

## **Title: Standardisation of number concentration, refractive index, and density measurements of complex nanoparticles**

### **Abstract**

Real-life high-value particulate products for applications including catalysis, optoelectronic and nanomedicines are increasing in complexity, with multicomponent structures and shape and porosity features. Such advanced materials require an update to existing standards for particle number concentration to make them relevant for current industrial needs. This requires the development of accurate and harmonised methods for measuring particle density and refractive index, that are required for measurements of number concentrations by methods well established in industry. This proposal delivers methods and documentary standards that de-risk innovation and enable regulatory compliance and commercialisation of high-value particle-based products.

### **Keywords**

Advanced materials, Nanoparticles, Particle density, Particle number concentration, Refractive index, Standardisation, Traceability, nanoparticle density measurements

### **Background to the Metrological Challenges**

Europe's average global market share in the nanomaterial market was estimated to be 20 % in 2016 and based on compound annual growth rate, the European market was estimated in 2020 to be 5.2 billion € and 141 kilotons. In addition to nanoparticle use in catalysis, optoelectronic and nanomedicines, detecting their presence and confirming their size is becoming increasingly important in food production, environmental monitoring, and product safety, whilst the accurate sizing of extracellular vesicle (EV) nanoparticles in body fluids offers the potential to detect disease. In a recently targeted Joint Research Centre stakeholder survey, respondents identified the need for particle size, effective particle density and particle complex refractive index (RI) to be stated on reference material (RM) certificates. For example, laser diffraction, the most widely sold instrument for particle characterisation, which is applicable also to inline metrology for quality control during manufacturing, requires the RI to link scattered intensity to particle size for sub micrometre particles. The need for number concentration and number-based size distribution measurements of (biological) particles with unknown RI is also relevant for clinical diagnosis to measure biological and therapeutical nanoparticles, such as viruses, vaccines and extra cellular vesicles.

There is a trend in nanoparticle development from passive towards active and hybrid nanomaterials, which leads to an increasing material complexity requiring an adaptation of the analytical techniques and respective standards to meet the needs of existing and future advanced materials. This trend in the field of nanomaterials is embedded in more fundamental changes in materials research to meet the requirements of the EC Green Deal & Digital Strategy, as worked out by the Advanced Materials 2030 Initiative. OECD released in 2022 an "Advanced Materials: Working Description" stating: "Advanced Materials under consideration of Working Party on Manufactured Nanomaterials are aimed to be assessed in order to improve their safety, sustainability and regulatory coverage within the strategic approach to identify knowledge gaps and recommendations for action". In this context, the EU is claiming this need for porous materials, composite materials, and particle system as advanced materials. This aligns with the European Metrology Network (EMN) for Advanced Manufacturing's cross-cutting topics for advanced materials.

The need for number-based concentrations is explained in the Commission staff working paper by the relevance of smallest particles for the toxicity properties and further work in metrological and standardisation aspects is demanded. This need for standardisation is addressed e.g. by CEN/TC352, ISO/TC 229 'Nanotechnologies' and ISO/TC 24/SC 4 'Particle characterization' and a "Guidance on the measurement of nanoparticle number concentration" (ISO/CD TS 24672.2 Nanotechnologies) is under development, which will provide an overview over both particle-by-particle methods such as particle tracking analysis (PTA), relative

pulse sensing (RPS), single particle inductively coupled plasma-mass spectrometry (spICP-MS) and differential mobility analyser and condensation particle counter (DMAS/CPC), and ensemble techniques such as dynamic light scattering (DCS), multi-angle dynamic light scattering (MADLS), small angle X ray scattering (SAXS) and UV-Visible. However, most if not all the methods are not sufficient for measurements of number concentration of advanced materials, because these methods require the input of material parameters such as density or RI that are typically unknown. In addition, because the existing standards and methods are based on idealised materials, there is a gap in addressing non-spherical, multi-component and multi-modal materials.

Research proposals are invited to address the standardisation requirements for metrological traceability of number concentration measurements of advanced particulate nanomaterials using combined approaches based on determining the related quantities density and refractive index.

## Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The JRP shall focus on [the traceable measurement and characterisation of particulate nanomaterials for number concentration for use in the standards being developed by ISO/TC229, CEN/TC352 and ISO/TC24/SC4 and related groups.

The specific objectives are

1. To develop representative test materials (RTMs) for number concentration measurements of nano- and sub-micrometre particles that go beyond spherical mono-disperse and mono-modal materials. These RTMs shall cover at least two of the following groups: porous, multicomponent, multi-modal size distributions and non-spherical shape.
2. To verify the performance of established reference and laboratory methods for relative and absolute number concentration measurements of complex samples using particle counting methods (e.g. PTA, spLS, spICP-MS, EM, FCM) and ensemble methods (e.g. SAXS, MADLS, DCS, UV-Vis) for particle sizes between 1 nm and 1 000 nm to meet present and future regulatory needs. This shall include the development of new, material-specific sample preparation protocols for imaging methods.
3. To develop traceable methods for particle density and RI measurements and to define uncertainty requirements for density and RI as input parameters for concentration measurements. The density measurements results are to be provided to ISO/TC 24/SG4 for consideration for the potential revision of the ISO 18747 standard. For RI measurements both ensemble and single-particle methods (e.g. FCM, UV-Vis, FFF-IR, light scattering, and laser diffraction) shall be considered.
4. To collaborate with the technical committees ISO/TC229, CEN/TC352 and ISO/TC24/SC4, and the users of the standards they develop to ensure that the outputs of the project are aligned with their needs, including the provision of a report on the results of a VAMAS pre-standardisation framework interlaboratory comparison study for nanoparticle number concentrations addressing the needs on reference material specifications identified by the JRC and recommendations for incorporation of this information into future standards at the earliest opportunity.

The proposed research shall be justified by clear reference to the measurement needs within strategic documents published by the relevant Regulatory body or Standards Developing Organisation or by a letter signed by the convenor of the respective TC/WG. EURAMET encourages proposals that include representatives from industry, regulators and standardisation bodies actively participating in the projects. The proposal must name a “Chief Stakeholder”, not a member of the consortium, but a representative of the user community that will benefit from the proposed work. The “Chief Stakeholder” should write a letter of support explaining how their organisation will make use of the outcomes from the research, be consulted regularly by the consortium during the project to ensure that the planned outcomes are still relevant, and be prepared to report to EURAMET on the benefits they have gained from the project.

Proposers should establish the current state of the art and explain how their proposed research goes beyond this. [In particular, proposers should outline the achievements of the EMPIR projects 14IND12 Innanopart, 18SIP01 ISOCONCur, 17NRM04 nPSize, 18HLT01 MetVes II and how their proposal will build on those.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.0 M€ and has defined an upper limit of 1.3 M€ for this project.

EURAMET also expects the EU Contribution to the external funded beneficiaries to not exceed 30 % of the total EU Contribution across all selected projects in this TP.

Any industrial beneficiaries that will receive significant benefit from the results of the proposed project are expected to be beneficiaries without receiving funding or associated partners.

## Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the 'end user' community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the "end user" community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Facilitate improved industrial capability or improved quality of life for European citizens in terms of personal health, protection of the environment and the climate, or energy security,
- Transfer knowledge to the nanoparticle chemical, optoelectronic industrial, and nanomedicine sectors.

You should detail other impacts of your proposed JRP as specified in the document "Guide 4: Writing Joint Research Projects (JRPs)"

You should also detail how your approach to realising the objectives will further the aim of the Partnership to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work.

## Time-scale

The project should be of up to 3 years duration.