Nanomaterials in Food – Prioritisation & Assessment

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Abstract

Nanomaterials (NMs) are of significant economic interest and have a huge impact on many industries including the food industry. The main application in food industry includes food additives and food packaging. However, the effects of NMs on human health are highly discussed, as well as the need of harmonised analytical methods and risk assessment methodologies. In line with these discussions, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) has started in 2017 a 2-year project focusing on NMs in food, to which the fellow was involved under the framework of the European Food Risk Assessment Fellowship Programme (EU-FORA). This technical report contains a description of the working program, the aims and the activities to which the fellow was involved during this placement. The main aims of the programme were to be involved in different steps of risk assessment process, to improve knowledge regarding food process, analytical and toxicological methods and to learn how to conduct expert assessments. All aims were linked with different kind of activities. Gaining hands-on experience on food risk assessment was achieved mainly by collecting occurrence data and performing exposure assessment calculations for the 'of concern' NMs, while scheduled visits to laboratories specialising in analytical methods of nanoparticles and toxicological studies helped to improve knowledge in these fields. Regular participation in the Working Group (GT) related to NMs in food and interaction with experts within ANSES facilitated the learning process of how to conduct collective expertise as well as to be further trained in risk assessment processes. Furthermore, apart from knowledge gained in risk assessment and NMs, the fellow was able to obtain transferable skills and knowledge that can be used to increase the scientific capacity of the fellow's home institute as well as to expand her scientific network, which could lead to collaboration opportunities in the future well beyond this fellowship.

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1. Introduction

Nanotechnology is a rapidly developing field and nanomaterials (NMs), are of significant technological and economic interest and have a huge impact on many industries including the food industry. The current use of NMs in the food sector is associated with three main areas: food additives and food packaging (Calzolai et al., 2012; Mattarozzi et al., 2017). While the nanotechnology has many applications and benefits for the food sector, there are also some concerns about their safety. The main concerns arise from the lack of knowledge regarding the interactions of NMs at the molecular or physiological levels and the fact that new NMs and applications are constantly being produced (Mattarozzi et al., 2017). Additionally, while the risk of particle inhalation has received much attention, there are still gaps of knowledge regarding possible adverse health effects due to oral exposure to nanoparticles (Winkler et al., 2018). Moreover, it is foreseen that due to the expanding commercialisation of NMs as part of the modern diet, their oral intake will increase worldwide (Winkler et al., 2018). In addition, since nanotechnology is a new field, there are still a lot of discussions on what is the definition of a NM especially from the regulatory point of view.

The International Organization for Standardization (ISO) has defined NM as a material with any external dimension on the nanoscale ('nano-object') or having an internal or surface structure in the nanoscale ('nanostructured material') (ISO, 2015). In particular, a nano-object is defined as a discrete piece of material with one, two or three external dimensions on the nanoscale. 'Nanoparticles' are nano-objects with all external dimensions on the nanoscale, where the lengths of the longest and shortest axes do not differ significantly. If the dimensions differ significantly, typically by more than a factor of 3, other terms, such as 'nanofibre' (two external dimensions in the nanoscale) or 'nanoplate' (one external dimension on the nanoscale) may be preferred to the termanoparticle. In turn, a 'nanostructured material' is defined as a material having internal or surface nanostructure, i.e. a composition of interrelated constituent parts in which one or more of those parts is a nanoscale region. 'Nanoscale' is defined as ranging from approximately 1 to 100 nm (ISO, 2015).

The European Commission issued a Recommendation (currently under review) for a definition of a NM in 2011 to provide a common basis for regulatory purposes across most areas of European Union (EU) policy where 'nanomaterial' means a natural, incidental or manufactured material containing particles in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number−size distribution, one or more external dimensions is in the size range 1−100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness, the number−size distribution threshold of 50% may be replaced by a threshold between 1 and 50%. Moreover, engineered NMs are a subset of the 'nanomaterial' that is defined in the European Commission's Recommendation of 2011 (European Commission, 2011).

In the Novel Food Regulation (EU) No 2015/22837 and referring to Regulation (EU) No 1169/20118 on the Provision of Food Information to Consumers, Engineered NM means 'any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale (European Union, 2011, 2015).

To ensure sustainable development and use of nanotechnology, especially in the food sector, this requires control and monitoring of NMs, as well as risk assessments on their application, which in turn requires information about their toxicity and an exposure assessment (Bouwmeester et al., 2009; Mattarozzi et al., 2017). Even though a number of analytical methods for the detection and characterisation of NMs exist (Calzolai et al., 2012; Mattarozzi et al., 2017), it is clear that it is necessary to improve and harmonise the analytical methods as well as to find methodologies to perform nanospecific risk assessments for the implementation of future regulations (Mattarozzi et al., 2017). In line with this, European Food Safety Authority (EFSA) has recently produced a guidance for the risk assessment of nanoscience and nanotechnology applications in the food and feed chain (EFSA, 2018a).

2. Description of work programme

In line of these discussions, French Agency for Food, Environmental and Occupational Health & Safety (ANSES) started at late 2017 a 2-year project focusing on NMs in food. The main objectives of this project are:

a) To identify the NMs present in food
b) To prioritise them in terms of potential health concern
c) To estimate exposures and if possible to perform a health risk assessment for the 'of concern' NMs in food.

A dedicated ad hoc working group (Nanomaterials in food) was set to deal with this issue and the project was split into two different phases:

First phase: The focus was on the use of NMs in the food industry in order to identify the type of NMs involved in the food process. For this, database analyses were performed (French and international, i.e. Global New Products Database, GNPD) as well as industrial and Non-Governmental Organisation (NGO) hearings.

Second phase: The focus was on the social impact of NMs as well as on the scientific and regulatory issues that arise from this. During this phase, based on literature searches, a prioritisation of the 'of concern' NMs concerning food safety was performed. Another aim of this working group is to coordinate specific research activities to complement information extracted from bibliography, in order to improve NMs dietary exposure data and if data allow it, to perform a health risk assessment for the selected NMs.

The fellow was involved in the second phase of the project, placed in the UERALIM unit (Food Risk Assessment Unit) at DER (Risk Assessment Department) for 1 year. During this period, the fellow was supervised by Dr Gilles Riviere and Dr Bruno Teste and the tasks of her work were under the framework of the working group (WG) (Nanomaterials in food) activities and in close collaboration with the experts. The work programme was set in collaboration with the Laboratory of Genetic Toxicology at the Institut Pasteur de Lille de Lille, led by Dr Fabrice Nesslany, who is also the chairman of the working group.

Prioritisation of nanomaterials in food

After the prioritisation of the substances containing nanoparticles, it has been decided that the work of the fellow would focus on the following food additives:

a) Titanium Dioxide, TiO_2 (E171)
b) Silicon Dioxide, SiO_2 (E551)

Titanium dioxide-TiO2-E171

TiO_2 is a white powder, which is mainly used in products to give a white background colour. Titanium dioxide in bulk form is approved as a food additive with number E171 and it is used on a large scale as a whitener and as a colorant to impart brightness to food products (Mattarozzi et al., 2017). More specifically according to the EC Regulation 1333/2008 (European Union, 2008), TiO_2 is authorised as a food additive (E171) in EU in quantum satis, in 51 food categories. Therefore, since there is no max permitted limit (MPL), the concentration in food can vary a lot. Examples of food products containing TiO_2 could be chewing gum, ice cream and confectionary products like candies, chocolate products, cakes pastries and biscuits (Lomer et al., 2000; Weir et al., 2012; Fiordaliso et al., 2018). Other food products could include sauces, dressings, spreads, cheese or even fish products like surimi (Yin et al., 2017).

The food additive E171 consists of TiO_2 particles and can be present in two major crystalline forms, anatase and rutile. Literature data show a great variability in the proportion of crystalline forms as well as in the particle size distribution in the different commercially available batches of E171 since the size of the particles can vary from a few dozen to several hundred nanometres (Weir et al., 2012; Yang et al., 2014; Fiordaliso et al., 2018). Therefore, since part of the food-grade TiO_2 material has been shown to be nanosized, this has created many discussions whether the food additive is considered as a NM or not and if it is safe for human consumption. (European Commission, 2017).

Silicon Dioxide-SIO2-E551-SAS

The food additive, silicon dioxide (E551 or SAS-synthetic amorphous silica), is used in the food industry as an anticaking agent, thickener or carrier of flavours, therefore is often added to foods that are in powder form e.g. salt, vegetable powder, egg powder, creamer, coffee powder etc. (Dekkers et al., 2011; Mattarozzi et al., 2017).

More specifically according to the EC Regulation 1333/2008 (Annex II), SiO_2 (E 551) is authorised as a food additive in 22 food categories. Several food categories are authorised at MPLs ranging from 2,000 to 30,000 mg/kg and others at quantum satis (QS). Silicon dioxide (E 551) can be authorised together with silicates (E 552, E 553a and E 553b) in different forms like fumed (pyrogenic) silica and hydrated silica (precipitated silica, silica gel and hydrous silica) depending on the process (thermal or

wet) used for their manufacture. In addition, E551 is authorised for other application in Parts 1–5 of Annex III e.g. as a carrier in emulsifiers and colours or as a food additive in nutrients.

According to EFSA Opinion, E551 is a material comprised of aggregated nanosized primary particles. These aggregates can further agglomerate to form larger structures. The sizes of the aggregates and agglomerates are normally greater than 100 nm. However, depending on the starting material and/or on the manufacturing process, it cannot be totally excluded that some aggregates of primary particles could be smaller than 100 nm in size (EFSA, 2018b).

2.1.   Aims

The main aims of the working program 'Nanomaterials in Food – Prioritisation & Assessment' were the following:

a) The fellow to be involved in different steps of risk assessment process (e.g. collection of occurrence data, hazard identification and characterisation, estimating exposures based on food consumption data and risk characterisation) according to specific guidelines (e.g. 'Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain') (EFSA, 2018a). More specifically, the idea was to perform literature searches (scientific and grey literature) to gather occurrence data, for the selected NMs, which can be used to calculate the exposure of the general French population and/or the exposure of specific populations (e.g. children).

b) To be further trained in current risk assessment methodologies in place at Anses (for nanotechnologies but also for non-nano chemicals) and to improve knowledge regarding food process, analytical and toxicological methods.

c) Learn how to conduct expert assessments in response to a request (public authorities, internal, stakeholders) based on compliance with ethical standards to prevent conflicts of interest and to ensure independence, collective multidisciplinary expertise, independency, quality etc.

2.2.   Activities/Methods

Learning objectives were achieved by the activities described below, in line with the aims of the program.

2.2.1.   Involvement in different steps of risk assessment process

The fellow was mainly involved in the collection of occurrence data and exposure assessment calculations for the selected NMs (TiO_2 and SiO_2) as described below. The remaining risk assessment steps: hazard identification, hazard characterisation and risk characterisation of the selected NMs are under process since the WG dealing with NMs in food is currently trying to set up a methodology for them. If time allows, the fellow will be further involved in these tasks for the remaining time of the EU-FORA fellowship.

2.2.1.1. Collection of occurrence data

As previously described, one of the aims of the ad hoc working group (Nanomaterials in food) was to improve NMs dietary exposure data and to perform a health risk assessment for the selected NMs, if data allow it. Along with this aim, the fellow undertook this task for collecting occurrence data for the food additives Titanium Dioxide (TiO_2) and Silicon Dioxide (SiO_2), in food products by performing a literature search.

The aim of this activity was to collect occurrence data for each food category for which TiO_2/SiO_2 is authorised according to the EC Regulation 1333/2008. For the collection of the occurrence data, two approaches were used: a) reported industry use levels of E171 and b) food analysis data corresponding to individual food products. For the literature search, the databases PubMed and Scopus were used and searches were restricted to the English language while no restriction was applied for the time of publication. Additional information was retrieved from: a) relevant web pages of National/ European Agencies/Bodies (e.g. EFSA, RIVM), b) grey literature from Google Scholar (e.g. Published NGO's data), c) data provided by DGCCRF (Directorate-General for Competition, Consumer Affairs and Fraud Control) inspections.

Information about each food product was individually collected (whenever it was possible) and registered in an excel file. Information included details about the product (description of product, labelling, photos, brand, point of sale, origin etc.), the concentration of the additive (in mg/Kg or mg/L)

as well as information about the method of analysis (validation data, LOQ/LOD) and sample preparation information. After registration, all food products were categorised according to Food Categorisation System (FCS) and sorted according to the number of the food category. The food categorisation was based on the 'Guidance document describing the food categories in Part E of the Annex II to Regulation (EC) No. 133/2008 on Food Additives' (European Commission, 2017). Finally, a min, mean and max value was calculated for the concentration of additive for each food category. For the mean value, the weighted approach was used to combine values between different sources when this was applicable.

Developing a methodology for the collection of occurrence data was the biggest challenge of this task, since many obstacles had to be overcome (combining data from different sources, quality/validity of data, food categorisation etc.) during the procedure.

Concerning TiO_2 the methodology used for the collection of occurrence data along with the results, the uncertainties and limitations of the study were published in an ANSES Opinion (ANSES, 2019) where detailed information can be found. According to these results, the highest concentrations of E171 are found in the following food categories: Confectionery products, dairy analogues, flavoured drinks, sauces, decorations coating and fillings as well as in food supplements in which the maximum concentration measured was 26,950 mg/kg.

The second aim of this activity was to collect information concerning the concentration of the nanoparticles of TiO_2/SiO_2 (either in food products or in the food additives itself) by performing a literature search. Concerning the concentration of Nps of TiO_2 expressed in % by number, the results were published in an ANSES Opinion (ANSES, 2019). These results indicate that on average 25% of the particles in E171 are nanoparticles (with a dimension less than 100 nm) while the min and max values reported in the literature were 6% and 55%, respectively.

Moreover, the fellow was involved in setting up a methodology to calculate a percentage of Nps by mass in E171 from available data and she was also involved in the final calculations.

The results of these tasks are not included in this report and are not discussed further since its part of the current work of the WG (NMs in food), the results of which will be published in an ANSES Opinion by the end of 2019.

2.2.1.2. Exposure Assessment Calculations

The fellow used the data collected for TiO_2/SiO_2 to perform an exposure assessment for different French population groups. The calculations for TiO_2 were performed by using the FAIM template (Food Additives Intake Model) for which an authorisation of use was requested form EFSA. Different scenarios were examined and the results shall be used for a future risk assessment of nano-TiO_2 in food. The calculations for SiO_2 are currently in progress.

The results obtained from the exposure assessment calculations are not included in the report and are not discussed further since its part of the current work of the working group (Nanomaterials in food), and the results of which will be published in an ANSES Opinion by the end of 2019.

2.2.2. Improve knowledge regarding food process, analytical and toxicological methods and further training in current risk assessment methodologies in place at ANSES

2.2.2.1. Improve knowledge on analytical methods for nanomaterials

The fellow visited the Laboratoire National de Metrologie et d' Essais-LNE (Paris, 27 of March, 2019) in order to gain further knowledge on the methods that can be used for the characterisation and quantification of nanoparticles in food products. This was very important for the fellow since the characterisation of NMs is an important step in nanospecific risk assessment and specifically for the steps of hazard identification.

During the visit, the principles of the main methods used by LNE (SEM-EDX, AFM, Zeta meter, DLS, BET instrument, XRD) to characterise the key parameters of NMs (size, shape, charge, concentration, specific surface, porosity, surface condition) were explained and a short demonstration of sample preparation procedure was performed (extraction of TiO_2 from a candy).

2.2.2.2. Improve knowledge on toxicological methods

The fellow was invited to visit the laboratory of Genetic Toxicology, Institut Pasteur de Lille (Lille, 18-20 of June, 2019), where she had the opportunity to gain knowledge on genotoxicity testing.

The principles of the main genotoxicity tests where explained and the guidelines associated with these tests were indicated (e.g. OECD). Moreover, it was explained how the interpretation of results is

done and what is required (e.g. criteria) in order to conclude that substance is genotoxic/mutagenic or not. During the visit, the fellow followed the laboratory procedure for the in vivo comet assay (Primary DNA damage) and part of the in vitro Ames test (Gene mutation test) and in vivo (bone marrow) and in vitro (mammalian cells) micronucleus assay (Chromosomal aberration test). Moreover, the principles of the in vivo Transgenic Mice and Pig-A tests (Gene mutation tests) were explained.

Overall, the visit to the Laboratory of Genetic Toxicology helped the fellow not only to increase knowledge on toxicological methods but also to better understand how these tests can be used for the hazard identification and characterisation. Moreover, the knowledge acquired from this training will help the fellow to be more familiar with toxicological results while reading literature in the future.

2.2.2.3. Further training in risk assessment methodologies in place at ANSES

During the 1-year's placement, the follow was encouraged to arrange independent meetings with ANSES colleagues, who have knowledge and expertise on different fields relevant with RA methodology. This interaction helped not only to increase knowledge of the fellow but enabled her also to extend her network within ANSES. Overall, the fellow was able to increase knowledge and to discuss on the following subjects:

  a) Collection of food consumption data at ANSES − INCA studies: The aims of the last survey (INCA3) were explained as well as the methodology used to collect the data and how these can be utilised. In addition, the fellow received information on how food products can be classified according to FoodEx2 categories and was able after to use the EFSA browsing catalogue for food categorisation.

  b) Total diet studies performed at ANSES (TDS): Several aspects concerning TDS were discussed. The fellow received information concerning the study design and the methodology used for this kind of studies (e.g. prioritisation of food and chemicals, sampling, food analysis etc.) as well as on the utilisation of these kinds of data for RA purposes. Moreover, the advantages of using TDS studies versus using data from monitoring and control programs were analysed.

  c) Database for occurrence data − CONTAMINE database: The data from national surveillance and control plans are collected and standardised by ANSES in contamine database, along with the data from TDS studies. The fellow discussed several aspects concerning the Contamine database like, its uses and applications, the quality of data as well as how the data are registered and categorised.

  d) Hazard identification and hazard characterisation: Members of the UERALIM unit devoted time to explain to the fellow the major toxicological studies and how their use for hazard identification and characterisation.

  e) PBPK models: The fellow received information on the most common uses and applications of PBPK models for chemical RA.

  f) Social aspects of NMs: The role of the Social Sciences, Expertise & Society Unit of ANSES was explained and information was provided for the activities of the unit concerning NMs.

Additionally, the fellow was involved in another project on the risk assessment of Cadmium (Cd) due to the consumption of seaweed food products. This arrangement was in agreement with the fellow, in order to get a broader knowledge on risk assessment methodologies in place at Anses and to have a better understanding on expert assessments processes. For that, the fellow had followed the procedures for the collection of occurrence and consumption data, which will be used for an exposure assessment calculation. During this process, the fellow gained knowledge on how you exclude or include occurrence data depending on the quality of results and on the criteria that is used for this decision.

2.2.3. Conduct expert assessments

ANSES provides collective expertise in the Agency's fields of competence in response to requests from the public authorities and stakeholders entitled to submit requests, as well as in the context of internal requests. The scientific expert assessments are conducted collectively in conjunction with Expert Committees (published as opinions on the ANSES website) and lead to recommendations designed to assist the competent authorities for risk management decisions.

During this 1 year of placement, the fellow attended several meetings of the WG (NMs in food) and was regularly presenting the results of her work to the experts. During these meetings, the fellow was involved in brainstorming processes and discussions with experts to determine the ways to conduct expertise. The fellow was therefore in this way taking part in the collective multidisciplinary expert

assessment process and has got hands-on experience and understanding of ANSES's expert assessment process which was a unique a highly valuable experience.

Moreover, she has followed the work of the ad hoc 'TiO$_2$' emergency collective expert appraisal group (GECU) which was created in response to a formal request in order to provide scientific and technical support on the risks associated with ingestion of the food additive E171. GECU's work was published in an ANSES Opinion (ANSES, 2019) which included the fellow's work results concerning the occurrence of TiO$_2$ in food as previously described. After the issue of this Opinion, the French Authorities decided to suspend the marketing of foods containing (titanium dioxide – TiO$_2$, E 171) as of January 2020 for 1 year, a decision that highlights the connection between risk assessment and risk management and the importance of risk assessment on policy decision.

2.3. Other activities

Learning objectives were further achieved by the following activities:

a) Participation in a symposium on 'Food Contaminants - Emerging Approaches to Know and Prevent Risk' (Paris, 19 December 2018)
b) A seminar on literature search called 'Agency Information Resources' given by a staff member at ANSES (ANSES, 31 October 2019)
c) Participation in Parma Summer School on Risk Benefit in food safety and nutrition (Parma, 11–13 June 2019)

3. Conclusions

The working program of 'Nanomaterials in Food – Prioritisation & Assessment' has provided a unique opportunity for the fellow to gain insights into the whole risk assessment process and linked principles and practices as well as to obtain knowledge in the field of NMs. NMs as a subject was the most challenging part of the project, since this is a new field with a lot of scientific interest. In addition, the obtained transferable skills and new knowledge could be further used to increase the scientific capacity of the fellow's home institute

The activities of the fellow proceeded in accordance with the work program. All aims were achieved and part of the fellow's work has been published in an ANSES Opinion and has been linked with a risk management decision as previously described.

Moreover, the EU-FORA program and this 1-year placement in ANSES provided an opportunity for the fellow to interact with experts having a long experience not only in NMs but also in risk assessment in general, enabling the fellow to expand her scientific network. Active participation in a WG was a unique and a highly valuable experience.

Finally, this experience gained at ANSES could also lead to future collaboration opportunities well beyond this fellowship.

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Abbreviations

AFM	Atomic Force Microscope
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
DER	Risk Assessment Department
DGCCRF	Directorate-General for Competition, Consumer Affairs and Fraud Control
DLS	Dynamic Light Emitting
EU-FORA	The European Food Risk Assessment Fellowship Program
FAIM	Food Additives Intake Model
FCS	Food Categorisation System
FoodEx2	Version 2 of the EFSA Food Classification and description system for exposure assessment
MPL	max permitted limit
NGO	Non-Governmental Organisations
NMs	Nanomaterials
OECD	Organisation for Economic Co-operation and Development
QS	quantum satis
RA	Risk Assessment
RIVM	Dutch Institute of Public Health and the Environment
SEM-EDX	EDX Scanning Electron Microscope Coupled with Energy-dispersive X-ray Spectroscopy
SiO_2	Silicon Dioxide
TDS	Total Diet Studies
TiO_2	Titanium Dioxide
UERALIM Unit	Food Risk Assessment Unit
XRD	X-Ray Diffraction