BLUE FROG SCIENTIFIC

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A Regulatory Framework for Assessing the Variability & Safety of Nanoforms

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Introduction

Are we overcomplicating nanoform regulation?

Nanomaterials are central to modern innovation, yet under EU REACH each nanoform is treated as inherently different.

This makes 'One Substance, One Registration' (OSOR) difficult, leading to duplicated data, increased cost, and significant delays – particularly for SMEs.

In extreme cases, a single registrant with 20 nanoforms could face over €6 million in testing costs and the use of more than 3,000 animals. At the same time, ecotoxicity guidelines were never designed for particulate materials, adding further complexity.

This project explores whether scientifically robust criteria can define "acceptable variation" between nanoforms – enabling more proportionate, ethical, and efficient regulation, aligned with REACH principles and the 3Rs.

Refining the Project

- Early analysis revealed that developing a comprehensive, enforceable framework for sets of similar nanoforms was not feasible within the project's timeframe.
- Focusing on acceptable variation within single nanoforms offered a more immediate path forward.

Is identifying acceptable variation grouping & read-across?

Simply... No.

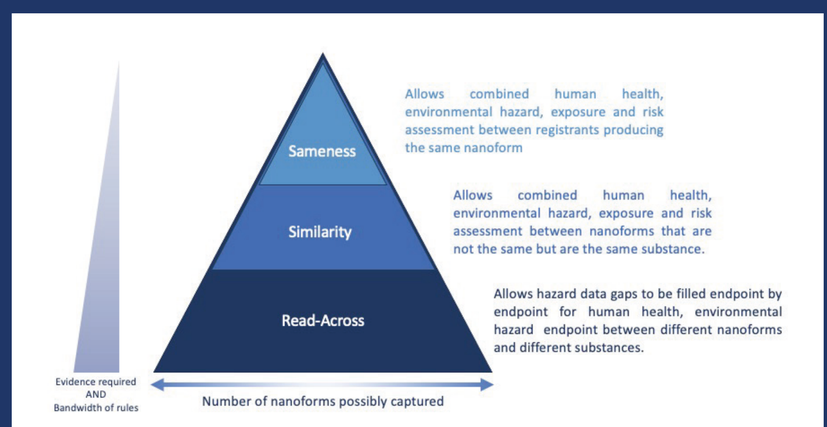

Figure 1: Schematic showing the inverse relationship between nanoform grouping/sameness, the required evidence (left) and the bandwidth of possible nanoforms included in a particular grouping strategy (middle). A brief explanation is given for each (right).

The Framework

- The Framework was based on established regulatory procedures (i.e. substance identification, GHS/CLP).
- Data was retrieved from 1,500 manuscripts (refined to 200), for rules, biological cut-offs and instrument repeatability.
- To use the framework all data as it corresponds to nanoform characteristics under REACH Annex VI, Section 2.4 i.e. size, shape, crystallinity, surface area and surface treatment/ functionalisation, is needed.
- There is at least one decision tree for each characteristic e.g. size and shape are combined, but consists of decision trees for spheroidal, elongated and platelet nanoforms.
- No specific decision tree is more important than the other, and all must conclude acceptable variation. Figure 2 shows an example decision tree for elongated nanoforms.

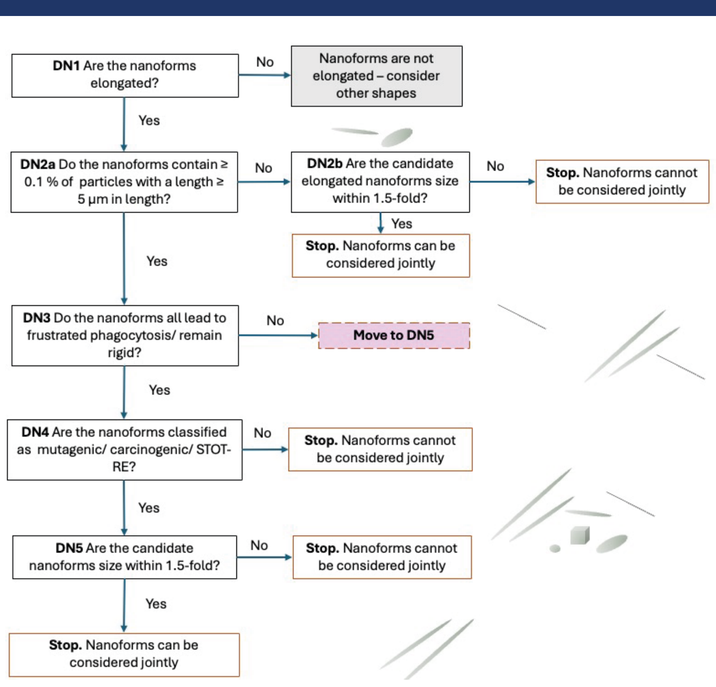

Figure 2: Example Decision Tree Elongated Nanoforms

Challenging the Framework

- The analysis showed that the decision trees are useful in determining nanoforms with and without acceptable variation.
- One conclusion highlighted possible conservatism – driven by differences in length but not diameter.
- Differences in length beyond a specific point may no longer have direct relevance.
- More limited environmental data than human – which makes sense considering the fibre paradigm.
- Lack of (particularly long-term) environmental and no developmental/ reproductive toxicity data.
- Macrophage aspect of the decision tree was not tested as there was no data.
- Rules were supported by the statistical approaches – giving some statistical validation.
- Limited number of nanoforms per group & more support required.

Endpoint	MWCNT Nanoform Pairwise G1 (4 NFs)	MWCNT Nanoform Pairwise G2 (3 NFs)	MWCNT Nanoform Pairwise G3a (2 NFs)	MWCNT Nanoform Pairwise G3b (2 NFs)	MWCNT Nanoform Pairwise G3c (2 NFs)
Annex VI					
Particle size distribution (incl. length) & Shape	*Not the same*		*Considered the same*		
Surface treatment/ functionalisation					
Surface Area					
Crystallinity					
Annex VII – X					
Dustiness					
Water solubility/ Dissolution		*No comparison possible*			
Dispersion Stability					
Short-term *Daphnia magna*					
Short-term toxicity to fish					
Long-term *Daphnia* sp.					
Long-term toxicity to fish					
Skin irritation/corrosion					
Skin Sensitisation					
Acute toxicity - inhalation					
Acute toxicity - oral					
Genotoxicity					
Carcinogenicity					
Repeated dose toxicity - inhalation					
Repro. & Develop. toxicity					

Conclusion

The **project achieved** the following key outcomes:

- Demonstrated proof of concept: The Decision Tree Framework provides a viable, science-based mechanism to assess acceptable variation among nanoforms using mandatory Annex VI data.
- Statistical and case study evidence supported several fold-difference thresholds (e.g., two-fold variation in surface area & 1.5-fold difference in diameter).
- The statistical models were useful for determining acceptable variation but often missed rejections of "sameness" due to the multi-faceted requirement of the assessment.
- Conservative framework and identified data gaps:
- Confirmed need for integration, not replacement of other frameworks e.g. sets.
- Advanced proportionality and the 3Rs - bringing back one substance one registration.

However, **the research also highlights the need** for:

- Broader validation: more diverse nanoforms and endpoints.
- Consistent data generation and sharing of nanoform characterisation data are essential to strengthen the empirical foundation for similarity/sameness assessments/validation.
- Mechanisms for maintaining and updating frameworks are required.

Recommendations for several strategic **priorities**:

- Integration of New Approach Methodologies (NAMs).
- International alignment: Promote coherence between EU approaches and global initiatives (e.g., OECD, ISO) to support global trade and regulatory acceptance.
- Implementation of these into the Decision Tree Framework forms the basis of a modernised, proportionate regulatory model for nanomaterials.

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