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A Regulatory Framework for Assessing the Variability & Safety of Nanoforms in the EU to Reduce Industry & Animal Burden

Authors: K. B. Paul[1], C. Shultz[2], R. Cross[2], G. Tsiliki[3], A. Zabeo[4], E. Moschini[5], V. Stone[5], W. Wohlleben[6], V. Rodriguez Unamuno[7], W. De Coen[7], D. Mestre[7], and C. Jacquet[7]

Affiliation: [1]Blue Frog Scientific Limited, Edinburgh, United Kingdom; [2]UK Centre for Ecology & Hydrology, Oxford, United Kingdom; [3]Purposeful IKE, Athens, Greece; [4]GreenDecision, Venice, Italy; [5]Heriot-Watt University, Edinburgh, United Kingdom; [6]ECETOC, Brussels, Belgium; and [7]European Chemicals Agency (ECHA), Helsinki, Finland.

*Corresponding Author: kai.paul@bluefrogscientific.com

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Introduction & Impact

Nanomaterials are key enabling technologies in modern innovation, yet their registration under chemicals legislations has presented major challenges globally. Why? Simply their unique properties that allow unheralded innovation, also give rise to unique problems. Under EU REACH each nanoform is currently assumed to be different, a priori, this is unlike non-nanoform substances, where One Substance, One Registration (OSOR) principles allow shared data between registrants with the same substance, streamlining registration, cost and time.

This presumption of difference means each nanoform should technically be supported by a full dataset, regardless of similarities in properties, creating significant barriers for industry, especially small and medium sized enterprises. For a registrant producing or importing multiple nanoforms of the same substance, this approach could result in dozens of separate dossiers, each requiring its own data set. For example, a registrant with 20 nanoforms at the 10–100 tonne/year band might need to conduct repeated dose and reproductive toxicity testing (OECD TG 422) on every nanoform—at an estimated cost exceeding €6 million and involving more than 3,000 animals. Beyond ethical and economic concerns, most standardised (eco)toxicological test guidelines were never designed for particulate materials, with test guidelines and guidance only now being adapted to be suitable for nanoform specific testing requirements, further complicating compliance.

This project explored whether clear, scientifically based criteria could be established to define acceptable variation among nanoforms, including that of their toxicology — a variation so limited that multiple nanoforms could be regarded as effectively the same concerning their hazard, exposure, and risk. Establishing such criteria would allow more proportional and ethical regulatory approaches, consistent with REACH's core aims, including the 3Rs principle while also leading nanoforms into a new regulatory era where the mechanisms of OSOR are once again established.

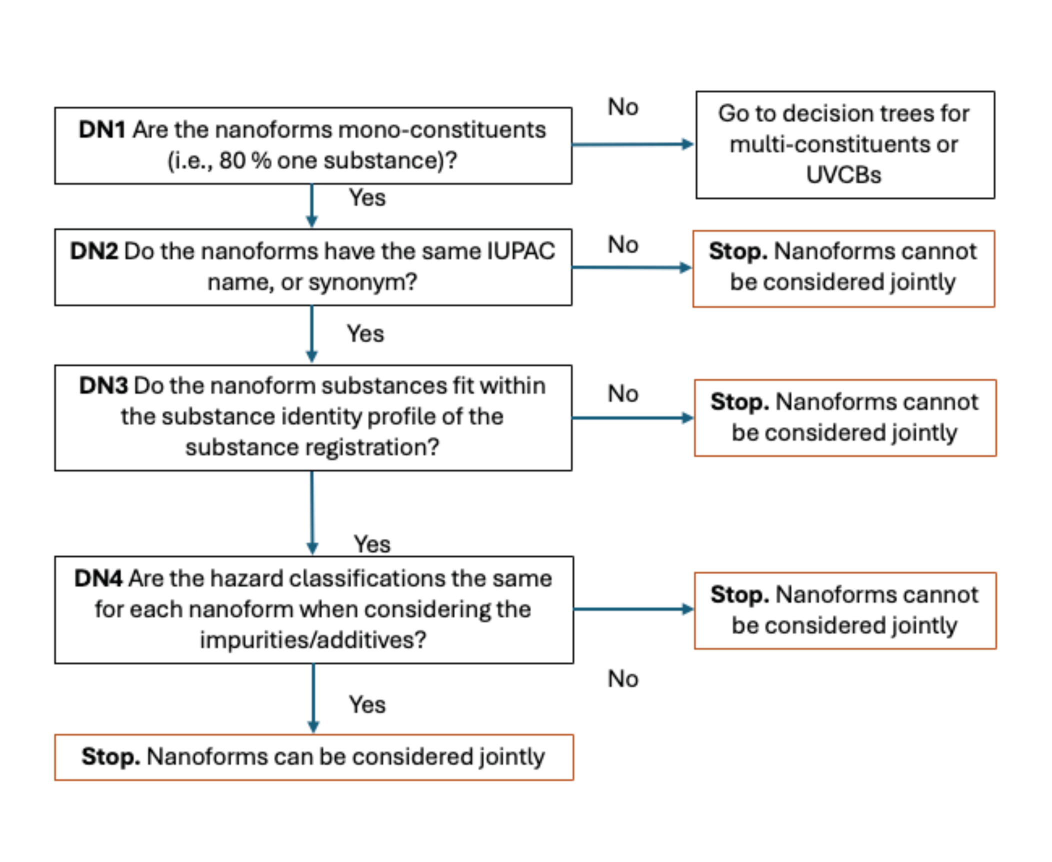

Figure 3: Example Decision Tree for Substance Identification

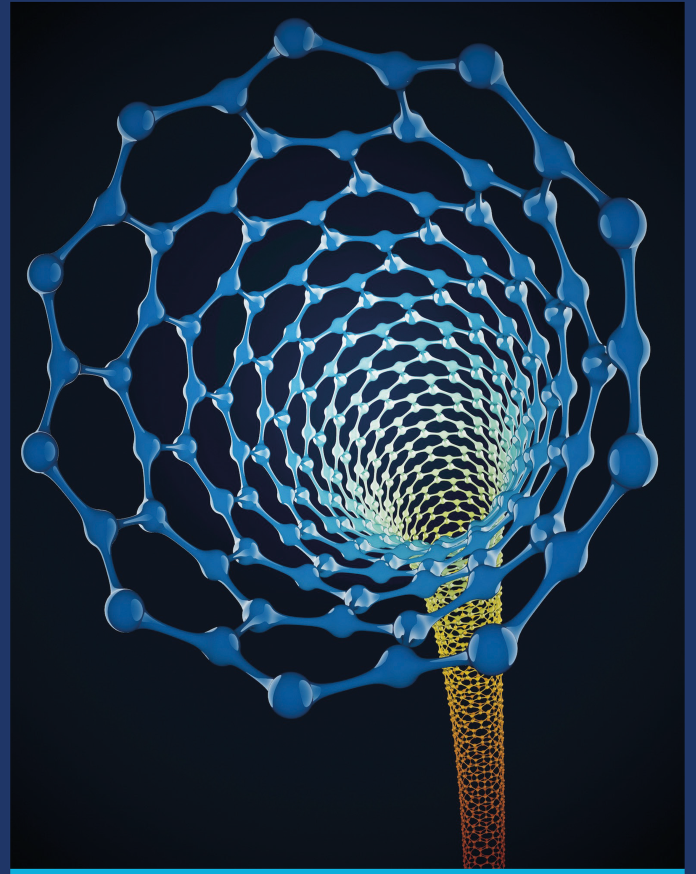

Image: Single Walled Carbon Nanotube

Project Refinement

Acceptable Variation Within Single Nanoforms

Early analysis revealed that developing a comprehensive, enforceable framework for sets of similar nanoforms was not feasible within the project's timeframe. The scientific literature showed insufficient and uneven data coverage across endpoints and nanoform types. Grouping criteria were inconsistently applied, and data were often not comparable due to divergent testing methodologies.

By contrast, focusing on acceptable variation within single nanoforms offered a more immediate path forward and delivering the basis to later approach the challenges represented by sets of similar nanoforms.

Is Identifying Acceptable Variation Grouping & Read-Across

Simply, NO. The premise, though it might be seen as grouping, is that the nanoform is the same, and therefore all are considered a single nanoform. By definition you cannot group singular substances. Due to this, data requirements to prove the acceptable variation are also more limited than e.g. read-across. Below is the schematic of where this might fit among other regulatory strategies under EU REACH for nanoforms (Figure 1).

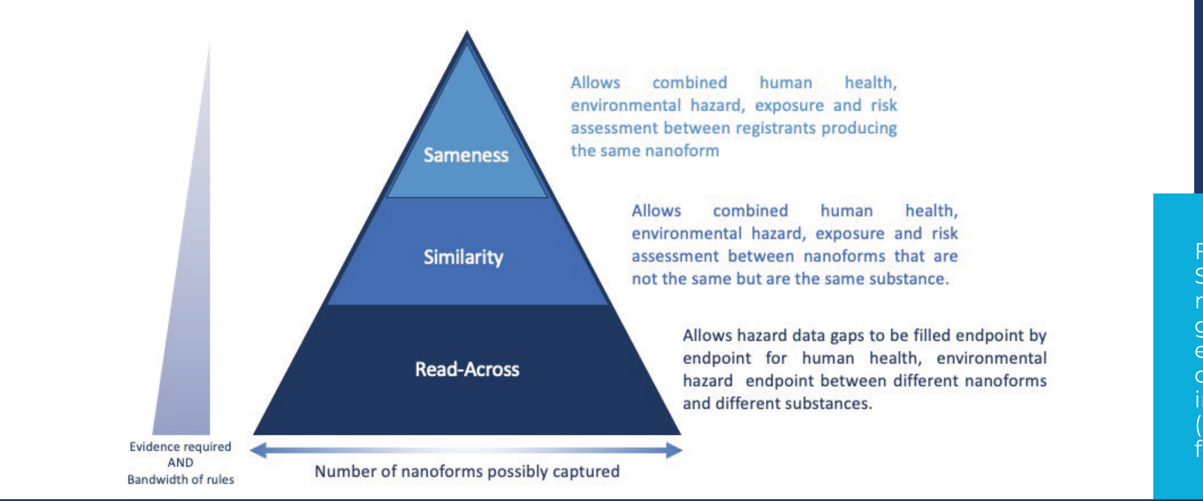

Figure 1: Schematic showing the inverse relationship between nanoform grouping/sameness, the required evidence (left) and the bandwidth of possible nanoforms included in a particular grouping strategy (middle). A brief explanation is given for each (right).

The Framework

The Framework was based on established regulatory procedures (i.e. substance identification, GHS/CLP) and data retrieved from 1,500 manuscripts (refined to 200), where rules were derived from biological cut-offs and instrument repeatability.

To use the framework all data as it corresponds to the required nanoform characteristics under REACH Annex VI, Section 2.4 i.e. size, shape, crystallinity, surface area and surface treatment/ functionalisation. There is at least one decision tree for each characteristic. For example, 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 decision trees must conclude acceptable variation for nanoforms to be considered single nanoforms. Figure 2 and Figure 3 give examples of the decision trees.

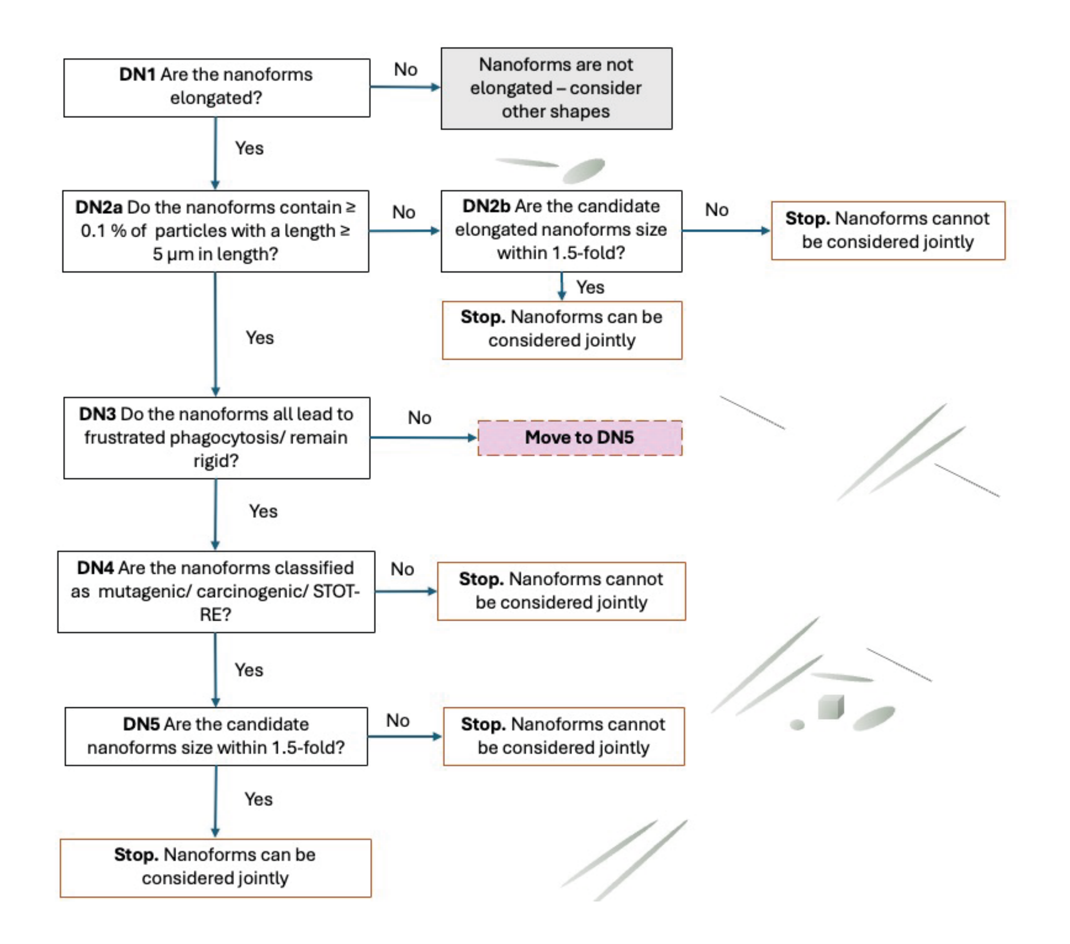

Figure 2: Example Decision Tree Elongated Nanoforms

Conclusion

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.

Framework Parameters

Statistical and case study evidence supported several fold-difference thresholds (e.g., two-fold variation in surface area & 1.5-fold difference in diameter), confirming that real-world nanoform variability can be captured within practical limits; however more detailed analysis is needed to potentially adjust fold-differences in the future when a broader and better comparable data base becomes available with time.

Statistical Models

The statistical models were useful for determining acceptable variation but often missed rejections of "sameness" due to the multi-faceted requirement of the assessment e.g. integrating variation with "hard cut-offs" from CLP.

Conservative Framework & Identified Data Gaps

While functional, the framework remains cautious—sometimes overly so—and limited by incomplete data, particularly for higher-tier toxicological and environmental endpoints.

Confirmed Need for Integration, Not Replacement

The framework should complement, not supersede, the "sets of similar nanoforms" concept, ensuring a coherent and flexible regulatory toolkit.

Advanced Proportionality & The 3Rs

By supporting shared registration of genuinely similar nanoforms, the approach contributes to reduced testing costs and animal use while maintaining protection for human health and the environment.

However, the research also highlights the continuing need for development and refinement. Specifically:

- Broader validation with more diverse nanoforms and endpoints is required to confirm general applicability.
- Consistent generation (e.g. through standardised and nanoform specific test guidance and guidelines) and sharing of nanoform characterisation data are essential to strengthen the empirical foundation for similarity assessments.
- Mechanisms for maintaining and updating frameworks—potentially through a "living guidance document" analogous to existing read-across or QSAR frameworks—should be explored.

Looking forward and based on the project outcomes the report recommends 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.

If these actions are implemented, the Decision Tree Framework and its derivatives could form the basis of a modernised, proportionate regulatory model for nanomaterials.