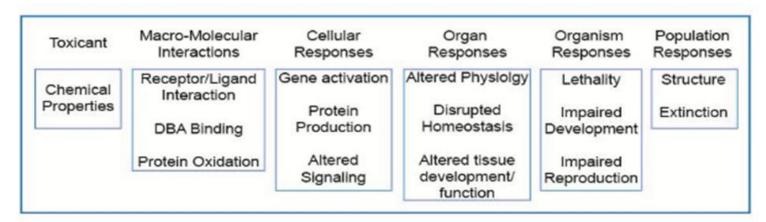
Using alternatives to animals where possible



OECD Integrated Approaches to Testing and Assessment IATAs



- Pragmatic, science based approaches for chemical hazard characterisation
- Rely on integrated analysis of existing information coupled with the generation of new information using testing strategies
- Can include a combination of methods
- Design can be informed by Adverse Outcome Pathways





GRACIOUS framework - Hypothesis Driven IATAs

- Existing AOPs will inform IATA design where possible
- 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

Lifecycle:

Human exposure and environmental release

What they are?
Physicochemical identity

Where they go?
Environmental fate, uptake and toxicokinetics

What they do?
Human and environmental toxicity

The IATAs will cover each aspect of the hypothesis

Integrated Approaches to Testing and Assessment

- The IATA format uses the format suggested by OECD
- Each IATA design is 'science based' and tailored to the specific hypothesis
- Tailoring IATAs for the obvious hypotheses will be more straightforward than for bespoke hypotheses
- More detail on the IATA is available on a poster by Fiona Murphy

Integrated Approaches to Testing and Assessment



- GRACIOUS partners are now
 - working on the development of the IATA's
 - Identifying relevant, reliable, robust SOPs with a clear evidence base
 - OECD, ISO, others...
 - Formulating an appropriate structure
 - Sequential testing strategy (STS)
 - Integrated testing strategy (ITS)
- Stakeholder engagement is essential in the design of the IATAs
- Breakout sessions 2 and 3

Summary



- The GRACIOUS framework provides a structure to guide the Grouping of nanoforms to support read-across
- ECHA guidance suggests grouping should be hypothesis driven
- GRACIOUS has developed a template for grouping hypothesis generation that incorporates
 - Purpose
 - Live cycle
 - What they are, where they go and what they do
- The hypothesis can then be tested by an IATA, using OECD guidelines
- The IATA use Sequential testing strategy (STS) or Integrated testing strategy (ITS) formats, feeding in the tests developed and recommended by other projects such as NanoReg2.



We look forward to hearing your ideas

Thank you!

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