Stakeholder Event, 24 November 2022

EFSA guidances on nano risk-assessment – Implementation to feed additives

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European Food Safety Authority

OUTLINE

- Implementation strategy – feed additives
- Specific considerations relevant to the risk assessment of feed additives

Implementation strategy – feed additives

- EFSA ensures fit for purpose assessments through its scientific guidance documents

Sectoral guidance documents

Technical guidance documents issued by the **FEEDAP Panel**
- 8 documents -

FEEDCO Unit

Cross-cutting Science

Guidance documents issued by the **Scientific Committee** applicable for all food sector areas

MESE Unit

https://www.efsa.europa.eu/en/applications/feedadditives/regulationsandguidance

Implementation strategy – feed additives

- Until today, no application for engineered nanomaterial as feed additive has been admitted to the risk assessment phase

- **Conventional materials** as feed additives might contain a fraction of small/nano-particles: to confirm if conventional risk assessment is sufficient or if a nano-specific risk assessment is needed

- Provision to investigate the presence of small particles is already included in the FEEDAP Guidance on characterisation (EFSA Journal 2017;15(10):5023)

GUIDANCE

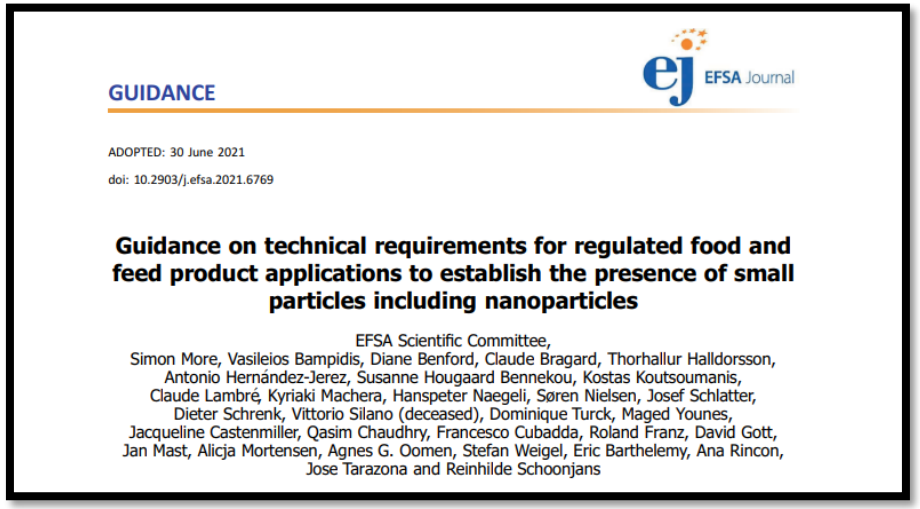
EFSA Journal

ADOPTED: 30 June 2021

doi: 10.2903/j.efsa.2021.6768

Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health

EFSA Scientific Committee,
Simon More, Vasileios Bampidis, Diane Benford, Claude Bragard, Thorhallur Halldorsson, Antonio Hernández-Jerez, Susanne Hougaard Bennekou, Kostas Koutsoumanis, Claude Lambré, Kyriaki Machera, Hanspeter Naegeli, Søren Nielsen, Josef Schlatter, Dieter Schrenk, Vittorio Silano (deceased), Dominique Turck, Maged Younes, Jacqueline Castenmiller, Qasim Chaudhry, Francesco Cubadda, Roland Franz, David Gott, Jan Mast, Alicja Mortensen, Agnes G. Oomen, Stefan Weigel, Eric Barthelemy, Ana Rincon, José Tarazona and Reinhilde Schoonjans



GUIDANCE

EFSA Journal

ADOPTED: 30 June 2021

doi: 10.2903/j.efsa.2021.6769

Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles

EFSA Scientific Committee,
Simon More, Vasileios Bampidis, Diane Benford, Claude Bragard, Thorhallur Halldorsson, Antonio Hernández-Jerez, Susanne Hougaard Bennekou, Kostas Koutsoumanis, Claude Lambré, Kyriaki Machera, Hanspeter Naegeli, Søren Nielsen, Josef Schlatter, Dieter Schrenk, Vittorio Silano (deceased), Dominique Turck, Maged Younes, Jacqueline Castenmiller, Qasim Chaudhry, Francesco Cubadda, Roland Franz, David Gott, Jan Mast, Alicja Mortensen, Agnes G. Oomen, Stefan Weigel, Eric Barthelemy, Ana Rincon, Jose Tarazona and Reinhilde Schoonjans

Implementation strategy – feed additives

Update the guidance on the Characterisation of feed additives

Send question to applicants to apply the Guidance on Particle-TR

Consult the cross-cutting WG on Nanotechnologies

Implementation strategy – feed additives

Update the guidance on the Characterisation of feed additives

- The requirement to assess the presence of nano/small particles has been already included in 2017
- The methodology used should be updated making reference to the Guidance on particle-TR
- This has been recorded in the Minutes of the 161st FEEDAP Plenary Meeting May 2022

Implementation strategy – feed additives

- **Guidance on the characterisation of feed additives**

EFSA Journal 2017;15(10):5023

- **Current text:**

"If the nature of the additive allows the possibility of the presence of nanoparticles, initially a particle size analysis of the additive by laser diffraction should be made. If the particle size analysis of the additive indicates that more than 1% of particles below 1 µm are present, this fraction should be further characterised by scanning electronic microscopy (wet method). Results should be expressed as a proportion of total number of particles. It should be clearly indicated if the product is a nanomaterial as defined by European legislation."

Implementation strategy – feed additives

- **Updated text:**

"For all additives (with the exception of additives consisting only of microorganisms), data should be provided to assess the presence of small particles including nanoparticles following the Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles (EFSA Scientific Committee, 2021a). In case the additive does not meet at least one of the Decision criteria listed in Table 1 of that Guidance, a full assessment for the fraction of small particles should be conducted in line with the requirements established in the Guidance on risk assessment of nanomaterials to be applied in the food and feed chain, human and animal health (EFSA Scientific Committee, 2021b) including additional information on the physico-chemical characterisation of the additive.

For additives consisting (or containing) engineered nanomaterials as defined in in Regulation (EU) No 2015/2283 (the Novel Food Regulation), the risk assessment including the physico-chemical characterisation of nanomaterial should follow the provisions of the Guidance on risk assessment of nanomaterials to be applied in the food and feed chain, human and animal health (EFSA Scientific Committee, 2021b)."

These changes will be revised and implemented in a future update of the guidance.

Implementation strategy – feed additives

Send question to applicants to apply the Guidance on Particle-TR

- For conventional materials: the applicant needs to provide information on the presence of small/nano particles in line with the EFSA SC Guidance on particle-TR
- For nanomaterials: the EFSA SC guidance on nano-RA should be followed
- Ongoing applications: during RA
- New applications: at the level of completeness check

Implementation strategy – feed additives

Send question to applicants to apply the Guidance on Particle-TR

- **Scope**
  - Technological feed additives
  - Nutritional feed additives
  - Sensory feed additives
  - Coccidiostats
  - Zootechnical feed additives

Feed additives consisting only of microorganisms are excluded from the scope!

Implementation strategy – feed additives

- To receive support in the assessment of the data in the light of the new EFSA nano Guidances
- To highlight feed-specific considerations

Specificities for feed additives

Appraisal routes proposed by the Guidance on Particle-TR

- **S.2** Solubility
- **S.2** Dissolution rate
- **S.3** Screening particle size
- **S.3** Quantification particle size
- **S.4** Coverage by existing studies

Aim: demonstrate that target species and consumers will not be exposed to small particles

Aim: demonstrate absence or quantify small particles in properly dispersed samples of feed additives

Aim: demonstrate that the fraction of small particles is properly covered by existing safety/ADME studies

S.2 Solubility

Aim: demonstrate that target species and consumers will not be exposed to small particles

Safety for the target species and consumers

Solubility of the feed additive

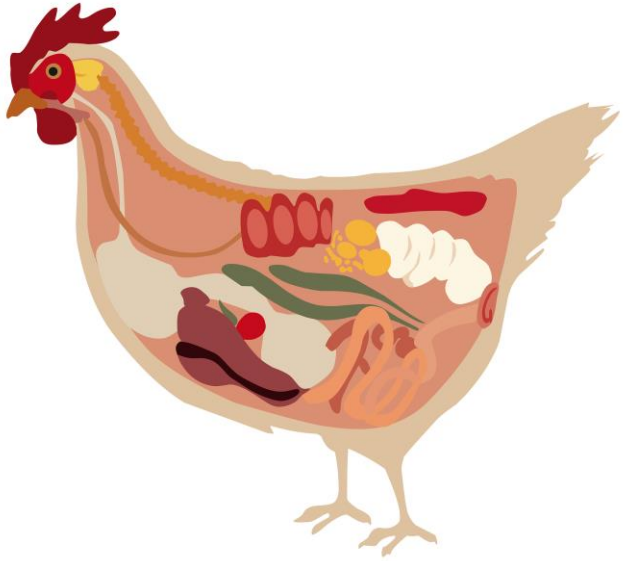
Solubility in water (Section 2.3.1)	Equal to or higher than 33.3 g/L	According to OECD TG 105 (OECD, 1995) with specific considerations for small particles	For multi-constituent substances and mixtures, the decision criterion has to be fulfilled for each constituent/component

Solubility of the residues

The solubility of the substance (or of the substances that constitute the residue) in water and/or lipids may be sufficient for confirming that, at the maximum residue levels of the substance, the residues in the treated animals will be fully dissolved. (see section 2.3.4.)

S.2 Dissolution rate criteria

- The dissolution protocol should be adapted in order to consider the physiological characteristics of each **target species**.
- The main elements to be considered are the gastrointestinal tract volume, the pH value of the different compartments, and the time required for the material ingested with the feed to reach the small intestine.



❖ Should the applicant choose the appraisal route via the demonstration of the dissolution rate criteria, he/she is invited to adapt the protocols to the target species: see questions sent to applicants during the risk assessment

Specificities for feed additives

S.3 Screening particle size

S.3 Quantification particle size

Aim: demonstrate absence or quantify small particles in properly dispersed samples of feed additives

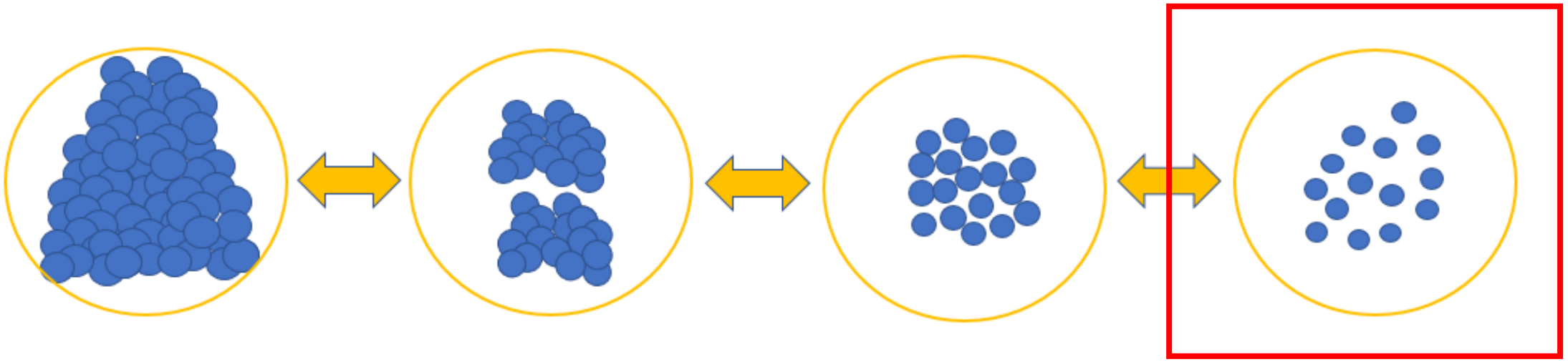
Particle size distribution can be measured for different purposes:

- **Oral toxicity**: the size of constituent particles should be determined
- **Inhalation exposure assessment**: the size of airborne particles should be determined

Specificities for feed additives

- For the assessment of **oral toxicity**, the focus of the measurement is on the size of constituent particles and their **smaller dimension**.

- **Ensuring proper dispersion is key for the risk assessment of nanoparticles** as allows to test a **nano-sized worst-case scenario**.



Specificities for feed additives

Proper dispersion of the material + **Proper technique/method of detection** → **Possible to apply the decision criteria**

Particle size distribution of the material (Section 3.3)	Particles equal to or larger than 500 nm The detection capability of the method(s) used for this assessment should provide convincing evidence that the material contains less than 10% of particles (number-based) with at least one dimension smaller than 500 nm	The method selection should be justified, and detection capability should be reported, examples of possible methods are: – centrifugal liquid sedimentation (CLS) – particle tracking analysis – descriptive EM – filtration complemented with chemical analysis	Proper dispersion of the material should be ensured (Section 3.2)

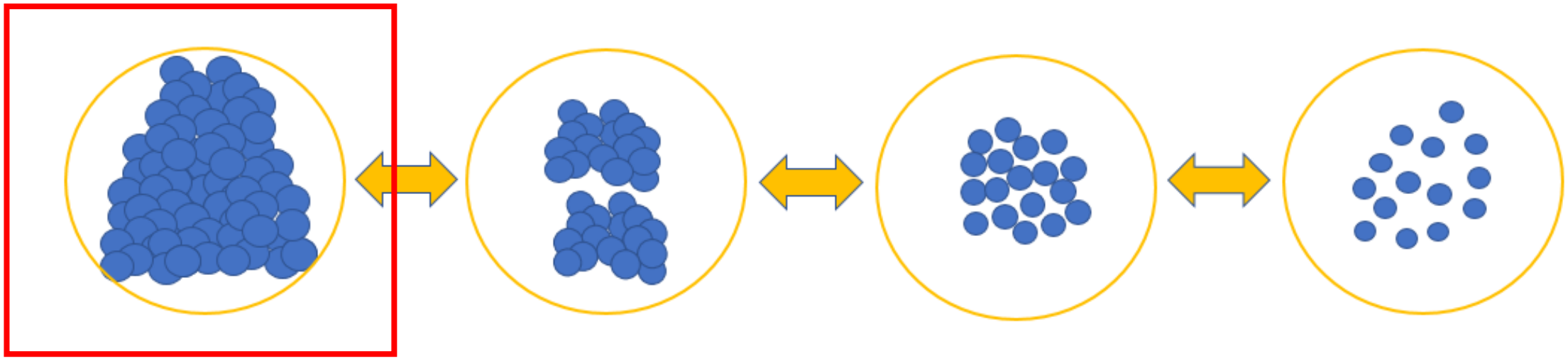
- Protocols and methods are described in Section 3.2 and 3.3 of the EFSA SC Guidance on particle-TR

Specificities for feed additives

- Users are likely exposed to airborne particles of feed additives during handling.

- For the purpose of the assessment of the **exposure of users by inhalation**, the level of agglomeration/aggregation of the airborne particles needs to be considered when the particle size measurement of the dust is performed.

- For conventional materials, the FEEDAP Guidance on user safety should be followed



S.4 Coverage by existing studies

Aim: demonstrate that the fraction of small particles is properly covered by existing safety/ADME studies

- **Applicable when the presence of small/nano particles cannot be excluded.**

there is no adequate information on the first two routes

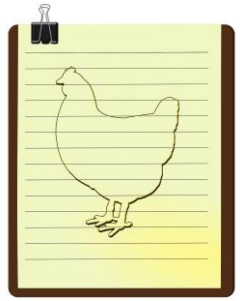
OR

the particle size data confirmed the presence of a fraction of small particles

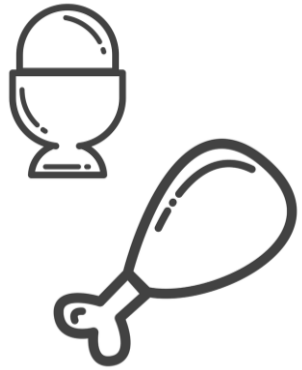
S.4 Coverage by existing studies

Aim: demonstrate that the fraction of small particles is properly covered by existing safety/ADME studies

- **Tolerance studies**
  - In general, tolerance studies are considered to sufficiently cover the hazard assessment of small particles present in conventional materials provided that the study conditions (including duration) is adequate. (See Section 4.2)



- **ADME studies and data on physico-chemical properties**
  - For example lipophilic organic substances can follow the uptake route of lipids: the available information on lipid-solubility, Kow, and toxicokinetic information, may be sufficient to conclude that, gastrointestinal uptake will be linked to the conventional processes. (Section 4.2)



Support initiatives to applicants

Stakeholder events

- March 2022 - *Stakeholder workshop on small particles and nanoparticles in food/feed*
  - Recording of the presentations are available at:

  https://www.efsa.europa.eu/it/events/stakeholder-workshop-small-particles-and-nanoparticles-food

- **November 2022 – *Info session on applications for feed additives (current)***

Other initiatives

- AskEFSA
- Telefonconference with EFSA

See EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products

https://www.efsa.europa.eu/en/supporting/pub/en-6472

Take-home message

- **Cross-cutting guidance documents are complementary to the sectoral ones**

- **For conventional materials:**
  - Use the Guidance on particle-TR to reply the question: ***Does a conventional risk-assessment sufficiently cover the additive under assessment or are nano-scale considerations needed due to the presence of small particles?***
  - Free choice between the appraisal routes:
    - Solubility/dissolution
    - Particle size
    - Existing studies
  - Compile the information supporting the selected appraisal route and provide a reasoned justification.

- **For nanomaterials:**
  - Use the Guidance on nano-RA to complete the dossier.

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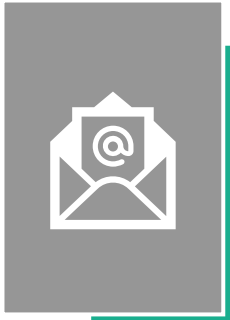

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