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EFSA Nano Guidances – Q&A

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Q&A session - OUTLINE

Questions and answers on the methodology

- Appraisal routes and decision criteria
- Risk assessment of nanomaterials

Questions and answers on the implementation

- Applicability/entry into force
- Scope
- Guidance update
- User safety

- **Other**

Q&A session – Questions on the methodology

TOPIC: Appraisal routes and decision criteria

Question

- For some products, even if they are less soluble and maybe contain small particles, the requirements for testing are very high and sometimes the need for such tests would be considered superfluous. The use of toxicity studies should be avoided where possible, but how does a company know what is the best choice?
- Can also a long history of safe use play a role, or does information of tolerance studies on target species with blood sampling contribute to answering questions on this issue?

Reply

- As elaborated in the Nano Guidances, the applicant can make use of the simpler appraisal routes proposed to exclude the need for nano-specific assessment. If this cannot be demonstrated, the applicant can check whether the existing tolerance/safety/ADME studies already cover possible nanospecific risks. Only in case of gaps not addressed by existing studies, there will be a need for any further study to address safety concerns related to nanoparticles exposure. Before conducting new *in vivo* studies, NAM-based approaches should be preferred.

Q&A session – Questions on the methodology

TOPIC: Appraisal routes and decision criteria

Question

- Since there is not any clear relation between number (%) of nanoparticles present in a material/feed additive and toxicity, what does EFSA think that might be the consequence of characterizing a feed additive "nanomaterial" (>50% nanoparticles)?

Reply

- Indication of median particle in terms of size number is to determine whether or not half (or more) of the particles in a material are in the nano range to be defined as a nanomaterial. Therefore, it has no 'risk implications' at this stage. After this step, risk assessment follows to consider the nano aspects as elaborated in the EFSA Nano Guidances.

Q&A session – Questions on the methodology

TOPIC: Appraisal routes and decision criteria

Question

- If possible, could you please explain different case studies / examples for powder and liquid substances in terms of the use of nanomaterial guidance.

Reply

- The Guidance on Particle - TR must be followed for all conventional materials (available either as powder or liquid). Therefore, the Guidance is also applicable to products marketed as liquid formulations unless it is confirmed (according to the methodology described in Section 2.3.1) that they do not contain small particles in suspension, and can therefore be considered as 'true liquids' or 'fully solubilised solids'. Substances that are true liquids or fully solubilised at normal conditions of oral ingestion are sufficiently covered by the sectoral guidance.

Q&A session – Questions on the methodology

TOPIC: Appraisal routes and decision criteria

Question

- For several feed additives, requests were received to submit analytical evidence for the solubility of the additive in water according to OECD TG 105 or equivalent, in line with the requirement of the Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles. However, we could not find any contract research laboratory that offers this kind of testing on a routinely basis.
- When receiving such a request for information, is there a possibility to discuss with EFSA the potential appraisal route, e.g. through a clarification telconference, to ensure that the data is not rejected due misinterpretation of the Guidance on Particle–TR?

Reply

- The Nano Guidances provide all necessary details on how to perform the assessment (i.e. OECD TG 105 integrated with the removal of particles in suspension by ultrafiltration), and further instructions for laboratories were provided during a dedicated Stakeholder Workshop (https://www.efsa.europa.eu/it/events/stakeholder-workshop-small-particles-and-nanoparticles-food).
- EFSA is available for clarification teleconferences as prescribed in 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)

Q&A session – Questions on the methodology

TOPIC: Appraisal routes and decision criteria

Question

- EFSA is proposing different appraisal routes in the recent guidance on the presence of nanoparticles. However, some of the appraisal routes (i.e. dissolution rate analysis) make reference on human physiological conditions although are requested for the safety of feed products. What route shall the applicant follow for the support of feed products, what protocol should be followed as representative for animal species? Shall we expect an update on the Guidance in regard to that?
- We need pragmatic solutions for dissolution rate testing with feed additives for all animal species

Reply

- EFSA acknowledges the lack of detailed provisions on the applicability of the dissolution rate appraisal route to target species. However, generic indications on the need to adapt the dissolution protocol to physiological conditions of target animals are provided, and based on the type of application (e.g. type of substance, number of target species for which the additive is intended) the applicant is free to select one or the best combination of appraisal routes to demonstrate that conventional risk assessment is sufficient.

Q&A session – Questions on the methodology

TOPIC: Appraisal routes and decision criteria

Question

- In the Guidance on technical requirements for product applications to establish the presence of small particles including nanoparticles, point 3.2 it is mentioned "the mean particle size should be measured by method such as....". For AF4 (Assymetric Flow Field Flow Fractionation) method as detection method, for ICP-MS it is mentioned "a single particle should be followed". Do we have the possibility to follow several particles for having more accurate data?

Reply

- The section mentioned refers to the methods, alternative to electron microscopy (EM), that can be applied to demonstrate the stability of the dispersion. AF4 and SP-ICP-MS are not suitable for measurement of constituent particle size distributions.
- Furthermore, it should be noted that SP-ICP-MS follows all particles but measures them in individual (single particle) capacity to derive range of size distribution.

Q&A session – Questions on the methodology

TOPIC: Appraisal routes and decision criteria

Question

- Will EFSA extend or elaborate on the list of accepted methods for solubility analysis and particle tracking analysis or descriptive EM? Laboratories seem not to be up to date with EFSA guidance and methodology may need to be adapted to type of product. This creates uncertainty on which and if the analysis will be accepted in any given application.
- In the guidance, 4 different examination methods are proposed. None of them seem to be equally suitable for all types of products. Third labs performing studies on particle size distribution (PSD) and on nanoparticle tracking analysis seem to have difficulties to decide which method to use, because they are not familiar with them, or because they do not offer all the methods to select the right one for a specific product.

Reply

- Both Nano Guidances provide extensive information on the techniques to be possibly selected, respective advantages and limitations. Also, the Guidance on Particle – TR includes a dedicated Appendix listing all different issues that should be considered when assessing the appropriateness of the analysis method and the outcome.
- However, EFSA acknowledges the intrinsic complexity of the topic and is considering to produce further guidance to provide additional indications on how to design and report results on particle size. Still, case by case considerations on the material under assessment remain key.

Q&A session – Questions on the methodology

TOPIC: Risk assessment of nanomaterials

Question

- If based on available information (or from literature), I know that my material has particle size in the nano range, or is a nanostructured material, which Guidance should I follow?

Reply

- In case of engineered nanomaterials, nanoforms, nanocarriers, nanostructured materials or conventional materials containing a fraction of nanoparticles requiring nano-specific assessment (as established by the Guidance on Particle-TR), the Guidance on Nano – Risk Assessment should be followed. The Guidance provides a tiered approach including waivers to simplify the assessment in case of non-persistent and non-toxic materials.

Q&A session - OUTLINE

Questions and answers on the implementation

- Applicability/entry into force
- Scope
- Guidance update
- User safety

- **Other**

Q&A session – Questions on implementation

Applicability/entry into force

- We would be very grateful if a reminder of key dates on the entry into force of the new regulation of nanomaterials could be included.
- I would like to learn about the intended date of entry into force/applicability of the new guidance and any transitional periods.

The need to identify and characterise small and nano particles has been already included in the currently applicable **FEEDAP Guidance on Characterisation of feed additives** (EFSA Journal 2017;15(10):5023).

The new guidance on particle-TR provide more detailed requirements how to establish the presence of small/nano particles and introduced a decision criteria and cut-off values that should be used to decide if a nano-specific assessment is needed.

The FEEDAP Panel in the minutes of its plenary meeting of May 2022 recorded that the new requirements outlined in the Guidance particle-TR substitute the former one and made reference to the two new nano guidance documents.

Q&A session – Questions on implementation

Scope

- My question will be focused on the relevance of technical requirements of small particles including nanoparticles specifically in enzyme preparations and in probiotics containing life microorganisms.

- What will be the status for microorganisms and enzymes. Argumentation could be provided that the nanoparticle assessment is not required. What type of argumentation would be accepted?

- Shall we expect the application of the new Guidance on nanoparticles in every new (Art. 4) or renewal (Art. 14) feed additive application regardless the type or category of the substance?

Additives consisting of only microorganisms are out of the scope.

Enzymes and microorganisms to be authorised with a formulation linked to a holder are within the scope: applicants should check if any of the ingredients could introduce small/nano particles in the additive to be authorised. The Guidance on particle-TR provides indications also for multi-constituent substances and mixtures.

All application types where EFSA is requested to assess the characterisation of a feed additive is included in the scope.

Q&A session – Questions on implementation

Guidance update

- Will new Guidances be released soon, to include the nano characterization?
- Is a new Guidance, describing the analytical methods to be applied, going to be published?
- Will the requirement for test for nano particles in connection with feed additives change from what is accepted at present?

The following guidance documents are applicable:

For conventional materials:

Guidance on particle-TR should be used to establish the presence of nano-particles. This contains all relevant analytical methods to be applied.

For nanomaterials:

Guidance on nano-RA should be used which provides detailed requirements for the characterisation of a nanomaterial

The Guidance on Characterisation of feed additives will be updated to redirect applicants to the two above-mentioned guidance documents (see FEEDAP Plenary minutes May 2022)

Q&A session – Questions on implementation

Guidance update

- If my feed additive contains no particle below 1µm, what should I do? Make particle size distribution characterisation or look at nanoparticles?

This provision, (i.e. 1 µm as cut-off value) still visible in the FEEDAP Guidance on characterisation, but it is not anymore valid. (see FEEDAP Plenary minutes May 2022)

The applicant should use the appraisal routes indicated in the Guidance on particle-TR to conclude on the presence/absence of small/nano particles and to decide if a nano-specific assessment is necessary.

Q&A session – Questions on implementation

User safety

- It seems that the Guidance is applicable to the feed additive, does the Guidance is applicable to the dust (from dusting potential analysis)?
- I would like to know, due to the new developments and current knowledge of the nanotechnology etc, what would the lowest particle sizes to be considered in the dust while evaluating the risks from inhalation exposure.

- The establishment of small/nano particles should be done **on the feed additive** that is subject of the application. The decision criteria and the cut-off values indicated in the **Guidance on particle-TR** should be followed and this is relevant to the additive to be authorised.

- For the **exposure assessment**, the applicant should follow the **FEEDAP guidance on user safety**. The relevant particle size for the exposure assessment is that of the airborne particles (i.e. particle size of the dust). Aggregates/agglomerates may be present in the dust. The PS analysis technique should allow to analyse the aggregated/agglomerated particles.

Q&A session – OTHER

- Clear rules on nano materials, update of Safety Data Sheet and labelling

We understand that this question refers to rules at regulatory level other than in the context of guidance for the risk assessment.

In general, the regulatory follow-up (including the labelling) stays with the risk manager.

The currently available documents provide guidance for the applicant and risk assessors related to the evaluation of presence of small particles and on the safety assessment of nanomaterials.

The Guidance on particle-TR was published following a mandate of the EC.

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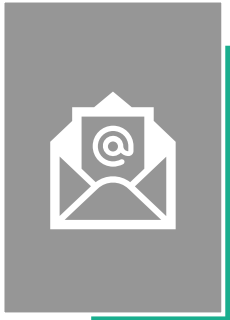

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