Grouping and read-across for nanoforms

Webinar: updated REACH Guidance for nanomaterials - what you need to know

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RX project and guidance development

RX project: usage of (eco)toxicological data for bridging data gaps between nanoforms of the same substance and grouping them. Report used as starting point for Guidance.

RX Project

Draft guidance (internal)

Formal consultation procedure

Collaboration with Nanomaterials Working Group

- Regulatory considerations
- Consistency with overall nanomaterials guidance

Scope of the guidance

- Grouping and read-across between nano and non-nanoforms of the same substance
- Does not cover different substances directly. Information given may be useful when attempting to read-across between nanoforms of different substances
- No specific advice on QSARs for nanomaterials

General issues

- Annex XI of REACH addresses read-across between substances and not read-across between forms of the same substance
- Similar principles, approach and terminology are used for nanoforms such as “source” and “target”
- General principles in the parent guidance (Guidance on IR&CSA Chapter R.6: QSARs and grouping of chemicals) and in Read-Across Assessment Framework (RAAF) are also applicable

Reminder on terminology

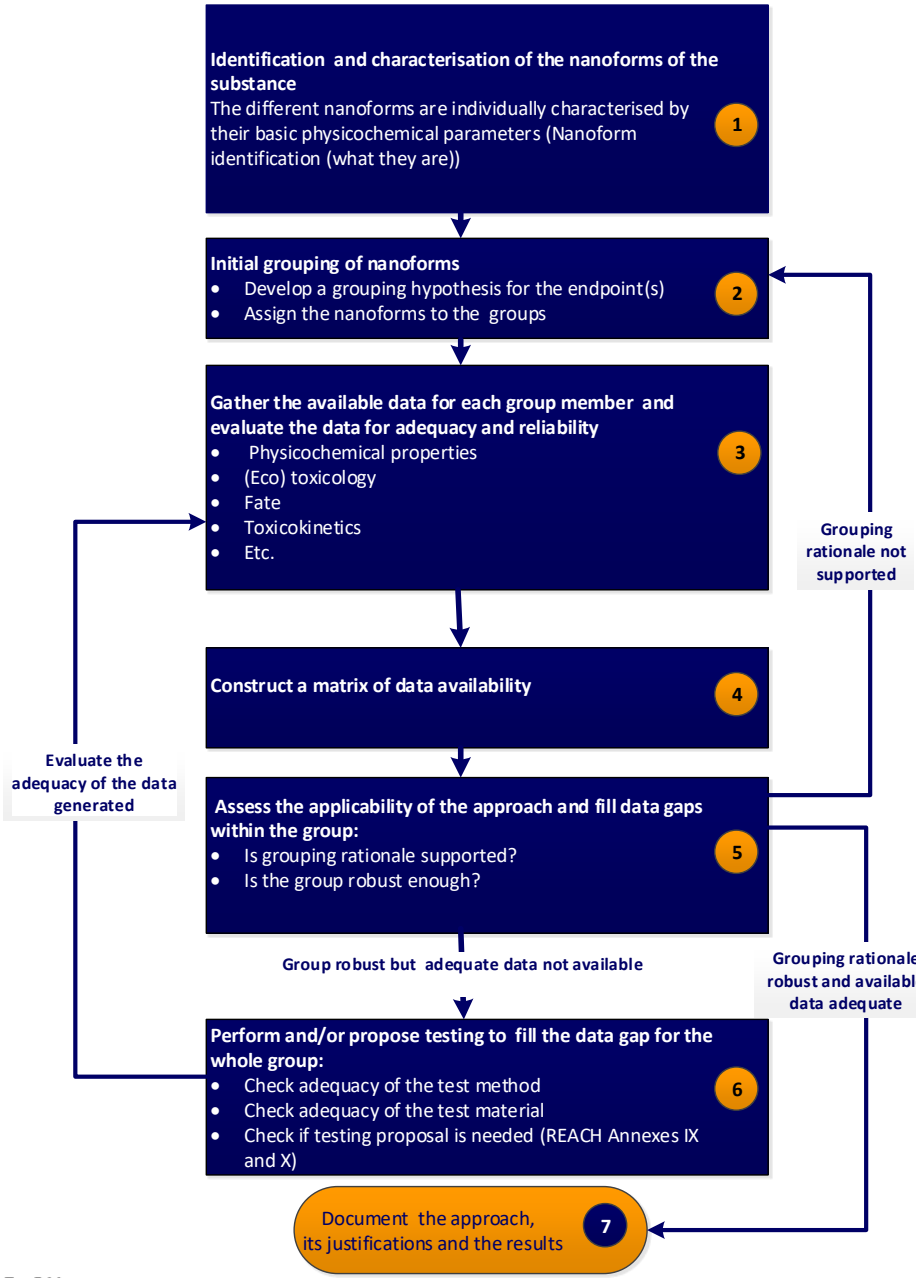
- Substances that have physicochemical, toxicological and ecotoxicological properties that are likely to be similar or follow a regular pattern may be considered as a group
- Read across is a technique used to predict endpoint information for one substance by using data from a same endpoint from another substance
- This guidance deals with grouping and read-across between nano and non-nanoforms of the same substance

Why guidance is needed?

- Nanoforms of substances registered together in the same registration
- Hazards posed by all possible forms of the substance covered by a registration must be addressed
- Guidance: pragmatic approach on how to assess differences in (eco)toxicological properties and fate of nanoforms and non-nanoform
- How to build a read-across justification and how to report it in the dossier

Stepwise approach

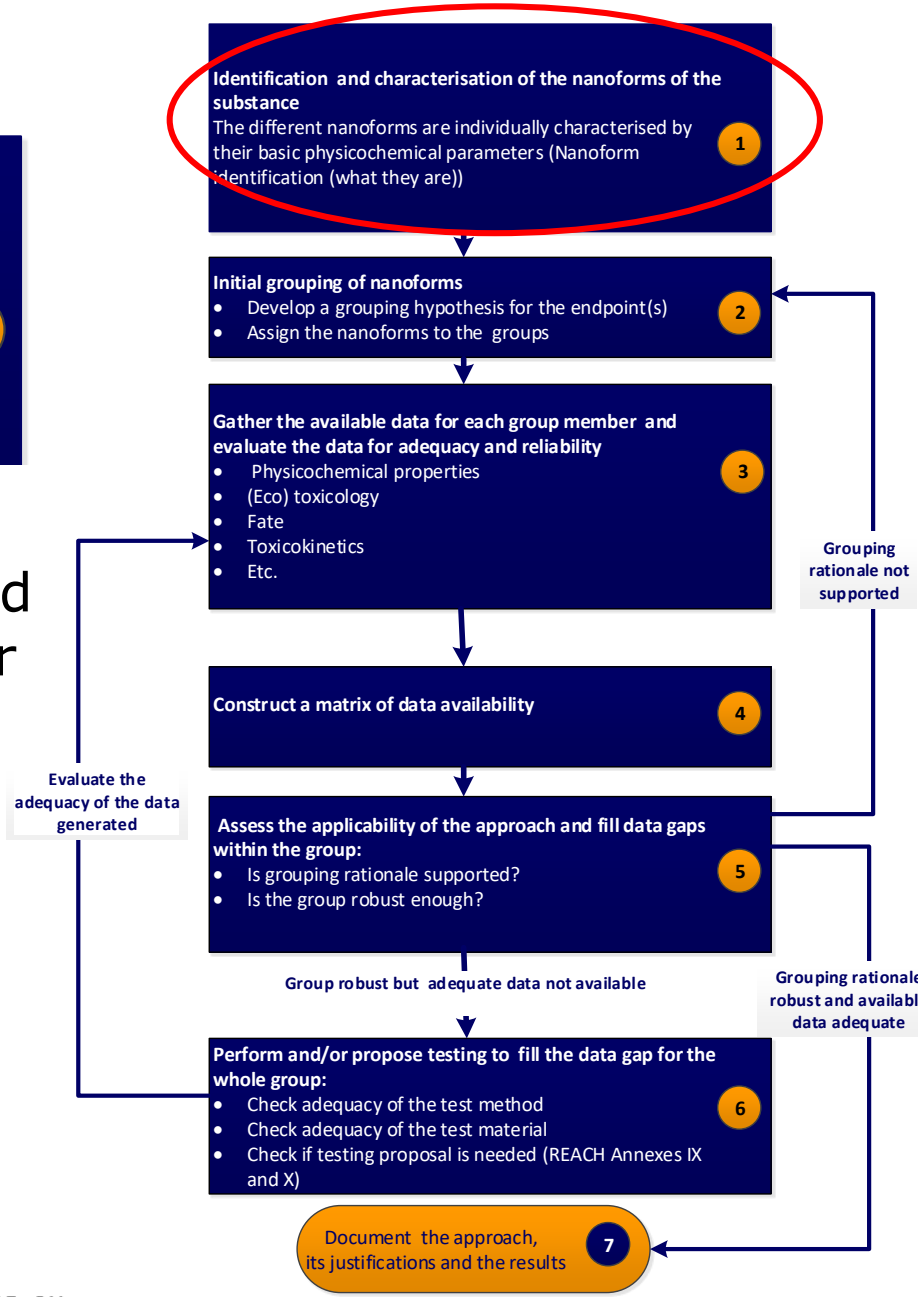
- Alternative approaches possible
- Steps may overlap or order may vary
- Endpoint specific, but several endpoints can be addressed together if hypothesis supports it
- Follows principles of OECD No. 194: Guidance on grouping of chemicals



Identification and characterisation of the nanoforms of the substance
The different nanoforms are individually characterised by their basic physicochemical parameters (Nanoform identification (what they are)) 1

Correct characterisation of nanoform to ensure proper hazard assessment. Basic information for nanoforms:

- Composition (including impurities and additives)
- Size
- Shape
- Surface chemistry



Initial grouping of nanoforms

- Develop a grouping hypothesis for the endpoint(s)
- Assign the nanoforms to the groups

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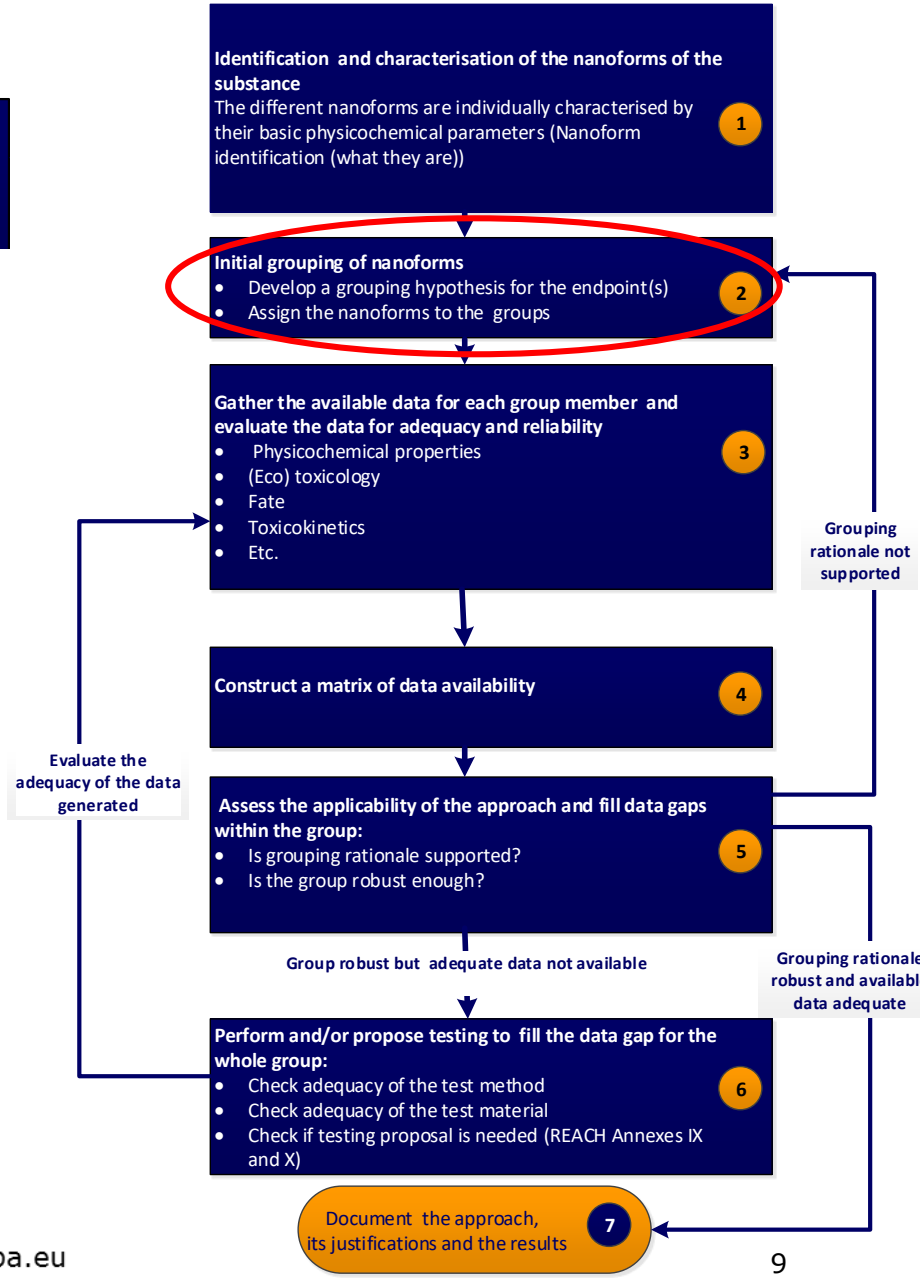
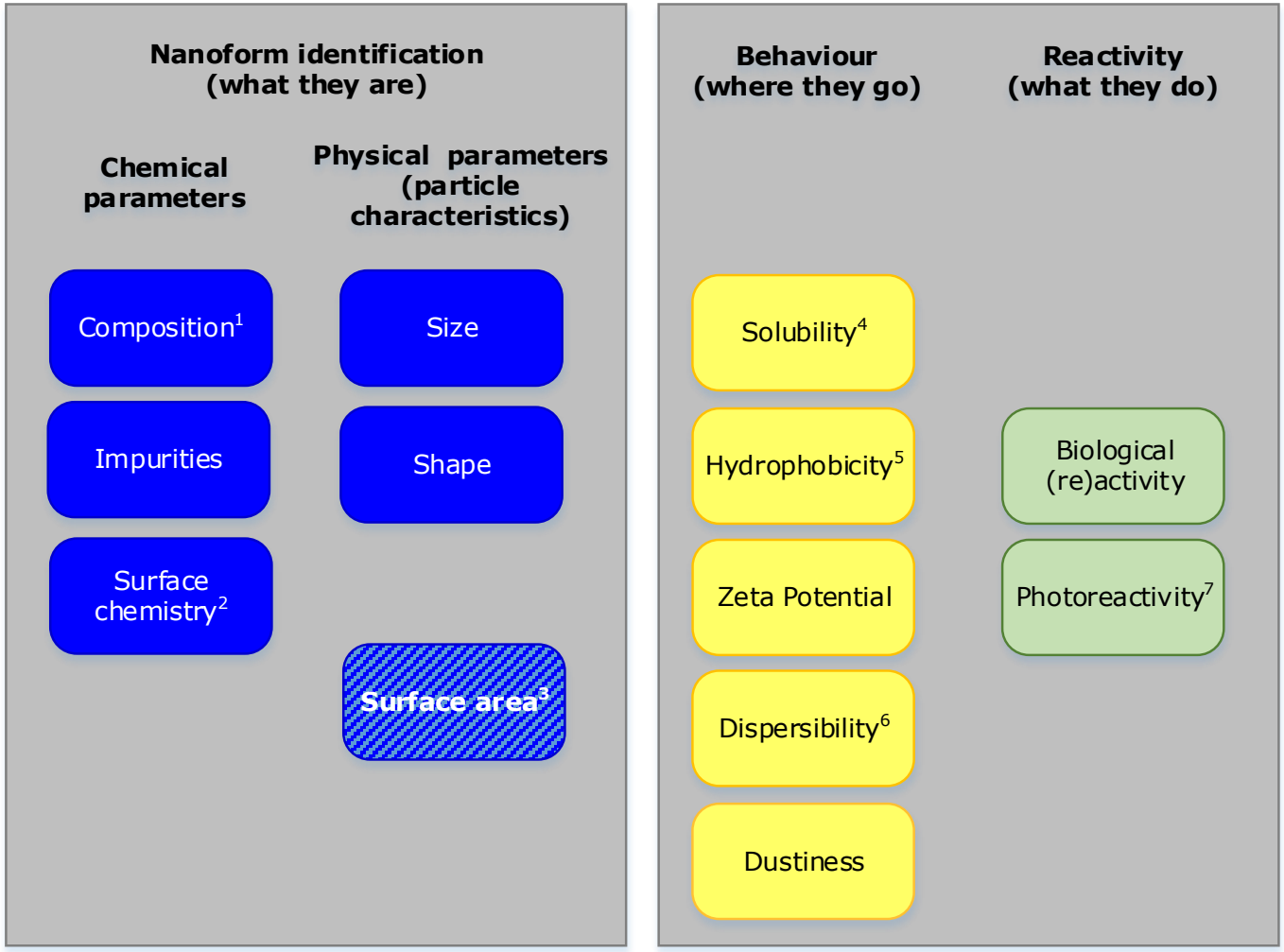
Define the scope (endpoint(s) covered) and develop grouping hypothesis by considering:

- Phys-chem parameters (step 1)
- "Reactivity" and "behaviour" parameters of the nanoforms
- Key parameters listed in Appendix 1
- Need to be taken into account, but may not be relevant for all assessments
- Depending on the hypothesis other phys-chem parameters, not included in Appendix 1 may be relevant (such as rigidity for fibres)



Key phys-chem parameters



Step 2: grouping hypothesis (I)

- Explains why similarities or differences between nanoforms in physicochemical properties allow predicting of specific (eco)toxicological behaviour
- Include a set of inclusion and/or exclusion rules that determine the ranges of applicability within which reliable estimation can be made for group members, for the given endpoint
- Physicochemical similarity not always enough justification. Consider to support hypothesis
  - Toxicokinetics data (route of exposure, ADME data)
  - Screening data (*in vitro*)
  - *In silico* models or predictions

Step 2: grouping hypothesis (II)

- To support hypothesis, consider processes that influence transport behaviour in different environmental compartments
  - adsorption
  - desorption
  - (hetero)aggregation
  - (hetero)agglomeration
  - sedimentation
  - dispersion
  - interaction with biomolecules

Example based on solubility

Available info (target nanoform(s)):

- High dissolution rate
- Similar water solubility to source
- Not surface treated
- Systemic toxicity driven by release of toxic ions

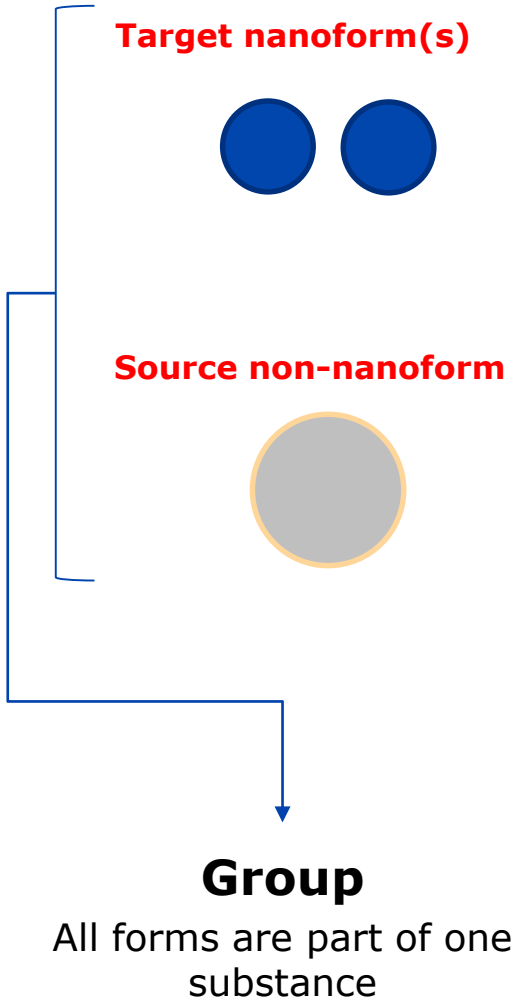
Basis for hypothesis:

Due to high dissolution rate and similar water solubility, it can be claimed that:

- Source and target have similar toxicokinetic behaviour and same toxicological effects (based on the hypothesis of ion driven toxicity)
- Systemic toxicity of target nanoform(s) can be predicted from available studies conducted with source

Further information needed:

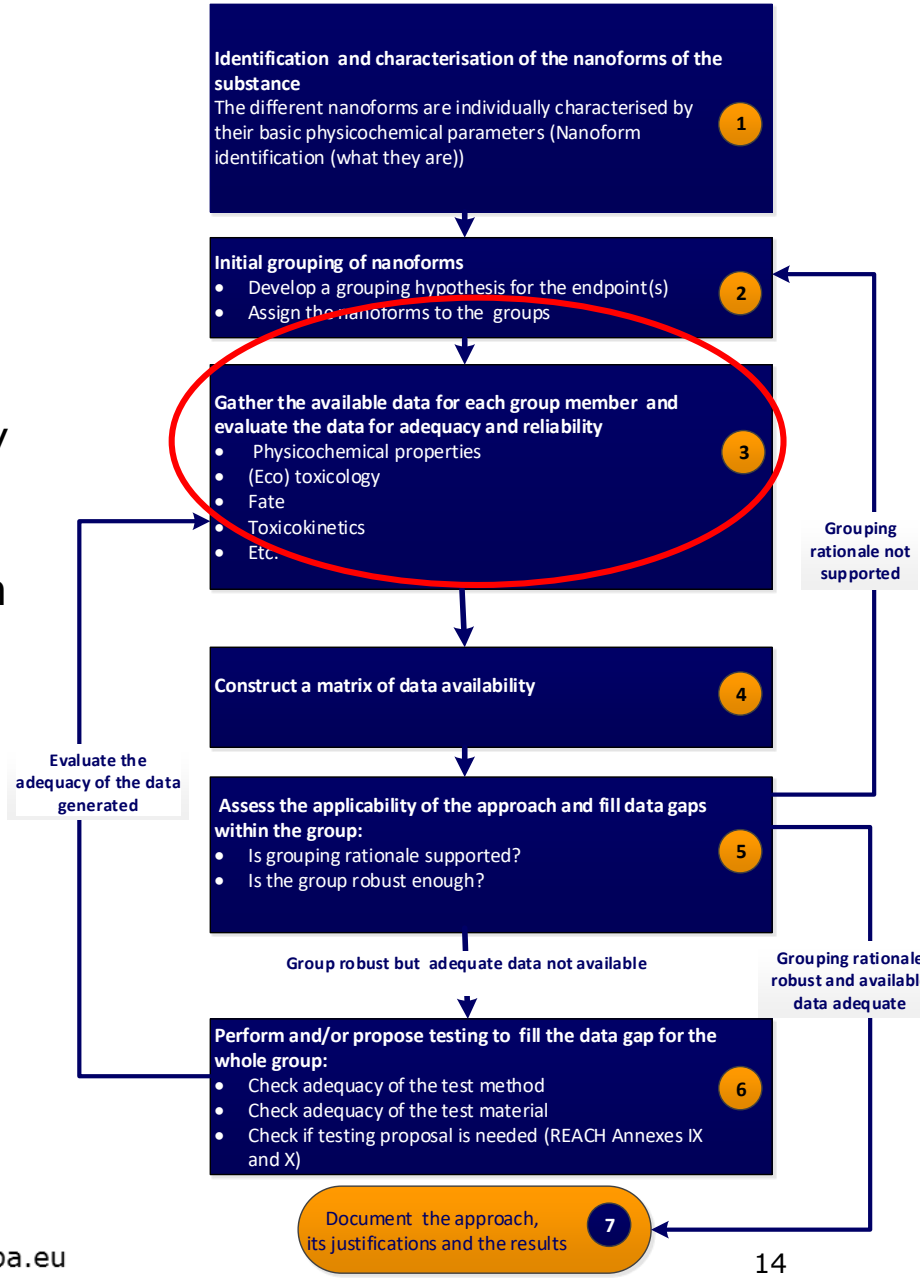
Information that demonstrates similar toxicokinetic behaviour, independent of particle size, of both source and target(s). E.g. **absorption studies** and/or **dissolution rate** studies in different media



Gather the available data for each group member and evaluate the data for adequacy and reliability 3

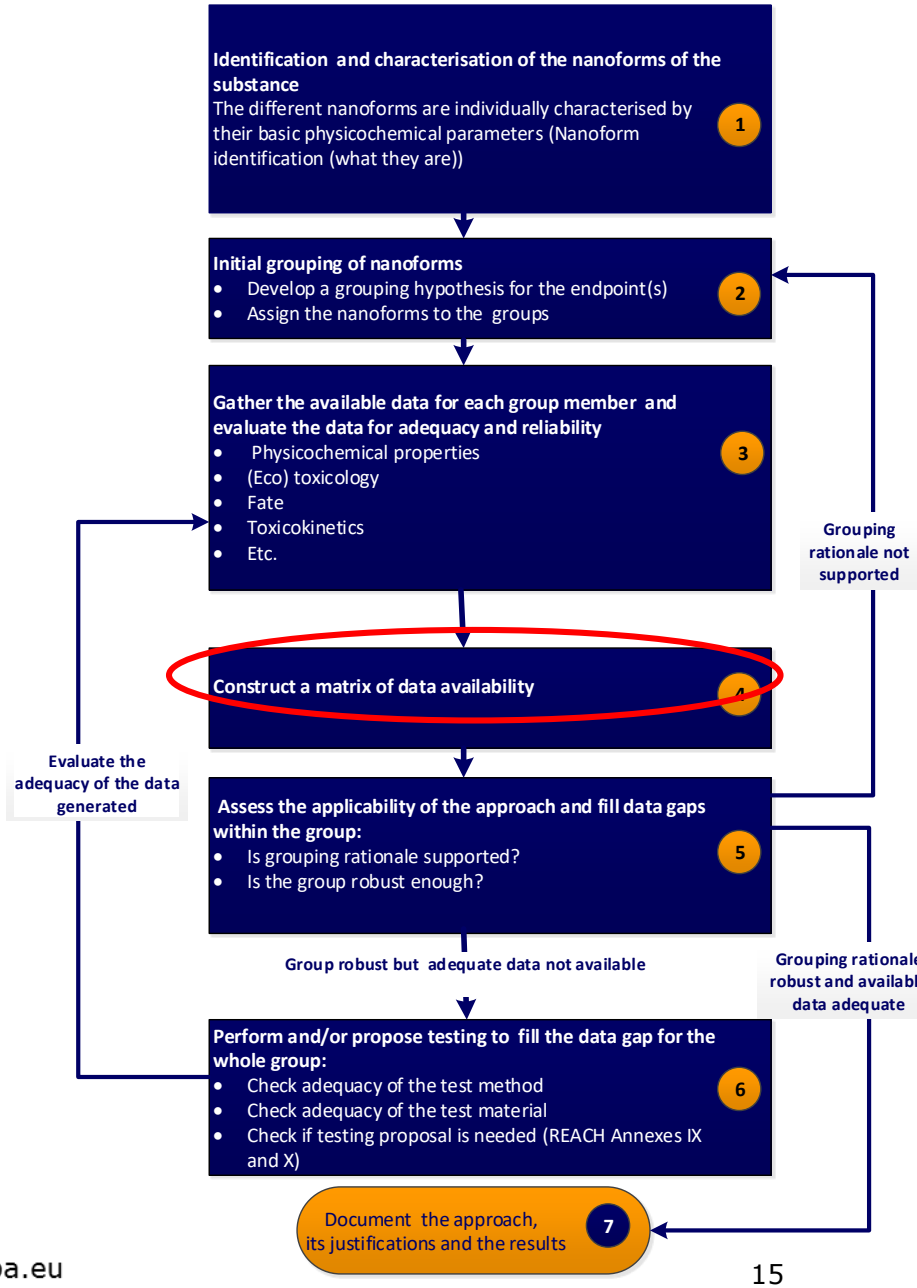
- Physicochemical properties
- (Eco) toxicology
- Fate
- Toxicokinetics
- Etc.

- Assessment of adequacy and reliability of available information for each nanoform (and not nanoform) that is part of the group to further strengthen hypothesis and justification (see Guidance R.3 and R.4)
- Consider similarities and differences in:
  - Behaviour in the test environments
  - Reactivity, fate etc. due to variable physchem properties
- Check whether a reliable study is available within the group for the specific REACH Information Requirement (generate it if needed)



Construct a matrix of data availability 4

- Data matrix to be prepared: endpoints versus group members
- Indicate whether data are available
- Identify data gaps
- Example of matrix in Appendix 2



Assess the applicability of the approach and fill data gaps within the group:
- Is grouping rationale supported?
- Is the group robust enough?

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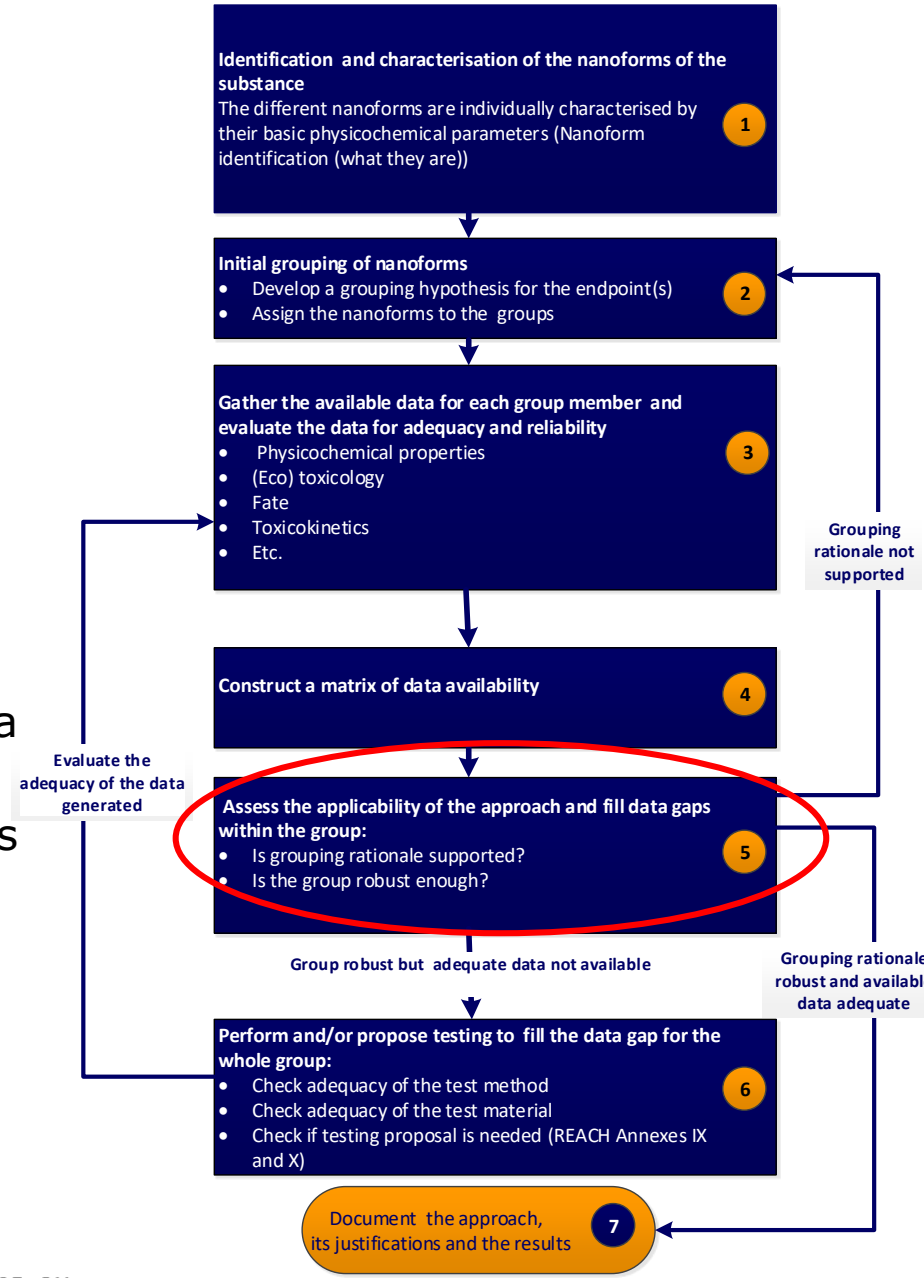
- Preliminary assessment of group:
  - Grouping hypothesis supported: does the group exhibit sufficient similarities in physicochemical properties based on available data in step 2
  - Group sufficiently robust: contains sufficient, relevant and reliable information on the members for assessment purposes



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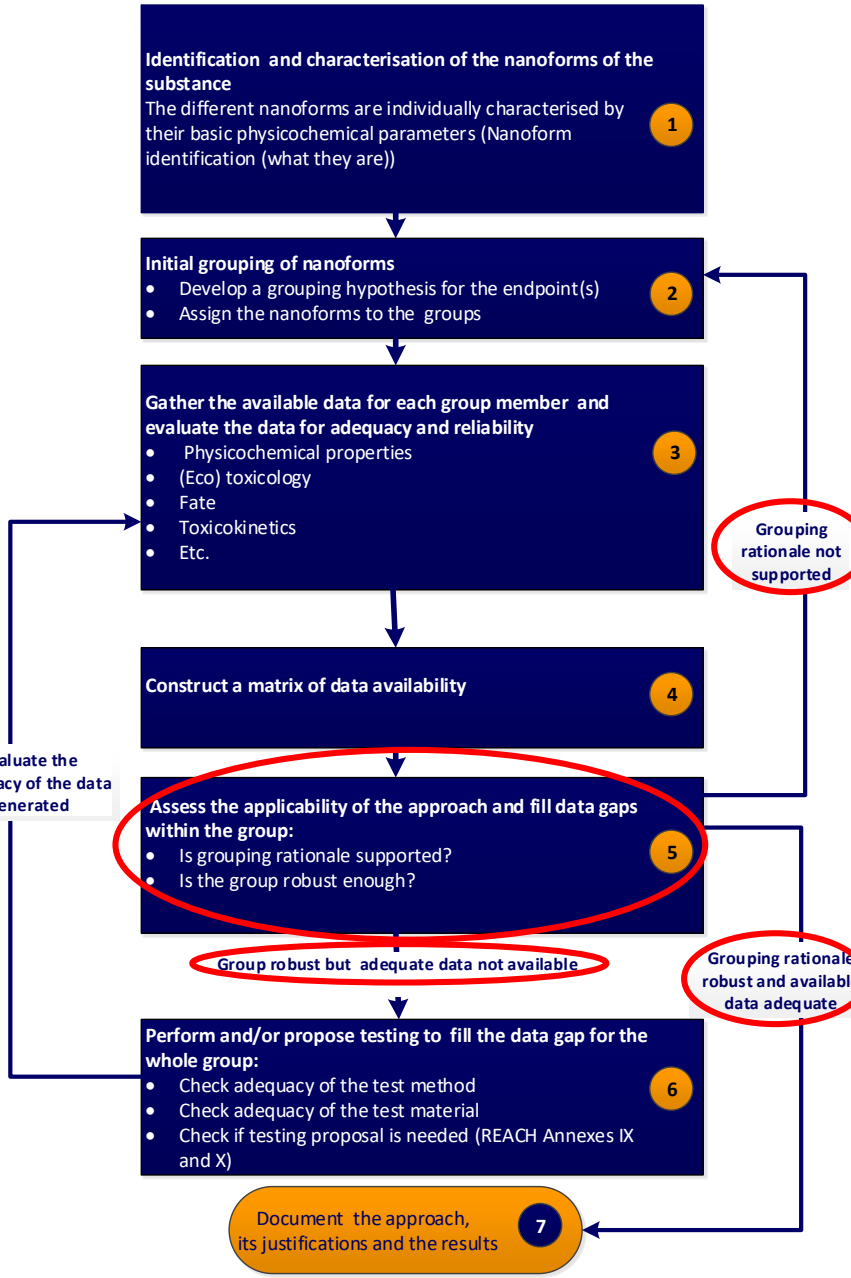
Three possible outcomes:

1. Grouping rationale not supported. Go to step 2 and modify hypothesis (e.g. divide the group)

2. Grouping rationale robust but adequate data not available: Go to step 6 and generate data

3. Grouping rationale robust and adequate data available. Go to step 7 and document your approach, justification and results



Perform and/or propose testing to fill the data gap for the whole group:

- Check adequacy of the test method
- Check adequacy of the test material
- Check if testing proposal is needed (REACH Annexes IX and X)

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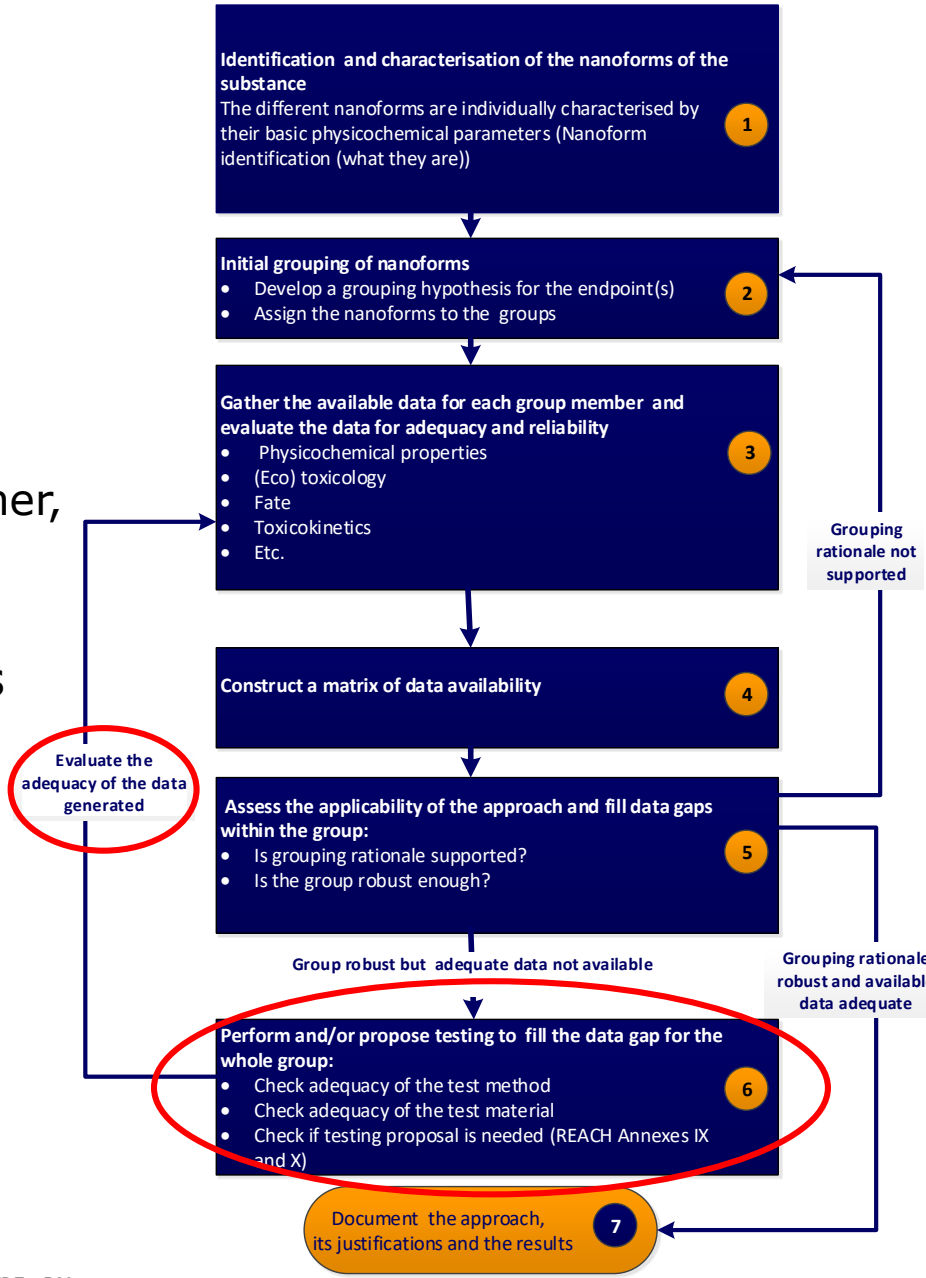
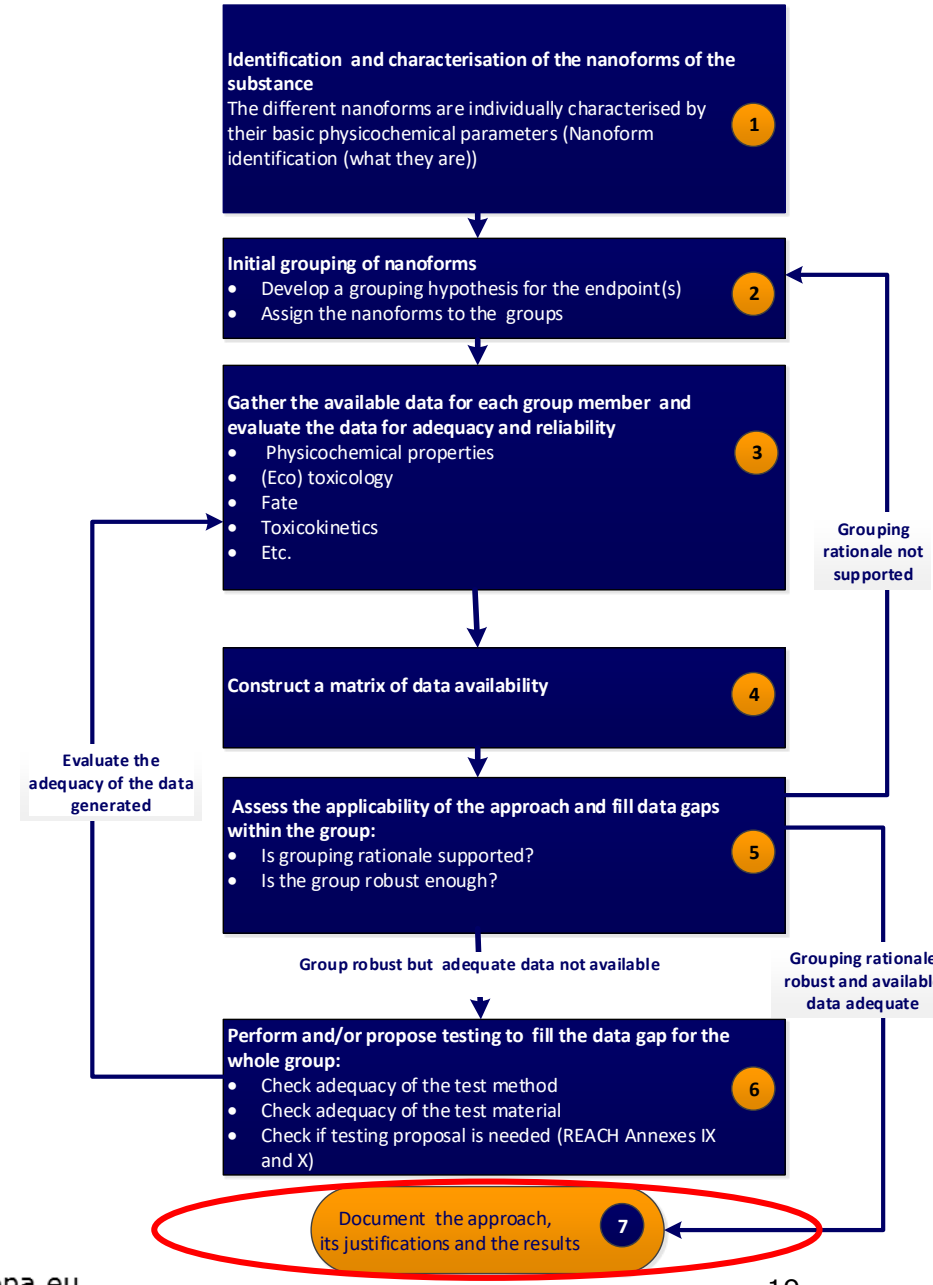
- Fill data gap:
  - Perform test in conventional manner, in accordance with Annexes VII-X
  - Use of adaptations (Annex XI)
- If tests performed, "normal" rules apply:
  - Adequacy of test method
  - Adequacy of testing material
  - Testing proposal may be required
- Once new data available, check adequacy



Document the approach, its justifications and the results 7

- Document assessment
  - IUCLID assessment entity functionality useful tool for reporting
  - Be transparent so assessor can follow your logic
  - Explain how uncertainty addressed



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