Stakeholder workshop on small particles and nanoparticles in food, 30 March – 1 April 2022

Examples related to other considerations

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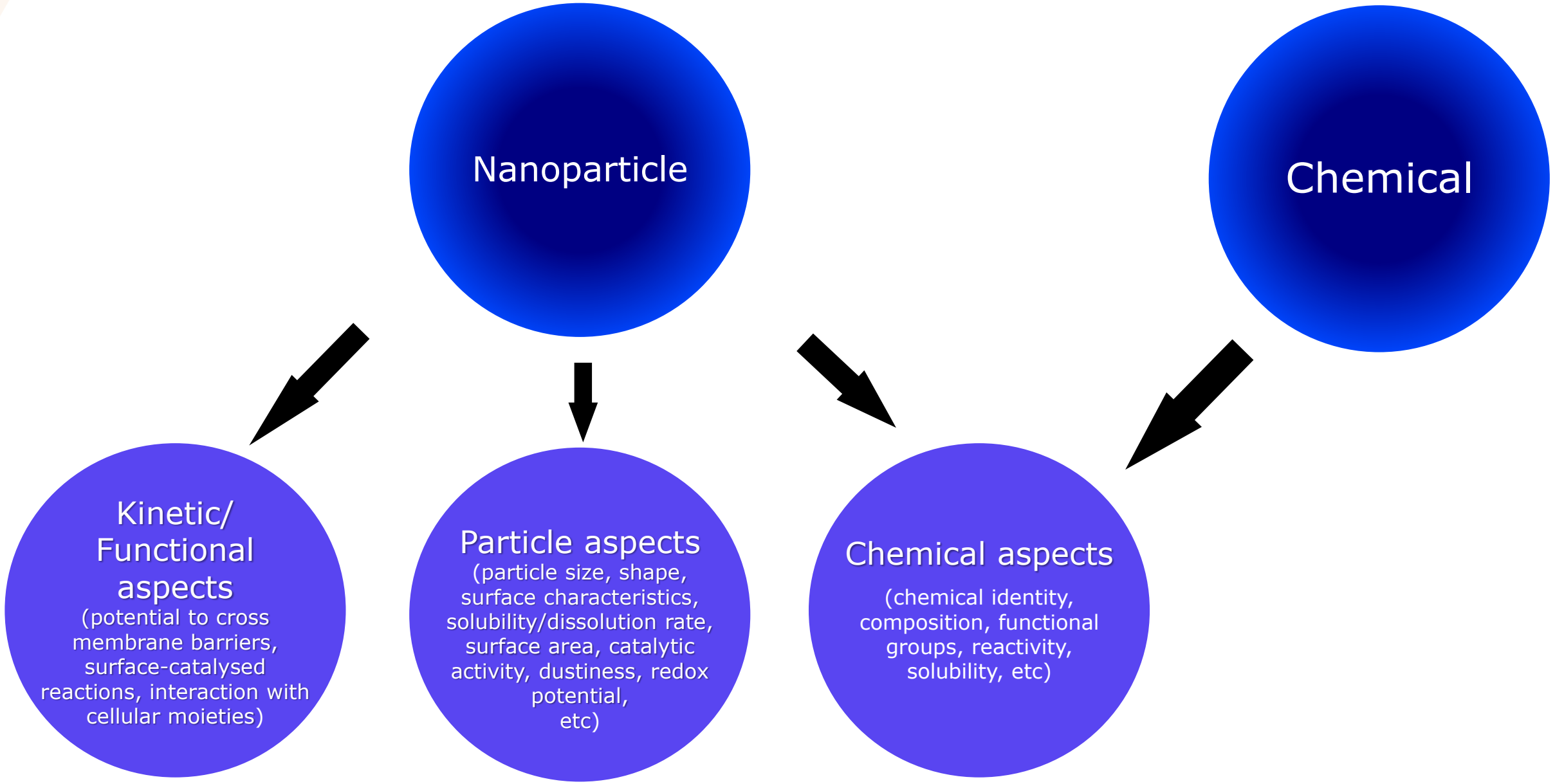
Trusted science for safe food

European Food Safety Authority

Specific Considerations for Nanomaterial Risk Assessment



Specific Considerations for Nanomaterial Risk Assessment: Physicochemical aspects

- **Agglomeration**: Due to high free energy at the surface, nanoparticles have a greater tendency of to stick together to form larger sized agglomerates. These can also de-agglomerate under certain pH/ionic conditions, or due to physical force.
  Adequate dispersion is therefore essential.
- **Solubility/dissolution**: Insoluble nanoparticles in a solvent form a dispersion/suspension - not a solution.
  Stability of a dispersion is therefore essential.
- Nanomaterials may stick to other surfaces, or sediment out of suspension.
  Uniformity of the dose under test conditions is therefore essential.
- **Surface characteristics**: nanoparticles may bind/adsorb other substances and act as a carrier of potentially harmful substances. They may also bind components of the test media and interfere with the assay read-out.
  Thorough characterisation of the test material is therefore essential.

Specific Considerations for Nanomaterial Risk Assessment: Toxicokinetic aspects

- **Bioavailability and biokinetic behaviour** of nanomaterials can be different from conventional forms:
  - Surface chemistry/surface modifications or coatings may influence properties, behaviour, effects of a nanomaterial;
    Consideration of surface characteristics is therefore essential.
  - Depending on the nanomaterial, and the route of exposure, nanoparticles may cross biological membrane barriers and reach various (unintended) parts of the body.
    Data on toxicokinetics of a nanomaterial are therefore essential.

Specific Considerations for Nanomaterial Risk Assessment: Toxicological aspects

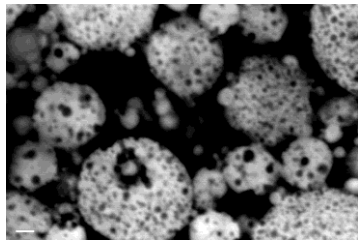
- **Dose metrics for toxicological testing**:
  - Mass-based dosimetry alone may not be appropriate; **Other metrics – such as particle number, surface area should be considered**;
  - Nanoparticles may have the potential to catalyse surface reactions; **Investigating surface reactivity is therefore essential**.
  - Nanoparticles may interact with biological entities close to molecular level; **Toxicological studies on the nanomaterial are therefore essential.**

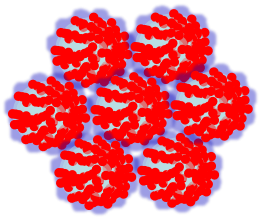
Specific Considerations for Nanomaterial Risk Assessment: Exposure aspects

- **Estimation of local and systemic exposure to**:
  - Nanoparticles;
  - Any released ions or other moieties.

Organic/natural substances

- **Nanomaterials are not always composed of inorganic substances**
  - They can also be made from **organic, or hybrid** (inorganic/organic) substances.
  - Numerous examples of **nano-forms of organic substances** are known – including those of certain food supplements, preservatives, nutraceuticals, vitamins, antioxidants, etc.
  - Organic nanomaterials have also been used to develop **nano-scale delivery systems** for other (bio)active substances, such as biocides, pesticides, human and veterinary medicines, etc.






Organic/natural substances

- In many cases, organic substances used are of natural origin, that are **claimed/assumed** by the applicants **as 'safe'**.

- Like inorganic nanomaterials, **safety concerns equally apply to organic nanomaterials**, because:

  - **properties, behaviour and toxicokinetics** of both organic and inorganic substances are prone to **change at the nano-scale** – compared to conventional bulk forms.

  - nano forms of many organic substances have been reported for **much greater absorption and bioavailability** compared to the same substances in conventional bulk form. Increased uptake/bioavailability of certain substances **may cause adverse health effects**.

  - organic substances in nanoparticle form may also **cross membrane barriers** to reach those parts of the body where their conventional bulk forms would have not reached.

  - if nanoparticles of an organic substance are internalised by cells and tissues, they may act as a reservoir that continues to **release molecular/ionic forms** over long periods. This may have positive as well as negative effects in a biological system.

Organic/natural substances

Therefore:

- Nano-forms of **organic or natural materials should not be automatically assumed as safe** on the basis of data corresponding to bulk forms;
- Safety assessment of nano-forms of organic/natural substances must also consider additional **small-particle related aspects**;
- A particular account should be taken of any changes in **physicochemical and biokinetic properties of the nano-form in comparison with the corresponding bulk form**.

Addressing small lipophilic organic particles

- A specific case is that of lipophilic substances present as small particles, including nanoparticles
- If they are not marketed in lipophilic media they maintain their particulate nature when ingested
- They do not dissolve in the GI tract and thus can be generally assumed to reach the human intestine as particles
- They can follow the uptake route of lipids and partition to physiological hydrophobic environments
- Information on the physicochemical properties (e.g. solubility and K_{ow}), toxicokinetic information and use levels

Addressing small lipophilic organic particles

- Based on this, GI uptake may be shown to be linked to conventional processes for the absorption of lipids and lipophilic materials by the intestinal epithelia, such as passive transport through the cellular membranes and partitioning to physiological lipophilic environments
- Endogenous substances (e.g. vitamin metabolites): conventional RA may be valid and information should be compiled supporting this appraisal route
- Exogenous components: special care has to be exercised in order to provide a reasoned justification, in which toxicokinetic information, uptake and distribution data are essential

Novel foods

- Nanoengineering means an ingredient is a novel food
- Thus to be assessed according to 2 guidances (NF and nano); if it is a nutrient source according to 3 guidances (NF, NS and nano)
- For nutrient sources it is essential to show if/when the nanomaterial joins the body pool of the nutrient and falls under control of homeostatic mechanisms
- Essential to demonstrate if particles may enter systemic circulation, differently from dietary sources of the nutrient
- IATAs including NAMs tackling the nano-aspects are essential to provide mechanistic knowledge underpinning the assessment

Why are nanomaterials used in FCMs?

Improved Packaging with Nanomaterial Additives:

- mechanical properties (flexibility, durability, tensile strength, temperature/moisture stability, etc.)
- barrier properties against gases, water, taint, organic chemicals, u.v. light

Active Packaging with Antimicrobial or Oxygen Scavenging Nanomaterials:

- to keep packaged food hygienic and fresh for longer

Smart/Intelligent Packaging with Nano(bio)sensors

- to indicate quality/freshness status of packaged foodstuffs

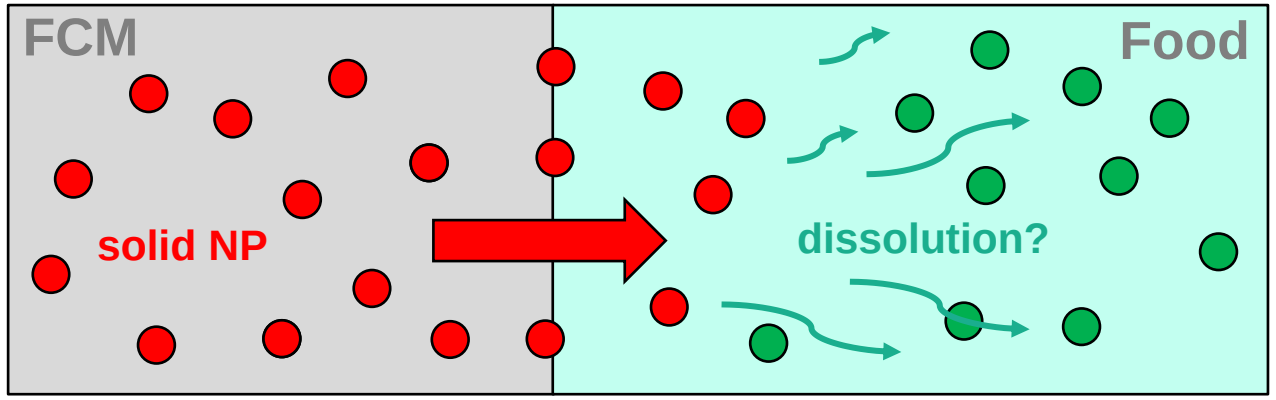
Nano-coatings:

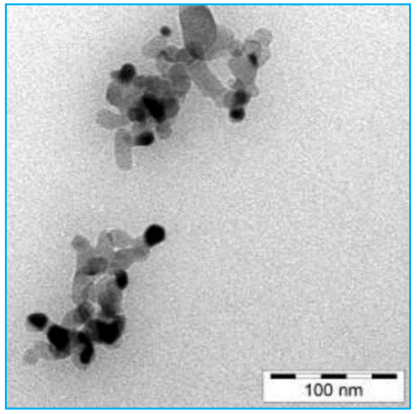
- to make antimicrobial and self-cleaning food contact surfaces
- to generate a barrier layer (reduce migration/adsorption)

Concerns over consumer safety from NP exposure arise only if NP are released (migration/abrasion) from FCM into food

Solubility threshold for FCM Nanomaterials

- Key aspect





TEM image
LDPE-nanocomposite

In case the **solid NP** is transferred into food:
is it sufficiently and rapidly dissolved into **ionic species (or molecules)**?
If no => nano-specific risk assessment
If yes => conventional risk assessment

Solubility threshold for FCM Nanomaterials

Adaptation of the solubility criterion to FCM substances

- The key consideration is that migration of nanoparticles from polymer based FCMs is generally very low (if any at all). This poses a low risk of consumer exposure to nanoparticles from the consumption of foods that was in contact with nano-composite based FCMs;
- Therefore, notwithstanding the solubility criterion provided in the Guidance, if a FCM substance has a solubility less than 33.3 g/L (i.e. not fully soluble), special considerations for small particles/nanoparticles in FCM should apply;
- However, an FCM substance may transfer from the FCM into food at a very low level that is solubilised (even though the intrinsic solubility may be <33.3 g/L);
- This discrepancy arising for the special case of FCM substances was addressed in the Guidance.

Solubility threshold for FCM Nanomaterials

Adaptation of the solubility criterion to FCM substances

- Under the EU Reg. 10/2011, migration limits for non-genotoxic substances are currently set at between 0.05 and 60 mg/kg (mg/L) food (food simulant).
  => 60 mg/kg is a generic upper migration limit for FCM substances.
- If a FCM substance has **solubility >60 mg/L**, then its **transfer from the FCM** to food will be in fully **solubilised form** and not as particles.
  Nota bene: If migration **exceeds 60 mg/L, then the FCM substance will not comply with the legislative limit and will not be allowed**.
- Therefore, RA Guidance was amended to say that a conventional RA should be sufficient for a FCM substance that has **solubility >60 mg/L**, where its levels migrating into food ....

  ….. can be considered to be in solubilised form on the basis of solubility/dissolution rate,
  ….. or can be demonstrated to be solubilised under worse-case time-temperature food contact conditions for the packaging before ingestion of the packed food.