Risks of nanotechnology in food

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European Food Safety Authority

Draft Opinion of the Scientific Committee on the

Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety

Public consultation:

17 October to 1 December, 2008

Outline

- Background
- Draft Opinion
  - Terms of Reference
  - Applications of Nanotechnologies in the food and feed area
  - Physico-chemical characterisation
  - Toxicokinetics
  - Toxicity
  - Environmental impact
  - Proposed Guidance for risk assessment
  - Conclusions
  - Recommendations
  - Public consultation

Terms of Reference (November 27, 2007)

European Food Safety Authority

The European Commission requested the European Food safety Authority (EFSA) to produce a scientific opinion

(1) On the need for specific risk assessment approaches for technologies/processes and applications including products of nanoscience and nanotechnologies in the food and feed area

(2) Identify the nature of the possible hazards associated with actual and foreseen applications in the food and feed area

(3) To provide general guidance on data needed for the risk assessment of such technologies and applications

EFSA Scientific Committee Working Group

- **15 experts in:**
  Nanotechnology, nanoscience, toxicology (including molecular toxicology and toxicokinetics), biochemistry, nutrition, exposure and risk assessment

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Introduction to the Draft Opinion

- **Focus on engineered (manufactured) nanomaterials (ENM) that are deliberately introduced into the food/feed chain**

- ***Excluded:*** **incidental ambient contamination of food/feed by nano-structured material, resulting from anthropogenic and natural sources**

- **ENM in feed treated in a similar way as those in food**

Terms

- **Nanoscale refers to a dimension in the order of 100 nm, and below.**

  Some latitude is allowed – there are size-related effects that can appear at larger size

- **Macroscale material ("bulk"), predominantly in sizes beyond the nanoscale**

- **"Dissolved chemical" describes a size smaller than the nanoscale**

Applications in food/feed area

European Food Safety Authority

Five broad categories:

- **Food contact materials (FCM).**
  Food packages, food processing equipment
  Probably most important
- **Food/feed ingredients processed to form nanostructures**
- **ENM added to food/feed**
- **Biosensors**
- **Other (agro-chemicals, pesticides, veterinary medicines)**

Present market status

- **EFSA is not aware of any database providing information on nanotechnology applications or products on the EU market**
- **Information from EU food industry organisations:**
  Currently no food products on the market
- **The current status of FCM or uses of nanotechnology processes is more uncertain, and such applications may be available on the EU market**
- **Available from outside EU**
- **Nanofraction (not ENM) present in conventional ingredients/ products?**

Physico-chemical characteristics

- **As size decreases, surface area increases dramatically**
- **ENM have novel properties because of high surface-to-volume ratios**
- **High surface reactivity**
- **ENM undergo dynamic changes in response to their environment. Free ENM tend to agglomerate and react with biomolecules**
- **Interaction with surroundings including food/feed matrix, gastro-intestinal tract content, biological tissues**
- **Translocation across biological membranes/distribution from portal of entry**
- **Differ from macroscale and dissolved chemicals of the same material – possibly altered toxicokinetics and toxicity profile**

Analytical tools for detection, quantification and characterization

- **Analytical tools exist for the qualitative and quantitative characterization of ENM**
- **Wide variety of ENM – no "best" technique for "all" situations**
- **Important to measure the ENM in the appropriate matrix – food/feed much more demanding than in simpler matrices**
- **Some ENMs cannot be distinguished from naturally occurring variants of the same material**
- **Analysing the chemical composition of the ENM possible, but not always information on whether still in nano-form**
- **Limited number of standardized reference materials for ENM**
- **Not possible to routinely determine ENM *in situ* in the food or feed matrix or biological tissues**

Exposure to ENM from food and feed

- **Relies on information provided by industry itself on use of ENM**
- **Migration from FCM into the food.**

  Only a few studies – some ENM may migrate while others not
- **Significant consumer and animal exposure to ENM ingredients in food and feed is currently not likely within EU, though there may be exposure to nanoscale fractions within other materials**
- **However, products are available outside EU; this contribution to consumer exposure is not quantified**

Toxicokinetics of ENM (1)

- **Limited information on oral exposure**
- **Mainly metals/metal oxides (i.e. insoluble)**
- **Likely changes of ENMs in food/feed and GI tract matrices**
- **Quantification through determination of the element in the ENM, without confirmation that nano-structure was preserved**
- **Limited absorption into portal circulation and lymph system**
- **Formulation at the nanosize may modify the toxicokinetic behaviour of ENM, as compared to the macroscale form or the dissolved chemical**
- **The liver and the spleen are major organs for systemic distribution of metallic ENMs. However, for certain ENMs, all organs may be targets**

Toxicokinetics of ENM (2)

- **Smaller-sized ENMs have a more widespread tissue distribution compared to larger, although data is limited**
- **There is some information that certain ENMs can pass across the placenta. There is no information on milk**
- **There are only limited data on potential, long-term accumulation/persistence of ENMs. However data suggest that insoluble ENMs may be retained and accumulate**

Toxicity of ENM (1)

- **The understanding of potential toxicity after oral intake of ENM is in its infancy. Data are insufficient to draw general conclusions**

- **Limited number of ENMs have been studied after oral administration, mainly metals and metal oxides.**
  Limited characterization of ENM used in toxicity studies

- **Only one study administration via feed. Other studies, administration via artificial dispersions (i.e. via gavage)**

- **Only a few studies have compared the toxicity of nano-formulated and conventional form of the same chemical**

- **Only a narrow range of effects have been studied in the toxicity tests**

Toxicity of ENM (2)

- **Most of the reported oral *in vivo* studies are on acute toxicity of ENMs.**

  Long-term studies have not been conducted

- **There is no adequate information that allows conclusions on the relationship between physico-chemical properties (size, surface properties, etc.) of ENMs and toxicity *in vivo* or *in vitro***

- **It is generally not possible to extrapolate the potential toxicity of ENM from information on dissolved or macroscale chemicals**

- **Numerous *in vitro* studies have shown that some ENMs induce oxidative stress at high concentrations. There are some data to indicate possible genotoxic and inflammatory responses *in vitro*. The studies have limitations.**

Environmental impact

- **Likely dispersal of ENMs to the environment during production, use and disposal of ENM in the food and feed area**
- **Possibility of re-entry of certain ENMs as contaminants in the food and feed chain.**

  Sewage
- **Recycling processes of food packaging material containing ENM should be considered, may affect the migration of the ENM in the recycled material**
- **Possible secondary environmental implications during disposal from possible release of antimicrobial ENMs from FCM**
- **Only limited information available of these processes related to ENM in food and feed**

Proposed Guidance on risk assessment (1)

- **General Risk Assessment Paradigm can be applied to RA of ENM** (Hazard Identification, Hazard Characterization, Exposure Assessment, Risk Characterization)
- **Lack of sufficient data and information of potential hazards of ENM**
- **Limited nano experience**
- **The adequacy of currently existing toxicological tests to detect all aspects of potential toxicity of ENM has yet to be established**
- **RA of ENMs will have to be carried out on a case-by-case basis**
- **Current guidance documents in the food and feed area do not address ENM. Modifications may be necessary**

Proposed Guidance (2)

- **Proper identification and detailed characterization of the ENM as used in food/feed, qualitatively and quantitatively**

- **Size (including distribution), mass, surface area, specific surface area, number, shape, chemical composition (including impurities and processing chemicals), surface properties (e.g. coating, charge) and solubility (including hydrophilicity)**

Proposed Guidance (3)

- **Difficult to analyse the presence of ENMs.**
  Conservative approach: Assume that the entire amount of ENM added to the food/feed, or migrating from FCM, is present in its nanoform

- **If demonstrated that the product does not contain nanomaterial, or that the ENM does not persist in the food/feed – likely no exposure and RA would not differ from that of a conventional chemical in the dissolved or macroscale form**

Proposed guidance (4)

- **If evidence is present that ENM dissolves in food/feed or the GI lumen, the RA can be based on the non-nanoform of the chemical. However, possible local exposure and effects should be considered**

- **If there is no information to prove the disappearance of the nanostructure, it shall be assumed that the nanoform may be absorbed**

Proposed Guidance (5)

- **Toxicokinetic data needed if the nano-structure may be absorbed**
- **Toxicokinetics will have to rely on *in vivo* studies. *In vitro* systems have not yet been validated for extrapolation to *in vivo* conditions**
- **The toxicokinetic studies supply information for decisions regarding further testing regimes and assessment**
- **If ENM intended to increase bioavailability:**
  Changes in bioavailability should be determined
- **RA should also be performed on the nanoscale carrier**

Proposed Guidance (6)

- **Toxicity needs to be assessed by *in vivo* assays**
- **Guidelines for toxicity testing of conventional chemicals (e.g. OECD) should be able to pick up important toxic effects of ENM.**
- **However, experience with ENMs is very limited and the adequacy of the existing toxicological tests to detect all aspects of potential toxicity of ENM has yet to be established**
- **Administration via feed is most relevant, but gavage may be considered.**

  The choice should always be justified

Proposed Guidance (7)

- **The risk characterization procedure (dose-response) would not, in principle, differ from that of dissolved chemicals or the macroscale material**

- **However, dose metrics is currently discussed, and several dose metrics may need to be explored in addition to mass (e.g. surface area and particle concentration)**

- **Finally, the limited database on ENM assessments should be considered in the choice of appropriate uncertainty factors in the risk characterization step**

Conclusions (1)

- **The opinion is generic in nature and not a risk assessment of nanotechnologies as such,**
  or possible uses thereof,
  or of specific products

- **The current usage of ENM in the food and feed area is unknown**

- **The nanospecific properties of ENMs are likely to affect their toxicokinetic behaviour and toxicity profile**

Conclusions (2)

- **Limitations and specific uncertainties:**
- **Difficulty to detect, characterize, and measure ENM in food/feed and biological matrices**
- **There is limited knowledge of (likely) exposure from possible applications and products in the food and feed area**
- **Very limited information on toxicokinetics and toxicology**
- **Environmental aspects unknown. Re-entry into feed/food?**

Conclusions (3)

- **The currently used risk-assessment paradigm is considered applicable for ENMs**
- **But adaptations are needed**
- **The risk assessment of ENM has to be performed on a case-by-case basis**
- **Current toxicity-testing approaches used for conventional materials are a suitable starting point**

Conclusions (4)

- **Comprehensive identification and characterization of the ENM should be requested from users/petitioners**

- **The physicochemical properties of ENM compared to conventional dissolved and macroscale chemical counterparts imply that their toxicokinetic and toxicity profiles cannot be fully inferred by extrapolation from data on their equivalent non-nanoforms**

Conclusions (5)

- **Information on whether it can be excluded that the ENM is absorbed in nanoform is important**

- **If this cannot be excluded, *in-vivo* studies on toxicokinetics and repeated-dose toxicity are needed, together with appropriate *in-vitro* studies (e.g. for genotoxicity).**

- **Current toxicity-testing methods should pick up important effects, but may need methodological modifications**

Conclusions (6)

- **Additional ("novel") toxic effects caused by ENM, which are not readily detectable by current standard protocols are possible. Additional endpoints, not routinely addressed, may need to be considered.**

- **For hazard characterization, different dose metrics may need to be explored, in addition to mass**

- **Uncertainty must be considered when choosing uncertainty factors (to arrive at acceptable daily intake, tolerable weekly intake, etc.)**

Recommendations

- **The opinion should be updated in the light of developments in the area**
- **When RA guidance documents in the food/feed area are reviewed, nanotechnology aspects shall be considered**
- **Particularly important research areas are:**
- **Methods for detection and analysis of ENMs**
- **Toxicokinetics and toxicity of a wide range ENMs, i.a. in relation to dissolved and macroscale forms of coprresponding chemicals**
- **Relationship between physico-chemical properties and toxicokinetics/toxicity**

Next steps

- **Public Consultation:**
  Start 17th October
  Deadline for comments Monday 1st December, 17:00 CET

- **Additional studies/data**

- **Comments on the proposed risk-assessment approach**

- **All contributions will be appreciated and considered**

- **Submission via the online commenting form found at**
  www.efsa.europa.eu
  Public Consultations and Calls for Contributions

  http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902132298.htm

- **Final adoption of opinion by Scientific Committee after public consultation**

Merci!