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A template for hypothesis generation to facilitate grouping and read-across of nanomaterials and support risk decision-making

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Introduction

In order to support nanotechnology industries in the sustainable commercialization of nanomaterials (NMs) and nano-enabled products (NEPs), there is an urgent need to streamline the risk assessment process both for regulatory compliance and to support innovation. The practical application of grouping similar nanoforms (NFs) of NMs and read-across from data-rich NFs to NF lacking sufficient fate and hazard data could be a useful strategy to reduce the burden of toxicity testing of individual NFs. It is crucial that any proposed grouping of NFs is hypothesis-driven and scientifically supported. Within the GRACIOUS project we have developed a template to guide hypothesis generation to facilitate evidence-based grouping and read-across for NFs.

Generating a Hypothesis

The initial step of generating a hypothesis is to define the **'purpose'** of grouping and/or read-across which may relate, for example, to regulatory, design and innovation, or precautionary needs of the user. Explicit inclusion of the purposes in the hypothesis template ensures the grouping will be relevant to the end-user.

The '**context**' identifies the use(s) of the NF, resulting in the identification of the likely exposure environment(s) (e.g. 'Occupational', 'Environment') and population(s) (e.g. 'Worker', 'Consumer') covered by the grouping hypothesis. This is the first step in defining the likely exposure scenario.

During the **life cycle** of a NF, many transformations may take place (which may alter some of the PC properties of the NF), and release may happen at several time-points. **Input from life cycle** describes the relevant exposure scenario under consideration and will clarify the potential level of released form and/or exposure dose which will subsequently feed into consideration of **What they are**?, **Where they go?, What they do**?.

The **'What they are', 'Where they go', 'What they do'** sections of the hypothesis template identify the considerations needed to establish a group (i.e. the linking of observed toxic responses to the PC properties of a NF, where possible).

The '**What they are**' section of the template specifically describes the PC characteristics shared between members of a group that determine the fate and hazard encompassing both the intrinsic material properties of a NF (such as chemical composition, crystallinity, and water solubility) and system-dependent (extrinsic) properties defined by the surroundings in which the NF is placed (e.g. dissolution rate in biological media, surface reactivity and dispersibility).

Consideration of both intrinsic and extrinsic properties is essential when developing a grouping hypothesis for exposure-relevant NFs.

Hypothesis Template

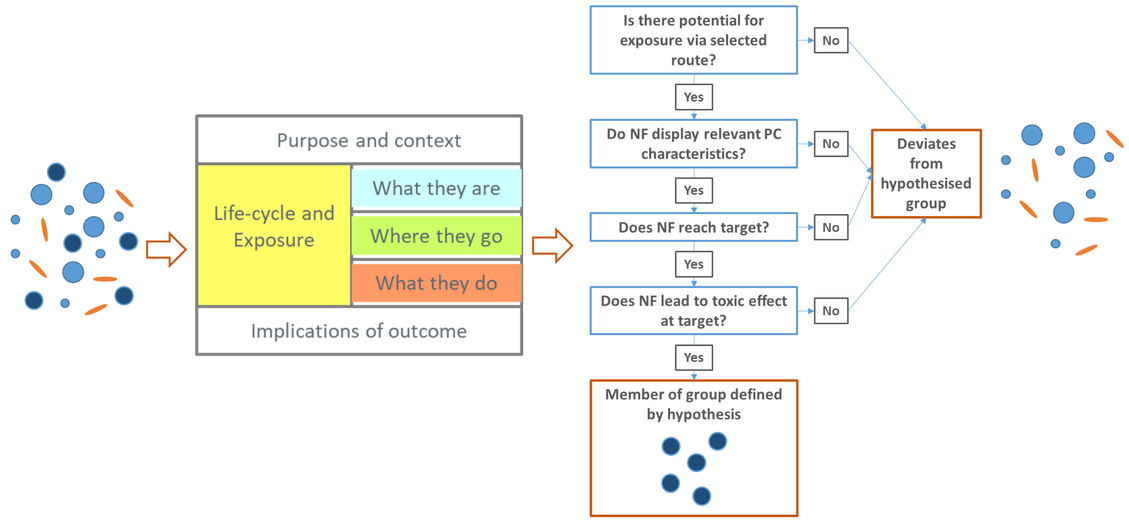
Purpose: Precautionary, Targeted testing, Regulatory, Safety by Design	
Context: Occupational, Consumer, Environmental	
Input from life cycle (WP2) Release and Exposure	**What they are? (WP3)** Physicochemical identity
	Where they go? (WP4) Environmental fate, uptake and toxicokinetics
	What they do? (WP5) Human and environmental toxicity
Potential implications: if in group: if not in group:	

Potential implications considers what action to take if your NF falls within/outside the group described in the hypothesis. Actions will depend on the initial purpose of testing. For example, if the purpose of testing is to ensure the development of a safe(r) innovative NF or NEP, the potential implications of adhering to a hypothesis that causally links a specific PC characteristic to an adverse health effect, may be to consider the impact of altering, if possible, a PC characteristic in the newly designed NF or NEP.

Tailored Integrated Approaches to Testing and Assessment

The format of the template is designed to directly inform the content of a tailored **Integrated Approach to Testing and Assessment (IATA).** An IATA will guide information gathering and the testing strategy required to make an evidence-based decision on whether the grouping hypothesis should be accepted or rejected. The representation of the pathway from exposure to the target site in a decision tree format allows the key PC characteristics directing fate and hazard to be identified along with potential points of departure where the user may deviate from, and therefore reject, the grouping hypothesis.

Nanomaterials → Template for generation of grouping hypothesis → Hypothesis-driven testing strategy to facilitate grouping



The adoption of the grouping hypothesis template by the GRACIOUS consortium has led to the generation of 35 hypotheses for grouping and associated IATA that are currently being tested and validated with case studies.

Conclusion

This template enables a consistent approach to hypothesis generation for the development of robust grouping and read-across arguments which require evidence-based, context-dependent hypotheses to establish a relationship between the physicochemical properties of substances and their hazard potential.

Continued use of the template by the wider nanosafety community will promote consistency in the design of grouping hypotheses and enable more rapid assessment and critique of the proposed grouping hypothesis, thereby helping to streamline the regulatory process in the future.

GRACIOUS partners

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