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Application of EFSA nano Guidance in the E171 opinion: a TDMA perspective

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EFSA Stakeholder workshop on small particles and nanoparticles in food

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TDMA represents the leading producers of titanium dioxide (TiO_2) in Europe

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Introduction

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- EFSA Nano guidance was applied to titanium dioxide/E 171 in the middle of an ongoing risk assessment
  - EFSA had previously considered E 171 as not meeting the definition of nanomaterial
- EFSA considered E 171 as safe in 4 opinions dating back to 2016
  - The studies requested by EFSA and submitted by TDMA showed no adverse effects
- EFSA then applied the new nano guidance when most of these studies had been completed
- 5th opinion published on 6 May 2021
  - Key conclusion is E 171 no longer considered safe due uncertainty for genotoxicity
  - The mandated application of the new nano guidance changed the outcome

Introduction (cont.)

- TDMA is committed to reduce the uncertainty related to E 171
- Continues to try to understand the main interpretation points but key questions remain open
- Presentation covers 3 of these areas:
  - Read-across
  - Nanoscale considerations (NSC)
  - New study design

Read-across

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- E 171 is a very specific form of TiO_2
  - Untreated/non-surface treated pigmentary non-nano grade with strict purity requirements
  - Representing less than 1% of TiO_2 produced
  - E 171 does not meet the EU recommendation of a nanomaterial
    - Not more than 50% of the number of particles below 100 nm
  - Though it does contain a fraction of nanoparticles
- EFSA Nano Guidance is clear related to different forms (page 3)
  - *Applicants must undertake a separate physico-chemical characterisation and specific risk assessment for each distinct nanomaterial/nanoform*

Read-across

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- In the 5th opinion, EFSA applied a read-across approach to consider other forms of TiO_2
  - Data on specialty industrial catalyst-type nano grades not used in food was relied on by EFSA in the evaluation for genotoxicity
- Read-across is foreseen in the EFSA Guidance (page 65)
  - *This justification must include detailed information on physico-chemical characteristics, as well as aspects related to toxicokinetic behaviour and toxicological hazard*
- The guidance/E171 opinion appears to be applied inconsistently
  - *A different threshold for read-across to show not safe?*

Nanoscale considerations

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- EFSA developed a comprehensive scoring for nanoscale considerations (NSC) in the 5th opinion on E 171 (Annex E)
- NSC1/highest reliability have the following criteria
  - Dispersion covered by a verified method (OECD) or a systematic approach
  - Sonication applying energy densities from 600 J/ml to 2500 J/ml sample volume plus confirmation of stability
  - Specific confirmation of sufficient level and stability of the dispersion such as electron micrograph, dynamic light scattering or zeta potential higher than 25 mV or lower than -25 mV
  - Use of demonstrably effective dispersing agents or surfactants
  - Information on the level of agglomeration in the stock suspension/powder in the treated feed

Nanoscale considerations (NSC)

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- Nanoscale considerations are not specifically included in the EFSA Guidance
  - Makes reference to *getting actual confirmation on exposure of cells/tissues to the nanoparticles or cellular uptake for in vitro studies is highly recommended to increase reliability* (page 48)
- Difficult to find justification that the use of high energy sonication and dispersing agents are a worst case
  - Certainly not representative of the use of E 171 in food
  - Arguably contrary to the Guidance itself
    - *Toxicological studies in which the exposure of laboratory animals mimics the consumers' exposure to nanoparticles are of relevance for risk assessment*. Point 1 on page 51 for in vivo studies.
- Nanoscale considerations (NSC) appear inconsistent
  - Particularly as there is nothing E 171 specific in the NSC

New study design

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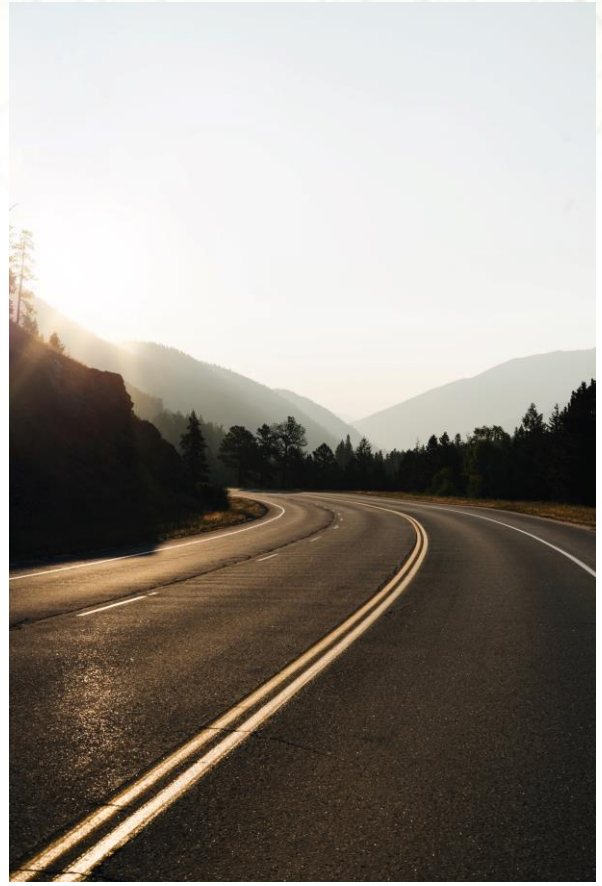
- Additional EFSA Guidance
  - *In specific cases, especially when exposure occurs mainly via solid and liquid foods, additional groups with dietary administration should be included in the study applying administration by gavage*. Point 6 on page 51 for in vivo studies.
- Does this mean that you should do 2 parallel 90 day oral toxicity studies for a substance such as E 171?
- Based on the precedent in the 5th E 171 opinion for nanoscale considerations
  - Should sonification and dispersing agents be applied?
  - In this confusing for other substances as it not clearly included in the EFSA Guidance?

Conclusions

- There appear to be inconsistencies in the application of the EFSA Nano guidance to E 171
- TDMA have found it difficult to apply the guidance for a new study
- Clarification would help in the assessment of food additives in the EU and beyond
- TDMA are willing to cooperate with EFSA and stakeholders to improve clarity



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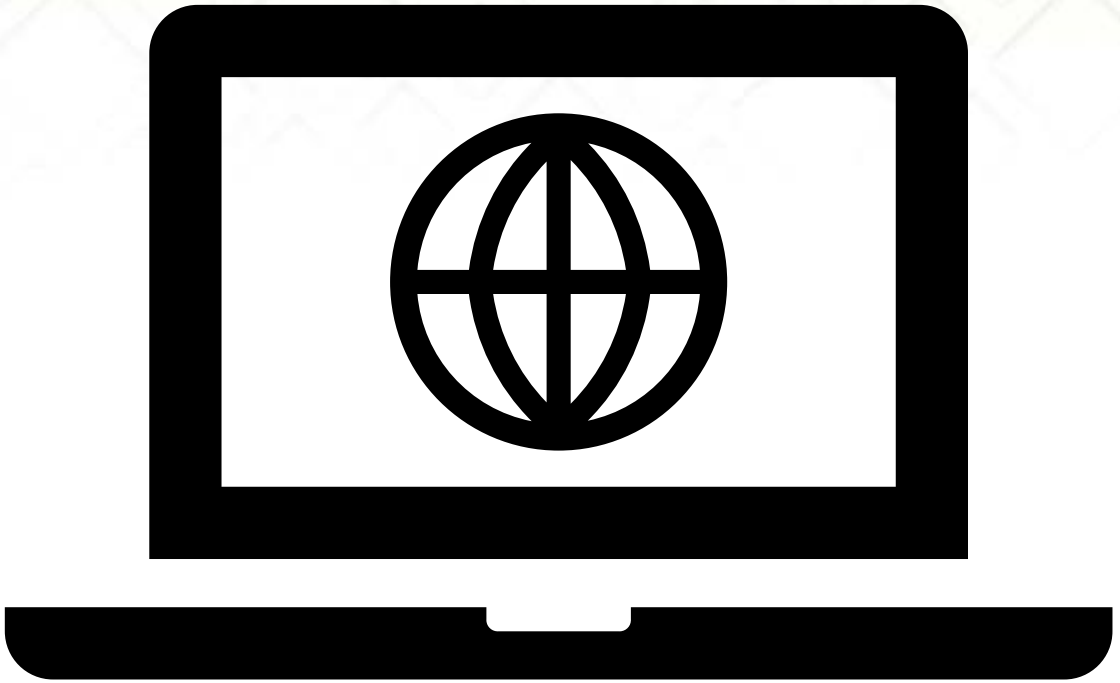
Thanks for your attention!

More information on tdma.info



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