EXTERNAL SCIENTIFIC REPORT

Inventory of Nanotechnology applications in the agricultural, feed and food sector

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Ruud Peters*, Puck Brandhoff, Stefan Weigel, Hans Marvin, Hans Bouwmeester

RIKILT: Wageningen UR, Wageningen, The Netherlands
*corresponding author; ruudj.peters@wur.nl

Karin Aschberger, Hubert Rauscher, Valeria Amenta, Maria Arena, Filipa Botelho Moniz, Stefania Gottardo, Agnieszka Mech

JRC: Nanobiosciences Unit, Institute for Health and Consumer Protection, Ispra, Italy
contact; karin.aschberger@ec.europa.eu

Acknowledgement: JRC Ispra: Teodor Ivanov, Aris Tsois, Laia Quiros Pesudo

ABSTRACT

The objective of this study was to prepare (i) an inventory of current and potential future applications of nanotechnology in the agri/feed/food sector and (ii) to review the regulation of nanomaterials in the EU as well as in non-EU countries. The first was achieved by preparing a Nano Inventory containing data extracted from four information sources: an extensive (structured) literature search, additional ad-hoc literature searches, company websites and questionnaires. From the Nano Inventory three inventory lists have been generated via dedicated queries: current and future nanotechnology applications, toxicological data and risk assessment status of nanomaterials in the agri/feed/food sector.

The results for nanotechnology applications show that nano-encapsulates, silver and titanium dioxide have the highest number of records in the Nano Inventory and that food additives and food contact materials are the most indicated current applications. Potential future developments are expected in the field of nano-encapsulates and nano-composites in applications such as novel foods, food/feed additives, biocides, pesticides and food contact materials. The query on toxicological data shows that most information is available for silica, titanium dioxide and silver to characterise their potential human hazard, including cytotoxicity, genotoxicity, repeated dose toxicity, and biokinetics. The inventory includes only a limited set of records for the risk assessment status of nanomaterials used in agri/feed/food applications showing that only a few materials have been evaluated according to the available literature. Finally, the review of legislation and regulation in the EU as well as in non-EU countries shows that currently a few EU legal acts incorporate a definition of a nanomaterial to enable specific provisions for nanomaterials. In many non-EU countries a broader approach with limited nanomaterial specific legislation and/or legally binding definition of nanomaterials is applied which mainly builds on guidance for industry.

Any enquiries related to this output should be addressed to FEED@efsa.europa.eu

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KEY WORDS

Nanotechnology, nanomaterial, agriculture, feed, food, inventory, toxicity, risk assessment, legislation.

DISCLAIMER

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SUMMARY

The objective of this study was (i) to prepare an inventory of current and potential future applications of nanotechnology in the agri/feed/food sector and (ii) to review how nanomaterials are regulated in the EU as well as in non-EU countries. The Nano Inventory developed for EFSA was implemented in a Microsoft Access environment and filled with data extracted from four sources of information: an extensive (structured) literature search, additional ad-hoc literature searches, company websites and two questionnaires. The extensive literature search was carried out for nanomaterials in the agri/feed/food sector and about 9000 references were found from different bibliographic databases. The application of selection criteria led to a final set of 896 references relevant for the purpose of the inventory. These included information on the application of nanomaterials in agricultural production, food and feed processing and additives, food packaging, the mode-of-action of nanomaterials, the eco- and human toxicology and the legislation of nanomaterials. Two questionnaires, one on production and use and one on regulation and safety assessment of nanomaterials in agri/feed/food applications were sent to companies, research institutes, authorities, consultants and other experts to gain additional information about the current and future production and use of nanomaterials, their regulation and safety assessment. In total over 1000 e-mail invitations were sent and about 80 reactions (responses to both questionaires and general statements in emails) were received.

Information from all sources was entered into the Nano Inventory resulting in 633 records of nanotechnology applications. Physico-chemical characteristics, product names, suppliers, information on (eco)toxicity testing, target species and exposure were entered, when available. From the Nano Inventory three types of information were retrieved via dedicated queries: (i) "*Current and future application*", (ii) "*Toxicological data*" and (iii) "*Risk assessment status*". These queries allow the creation of inventory lists with various types of information on the nature of the nanomaterials, their application, eco- and human toxicological profiles, implications for safety and exposure scenarios. The inventory lists cover 55 different nanomaterials and 12 different applications.

The results for "*Current and future application*" show that nano-encapsulates, silver and titanium dioxide have the highest number of records in the Nano Inventory and that food additives and food contact materials are the most indicated applications. Currently, 276 nanomaterials are confirmed to be available on the market, however, an exact distinction between those that are confirmed to be on the market and potential nanomaterial applications cannot always be made. In addition, there are some particles, such as silica, that have a long history of application and may therefore be considered as non-nano, even if they contain a fraction in the nanosize. In total 633 nanotechnology applications were found and 55 types of nanomaterials for agri/feed/food were identified. The nanomaterials are very diverse, including metals, metal oxides, clay and full-carbon materials and organic nanomaterials consisting of nano-encapsulates and nano-composites. Less than 20% of the different nanomaterials are involved in more than 80% of the applications and only a limited number of nanomaterials are involved in most of the applications. A comparison between current and future applications indicates a trend from inorganic materials like silver towards organic materials like nano-encapsulates and nano-composites. The results also indicate that applications in novel foods, feed additives, biocides and pesticides are currently mostly at a developmental stage. No information was found that would allow an extrapolation of nanotechnology applications from the food to the feed sector. However, some food applications may be expected to be used for feed as well.

The query on "*Toxicological data*" provides information about the type of toxicity tests performed with the different nanomaterials that were included in the inventory lists. Although the inventory lists were not constructed as an exhaustive source of toxicity data of a particular material, still 691 nanomaterial-toxicological data combinations were found. The data included in the Nano Inventory

mostly involve endpoints like cytotoxicity, genotoxicity and repeated-dose toxicity for silica, titanium dioxide and silver. In addition, it can be concluded that the lack of systematic reporting of the full set of physico-chemical properties reduces the usefulness and comparability of the toxicity data. Improvement of this aspect would facilitate the use of the studies in risk assessment processes. The potential toxicity of a few relevant nanomaterials (silver, titanium dioxide, zinc oxide, silica and carbon nanotubes) is presented. The effects of silver nanomaterials seems to be related with the release of silver ions from these materials. Studies also suggest the *in vivo* formation of silver nanoparticles following absorption of silver ions. Toxicity studies of titanium dioxide show that it may be bioavailable upon oral exposure, but that the translocation rate is unknown and that the genotoxicity shows conflicting results. From orally administered zinc oxide only minor amounts seem to be absorbed, most likely in ionic form. Absorbed zinc seems to be cleared from organs after 7 days. Synthetic amorphous silica is an important form of silica used in many food items and the most recent reviews suggest safety for consumers when exposed via food. *In vivo* studies with carbon nanotubes show no uptake while *in vitro* studies suggest the uptake in cells, however no ability to cross the intestinal wall. In all cases uncertainties and conflicting results remain and further studies are recommended to conclude on the possible uptake and toxicity of these nanomaterials.

The *“Risk assessment status”* query was retrieved from a very limited number of studies found in the literature search. A complete risk assessment of a specific nanotechnology application in the agri/feed/food sector including exposure and hazard assessment could only be retrieved for a few nanomaterials, e.g. on silica and titanium dioxide. Most studies reported in the literature focus either on hazard assessment (toxicity) or release (exposure) of nanoparticles. A complete risk assessment is available for only a few studies, one being synthetic amorphous silica in food, the other titanium dioxide in packaging materials. Such risks assessments are made very carefully because of the uncertainties in both the hazard and the human exposure data. There is some risk assessment data on silver and zinc oxide but mostly incomplete which resembles the current situation on the risk assessment of nanomaterials. The main reason for carrying out a risk assessment was "self assessment"; risk assessments because of regulatory requirements or as part of the submission of nanomaterials to the authorities were not found.

Legislation and regulation of nanomaterials were reviewed in EU as well as non-EU countries based on literature research and a questionnaire. Currently, only a few EU legal acts incorporate a nanomaterial definition: No 1169/2011 and 10/2011 on food information to consumers and plastic food contact materials, respectively, and No 1223/2009 and 528/2013 on cosmetic and biocidal products, respectively. Interestingly the definition in two former regulations is different from the one in the two latter definitions. In 2011 the European Commission published a Recommendation on the definition of a nanomaterial (2011/696/EU). A draft law on novel food (COM/2013/0435) also provides a legal basis to regulate nanomaterials or the application of nanotechnology in food products. The review of existing legislation in non-EU countries shows that other countries have limited nanomaterial specific legislation and no legally binding definition. They have rather adopted a broader approach which builds mainly on guidance for industry.

In conclusion, the results extracted from the Nano Inventory provide an overview on nanomaterials presently on the market for use in the agri/feed/food sector and their purpose. The comparison between products already on the market and products currently in research and development stage, suggest that in the near future nanotechnology applications in the agri/feed/food sector will include increasingly organic nanostructures such as emulsions and micelles in food processing, nano-encapsulates for the delivery of vitamins and nutrients, and encapsulation of pesticides and fertilizers in agriculture. Other foreseeable applications are in nano-sized adsorbents in feed for specific problems such as pathogens and mycotoxins. Beacause technological developments go fast, reports on new and potential applications of nanomaterials are not always accompanied by thorough/uniform physico-chemical characterisation of the nanomaterial, nor by safety tests representative for their ingestion. However, such information is vital to develop safe applications of existing nanomaterials or new nanomaterials safe by design.

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BACKGROUND AS PROVIDED BY EFSA

On 18 October 2011 the European Commission published the following Recommendation[1] on the definition of nanomaterial: '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 nm-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 %. According to it Member States, the Union agencies and economic operators are invited to use the definition of the term "nanomaterial" described in the above recommendation in the adoption and implementation of legislation and policy and research programmes concerning products of nanotechnologies.

In addition, Regulation (EU) N° 1169/2011 (of 25 October 2011)[2] has introduced the definition of engineered nanomaterial (ENM) as follows: 'engineered nanomaterial' 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. Properties that are characteristic of the nanoscale include: (i) those related to the large specific surface area of the materials considered; and/or (ii) specific physico-chemical properties that are different from those of the non-nanoform of the same material.

Nanotechnology applications for the food sector (food additives and food contact materials) are relatively recent. The main developments so far aim at altering the texture of food components, encapsulating food components or additives, developing new tastes, controlling the release of flavours, developing nano-sensors for traceability and monitoring the condition of food during transport and storage, and/or increasing the bioavailability of nutritional components.

There are a few examples of available products where a nano-sized additive has been specifically developed for animal feed. For example, certain mono-grade vitamin mixes are commercially available for use in poultry and livestock feed. Examples of research and development in this area include a feed additive comprising a natural biopolymer from yeast cell walls that can bind mycotoxins to protect animal against mycotoxicosis, and an aflatoxin binding nano-additive for animal feed. Although the feed additive sector is currently far behind in the application of nanotechnology and nanomaterials in the future it could benefit from the development of further applications in this sector. Theoretically, any nano-sized mineral, vitamin or other additive developed for a food application could equally be used for animal feed.

EFSA's Scientific Committee (SC) published in 2011 a guidance document on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain.[3] In this guidance it is noted that EFSA Panel on additives and Products or Substances used in Animal Feed (FEEDAP), assessing the safety and efficacy of feed additives, has already included the concept of "size" of substances in its technical guidance documents for the preparation of dossiers for feed additives. Also the Panel on Food Additives and Nutrient Sources added to Food (ANS) has in its draft "Guidance for

[1] OJ L 275, 20.10.2011, p.38 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:275:0038:0040:EN:PDF)

[2] Regulation (EU) N° 1169/2011 (of 25 October 2011)3 on the Provision of Food Information to Consumers which requires the mandatory labelling of nano ingredients in foods placed on the EU market as of 13 December 2014OJ L 304, 22.11.2011 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:304:0018:0063:EN:PDF)

[3] http://www.efsa.europa.eu/en/efsajournal/doc/2140.pdf

submission for food additive evaluations"[4] addressed data and information requirements for nanomaterials.

TERMS OF REFERENCE AS PROVIDED BY EFSA

Considering the constant development in the field, more up-to-date information on the state of the art would be required on food additives/food contact materials/feed additives applications in the area of nanotechnology. Also the EFSA Scientific Network for Risk Assessment of Nanotechnologies in Food and Feed has identified at its 2012[5] meeting the need for an inventory of nanomaterials used in the food/feed chain as a priority.

Therefore, the EFSA FEED Unit (in coordination with FIP Unit, NUTRI Unit, SCOM and EMRISK Unit) is requested to launch a procurement call for the preparation of a background document on the current knowledge in the field of nanotechnology and prepare an inventory of food additives/food contact materials/feed additives applications of nanotechnologies currently used and/or reasonably foresee to be used. The background document could then be used by EFSA's Panels for consideration and potential update of the specific guidance documents.

In addition, this information would allow the SC and its Network to describe further best practice for safety assessments before placing nanomaterial on the market and/or update the horizontal SC Guidance Document of 2011, when needed.

This contract was awarded by EFSA to:

Contractor: RIKILT: Wageningen UR, Wageningen, The Netherlands.
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Contract/grant title: Inventory of food additives and other food ingredients, food contact materials, and feed additives applications in the area of nanotechnologies

Contract number: CFT/EFSA/FEED/2012/01-CT01

[4] http://www.efsa.europa.eu/en/consultations/call/111117.pdf

[5] http://www.efsa.europa.eu/en/events/event/120403a.htm

1. INTRODUCTION AND OBJECTIVES

1.1. Nanotechnology and the agri/feed/food sector

Nanotechnology is defined by the International Organization for Standardization as the "application of scientific knowledge to manipulate and control matter at the nanoscale in order to make use of size- and structure-dependent properties and phenomena, as distinct from those associated with individual atoms or molecules or with bulk materials" (ISO, 2010). The word "nano" refers to a billionth of a meter (10^{-9} m) and nanotechnology can be understood as the fabrication, characterisation and manipulation of particles with sizes <100 nm (ASTM, 2012: Nanowerk, 2010).

Although the size limit of below 100 nanometres is fairly arbitrary, it is generally accepted and has been suggested or adopted by several bodies to define nanoparticles, or nanomaterials consisting of such particles. There has also been debate whether concentration limits to define nanomaterials should be expressed on a mass basis or on a particle-number basis. In this respect, the European Commission adopted a Recommendation on the definition of a nanomaterials 2011/696/EU on 18 October 2011 (European Commission, 2011b). According to this recommendation, a "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 are in the size range 1 nm - 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 %.*

- *By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.*

It is expected that this definition will be used primarily to identify materials for which special provisions might apply (e.g. for risk assessment or ingredient labeling). However, there are various scientific and/or technical challenges related to the measurement of materials in the implementation of the recommended nanomaterial definition. In particular, the requirement of measuring the constituent particles inside aggregates, the difficulty to convert experimentally measured signals into accurate number-based size distributions, and to detect and count particles at the lower size range of the definition, i.e. smaller than 10 nm. Analytical methods able to identify materials as nanomaterials according to the recommended nanomaterial definition are in development. However, most current methods have a detection limit higher than 1 nm or a lower sensitivity for smaller particles. As a consequence, they can only be used for a positive test to prove that a material is a nanomaterial, but not for a negative test to prove that a material is not a nanomaterial. Presently, none of the currently available methods is able to determine for all kinds of potential nanomaterials whether they fulfil the definition or not. Therefore a range of measurement methods is required to investigate whether nanomaterials fulfil the regulatory definition (Linsinger et al., 2012).

Nanotechnology offers substantial prospects for the development of innovative products and applications and it is expected that the number of products and production volumes involving nanotechnology will increase in the future. The advantages that nanotechnologies offer arise from the unique functional properties of nanosized particles and materials, collectively called nanomaterials, which have a much larger surface to mass ratio compared to bulk materials. These unique functionalities of nanomaterials are being used by many industries, including the food and agriculture sectors. Nanomaterials are used in food to prevent microbial spoilage of packaged food, to improve colours, flavours, taste and texture and increase the bioavailability of vitamins and minerals. The application of nanomaterials has also enabled the development of innovative packaging materials that can improve the safety and shelf life of products. These prospects have led to innovative developments in the agriculture, food and related sectors.

However, due to the special properties of nanomaterials there are concerns about their safety, especially because of our limited knowledge of human health effects of these materials and the fact that new nanomaterials and applications thereof are constantly being produced and thus exposure to them are increasing. In response to this uncertainty more up-to-date information is required on the state-of-the-art of applications of nanotechnology as pesticides, food additives, food contact materials and feed additives, i.e. the use of nanomaterials in the agricultural, feed and food sector (thereof agri/feed/food sector). Nanotechnology applications are currently being studied, developed and in some cases already used in the different parts of the agri/feed/food sector (different stages of the food production chain are illustrated in Figure 1).

Figure 1: The food production chain, possible applications of nanotechnology is mentioned in the text.

Examples of different (future) applications in the agri/feed/food sector are:

Agriculture:
- Nanocapsules for more efficient delivery of pesticides, fertilizers and other agrochemicals
- Nanomaterials for detection of animal and plant pathogens
- Nanomaterials for identity preservation and tracking and tracing

Food and feed:
- Nanocapsules to improve dispersion, bioavailability and absorption of nutrients
- Nanomaterials as colour enhancers
- Nano-encapsulated flavour enhancers
- Nanotubes and nanoparticles as gelation and viscousifying agents
- Nanoparticles for selective binding and removal of chemicals and pathogens from food

Food packaging:
- Nanoparticles to detect chemicals of foodborne pathogens
- Biodegradable nanosensors for temperature and moisture monitoring
- Nanoclays and nanofilms as barrier materials to prevent spoilage and oxygen absorption
- Nanoparticles for antimicrobial and antifungal surface coatings

Food supplements:
- Nanoparticle suspensions as antimicrobials
- Nano-encapsulation for targeted delivery of nutraceuticals

1.2. Types of nanomaterials

Nanomaterials can roughly be divided into three categories: organic nanomaterials, combined organic/inorganic (surface modified) nanomaterials and inorganic nanomaterials as shown in Figure 2. In recent years all these materials have attracted great interest. Organic nanomaterials are developed as nano-encapsulates for vitamins, antioxidants, colours, flavours and preservatives. The production of organoclay is of interest for making polymer/clay nano-composites with improved physical and mechanical properties (Singla et al., 2012). Inorganic nanomaterials as such are used in food and food supplements, while embedded in polymer matrices they are used in food packaging applications. The conventional form of materials as silica and titanium dioxide are approved as a food additive but do contain a nanosized fraction (Peters et al., 2012; Weir et al., 2012). The use of these different nanomaterials in the agri/feed/food sector is described briefly below.

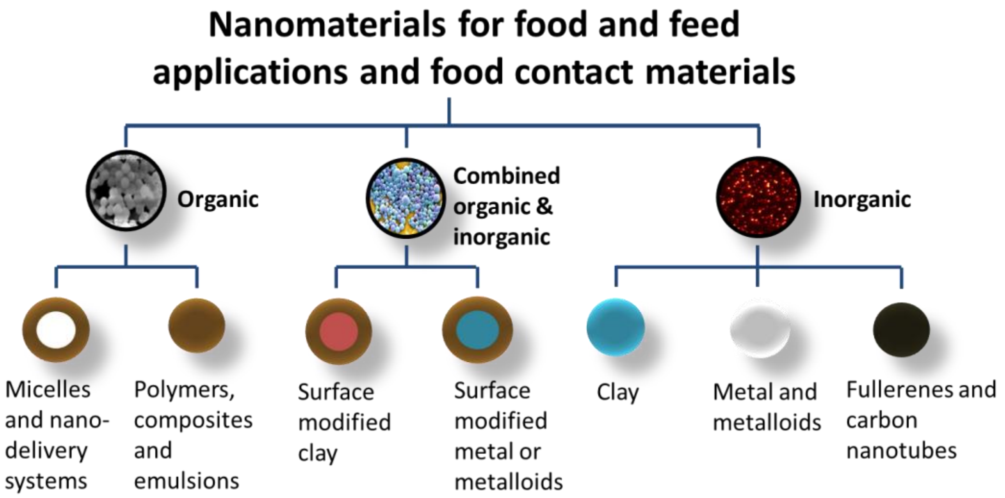

Figure 2: Types of nanomaterials for (future) food and feed applications and food contact materials.

1.2.1. Organic nanomaterials

A major (future) application area of organic nanomaterials is in the encapsulation of additives, but also pesticides and veterinary drugs. These so-called nano-encapsulates consist generally of micelles, liposomes or nanospheres, and are composed of materials which are generally regarded as safe (GRAS) (Peters at al., 2011). The structure of two common types of nanomaterials, micelles and liposomes are shown in Figure 3. In general, three types of organic nanomaterials can be distinguished, lipid-, protein- and polysaccharide-based nanomaterials. Lipid-based nanomaterials are among the most applied organic nanomaterials since they can be produced using natural ingredients on an industrial scale and have the ability to encapsulate compounds with different solubilities. Protein-based nanomaterials are often prepared using a ‘bottom up’ approach, where structures are built from molecules capable of self-assembly. For example, globular proteins such as whey proteins from milk have the ability to form particles with sizes of 40 nm while 95% of the caseins are naturally self-assembled micelles with a 50-500 nm diameter. Polysaccharides are naturally occurring compounds in plants (e.g., pectin, guar gum), animals (e.g., chitosan, chondroitin sulphate), algae (e.g., alginates) and microorganisms (e.g., dextran). Up to now, chitosan, a naturally biodegradable and biocompatible polysaccharide, and starch appear to be the most used polysaccharides for nanomaterials in pharmaceutical and biomedical applications.

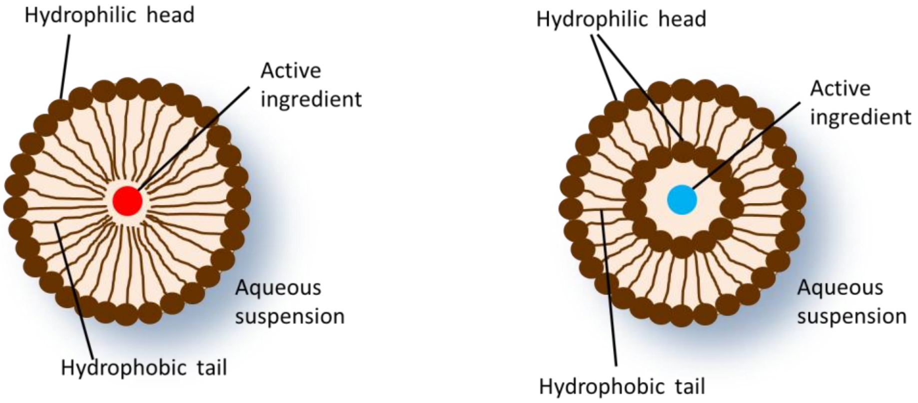

Figure 3: Active ingredients are trapped inside the sphere of the nanoparticles protecting them from unwanted physical or chemical changes before reaching their destination. Sizes of micelles and liposomes are typically in the range of 10-100 nm and 100-300 nm, respectively (Peters et al., 2011).

Various ingredients like vitamins, antioxidants, colours, flavours and preservatives, but also pesticides and veterinary drugs can be encapsulated within these nanomaterials thereby improving the stability and bioavailability of substances or ingredients which have poor intrinsic stability or bioavailability. The modified optical characteristics of nano-encapsulated materials mean that they can be used in a wide range of products, especially clear beverages. The improved bioavailability and uptake especially opened up a large area of applications in food products and supplements that incorporate nanosized vitamins, nutraceuticals, antimicrobials, antioxidants etc.

1.2.2. Combined organic/inorganic (surface modified) nanomaterials

Combined organic and inorganic nanomaterials, also called surface modified nanomaterials, are nanomaterials that add certain types of functionality to the matrix, such as antimicrobial activity or a preservative action through absorption of oxygen. In food packaging, functionalised nanomaterials are incorporated in the polymer matrix to offer mechanical strength or a barrier against gases, volatile components (such as flavours) or moisture. One example is the use of functionalised nano-clays in food packaging to develop materials with enhanced gas-barrier properties. The nano-clay mineral is mainly montmorillonite; natural clay obtained from volcanic ash/rocks (also termed bentonite). Organo-clay has a natural nano-scaled layer structure and is organically modified to bind to polymer matrices (Betega de Paiva et al., 2008).

1.2.3. Inorganic nanomaterials

Only a limited number of inorganic nanomaterials are known to be used in food, food additives, food supplements and food packaging applications although some of them might be used in high volumes and several different applications. These include nanomaterials of silver, iron, calcium and magnesium, selenium, silicates and titanium dioxide. Food packaging is the major area of application of inorganic nanomaterials and includes combinations of polymers (as described in the previous section) as a gas barrier, nano-silver and nano-zinc oxide for antimicrobial activity, and nano-titanium dioxide for ultraviolet protection. Silica in nano-form is used for surface coating of packaging materials. Titanium nitride is authorised in the EU for its use as additive or polymer production aid in plastic food contact materials (EU Regulation 1183/2012). While nano-silver has the fastest growing number of applications, it is by volume not the most used material. It is used in food supplements, in food packaging, storage boxes and refrigarators as an antimicrobial. The Woodrow Wilson database lists about 40 applications of silver in food and food-related products, most of them in food supplements (Woodrow Wilson, 2012). Patents also mention silver for the preparation of antibacterial wheat flour and as an animal feed additive, however, this is still in the research phase (Park et al., 2006). More recently silver has been studied as an alternative for the antibiotics used in the poultry production (Pineda et al., 2012a, 2012b).

Silicon dioxide, or silica, has been used in food processing and food applications for many years in a form which is called synthetic amorphous silica, or SAS. It is used in the clearing of beverages and as an anti-caking agent in many powdered food items. The bulk material is known as food additive E551 and consists of primary particles, aggregates and agglomerates. The primary particles and part of the aggregates consist of materials with sizes <100 nm (Peters et al., 2012). E551 is one of the most important anti-caking agents.
Other manufactured anti-caking agents include calcium silicate (E552), sodium aluminosilicate (E554), dicalcium phosphate (E341), sodium ferrocyanide (E535) and microcrystalline cellulose (E460). There is no information whether these materials or a part of them have a particle size in the nanosized range.

Titanium dioxide in bulk form is approved as a food additive with number E171. It is used as a whitener, as a colorant to lend brightness to food products, especially confectionary products, and it is used in toothpastes, paints and coatings. While the average particle size is 200-300 nm, part of this bulk material may contain a fraction of particles with sizes <100 nm (Weir et al., 2012). Nano-sized titanium dioxide, e.g. with particle sizes <100 nm, is being used as a photo catalyst in water treatment processes, in packaging and as a coating for self-cleaning windows.
Other metals in the form of nano-sized particles are available as food- or health supplements. These include nano-selenium (Xu et al, 2007), nano-calcium (Hannig et al., 2010), nano-iron (Sekhon, 2010), and colloidal suspensions of metal particles, e.g., copper, gold, platinum, silver, molybdenum, palladium, titanium, and zinc (Fung et al., 1996: Park et al., 2006: Purest Colloids, 2013).

1.3. Scope of the study

The objectives of this study are to prepare (i) an inventory of the currently used and potential future applications of nanotechnology in the field of agriculture, feed and food (thereof agri/feed/food) and (ii) a review of the existing legislation in EU and non-EU countries on the authorisation of food additives/food contact materials/feed additives applications in the area of nanotechnology. Information for reaching the abovementioned goals is described in section 2. For each of the application, the inventory also includes, when available, the physical-chemical characterization and the mode of action of the nanomaterial, the current knowledge on (eco)toxicity and the status of the risk assessment.
A strict definition of a nanomaterial, as particles with one size <100 nm, was not followed to avoid the exclusion of potential nanomaterials. This means that larger particles that are considered or mentioned as nanomaterials, or potential nanomaterials for which the particle size is not clear are included in the study.

2. SOURCES OF INFORMATION

The objective of this study was to prepare (i) an inventory of the current and potential future applications of nanotechnology in the agri/feed/food sector and (ii) a review of the regulation of nanomaterials in the EU as well as in non-EU countries. Information employed in the Nano Inventory (i) comes from 4 different sources as schematically presented in Figure 4 and described in more detail below.

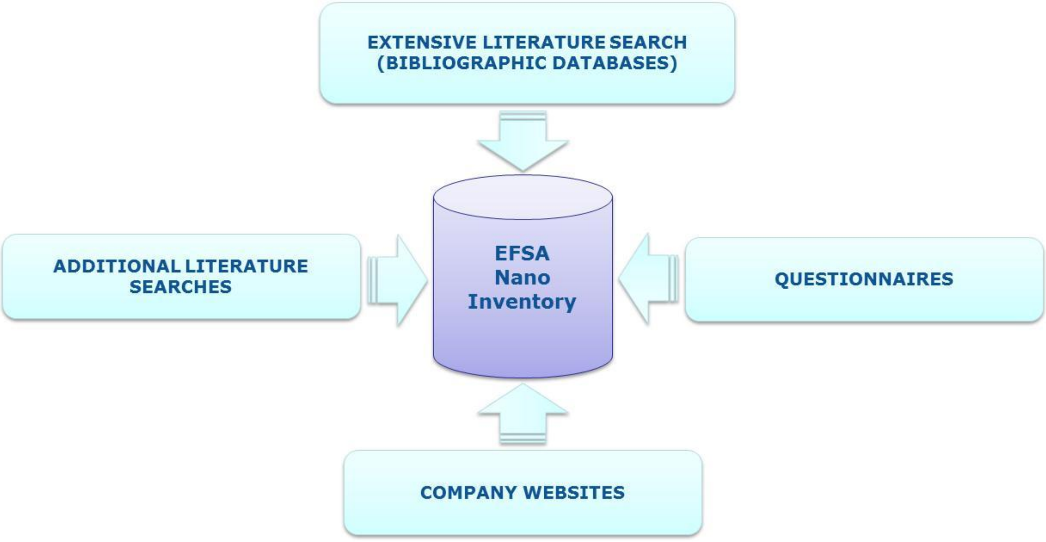

Figure 4: Schematic presentation of information sources that feed the Nano Inventory.

With exception of the company websites, the same information sources are also used to collect information for the review on legislation of nanomaterials in EU and non-Eu countries (ii) as illustrated in Figure 5.

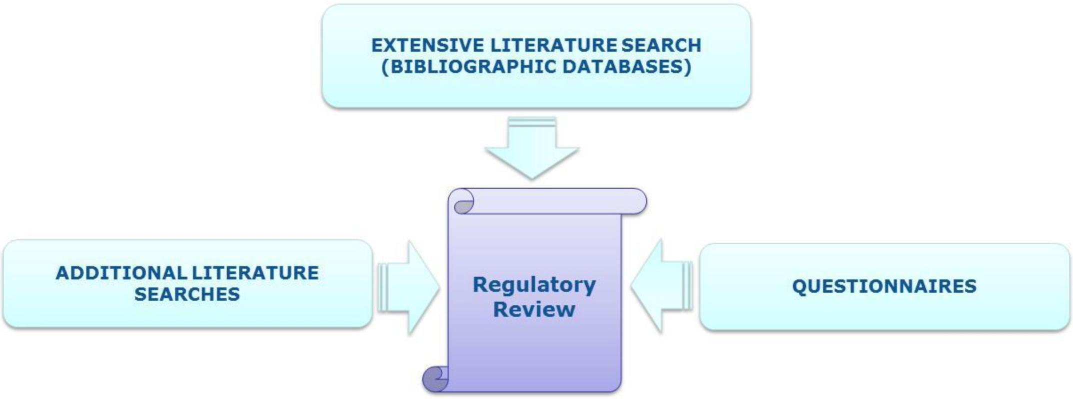

Figure 5: Schematic presentation of information sources that feed the review on regulation and legislation.

Each of the information sources is described in detail in the following sections.

2.1. Extensive literature search

2.1.1. Bibliographic databases

To assess the state of the application of nanotechnology in the agri/feed/food sector an extensive literature search was performed with documented sources, search terms, and inclusion criteria. The bibliographic databases that were selected include:

- **Scopus**. This is a well-known abstracting database designed to provide expert results. It includes abstracts and cited references of over 16,000 peer-reviewed science journals from more than 5,000 international publishers, including Open Access and electronic-only titles.
- **Web of Science**. This database is part of the ISI Web of Knowledge, a leading citation database with multidisciplinary coverage of over 10,000 high-impact journals in the sciences, social sciences, arts and humanities, as well as international proceedings coverage for over 120,000 conferences.
- **PubMed Central**. This database is an archive of biomedical and life sciences journal literature developed and managed by the U.S. National Centre for Biotechnology Information (NCBI). This database was selected since it was expected that there is a certain degree of overlap between the food and medicine sectors. Many food products are marketed as a means to enhance nutrition and as an aid to health. Therefore, food supplements and nutraceuticals are likely areas for the application of nanomaterials.
- **NANOnetBase**. NANOnetBase gives access to thousands of pages of theory, data, and experimental results on nanoscale modelling, analytical determination, characterization, and fabrication techniques of nanomaterials.
- **SciFinder Scholar** (only for patents). This provides access to several Chemical Abstracts Service databases, including Chemical Abstracts, Registry, CASREACT, CHEMLIST, and CHEMCAT. It includes nanotechnology, the application of nanomaterials, many articles covering the detection and quantification of nanomaterials as well as their toxicology and risk assessment and a patent section.

2.1.2. Search terms

The search strategy consisted of three major steps. Combinations of keywords were used, starting with a broad screening on nano, nanotechnology and nanomaterials, then focusing on application of these materials in the agri/feed/food sector, and finally focusing on the type of application, the properties of the nanomaterials, the safe application of these nanomaterials, analytical and toxicological aspects and risk assessment. The strategy and used keywords are as follows:

- Step 1 was designed to capture titles/subject headings that studied nanomaterials, nanoparticles or materials which may not necessarily be named “nano”, e.g. micelles, SAS, CB, ultrafine, sub-pigmentary and micro emulsions. In this step the following search terms were used (“*” indicates that the search term includes all words containing additional characters following the “*” symbol):

  Nano* OR nanotechnology* OR nanomaterial* OR nanoparticle* OR micelles* OR SAS* OR CB* OR ultrafine* OR sub_pigmentary* OR micro_emulsions*

AND

- Step 2 was designed to capture among the titles retrieved from step 1 those that investigated the application of nanomaterials in the areas agriculture, food additives, food contact materials and feed additives (“()” indicates that two adjacent terms are next to each other in that order [i.e., a space or a punctuation mark such as a hyphen can be found between the search terms) (application) AND (food()additive OR food contact material OR feed()additive OR agriculture OR agro()chemicals OR pesticides OR novel()food OR flavouring or enzyme) OR food()packaging OR food()processing OR feed()processing OR delivery()system OR delivery()systems OR nanocides OR analysis OR analytical()determination OR detection OR characterization OR analytical()characterization)

AND

- Step 3 was designed to capture title/subject headings from step 2 hits that investigated one of the physical, chemical, biological or toxicological properties ("()" indicates that two adjacent terms are next to each other in that order [i.e., a space or a punctuation mark such as a hyphen can be found between the search terms)

  (composites) OR (metal()oxide) OR (inorganic) OR (organic) OR (agglomerates) OR (aggregates) OR (efficacy) OR (exposure) OR (exposure()assessment) OR (translocation) OR (biological()interactions) OR (chemical()interactions) OR (toxic()toxicity) OR (safety) OR (risk assessment) OR (mode of action) OR (antibacterial OR antimicrobial OR antiviral)

In an additional search a number of search terms were replaced by others to investigate whether the use of certain abbreviations and terms in earlier searches, e.g. "SAS", "CB" and "Application" had limited the number of relevant results. This additional search was done using all of the bibliographic databases, except SciFinder Scholar. The following alternatives were applied:

- Alternative 1: "CB" was replaced by "carbon black"
- Alternative 2: "SAS" was replaced by "silica" or "silicate" or "SiO2"
- Alternative 3: "application" was replaced by "apply" or "applied"
- Alternative 4: "application" was replaced by "used"

The additional number of references was determined by removing the results in common with the initial literature searches.

2.1.3. Criteria used for selection of relevant references

The initial search results were merged to remove duplicate records of the same reference. The selection of relevant papers followed different phases. First of all, references were included/excluded based on the title and to which extent it answered the objectives of the project. For the latter the following descriptions were used to classify the papers:

- The paper describes the application of existing/real nanomaterials in agri/feed/food. If YES assign the paper to the category (a) "agriculture (incl. feed)", (b)"food", (c) "food packaging". If NO go to:
- The paper describes developments, research or future applications of nanomaterials in agri/feed/food. If YES assign the paper to the category (a) "agriculture (incl. feed)" (b)"food", (c) "food packaging". If NO go to:
- The paper describes the mechanism or mode-of-action of nanomaterials. If YES assign the paper to the category (d) "mode of action". If NO go to:
- The paper describes the legislation and regulatory aspects of nanomaterials If YES assign the paper to the category (e) "legislation/regulation". If NO go to:
- The paper describes eco- and human toxicity of nanomaterials. If YES assign the paper to the category (f) "toxicity (eco- and human tox)". If NO reject the paper.

If the title and description were not conclusive, abstracts and/or full texts were reviewed to assist in the classification. This led to a set of papers that were fully reviewed for inclusion in the inventory and for the production of the review on regulation and legislation. For the eligibility of the full text some additional exclusion criteria have been applied:

General Criterium:
- Exclusion of papers in languages other than English, German, French, Italian, Spanish or Dutch

Criteria for the exclusion of papers in the categories agriculture, feed, food and food contact materials:
- No description of application in one of the following fields: Food additive, Food contact material, Novel food, - Food ingredient (not specified), Feed additive, Pesticide, Flavouring, Enzyme, Fertiliser, Supplement, Veterinary Drug, Biocide;
- General overview on nanotechnology applied to agri/feed/food without any description of the nanomaterials.

Criteria for the exclusion of papers in the categories toxicity, risk assessment and effct/mode of action:
- Description of a nanomaterial of low relevance for agri/feed/food (no application found in papers of categories agriculture, feed, food and food contact materials);
- Routes of exposure not relevant for food

Criteria for the exclusion of papers in the category legislation:
- No information on regulation of nanomaterials in agri/feed/food.

2.1.4. Selected relevant references

The initial search was carried out on 13-04-2013, followed by further searches on 24-04-2013 and 07-05-2013. An additional search in which a number of search terms were replaced was conducted on 28-08-2013. No special time range was selected since the term “nano” and “nanotechnology” are used only since about 1990. Before 1990 the term “colloidal particles” was used and nanotechnology was not yet recognised as a new expertise or technological field. The oldest article in the literature search originates from 1992 and therefore a time range starts from 1992 to the present date. Table 1 gives an overview of the number of references that were identified in the different bibliographic databases.

Table 1: Number of references that were identified in each bibliographic database, and number of references that were selected after applying the exclusion criteria and after removal of duplicates.

Bibliographic database	Identified records	Selected relevant records
Scopus	3791	393
Web of Science	2151	134
PubMed Central	1608	64
NANOnet Base	12	4
SciFinder Scholar	736	55
Alternative search 1	18	1
Alternative search 2	604	6
Alternative search 3	48	5
Total	**8968**	**662**

Scanning through the references shows that while almost all have nano, nanotechnology or nanomaterials in the title and/or abstract, only a very limited number describe the actual application of nanomaterials in the agri/feed/food sector. More references describe potential applications or represent reviews of nanomaterials, their properties and applications in general. However, most references describe pharmaceutical and medical applications, the (green) synthesis of nanomaterials, the analysis of nanomaterials and the analysis of chemical contaminants using (magnetic) nanoparticles. The additional searches in which search terms were replaced resulted only in a limited number of additional references. Replacement of "SAS" by "silica" or "silicate" or "SiO_2" resulted in more additional references, however, almost all address clean-up procedures in chemical analysis. Replacement of the term "application" by "apply" or "applied" resulted in a limited number of additional references while replacement by "used" resulted in >25,000 references. As a test about 1% of these references were evaluated and of these <1% would be included following the criteria used for selection of relevant references. Accordingly, this group of additional references were rejected.

2.2. Additional searches

In addition to the extensive literature search (Section 2.1), ad-hoc literature searches were made via Google to retrieve specific relevant peer reviewed and/or non peer reviewed references. Moreover, webpages of international organisations such as EFSA, FAO/WHO and OECD or national organisations such as FDA, Health Canada, etc. were screened for relevant reports. These additional literature searches were triggered by specific needs arisen during the project and should be considered as complementary to the extensive structured literature search, for example some literature as used in the section on toxicology 3.3.2.1-3.3.2.5. In addition, information from EFSA Register of Question database was checked (http://www.efsa.europa.eu/en/request/requests.htm). Infromation on nanomaterials currently under assessment by EFSA was included . These additional searches confirmed that most of the scientific literature had already been identified in the bibliographic databases. Nevertheless, a total number of 117 publications were added to the list of relevant references. The additional relevant references are listed in Appendix A.

Table 2: Number of gray literature and additional references that were collected from the internet.

Bibliographic database	Identified records	Selected relevant records
Internet, Grey literature	-	117
Total	**8968**	**779**

2.3. Company websites

A targeted internet search was also performed on a number of product databases where various products containing nanomaterials are reported. These product databases included:

- The Woodrow Wilson database (The Project on Emerging Nanotechnologies), the first publicly available on-line inventory of nanotechnology-based consumer products (Woodrow Wilson, 2012). The inventory claims to be an important resource for consumers, policymakers, and others interested in how nanotechnology enters the market. The most recent update originates from 10 March 2011 and was inspected on 14-05-2013.
- The ANEC-BEUC 2010 database, a European inventory of consumer products claiming to contain nanomaterials (ANEC/BEUC, 2013). The inventory has the form of a Microsoft Excel table and was downloaded from the site on 14-05-2103.

- The on-line database of the German Environmental NGO 'BUND'(BUND, 2013) assessed on 15-05-2013.
- Nanotech-data.com, the database of nanotechnologies for Luxembourg and areas in Germany and Belgium (Nanotech-data, 2013) assessed on 15-05-2013.
- Nanoproducts.de (Nanoproducts, 2013), a freely accessible database that deals with the marketing of products containing nanomaterials and was assessed on 15-05-2013.

The concepts underlying the databases were investigated to determine whether they could be used in the project and whether the products could be added to the Nano Inventory or the company websites could provide additional data on certain products for the Nano Inventory. In general, products in these databases; 1) are readily purchased by consumers; 2) are identified as "nano" by the manufacturer or by another source; 3) have a "nano" claim that appears reasonable. Notice that the "nano" claim of the products is not verified in any of the databases. This means that there may be false positives in these internet databases (products which are claimed to contain nanomaterials, but which do not). In addition, the databases include nanomaterials that are produced by companies as well as products (mainly food supplements) sold by all kind of shops. Based on these consideations, these product databases were used to retrieve additional information only on those products that are intended for the agri/feed/food sector and were mentioned in the relevant literature selected according to the search strategy described in Section 2.1 and 2.2. only. In all the cases, the websites of the related suppliers were cross-checked and any further information was included in the Nano Inventory. The list of company websites explored is reported in Appendix B.

2.4. Questionnaires

Two questionnaires were prepared with the objective to collect additional information: Questionnaire 1 on "*Production, use, import, research and development of nanomaterials*" and Questionnaire 2 on "*Regulation of nanomaterials in non-EU countries"* consisted of 25 and 24 questions respectively, most of them containing a list of optional answers. A functional mailbox was created to allow respondents to send additional information. The questionnaire could be filled in anonymously.
A size range up to 1 µm, which for the purpose of the survey was called "nanomaterial", was selected to increase the chance of receiving more information on potential nanomaterials. As explained to recipients the choice for this size range was not intended to have any implication on the current discussion of a definition of nanomaterial in the EU, nor would it trigger any regulatory requirements or consequences for the reported materials. The cover letter and the final version of the questionnaire on the production and use of nanomaterials can be found in Appendix C.
The recipients (1024 addresses) received both questionnaires on 11 October 2013 via e-mail with the request to fill them out according to their expertise. The deadline was 4 November 2013.

3. NANO INVENTORY

The 'Nano Inventory' was created using data and information on applications of nanotechnology in agri/feedfeed/food retrieved from the extensive literature search and other sources during the project (Chapter 2). This Inventory was developed in a Microsoft Access environment to facilitate collection, storage and extraction of data and information during the project[6] (see Section 3.1 and 3.2). Three predefined queries were developed to generate Inventory lists[7] (see Section 3.3).

3.1. Development of the Nano Inventory and predefined queries

The conceptual design of the Nano Inventory started from the objectives and requirements as defined in the project proposal. Specifically, the Inventory was meant to include applications of

[6] The entire Nano Inventory can be made available upon request in a read-only version.
[7] The Inventory lists are publicly available and can be downloaded from the EFSA website in a Microsoft Excel format together with this report.

nanotechnology that are currently used and/or expected for future use in several application fields related to agri/feed/food sectors. The considered application fields are listed for each sector in Figure 6.

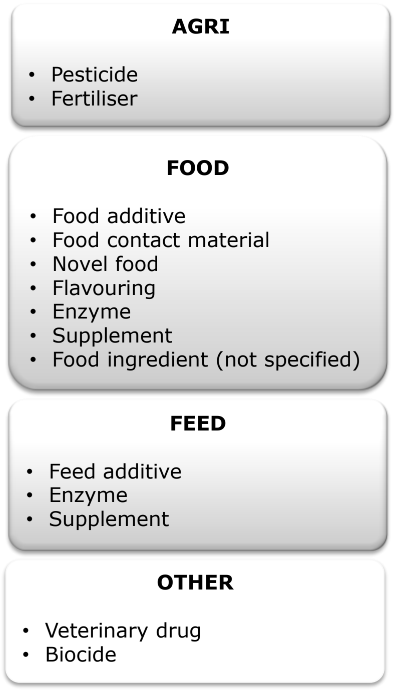

Figure 6: Application fields by sector. 'Other' includes application fields that are not directly related to agriculture, food and/or feed sectors but may be relevant and should therefore also be considered.

The structure of the Inventory is illustrated in a tabular form in Appendix D. It lists all the fields and related organisation into thirteen groups. It also contains a short description of the meaning of each field and an indication of the value to be inserted in each field based on the information retrieved from the literature. The content of the entire Inventory is analysed and discussed in Section 3.2.

A set of predefined queries were developed to generate the Inventory lists. The Inventory lists can be downloaded from the EFSA website in a Microsoft Excel format together with this report.

The first query is called *'Current and future applications'* and aims at providing lists of current and/or future applications of nanomaterials by field (e.g. food contact material, food additive, etc.) and nanomaterial name including information on availability on the market and authorisation for the use in the EU.

The second query is called *'Toxicological data'* and aims at retrieving all the toxicological data that have been entered for each nanomaterial from the Inventory.

The third query is called *'Risk assessment status'* and aims at giving an overview on the possible implications for safety and related human health and environmental risks for each nanomaterial based on the retrieved information on hazard and exposure.

The fields extracted for the individual queries are presented in Table 3. Squared brackets specify the related group (e.g. HH as hazard for Human Health or ENV for the Environment) (refer to Appendix D for description and more details on the fields).

The main findings from the predefined queries are analysed and discussed in Section 3.3.

Table 3: Overview of fields extracted for predefined queries.

Current and future applications **Query 1**	**Toxicological data** **Query 2**	**Risk assessment status** **Query 3**
Nanomaterial	Nanomaterial	Nanomaterial
CAS number	CAS number	CAS number
Origin	Parameter (size related) [Physico-chemical parameters]	Application field
Application field	Use stage	Availability on the market
Availability on the market	Value/description	Implication for safety
Product name	Mode (mechanisms) of action (incl. comparison to non-nano form)	Endpoint [hazard for HH]
Type of product	Endpoint [hazard for HH]	Results [hazard for HH]
Country of use (or territory)	Results [hazard for HH]	Endpoint [hazard for ENV]
Authorisation for the use in EU	Endpoint [kinetics HH]	Results [hazard for ENV]
Reference	Results [kinetics HH]	Endpoint [kinetics HH]
	Target species	Results [kinetics HH]
	Target population	Scenario [exposure]
	Reason for the assessment	Outcome [exposure]
	Reference	Reason for the assessment
		Reference

The Nano Inventory in Microsoft Access® has also been mapped to IUCLID 5.5. This will enable future migration of Inventory data to IUCLID 5.5 if needed (e.g. for use in other contexts such as the European Commission Web Platform on Nanomaterials[8] or for incorporation into NANOhub[9] for regulatory purposes).

[8] The European Commission Web Platform on Nanomaterials (http://ihcp.jrc.ec.europa.eu/our_databases/web-platform-on-nanomaterials) is a single-entry point to references (web links) to as much information sources as possible that are relevant to nanomaterials. The first version was released in December 2013.
[9] NANOhub (http://www.napira.eu/) is a database and information platform based on IUCLID developed to address and host nano-specific information and methodology. The roadmap for development of NANOHub is defined by ECHA, OECD, and JRC.

3.2. Analysis of the Nano Inventory

The Nano Inventory contains 633 records originating from 478 documents that were entered into the inventory. Table 4 gives an overview of the sources and types of documents. About 75% of the documents are peer reviewed literature, while the remaining consists of comparable numbers of records filled with non-peer reviewed (grey) literature, patents, company websites and information from questionnaires. About 50% of these documents originate from the European region, 30% from the Asian region and 20% from the Americas. The number of papers can also be differentiated per year and Figure 7 shows that the oldest publication originates from 1992 and that the number of publications increases over the years to a number of 117 in 2013. Note that the number of papers in 2013 is already higher than the number in 2012 while the literature search was only carried out at the end of April 2013.

Table 4: Overview of the information that was entered into the Nano Inventory

Source		**No. of papers**
	Type of paper/document	
Library search		
	Peer reviewed literature	365
	Non-peer reviewed literature	21
	Patent	24
Internet		
	Company websites	42
Other		
	Questionnaires	17
	Others	9

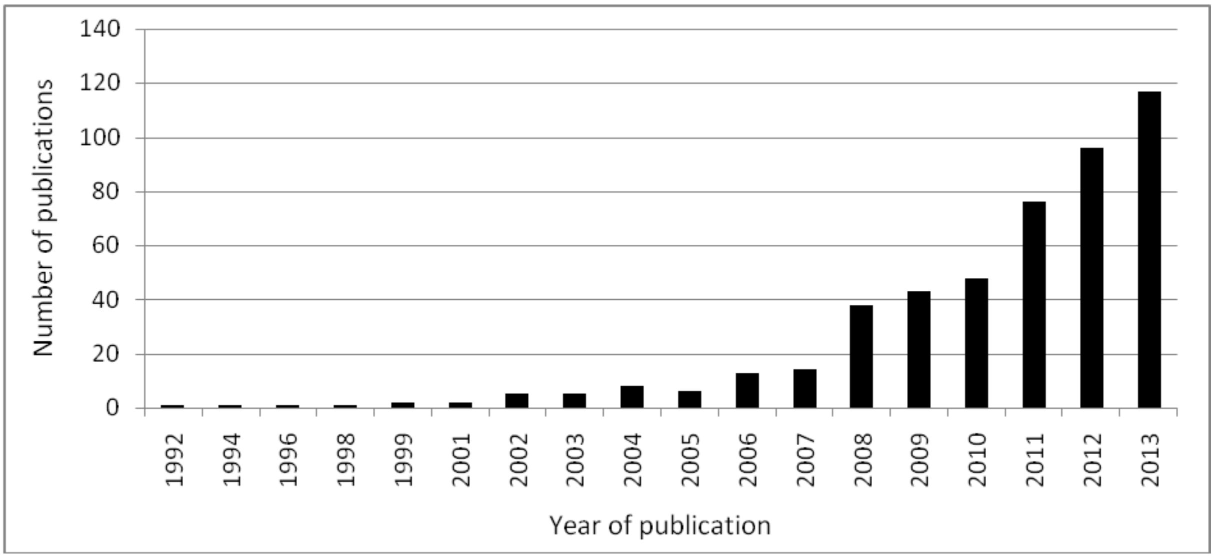

Figure 7: Number of papers over the years in the Nano Inventory (note that 2013 is not for the complete year).

In total 55 types of nanomaterials can be extracted from the Nano Inventory. Table 5 gives an overview of these nanomaterials showing that 50% of them are only reported once. The materials in the left column are reported more frequently with nano-encapsulates the most often, 149 times. Note that nano-encapsulates is used here as the term for micelles, nanocapsules, nanocarriers and nanoemulsion. In the same way the term nano-composite is used for nanocomposite, nanolaminate and nanopolymer. These numbers may give an indication on the frequency of the materials used, with nano-encapsulates and silver being the most frequent ones. However it should be noted that these numbers refer to the entries into the Nano Inventory, which is influenced by the frequency by which the materials are reported in publications and the criteria applied to select the information to be inserted into the Nano Inventory. Information about the tonnage used in the Nano Inventory is found only for silica and titanium dioxide, so no comparison can be made. Since these are classically used materials in many food products the amounts of silica and titanium dioxide used are expected to be much higher than nano-encapsulates and silver.

Table 5: Types of nanomaterials and the number of them that are in the Nano Inventory.

Nanomaterial	No.	Nanomaterial	No.
Nano-encapsulates	149	Calcium	1
Silver	122	Calcium phosphate	1
Titanium dioxide	65	Calcium silicate	1
Nano-composite	41	Carbofuran	1
Zinc oxide	34	Carbon dioxide	1
Clay	29	Carbon nano-onions	1
Synthetic amorphous silica	25	Casein	1
Carbon nanotubes	23	Cellulose	1
Silicon dioxide	17	Chromium	1
Gold	13	Fly ash	1
Iron	12	Fullerol	1
Nanosensor	11	Green tea	1
Copper	9	Lead	1
Chitosan	8	Lignan glycosides	1
Quantum dot	7	Lysozyme	1
Fullerene	5	Membrane-structured solid nanoparticles	1
Nisin	5	Nano solution	1
Selenium	5	Nanodroplets	1
Calcium carbonate	4	Nanolipids	1
Copper oxide	4	Nanosalt	1
Protein	4	Nickel	1

Cerium oxide	3	Organic pigment	1
Starch	3	Platinum	1
Aluminumoxide	2	Sulfur nanoparticles	1
Carbon black	2	Synthetic Amorphous Sodium Aluminium Silicate	1
Nanoscale enzyme support systems	2	Titanium nitride	1
Aluminium	1	Zeolith	1
Bifenthrin	1		

The nanomaterials are used in different types of applications (linked to uses in the agri/feed/food sector), or are intended to be used so in the future. The Nano Inventory was designed to contain 12 types of applications (See Table 6). The frequency with which these applications are encountered is also of interest and is shown in Table 6. A category "Not clear" was added to include the nanomaterials for which the type of application field was not clear.

Table 6: Types of applications and the number of them that are in the Nano Inventory.

Application	No.	Application	No.
Food contact material	213	Biocide	12
Food additive	153	Fertiliser	10
Not clear	78	Veterinary drug	7
Food ingredient (not specified)	51	Novel food	5
Supplement	45	Enzyme	1
Pesticide	39	Flavouring	1
Feed additive	18		

The types of applications most frequently encountered in the Nano Inventory include food contact materials and food additives. For 78 entries in the Nano Inventory the type of application was not clear while for 51 it was clear that it concerned a food ingredient but not exactly what kind. The results in Table 6 also show that most nanomaterials in the agri/feed/food sector are associated with food and not with agriculture or feed.

Figure 8 is a combination of Tables 5 and 6, showing the frequency of nanomaterials used in specific types of applications. For reasons of clarity, nanomaterials that were listed only a few times (generally <5) are not shown and as a consequence Figure 8 describes about 75% of the nanomaterial-application combinations in the Nano Inventory. Again it becomes clear that food additives and food contact materials are the major application fields and that nano-encapsulates and silver are the most frequently used nanomaterials.

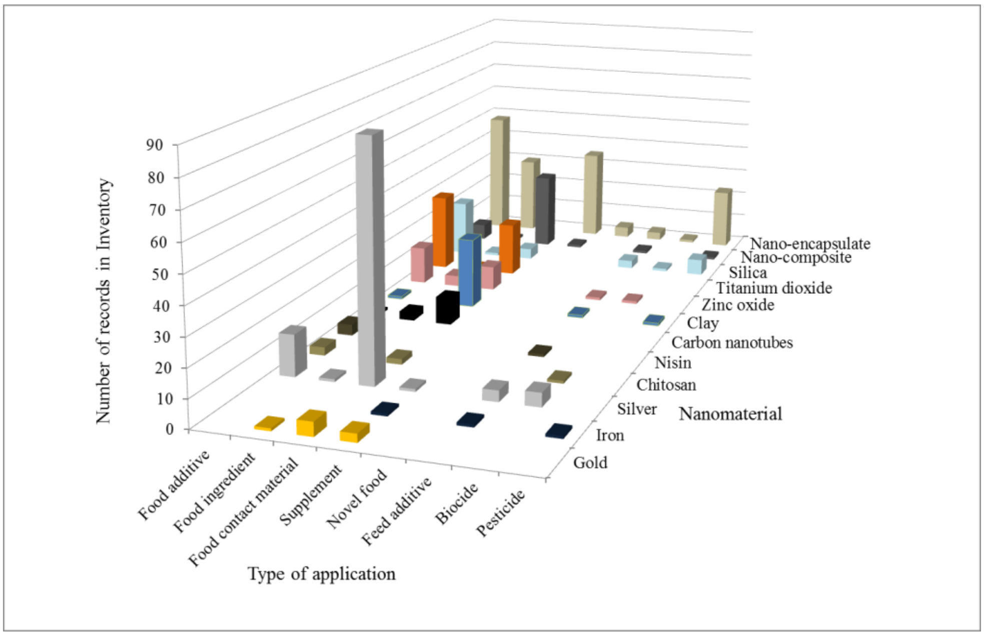

Figure 8: Information extracted from the Nano Inventory shows the number of records of the most used nanomaterials in the most common types of applications. For reasons of clarity not all nanomaterials and applications are shown. "Silica" is the sum of synthetic amorphous silica and silicon dioxide.

It should be noted that the nanomaterial applications in Tables 5, 6 and Figure 8 include both, those already available on the market and those still in the development stage. A differentiation between these two is made in the next section, but for the totals it can be added that 40% of the nanomaterial applications are available on the market, 20% of the nanomaterial applications are in development while for 40% of the nanomaterial applications that were identified in the literature that entered the Nano Inventory the status is not clear.

An important element of any nanomaterial toxicity screening is a detailed and comprehensive physicochemical characterization of the test material being studied. This is a critical factor for correlating the nanoparticle surface characteristics with any measured biological/toxicological responses, as well as to provide an adequate reference point for comparing toxicity results with the hazard-based findings of other investigators. This can only be accomplished if rigorous characterization is conducted. In the absence of an adequate assessment of the physical characteristics, it is easy to draw general conclusions on nanoparticle-types which may have similar chemical compositions but, in fact, have different sizes, shapes and surface areas. One obvious physical characteristic is the size, size range or size distribution, others are shape, surface area, zeta potential and aggregation state. Using the Nano Inventory it is possible to make an estimation to which extent the nanomaterials in the records are characterised. Figure 9 gives an overview of a number of the most important physicochemical characteristics reported in the 633 records in the Nano Inventory.

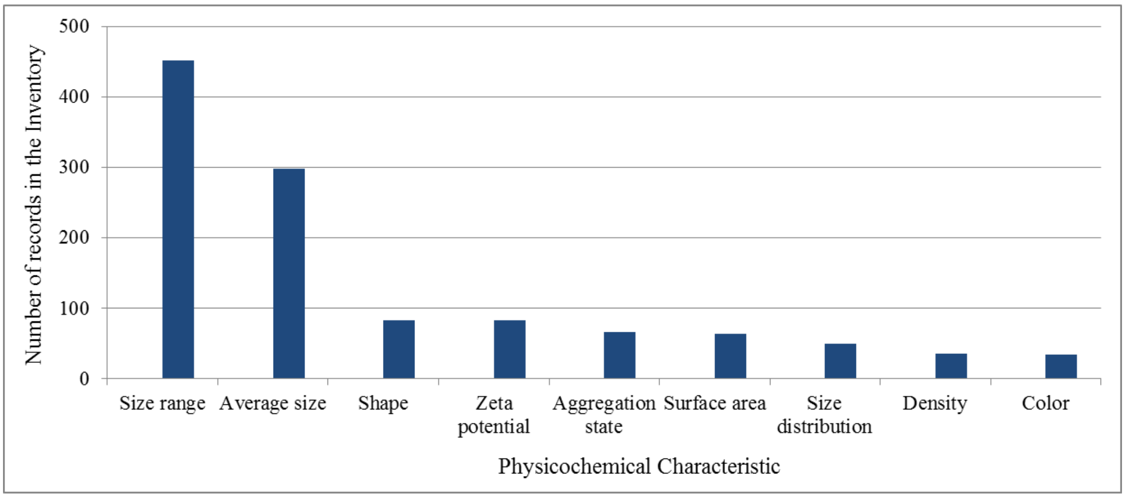

Figure 9: Physicochemical characteristics provided for nanomaterials in the Inventory.

A size range or average particle size is reported most often, in 451 and 298 of the 633 records respectively. Only in a limited number of papers these sizes are measured, more often the size of the nanomaterials as stated by the supplier is given. A size distribution is reported in only 49 records in the Nano Inventory. Other important physicochemical characteristics like shape, zeta potential and aggregation state are reported in 84, 82 and 66 records, respectively.

3.3. Results from predefined queries

3.3.1. Current and future applications query

A number of predefined queries were prepared for the Nano Inventory. The first query is called '*Current and future applications*' and aims to provide a lists of current and future applications of nanomaterials. The query consists of an alphabetic listing of nanomaterials, their CAS number, application field and other fields as given in Table 7.

Table 7: Overview of fields in the *"Current and future application"* query.

Field in "Application" query		Number of entries
Nanomaterial name		633
CAS number		32
Origin manufactured		481
Application field		see Figure 11
Availability on the market	confirmed	276
	in development	136
Product name		169
Type of product		170
Country of use (territory)	Asia	6
	EU	9

	USA	8
Authorisation for use in the EU		22

The list consists of 633 individual entries including information from the documents listed in Table 4 and contains 55 different types of nanomaterials both, inorganic and organic. Around 80% of the nanomaterials are found only a limited number of times (<10) in the Nano Inventory and 50% of the nanomaterials are found only once, i.e. more than 80% of the entries are determined by only 20% (i.e. 12) of the different types of nanomaterials. These are mostly nano-encapsulates (149), silver (122), titanium dioxide (65), nano-composites (41) and zinc oxide (34), as shown in Figure 10.

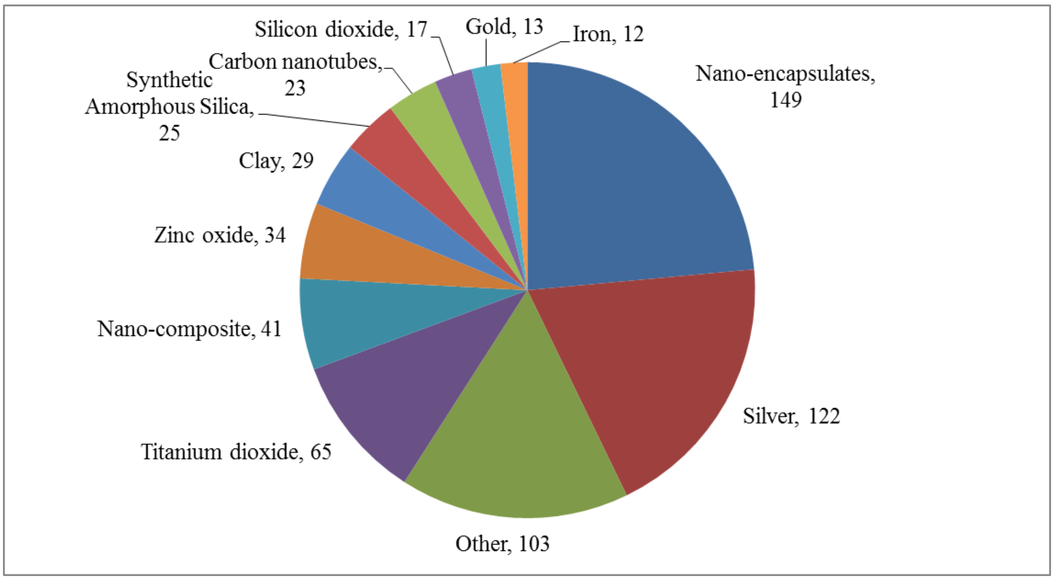

Figure 10: Overview of the type of nanomaterial mentioned in 633 records of the Nano Inventory (filtered with the query *"current and future applications"*).

Since most news in the popular media concerns the application of inorganic nanomaterials, it is somewhat surprising to see that organic nanomaterials are in fact the majority when it comes to application in the agri/feed/food sector. The applied inorganic nanoparticles are very diverse, including metals, metal oxides, clay and full-carbon materials, while the vast majority of the organic nanomaterials consists of nano-encapsulates and nano-composites. As for the application fields it is already shown in the previous section that "food contact materials" and "food additives" are by far the mostly used type of applications of nanomaterials while the other types of applications are of minor importance.

The query also differentiates between combinations of nanomaterial-application which are "confirmed", meaning that these are available as commercial products (Figure 11), and those which are "in development", meaning that they have not yet reached the marketplace (Figure 12). About 40% of the nanomaterial–application combinations are available on the market while 20% are still in the development stage. Apart from this there is a third category of about 40% for which the status in the Nano Inventory is not known, i.e. "not clear". Again, it can be noticed that materials that are available on the market are mainly applied in the categories "food additives", "food contact materials" and "supplements" and that these are mainly organic and clay nanomaterials.

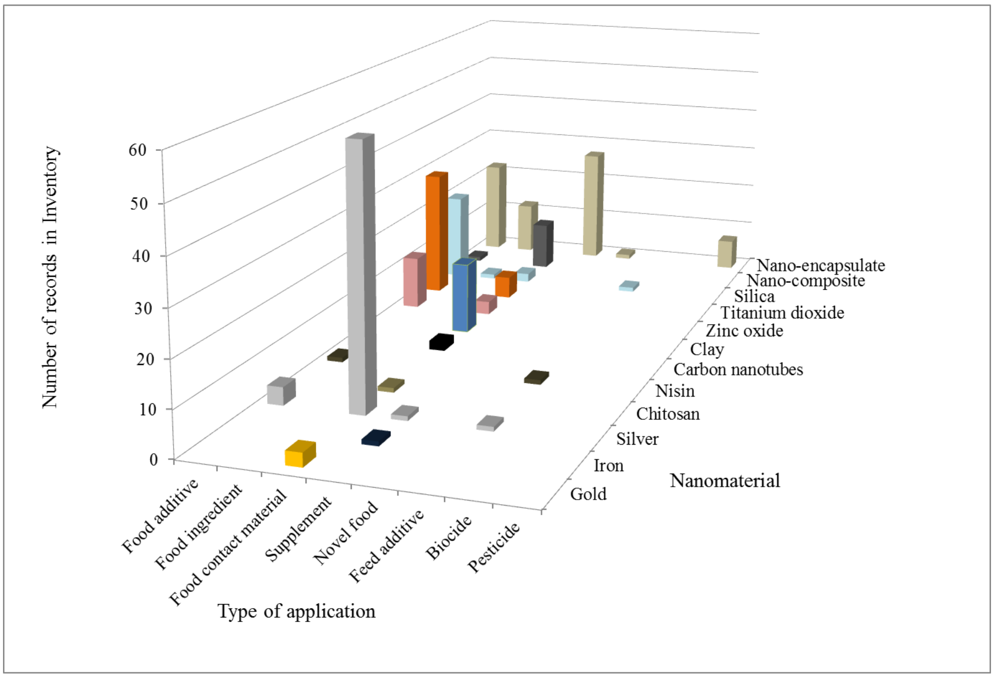

Figure 11: Nanomaterial-application combination which are available on the market.

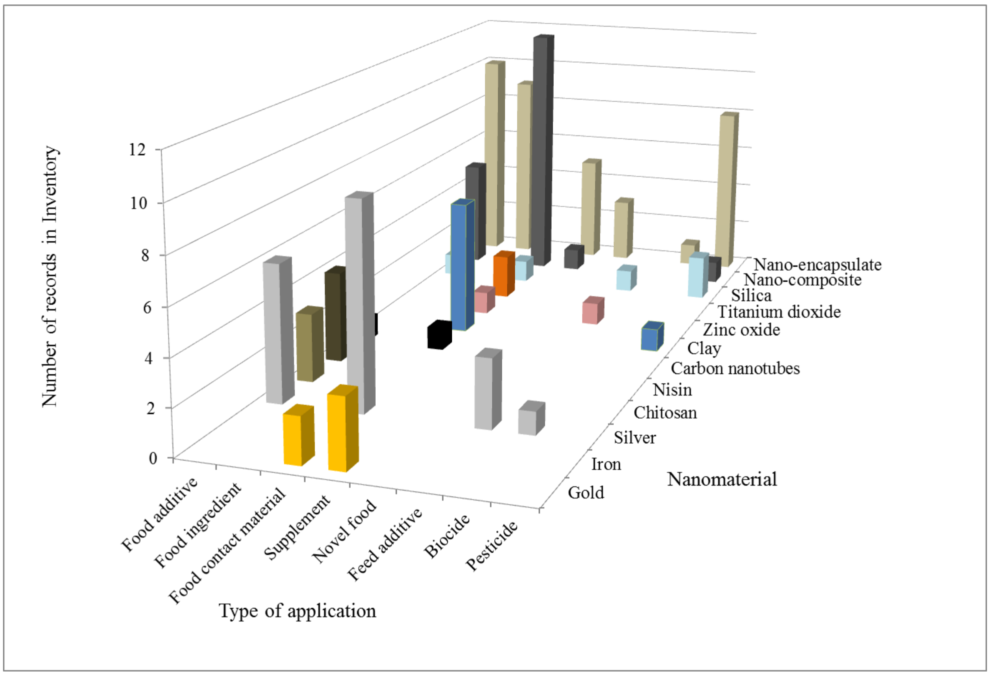

Figure 12: Nanomaterial-application combination which are in development.

When comparing Figures 11 and 12 it is clear that the majority of nanomaterials in Figure 11 consist of inorganic nanomaterials while the majority in figure 12 are organic nanomaterials suggesting that future developments may very well be in the area of organic nanomaterials. Many of these are nano-encapsulates for food additives and supplements, but also for pesticides and fertilizers in the agricultural sector. Especially the fact that the properties of such organic nanoparticles can be "tuned" to the application makes them very attractive.

The "*Current and future application*" query shows that 22 of the nanomaterial/application field combinations have been reported to be approved for use in the EU. These include: an application of a carbon nanotube in food packaging (Duran et al., 2013); the pesticides Apron MAXX, Banner MAXX and Primo MAXX in the form of a nanoemulsion (Kah et al., 2012); a nanopolymer or –laminate for which the application was not clear (but probably food contact materials) (Lagaron et al., 2011), several synthetic amorphous silica and silver materials, nanosensors as part of food contact materials (Sekhon, 2010; Ravichandran, 2010), calcium carbonate (E170) as a food additive (EFSA, 2011), an organic pigment with a food contact material application and a bentonite clay (E558) as a feed additive (EFSA, 2010). It should be kept in mind that the information that these materials are authorized for use in the EU comes from the consulted literature as cited. The claims were not verified. The following sections give a description of current and future applications of nanomaterials in the agri/food/feed sector based on the search exercise performed in this procurement call.

3.3.1.1. Current and future application of nanomaterials in agricultural production

During primary production nano-formulated agro-chemicals are employed to increase the efficacy of the agro-chemicals compared to conventional formulations. For example, nano-encapsulated and solid lipid nanoparticles have been explored for the delivery of agrochemicals (Frederiksen et al., 2003). The application of novel nanotechnology techniques in agriculture has recently been reviewed by a number of authors (Gogos et al., 2012: Narayanan et al., 2012: Kushwaha et al., 2012: Shrivastava et al., 2009: Shamim, 2011: Mahalik et al., 2010) and can be divided into three main categories; pesticides, plant growth promoters and animal feed additives. Most search results in this category deal with organic nanomaterials, followed by titanium dioxide, silver, silica, and alumina. Nanomaterials come in many diverse forms (surprisingly often >100 nm), from solid doped particles to (often non-persistent) polymer and oil–water based structures.

Pesticides are chemical substances which are meant to prevent, destroy or mitigate pests. Nanotechnology shows great promise to improve pest management strategies through the formulations of nanomaterial-based pesticides. Nano-encapsulates are used for delivering pesticides and other agrochemicals (Kah et al., 2012: Maysinger, 2007: Torney et al., 2007: Chaudhry et al., 2008: Mukal et al., 2009: Perea-de-Lugue et al., 2009). A surfactant based nano-emulsion has been described as a delivery system for the pesticide beta-cypermethrin (Wang et al., 2007) as are porous hollow silica and surface modified nanomaterials for controlled release of the pesticide validamycin and the herbicide 2,4-dichlorophenoxyacetate (Liu et al., 2006). The interesting results obtained in academic researches over the last few decades have been closely followed by several companies. Some companies over the last decade, such as Syngenta, Bayer, Monsanto, Sumitomo, BASF, and Dow Agrosciences have already deposited several different patents comprising a wide range of protocols for production and application of encapsulated formulations, which can be used to produce nanoinsecticides (Perlatti et al. 2012). Despite the hard work and heavy investment, no commercial nano-insecticide formulation has been extensively commercialized up to 2012 (Perlatti et al., 2012). Some nano-products are already being applied, like e.g. Nanocid® based pesticides (Alavi et al., 2010: Gholami-Ahangaran et al., 2013) and Chitosan (Cota-Arriola et al., 2013), however, most of the applications are still in the developmental stage. For example, the preparation of the commonly used conventional chemical pesticide permethrin on a nano-scale by Suresh Kumar et al. (Suresh Kumar et al., 2013), showed that the resulting nanopermethrin could be potentially used as a safe and effective alternative. Also the use of the pheromone methyl eugenol as a nanogel proved to be a low cost approach (Bhagat et al., 2013), due to lower applied doses without losing efficacy (Chin et al., 2011). Another group of nano-agents with insecticidal, antimicrobial or antifungal properties are naturally occurring ashes and green produced inorganic metal nanoparticles (Sonkar et al., 2012: Yildiz et al., 2012: Gunalan et al., 2012: Debnath et al., 2011: Stadler et al., 2010: Choudhury et al., 2010: Rajakumar et al., 2013).

Nanotechnology can not only protect crops and food products from pests but also boost crop production and quality (Kole et al., 2013: Wang et al. , 2012: Mondal et al., 2011). Fertilizers in the form of nano-emulsions are used to increase the potency of active ingredients, or potentially reduce the quantity of fertiliser that has to be applied (Barati, 2010: Pandey et al., 2010). An example of this is a nanoclay for the slow release of growth stimulants and biocontrol agents (Friends of the Earth, 2008). Nanotechnology also offers a wide array of opportunities to further improve the overall properties of agricultural products (e.g. better nutritional values). Some examples include using bio conjugated nanoparticles (encapsulation) for the slow release of nutrients, food additives like vitamin A and omega-3 fatty acids, or active compounds used in veterinary medicine (Sauvant et al., 2012: Gökmen et al., 2011: Scott , 2007: Xun et al., 2012: Wanyika et al., 2012: Nguyen et al., 2012: Verma et al., 2012: Varma, 2012).

Other applications of nanomaterials in agriculture are agri-waste management and water and soil cleaning purposes. Nanofibers produced from cotton fibres have apparently been used for agri-waste management while aluminium oxide, lanthanum particles and nanoscale iron powder have been used in the process of water purification and/or soil cleaning (FAO, 2010: Bouwmeester et al., 2009). It is expected that these materials will not enter the food- or feed chain and they are therefore not discussed further.

No currently applied feed additives are identified in the Nano Inventory and there appear to be only a limited number of nanomaterials in development for feed additives. In addition, no information was found that certain food additives will also be used as feed additives, e.g. encapsulated vitamins or nutrients. However, nanomaterials are being developed and tested for efficacy to replace antibiotics, to absorb bacteria and toxins, and to improve digestibility of feed. Antibacterial nanosilver is believed to have a similar effect as the usual antibiotics and is being added to drinking water for chickens (Pineda et al., 2012a,b) and pigs (Fondevila et al., 2009). Somewhat surprisingly, nanosilver has also been tested to reduce the toxicity of aflatoxin in chickens (Gholami-Ahangaran et al., 2011). In another potential application polystyrene-based particles are added to chicken feed to bind bacteria. These particles with the bound bacteria clump together when passing through the gastrointestinal tract of the chicken along with other fecal matter (Kuzma et al., 2008). Another development is the potential use of nanoclay as a feed additive. The contamination of animal feed with mycotoxins represents a worldwide problem for farmers and can cause serious diseases in farm animals. Researchers have developed a montmorillonite based nanoclay specifically to absorb mycotoxins in the gastrointestinal tract of animals to protect them from mycotoxosis (YingHua et al., 2005). As a specific example, Shi et al. tested the efficacy of a modified montmorillonite nanocomposite to reduce the toxicity of aflatoxin in chickens (Shi et al., 2006). Finally, the effect of high dose of nano-selenium on feed digestibility was tested with sheep (Xun et al., 2012). The results indicated that supplemental selenium in the form of nano-selenium significantly improved the feed digestion in sheep.

3.3.1.2. Current and future application of nanomaterials in food processing/additives

Nanotechnologies are applied in food production machinery and in food additives. Examples of nanotechnology in food production machinery are coatings of machines, or the use of nano-sieves (e.g., to filter out bacteria). While direct food contact is evident, this application of nanotechnology is expected to have very low additional safety concerns, because migration or carry-over to food should be excluded and exposure is therefore expected to be negligible. An exception may be cooking equipment, crockery and other kitchenware that may have been treated with nanomaterials to provide it with antibacterial properties (Chen et al., 2010) as in that case the particles are on the surface to exert their microbial activity.

Of more importance are food additives which are substances added to food to improve the stability of foods during processing and storage, to improve certain product characteristics, or to increase the potency and bioavailability of nutrients in the food product. A number of such additives have been identified in the literature and are discussed below.

Synthetic amorphous silica (E551), mostly used in the form of precipitated and fumed silica, consists of primary particles in the size range around 5-100 nm (European Commission, 2012). The aggregates, which are fused and chemically bonded primary particles, typically are of size between 30 and 50 nm. These aggregates in turn form physically bonded agglomerates (by van der Waal's forces) in the range of 100 nm to 100 µm. Synthetic amorphous silica is in use since the 1920s and has numerous applications. It is used as a free-flow, anti-caking agent in powdered food items and animal feed. A recent study showed that at least a part of the silica material in powdered food items is in the nano-size range (Peters et al., 2012). Apart from that, the fact that the primary particle size is <100 nm already indicates that E551 is a nanomaterial according to the nanomaterial definition.

Titanium dioxide (E171) is also a common food additive. As a pigment, titanium dioxide is used to enhance the white colour of certain foods, such as dairy products and candy. It also lends brightness to toothpaste and some medications. However, it is also used as a food additive and flavour enhancer in a variety of non-white foods, including dried vegetables, nuts, seeds, soups, and mustard, as well as beer and wine. As with silica, titanium dioxide particles are referred to as primary particles, aggregates or agglomerates. Scattering of light by titanium dioxide is maximized in particles that are 200–300 nm in diameter, and most commercial products that are used as pigments have primary particle sizes within this range. The size distribution of ultrasonically dispersed primary particles and aggregates generally ranges from <100 to 500 nm. Exposure to titanium dioxide from foods and consumer products and its risk for humans is of increasing interest; a recent study showed that 5 to 36% of the titanium dioxide in common food products is in the nano-size range (Weir et al., 2012).

Iron in the form of iron oxides (E172) is used as a food colorant. Although there is no information about the size of these particles, they are likely to be in the micron-size range since they are produced top down, i.e. by grinding larger particles. Besides improving certain product characteristics, other forms of iron are being studied as a health-promoting food additive since iron deficiency is one of the most common micronutrient deficiencies worldwide. Food fortification can be an effective and sustainable strategy to reduce iron deficiency but selection of iron fortificants remains a challenge. The solubility and the bioavailability of poorly acid-soluble Fe compounds can be improved by decreasing their primary particle size and thereby increasing their specific surface area. Nanostructured iron may prove useful for iron fortification of certain foods and compounds containing are already being produced (Hilty et al., 2011: Zimmermann et al., 2011).

Nano-encapsulation involves the incorporation, absorption or dispersion of bioactive compounds in, at or on small vesicles with nano (or submicron) diameters. This type of application is especially important in food and is discussed here more in-depth. The incorporated bioactive compounds may be protected against degradation, have improved stability and solubility (e.g., solubilizing a hydrophilic compound in hydrophobic matrices and vice versa) and therefore might increase bioavailability and delivery to cells and tissues (Taylor et al., 2005: McClements, 2010: Magnuson et al., 2011). For example, a bakery firm has been reported to successfully incorporate microcapsules containing tuna fish oil (a source of omega-3 fatty acids) in bread. The capsules are designed to break up only after they reached the stomach, thus avoiding the unpleasant taste of the fish oil (Joseph et al., 2006).
Nano-encapsulates generally consist of a core composed of one to several types of compounds surrounded by a wall or barrier and have their roots in the pharmaceutical industry, where synthetic polymeric nano-encapsulates are often employed (Puri et al., 2009: Antunes et al., 2013). Various types of organic nanomaterials are used for nano-encapsulation, which are often based on lipids, proteins, polysaccharides, polymeric networks, or combinations thereof. Polymer-based nanomaterials have been developed extensively for the biomedical and pharmaceutical sectors to protect and transport bioactive compounds to target functions. However, synthetic polymer-based nanomaterials cannot be used for food applications, as food-grade polymers have to be utilized, so only

nanomaterials based on lipids, proteins and polysaccharides are suitable for applications in food (Chen et al., 2006: Graveland-Bikker et al., 2006: Mozafari et al., 2006). A special case of non-organic encapsulate is the use of nano-sized silicon as a food additive to improve the stability of hydrophobic nutrients during processing and storage through a combined effect of nanostructuring and solid state modification (Canham, 2007).

In recent years a large amount of studies and reviews have been published that describe the potentials of nano-encapsulation in different applications (Durán et al., 2012: Esmaeilzadeh et al., 2011: Esmaili et al., 2011: Ezhilarasi et al., 2013: He et al., 2013: Kuan et al., 2012: McClements, 2011a: McClements et al., 2011b: McClements, 2012: Severino et al., 2012: Pavankumar et al., 2012). As a consequence there is a relative large number of these organic nanomaterials available and used in products and a few of them are mentioned here. Nano-sized self-assembled liquid structures are produced by a company called NutraLease™ (NutraLease, 2013). The 30 nm particles consist of micelles, lipid-based hollow spheres, that can contain a whole set of hydrophobic nutrients. AquaNova™, a company in Germany, uses nanotechnology to produce similar nanomicelles to improve the solubility of bioactives and change water/fat solubility of nutrients, such as vitamin A, C, D, E and K, coenzyme Q10, β-carotene, isoflavones, α-lipoic acid and omega-3 fatty acids (AquaNova, 2013). The size of these micelles is claimed to be around 30 nm. LycoVit™, produced by BASF is a gelatine based nanoparticulate material containing synthetic lycopene. While the bioavailability of lycopene from fresh, non-processed tomatoes is poor, the bioavailability of this synthetic nanoparticulate material is claimed to be similar to that found for formulated natural tomato extract (Hoppe et al., 2003). The size of these particles is claimed to be 200-300 nm. LifePak Nano™ by Pharmanex contains nano-encapsulated (fat-soluble) vitamins like carotenoids and CoQ10. In the case of coenzyme Q10 it is claimed that the process of nano encapsulation increases the bioavailability by 5-10 times (Pharmanex, 2013). There is no information about the size of the material. MicroHydrin™ by RBC Life Sciences is claimed to consist of molecular cages, 1-5 nanometers in diameter, made from a silica-mineral hydride complex and is used as an antioxidant dietary supplement. The same company also produces Artichoke Nanoclusters and Slim Shake Chocolate, both coated nano-size silica particles (RBC Life Sciences, 2013). Empty liposomes are also available on the market to form encapsulation micelles. An example is nanocapsules marketed under the name Coatsome™, a phospholipid-based micelle mainly meant for research studies, consisting of cholesterol, L-(α)-dipalmitoylphosphatidylglycerol (DPPG), and L-(α)-dipalmitoylphosphatidylcholine (DPPC) that spontaneously forms liposome micelles upon suspension in water (CoatSome, 2013).

3.3.1.3. Current and future application of nanomaterials in food contact materials

Incorporation of nanomaterials or nanotechnological devices in packaging materials or storage containers in order to lengthen the storage time while keeping the products fresh are considered the most important type of nanotechnology application in the food area for the near future (Chaudhry et al., 2008). Nanocomposites can improve mechanical strength; reduce weight, increase heat resistance, and improve barrier against oxygen, carbon dioxide, ultraviolet radiation, moisture, and volatiles of food package materials. The main nanoparticles that have been studied for use in food packaging systems as well as their effects and applications were reviewed recently (Papaspyrides, 2010: Silvestre et al., 2013). Fine nanoparticulates (100 nm or less) are incorporated into plastics to improve the properties over those of conventional counterparts. These so-called nano-composites are thermoplastic polymers that have nanoscale inclusions, 2%–8% by weight. Nanoscale inclusions consist of nanoclays, carbon nanoparticles, nanoscale metals and oxides, and polymeric resins. An example of this is a butadiene, ethyl acrylate, methyl methacrylate, styrene copolymer, either not crosslinked or crosslinked with divinylbenzene or 1,3-butanediol dimethacrylate, in nanoform, intended to be used up to 10% w/w as an impact modifier in rigid PVC that is used as a food contact material. This material is currently under assessment of EFSA (EFSA, 2014). Under EFSA assessment are also nano-hexadecyltrimethylammonium bromide modified montmorillonite organoclay for use as additive in plastics[10]. Nanocomposites are characterized by extremely high surface-to-volume ratio, making them highly reactive in comparison to their macroscale counterparts, and thus presenting fundamentally different properties. Moreover, nanocomposites can also have biodegradable (Pillai et al., 2013) and antimicrobial properties (Lagerón et al., 2005: Li et al., 2011: Martínez-Abad et al., 2012).

The permeability of the food packaging materials for atmospheric oxygen can be reduced by adding nanomaterials to polypropylene-based nanocomposite films, which makes it more difficult for oxygen to pass through to the packaged goods than through conventional polymer films thus improving the preservation of food (Schirmer et al., 2008: Manikantan et al., 2011: Duraccio et al., 2013). An added benefit of adding nanoclays is an improvement in tensile strength and thermal properties and therefore polymer-clay nano-composites have emerged as a novel food packaging material. Other forms of nanomaterials such as nano wheels, nanofibers and nanotubes, are being investigated for application in nanocomposites to improve the properties of food packages (McHugh, 2008). Materials with similar properties but comprising of polyamide with layered silicate barriers have additional properties such as thermal buffering (Johnston et al., 2008a/b). Durethan, from BayVillaer Polymers is a nanocomposite film enriched with silicate nanoparticles that reduce entry of oxygen and other gases and the exit of moisture, thus preventing food from spoiling. Nanocor has developed nanocrystals to be used in nanocomposite plastic beer bottles to minimize loss of carbon dioxide and entry of oxygen into beer bottles (Plastimart, 2010). Natural biopolymer-based nanocomposite packaging materials with bio-functional properties have a potential for application in the active food packaging industry. Advances in the preparation of natural biopolymer-based films, their nano-composites, and their potential use in packaging applications were reported (Lageron et al., 2011: Sanchez-Garcia et al., 2010). Other improvements in nanotechnology for food packaging include carbon nanotubes that can be used in food packaging to improve its mechanical properties and for its antimicrobial effects (Casals et al., 2008: Rungraeng et al, 2012).

Nanoparticles can also be used to improve biodegradable food packaging. This type of food packaging can be made of biodegradable polylactide (PLA) composite films containing ultraviolet radiation absorbing inorganic nanofillers such as Ag-TiO_2 nanoparticles. The thermal properties and thermo mechanical stability of the composite film is much higher than that of regular PLA and the photo degradability is significantly improved by adding the Ag-TiO_2 nanoparticles (Pillai et al., 2013).

The most common nanoparticles added to food packaging to confer antimicrobial properties are silver, chitosan, zinc oxide and nisin (Rai et al., 2011: De Azeredo, 2013). Chitosan is a very promising option for antimicrobial food packaging. Thus chitosan (nano)films are very effective for food preservation, and have great potential for a wide range of applications due to the biodegradability, biocompatibility, antimicrobial activity, non-toxicity and versatile chemical and physical properties (Tripathi et al., 2008: Dutta et al., 2009: Lima et al., 2009: Aresta et al., 2013). Nanoparticles coated with poly-ethylene-glycol and loaded with garlic essential oils have been studied to control the stored-product pests (Yang et al., 2009). Phytoglycogen octenyl succinate, an amphilic carbohydrate nanoparticles loaded with ε-polylysine improved the shelf life of the lipid products to oxidation (Scheffler et al., 2010). Zinc oxide has also been tested in antimicrobial food packaging films (Li et al., 2011: Espitia et al., 2012) aswell as nano-emulsions of the antimicrobial peptide nisin (Imran et al., 2012). Nisin is a polycyclic antibacterial peptide with 34 amino acid residues used as a food preservative. Nisin is a rare example of a "broad-spectrum" bacteriocin and is used in processed cheese, meats, beverages, etc. during production to extend shelf life. As a food additive, nisin has E(uropean) number E234.

[10] http://www.efsa.europa.eu/en/request/requests.htm

At present, silver is the most investigated antibacterial nanoparticle. Silver nanoparticles are added to food packaging materials in several ways, for instance as finely dispersed nanosilver particles embedded in containers and coatings (Benelmekki et al., 2012: Martinez-Abad et al., 2012: Llorens et al., 2012), as a silver-based zeolite in polylactic acid biocomposites (Busolo et al., 2010: Fernandez et al., 2010), and as gelatin-silver nano-composites (Halder et al., 2011). The antimicrobial properties of the food packaging materials were improved by incorporating any of these methods but only the finely dispersed nanosilver particles embedded in the containers are currently used in food packaging, the other methods are still in the research stage.

3.3.2. Toxicological data query

All the information collected by the Nano Inventory on toxicology was included in the query called '*Toxicological data*'. Specifically, this query includes fields about physico-chemical properties of the tested nanomaterials, when available, mode of action intended as the mechanism by which the nanomaterial explicate its function, human toxicology, including both the toxicity and the kinetic, target species and population (Table 3). While the total number of entries in the '*Toxicological data*' query is 1942, the query consists of 691 toxicological tests. The higher total number results from multiple entries, for instance, when more than one physical property was entered in the Nano Inventory for one and the same particle. To get meaningful numbers blank Endpoint [hazard for HH] were removed as were multiple entries for one and the same particle in the Parameter field. The resulting numbers for this query are presented in Table 8.

Table 8: Overview of fields in the "Toxicological data" query.

Field in "Toxicological data" query		Number of entries
Nanomaterial		691
CAS number		32
Parameter		418
Use stage		
	As pristine	155
	As delivered for application	54
	As used in toxicological test	65
	As used in efficacy test	6
Mode of action		194
Endpoint [hazard for HH]		691
Endpoint [kinetics for HH]		445
Target species		7
Reason for the assessment		
	Self-assessment	442
	Regulatory requirements	132

For many nanomaterials a CAS number is given which indicates that the nanomaterials used in toxicological tests have a known chemical composition, e.g. materials like silica, titanium dioxide and silver. As mentioned before, for correlating any measured toxicological response with nanoparticle properties it is most important to know the physico-chemical properties of the particles, in-situ, i.e. as used in the toxicological test. Table 8 shows, this is often not the case and only in 20% of the records particles characteristic are reported for the toxicological test system. In most studies the properties of the nanomaterials as manufactured (pristine), or as delivered, are reported. In the absence of a good assessment of the physico-chemical properties in the toxicological test medium it is not possible to draw general conclusions on nanomaterials which may have similar chemical compositions but, in fact, have different sizes, shapes and surface areas. Different types of toxicity tests have been carried out with different nanomaterials; the results are presented in Figure 13. The field “Endpoint [hazard for HH]” has a total of 691 records and ranks 10 types of toxicity testing. While silica, silver and titanium dioxide are the most tested nanomaterials, genotoxicity, acute toxicity, cytotoxicity and repeated dose toxicity, are the most tested toxicity endpoints.

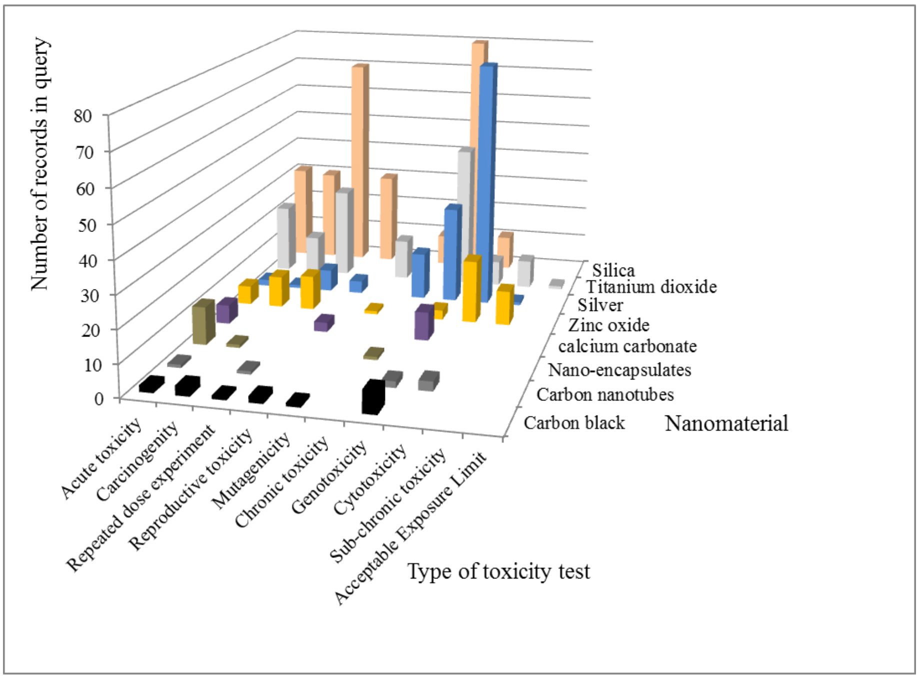

Figure 13: Overview of the 10 different types of toxicity testing and most reported nanomaterials reported in the Toxicological data query of the Nano Inventory.

For the field “Endpoint [kinetics for HH]” 445 records are found ranking 5 types of kinetic processes, absorption, distribution, and elimination. In more than 50% of these studies in the inventory the distribution of nanomaterials over the different organs and tissues is discussed. Absorption and elimination studies make up most of the other 50%.

As described above, the primary focus of the inventory was to give an overview of current and potential future applications in the area of nanotechnology. Secondary to that, toxicological data on the different nanomaterials used for those applications have been collected. Consequently, the inventory is not to be considered as an exhaustive source of toxicity data and it is not intended to cover all the available knowledge in that field. In the last years several reviews have been published reporting the human effects of some of the main applied nanomaterials in agri/feed and food applications, like silver, TiO_2, SAS (Synthetic Amorphous Silica), CNTs, etc. Such reviews, if considered reliable were utilised for the descriptions in the below paragraphs and have been supported by information from additional searches as described in section 2.2 and Appendix A.

3.3.2.1. Potential toxicity of silver nanomaterials

The systemic absorption after oral exposure and the safety, health and environmental effects of nanosilver have been recently reviewed by the Danish Environmental Protection Agency (Danish EPA, 2013), the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR, 2013). An 28-day oral study in rat comparing coated and uncoated silver nanomaterials with soluble silver compounds ($AgNO_3$) showed that nanoparticles were found in all three groups, suggesting the possibility of *in vivo* formation of silver nanoparticles following absorption of silver ions (van der Zande et al., 2012). In general, it is believed that silver ions are released from silver nanomaterials and are absorbed in the gastro intestinal tract of experimental animals. Several studies reported that after the detection in the blood, silver was further distributed to organs (Danish EPA, 2013). Liver seems to be a target organ for toxicity as indicated by the effect of silver on various liver enzymes (SCENIHR, 2013). Levels in blood and organs depend both on the dose and on the size of the silver nanomaterials used (i.e. larger particles seem not to be absorbed, while a high absorption has been reported for silver nanomaterials smaller than 100 nm). Some excretion of silver has been reported to occur via feces. No significant difference in the absorption of silver nanomaterials in the Gastro-Intestinal tract or in the deposition in various organs has been identified when compared to different polymeric coatings/stabilizers (Danish EPA, 2013). Overall, human toxicity of both silver and nanosilver has been reported as low. While *in vitro* studies with silver nanomaterials reported cytotoxic effects, genotoxic DNA damaging capacity, and developmental toxicity; the *in vivo* studies could not confirm the same effects. *In vivo* repeated dose toxicity studies did not result in alterations in the specific immune responses, although, in contrast, the *in vitro* studies reported an induction of cytokine in macrophages and natural killer cell activity. Thus, further studies on the effects on the immune system and its functionality after exposure to silver nanomaterials are recommended (SCENIHR, 2013).

3.3.2.2. Potential toxicity of titanium dioxide nanomaterials

The toxicological data on TiO_2 nanomaterials has been reviewed by Shi et al (Shi et al., 2013) and the Danish EPA (Danish EPA, 2013). Shi et al. conclude that TiO_2 might be bioavailable upon oral exposure, but that the translocation rate is unkown. They also state that the genotoxic potential of TiO_2 nanomaterials has been studied extensively, but that the results are conflicting and the used doses were high. Therefore, the authors call for more hazard assessment studies with a focus on long-term animal studies comparing the toxicity and carcinogenicity of TiO_2 fine and ultrafine (= nano)particles. The focus of these studies must be aimed at both occupational and consumer relevant doses and routes of exposure. The Danish EPA review reported only one study that addressed the influence of crystal structure of TiO_2 nanoparticles on absorption after oral exposure. The result from this study indicated that the rutile form is better absorbed than the anatase form which is generally considered more toxic. Agglomeration of the anatase form could be one of the possible explanation for the low absorption of these particles, this being in line with the general agreement that absorption of nanomaterials is inversely correlated to the their size. However, in the case of TiO_2 nanoparticles this mechanism is not entirely understood (Danish EPA, 2013).

3.3.2.3. Potential toxicity of zinc oxide nanomaterials

Apart from the study by the Danish EPA (Danish EPA, 2013), no recent review on the oral toxicity of zinc oxide (ZnO) nanoparticles was identified. The studies included in the Nano Inventory assessed the toxicokinetics after oral exposure. Only a minor amount of orally administered ZnO is absorbed, most likely in the ionic form, and distributed to organs, mainly liver, lung and kidney. The uptake of smaller particles is larger than that of larger particles. An important observation was also that Zn was cleared from the organs after 7 days (Baek et al., 2012: Li et al., 2012). Lee et al conducted two studies to determine the behaviour and accumulation of nano- and submicron-sized ZnO particles (Lee et al., 2012a,b). The first study revealed that the highest concentrations in blood were reached 5-7 hours after administration of labelled ZnO nanomaterials. Smaller particles were absorbed at a faster rate than larger particles. The second study showed that larger particles were mostly found in the liver and kidney while smaller particles were taken up faster and also reached other organs. However, a recent paper (Peak et al., 2013) concludes that the major biological fate of ZnO nanoparticles in tissues was the ionic form, not the particulate form.

3.3.2.4. Potential toxicity of silica nanoparticles

In discussing the literature on silica nanoparticles it is important to realize the different types of silica. This ranges from synthetic amorphous silica (SAS) to colloidal silica. For both silica and SAS much information is available in the "Toxicological data" query. This concerns particle properties as size and specific surface area, as well as information about toxicity testing. SAS is an important form of silica that is used in many food applications as E551 and consists of aggregates and agglomerates of primary particles with sizes around 10 nm. The most recent review of the literature was performed by (Fruijtier-Pölloth, 2012) suggesting safety for consumers when exposed to SAS via food, as indicated by a LOAEL (based on liver toxicity in rats) of 1500 mg/kg bw/day (Dekkers et al., 2011, 2012). In a recent *in vitro* study reported by the Danish EPA (Danish EPA, 2013) it was shown that a high amount of SiO_2 nanoparticles was present in the gut after complete digestion of foods containing those NPs. Only very recently (and therefore not included in the Nano Inventory) Van der Zande et al. performed an oral feeding study using SAS in which rats were exposed for 28 days, and to only the highest dose for 84 days (Van der Zande et al., 2014). The authors conclude that although only few adverse effects were observed, additional studies are warranted to further evaluate the biological relevance of the observed fibrosis in liver and possible accumulation of silica in the spleen.

3.3.2.5. Potential toxicity of carbon nanotubes

The applications of carbon nanotubes (CNTs) collected in the inventory refer to food packaging materials. Risk to humans would only occur if nanotubes embedded in food packing material was released into food and or feed. Strikingly this was not studied in any of the papers that evaluated the use of carbon nanotubes in food packing material. While, the absorption of CNTs after oral exposure from *in vivo* studies has not been reported by the Danish EPA(Danish EPA, 2013), *in vitro* observations suggest in principle the ability to enter the cells however not to cross the intestinal wall and enter into circulation . A study by Kolasnjajtabi did not reveal the formation of granuloma after oral exposure to CNTs (Kolosnjajtabi et al., 2010). Other *in vivo* studies were performed but did not prove any uptake of CNTs (Matsumoto et al., 2012: Awasthi et al., 2013).

3.3.3. Risk assessment status query

The third query is called '*Risk assessment status*' and aims to give an overview on the possible implications for safety and related risks for each nanomaterial based on the retrieved information on hazard (toxicity) and exposure. Specifically, this query includes information about identified hazards for human health and the environment, kinetics for human health and exposure scenarios. The query consists of 203 entries that include information on exposure. Silica, titanium dioxide, nano-encapsulated pesticides and silver are the most frequently found nanomaterials. To get meaningful numbers multiple references/entries in the query have been removed and Table 9 gives an overview of the number of entries for each field in the '*Risk assessment status*' query.

Table 9: Overview of fields in the '*Risk assessment status*' query.

Field in *"Risk assessment status"* query	**Number of entries**
Nanomaterial	203
CAS number	32
Application field	203

Availability on the market		
	confirmed	42
	in development	158
Implication for safety		160
Endpoint [hazard for HH]		175
Endpoint [hazard for ENV]		148
Endpoint [kinetics HH]		24
Scenario [exposure]		203
Reason for the assessment		
	Self-assessment	178
	Regulatory requirement	0

The fields ‘Application field’ and ‘Availability on the market’ are already discussed in section 3.3.1. The fields ‘Endpoint [hazard for HH]’, ‘Endpoint [Kinetic HH] and ‘Reason for assessment’ are already discussed in section 3.3.2. The field ‘Implication for safety’ has 160 entries and gives potential information whether a certain nanotechnology application results in a lower or higher safety compared to the related bulk form. The field ‘Endpoint [hazard for ENV] has 148 entries reporting data on 11 persistence and accumulation properties as well as potential effects as shown in Figure 14.

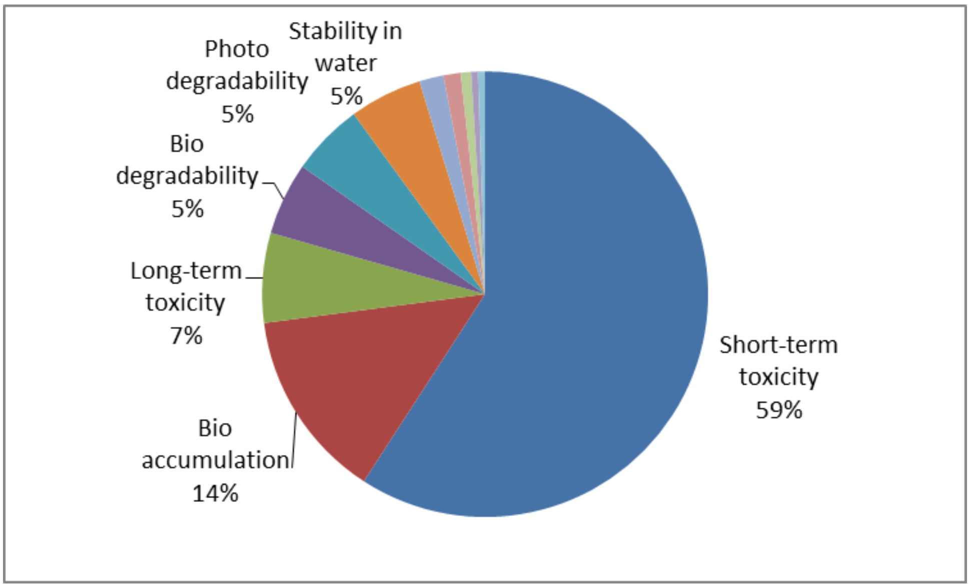

Figure 14: The major properties in the field ‘Endpoint [hazard for ENV]’.

In a traditional risk assessment, information on hazard is combined with exposure. The analysis of the query often shows incomplete records, because only limited information is provided on exposure (fields ‘scenario’ and ‘outcome’). In that context it should be noted that the main source of information for the Nano Inventory is open literature. Scientific studies or other open literature usually cover only parts of the risk assessment, i.e. toxicological tests for the hazard assessment or migration studies to assess the potential exposure. Full risk assessments are usually prepared for as part of an evaluation for authorisation or any other approval. Such complete information may not be disclosed before submission to an authority and was therefore not available for the assessment. The major exposure scenarios in the Nano Inventory are presented in Figure 15.

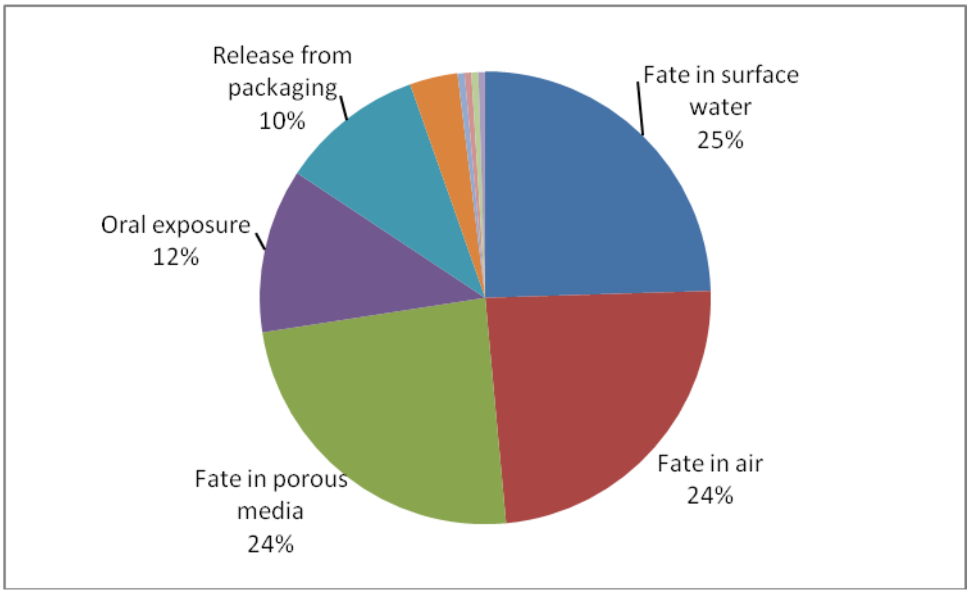

Figure 15: The major exposure scenarios in the Nano Inventory.

As can be seen in Figure 15 there are only a few major exposure scenarios which in fact originate from only three studies. The first is a complete risk assessment for silica, presented by Dekkers et al. (Dekkers et al., 2011), but even for this risk assessment the authors are very careful because of the uncertainties in both the hazard and the human exposure data. For titanium dioxide the *"Risk assessment status"* query mostly reveals records from one source on one specific material; DuPontTM Light Stabilizer. The information in these records is derived from an EPA Nanomaterial Risk Assessment Worksheet presented by DuPont. It summarizes that DuPontTM Light Stabilizer may be used as a component of polymers used as food and beverage containers which raises the possibility of ingestion should it somehow migrate from the polymer to the content. Once incorporated into polymer, DuPontTM Light Stabilizer is encapsulated by the polymer and the exposure potential for consumers is expected to be low. Based on hazard studies performed by DuPont itself, DuPontTM Light Stabilizer has a low acute oral and pulmonary toxicity, and is not a skin irritant or sensitizer. Chronic toxicity testing has not been conducted because of the expected low level of exposure as well as the lack of adverse effects seen in acute studies.

The records on carbon nanotubes are limited to the release from packaging or only contain information on its application, but not on potential exposure or risk assessment.

For nano-encapsulates no risk assessment data is available with the exception of a material which is intended to be used as a veterinary drug and was tested for bioaccumulation.

For silver risk assessment information is available from the Nano Inventory, but the records reveal mostly toxicological data and not data from risk assessment studies. Some data are available for zinc oxide but this mainly concerns toxicity studies and release from packaging and only provides limited information on the risk assessment status. In conclusion, only in a few cases an outcome from a risk assessment of a nanotechnology application is presented. This resembles the current situation on the risk assessment of nanomaterials: only silica and titanium dioxide have been evaluated. The field 'Reason for assessment' contains 180 entries, 178 times "self assessment", 2 times "not clear". Apparently in no case a risk assessment was carried out because of regulatory requirements.

3.4. Other results

3.4.1. Mode of action of nanomaterials

It is evident that the metal and metal oxide based nanoparticles constitute an effective antimicrobial agent against common microorganisms. Therefore, some of the nanoparticles such as silver, titanium dioxide and zinc oxide are receiving considerable attention as antimicrobials and additives in consumer, health-related and industrial products (Ravishankar et al., 2011; De Stefano et al., 2012; Manke et al., 2013). The same is true for some of the organic nanoparticles although these are mainly used to stabilize drugs or nutrients with the idea to increase the uptake of such drugs or nutrients. The mode of action of nanomaterials is one of the fields in the "Toxicological data" query and in total 235 entries can be found in the Nano Inventory. Figure 16 gives an overview of the most prominent nanomaterials for which an entry in the mode of action field is given and not surprisingly, the majority are related to nanosilver.

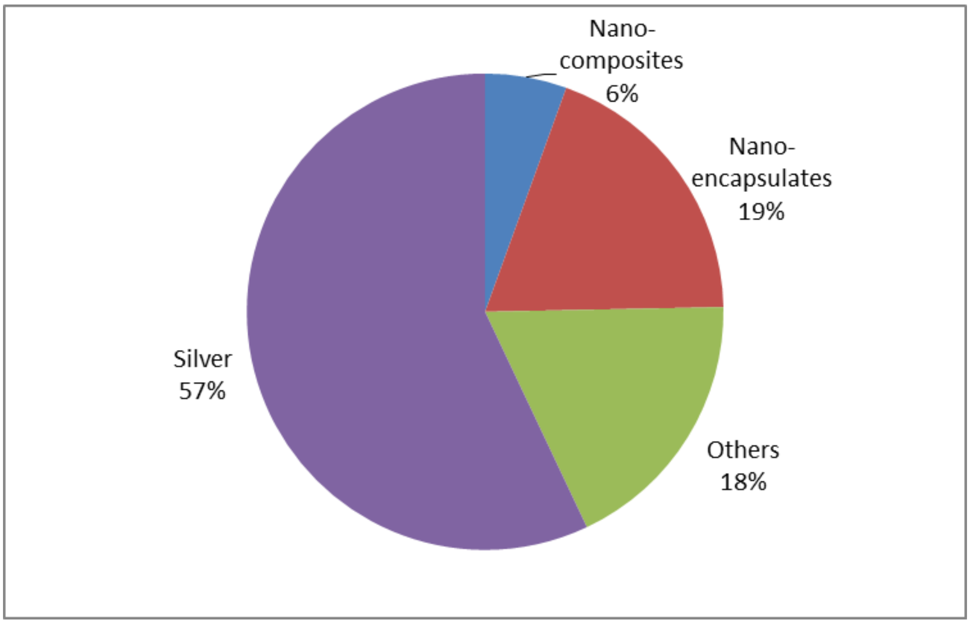

Figure 16: Nanomaterials for which a mode of action is found in the Nano Inventory

While short descriptions of the mode of action are given in the Nano Inventory, this section presents a more elaborate overview of the mode of action of different types of nanoparticles.

Silver nanomaterials have a broad spectrum of antimicrobial activity against pathogens and therefore are increasingly incorporated into various matrices and materials (Ravishankar et al., 2011; Khan et al., 2011). Often composites of silver nanoparticles in polymers are used, for instance in fridges or food packaging materials. Several mechanisms have been proposed to explain the inhibitory effect of nanosilver on bacteria. It is assumed that the high affinity of silver towards sulphur and phosphorus is the key element of the antimicrobial effect. It is also suggested that silver ions (particularly Ag^+) released from nanosilver can interact with phosphorus moieties in DNA, resulting in inactivation of DNA replication, or can react with sulphur-containing proteins, leading to the inhibition of enzyme functions. The general understanding is that silver nanoparticles of less than 20 nm diameters get attached to sulphur-containing proteins of bacterial cell membranes leading to greater permeability of the membrane, causing the death of the bacteria. The size and shape of nanoparticles also plays a role in its antimicrobial activity with small particles exhibiting a higher antimicrobial activity than big particles. This result can be due to a higher particle penetration of small particles, or to an increase of released Ag^+ ions due to the increased surface area. In some cases it is claimed that composites result in improved antimicrobial activities. Chitosan-bound silver nanoparticles have enhanced antimicrobial activity compared to the individual components, i.e. chitosan and silver. In the composite, the essential function of the positively charged chitosan matrix is to capture negatively charged bacteria on its surface, while the nanosilver created pores in the bacterial wall, thereby causing disintegration of the bacteria (Georgios et al., 2011).

TiO_2 nanoparticles are used as antimicrobial agents, sometimes in combination with other elements as nickel oxide and cobalt for the inactivation of foodborne pathogens (Amna et al., 2013). The inhibitory activity of TiO_2 is due to the photo-catalytic generation of strong oxidizing radicals when illuminated with UV light at wavelength of less than 385 nm. TiO_2 photo-catalysts can also be used as effective biofilm disinfectant in food processing industries. It has been suggested that nanostructured TiO_2 on UV irradiation can be used as an effective way to reduce the disinfection time, eliminating pathogenic microorganisms in food contact surfaces and enhance food safety (Ravishankar et al., 2011).

Studies have shown that some metal oxide nanomaterials like ZnO and CuO nanoparticles have a selective toxicity towards bacteria and only exhibit minimal effect on human cells, a property which makes them interesting for applications in the agricultural and food industries (Ravishankar et al., 2011). The generation of hydrogen peroxide from the surface of ZnO is considered as the mean reason for the inhibition of bacterial growth. As with silver it is observed that smaller particle size results in higher activity, probably as a result of the increased surface area and therefore increased generation of hydrogen peroxide. Another possible mechanism for ZnO antibacterial activity is the release of Zn^{2+} ions which can damage cell membranes and interact with intracellular contents. Studies show that ZnO nanoparticles can potentially be used as an effective antibacterial agent to protect agricultural and food products from foodborne pathogens (Sinha et al., 2011).

Pure nano-silica used as an antibacterial agent was not identified in the investigated literature. Nanosilica does however show antibacterial applications when nano/micro silica is used as a carrier. SiO_2/Ag composites are produced by the adsorption of silver salts on nanosilica and subsequent chemical reduction. The mode of action is the same as that for silver nanoparticles (Das et al., 2013).

Nano-encapsulates are used to stabilize active ingredients, as for example vitamine C. Overall, vitamin C is labile and most of its functionality is lost during processing and storage of food and feeds because of the exposure to high temperature, oxygen and light. Encapsulation is a suitable technique to isolate vitamine C from these environmental conditions and thus enhance the vitamin C stability (Alishahi et al., 2011). Encapsulated nisin was compared with non-encapsulated (free) nisin for its antimicrobial capacity in skimmed milk inoculated with Listeria. At higher temperatures free nisin showed better inhibitory properties, however, at lower temperatures (refrigeration) encapsulated nisin showed better results (Malheiros et al., 2010). Similar results are reported for cheese, encapsulated nisin showed better antimicrobial effects than free nisin (Malheiros et al., 2012). Encapsulation of antimicrobial peptides with an organic nanoparticle also showed to be important to overcome stability issues and interaction with food components.

3.4.2. *Results from questionnaire on "Production, use, import, research and development"*

Questionnaire 1 on production, use, import, research and development of nanomaterials in agri/feed/food applications (see Appendix C.1) was addressed to:

- companies (including their representatives, industrial or trade organisations) producing, importing or using materials and/or products containing materials with size < 1 µm in agri/feed/food applications and/or
- research institutes (private, public), research and development departments of industry, or others active in research and development of materials and/or products containing materials < 1 µm in agri/feed/food applications.

A total of 35 answers were received to questionnaire 1 on "Production, use, import, research and development". In addition 11 emails from industry representatives were received providing additional information or statements for not filling out the questionnaire. From the 35 individual answers to the questionnaire most (18) were from public research or control institutes or universities, 8 from private companies, 5 from industrial or trade associations and 1 each from a private research institute and an industrial R&D department (see Figure 17). Mainly researchers (15) and managers (11) answered to the questionnaires. 25 of the responding institutions were located in the EU (5 in Belgium, 3 in Croatia and 1 each from other countries), 5 outside Europe (USA, Australia, Brazil, Mexico) and 5 were active in- and outside the EU (see Figure 18). Mainly larger companies/institutions responded, half (17) of them having more than 250 employees and only 3 less than 10.

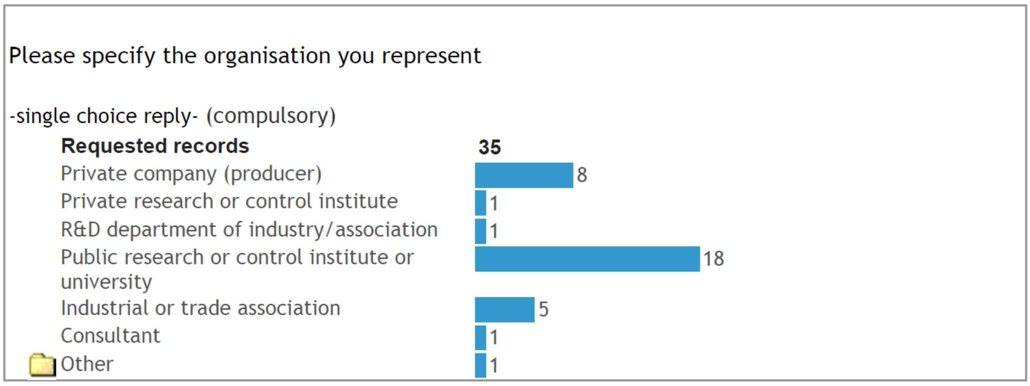

Figure 17: Statistics of organisations responding to the questionnaire on "*Production, use, import, research and development of nanomaterials*".

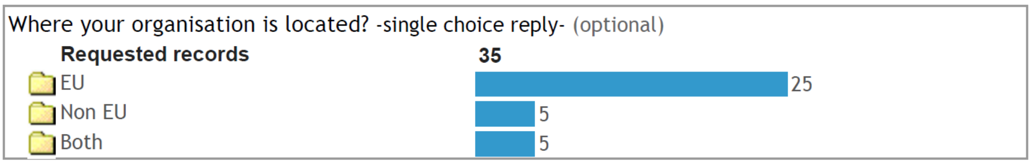

Figure 18: Statistics of respondents of questionnaire 1 according to regions.

Most of the responding companies are active in the field of food additives (18), food contact materials (15), feed or feed additives (14) and agri (pesticides (11)/biocides (11)). Some of the respondents (12) are also active in the production of (raw) material used for one of these applications (see Figure 19). More than half of those responding to the questionnaire said that they are not active and do not plan activities to produce/import (21), use (24) or perform research and development (14) on nanomaterials. About one third stated that they are currently active but only one reported the plan to produce/import or develop nanomaterials for agri/feed/food applications. Those who selected the option 'other' (3) were active in collecting scientific information and/or giving scientific and technical expertise/opinions related to nanomaterials in agri/feed/food applications.

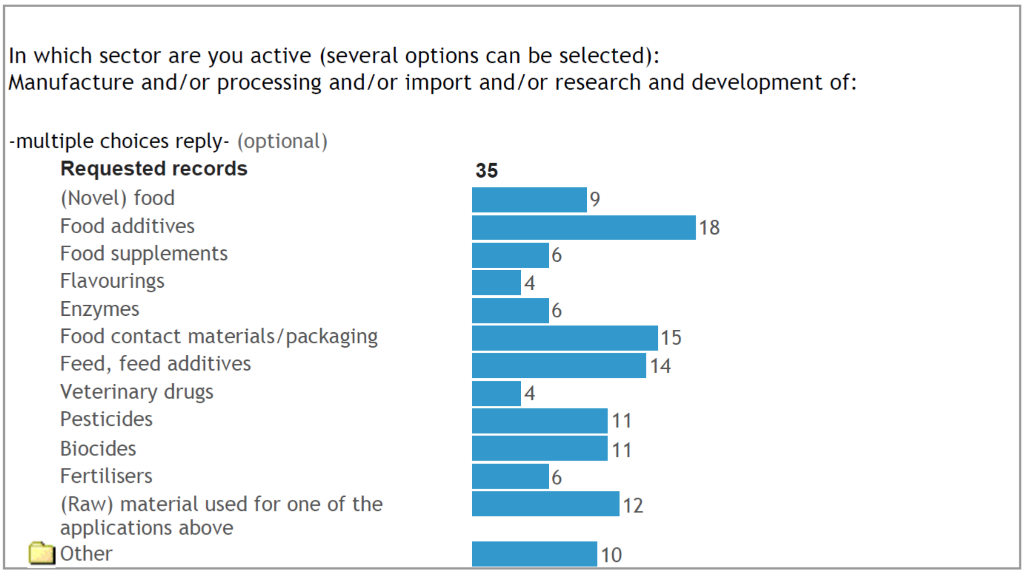

Figure 19: Statistics of the activity of the organisation of responders of questionnaire 1.

Most of the nanomaterials described by participants are used as food contact materials (14), food (7) and feed additives (5), pesticides (4) and biocides (5), whereas minor applications address novel food (2) and veterinary drug (1). Nanomaterials used or developed for applications such as food supplement, flavouring, enzyme or fertiliser were not reported at all. Information was provided in total for 19 substances, however, most of the descriptions were, not very detailed (only names and application reported). Two respondents attached a detailed description of the material to the questionnaire. The described nanomaterials include:

- Nanoemulsions containing essential oils or beta carotene to be used as (novel) food, food additive or biocide.
- Liposomes (spheroidal shape) as food additive
- Calcium carbonate (< 1um) natural ground as food and feed additive
- SAS as food additive (anti-caking), food contact material (reinforcing filler in rubber goods) and feed additive.
- Synthetic amorphous sodium aluminium silicates, carbon black, nanofillers and modified montmorillonite with ammonia salt of tallow fatty acids as food contact material
- TiO_2 for non-stick surfaces or as UV absorber
- Nano-Silver as food contact material, biocide, feed additive, veterinary drug
- Fullerenes, single walled carbon nanotubes or graphene ribbons used as biocide
- Silica, kaoling (clay), pigments, finely milled solids, artificial silica, copper oxide and other pesticidal metallic compounds and defoamers (emulsions) used in/as pesticide

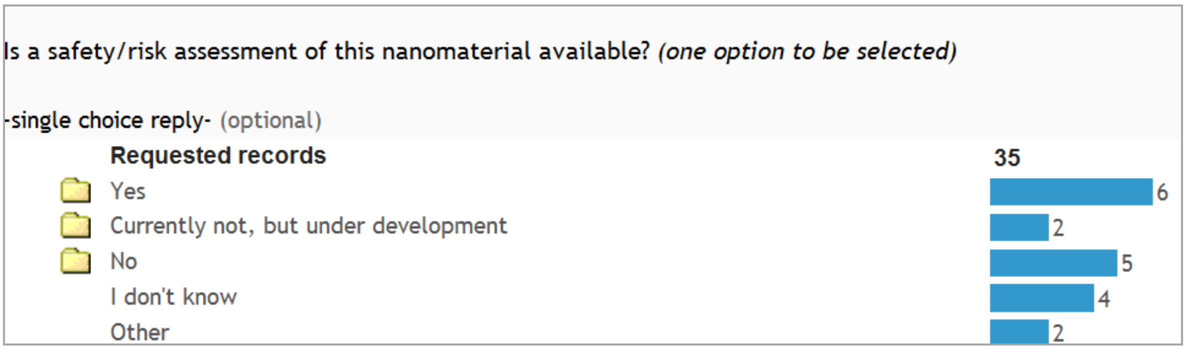

Figure 20: Overview of the availability of a safety/risk assessment (collated results for one nanomaterial per questionnaire).

Safety assessments collated for all three reported nanomaterials were available for 11 nanomaterials or are in development for 2 nanomaterials (Figure 20 shows results for only on nanomaterial). The main motivation given as justification for performing a risk assessment is the REACH requirement. However, for most of the reported nanomaterials no safety assessment is available (7) or the responders did not know (9). Finally, the majority did not answer this question at all.

In general, it was positive to notice that most of the responders (21) were willing to be contacted to provide further information. Representatives of food, plastic, pigment, mineral, crop, feed and nanotechnology industry or associations therof responded to the questionnaire invitation mostly via email, confirming that we have reached most relevant industry associations. Some of them provided rather general information to the questionnaire (on their activities and less on specific materials), others only provided comments or general information in an e-mail. All made an effort to show that they support the idea of improving transparency regarding the use of nanotechnology or nanomaterials in the food chain, but most also provided justifications for not reporting specific information. The main issue for not filling out the questionnaire was the (too) wide materials size range used in the questionnaire (materials <1 µm), which is not in line with the EU or ISO definitions, although a justification was provided for that choice. The lack of explanation to which the selected nanosize range refers (e.g. primary particle, aggregates/agglomerates, external particle size or internal structure based on agglomeration) and to which percentage this would apply was also mentioned. It was argued that the implementation of an inventory based on such a size range is not possible. Intellectual property law and/or related issues for materials in research and development were mentioned as reasons for not-disclosing information as well as that not all of the development efforts would lead to new materials/products on the market. Some producers/associations of mineral powders including silicon dioxide, kaolin powder, bentonite, kaolin, clays, calcium carbonate, calcium oxide, calcium dihydroxide, diatomite, quartz, or organic pigments stated that they are not intentionally producing nanomaterials but due to the production process and variable size distribution a fraction of the particle size may be <100 nm. The applications for mineral powders include: food additives, pesticides, biocides, fertilisers or in case of organic pigments food/feed additives or food contact materials. Two of the contacted producers explained that their nanomaterials (i.e. titanium dioxide) have no application in the agri/feed/food sector.

4. REVIEW OF EXISTING LEGISLATION ADDRESSING NANOTECHNOLOGY IN THE AGRI/FEED/FOOD SECTOR

The literature review on existing legislation with regard to nanomaterials and nanotechnology in food additives/food contact materials/feed additives and agriculture applications was focused on non-EU OECD countries including Switzerland, USA, Canada, Australia Japan, Korea, non-OECD countries covering other European countries, BRIC-countries (Brazil, Russia, India and China) and other non-

European countries (e.g. Malaysia and South Africa). Information on relevant regulations was gathered from appropriate recently published reports, such as the 2013 WHO/FAO report “State of the art on the initiatives and activities relevant to risk assessment and risk management of nanotechnologies in the food and agricultural sectors” and FDA Guidances Related to Nanotechnology. Appendix A shows a complete list of reports that have been consulted for preparing the regulatory review. Peer-reviewed publications were retrieved from the bibliographic databases search (see paragraph 2.1.1) and a few additional papers were selected from additional sources (e.g. Google search - see Appendix A). Information on regulation was also gathered from websites of governments, organizations, national and international institutions and from responses to the questionnaire on "Regulation and Safety Assessment of Nanomaterials in Agri/feed/food Applications" (see paragraph 4.1.5).

4.1. Implementing nanomaterials regulation and assessment

A clear definition is required to discriminate nanomaterials from other materials. Some countries have already introduced definitions, although not necessarily in a regulatory framework but as a working definition (NICNAS 2010; Australia 2011), a policy statement (Health Canada 2011), or presented as a general description in guidance (US-FDA 2011). International organizations such as the International Organization for Standardization (ISO), the International Risk Governance Council (IRGC) and the OECD (Bugusu, 2009, OECD, 2010) have also published definitions for nanomaterials or nanotechnology. The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) of the European Commission has published the scientific basis for the definition of the term nanomaterial (SCENIHR, 2010). In October 2011 the European Commission published the “Recommendation on the definition of a nanomaterial’, primarily intended to provide unambiguous criteria to identify materials for which special regulatory provisions might apply, but also to promote consistency on the interpretation of the term ‘nanomaterial” (European Commission, 2011a). In order to balance technology development with EHS (Environment, Health and Safety) regulation, most governments in leading industrialised countries follow an incremental, case-by-case approach to risk assessment and management ((SCENIHR 2009).

4.2. EU Legislation

Nanomaterials are covered in the EU by different **pieces of legislation**, which either implicitly or explicitly address NMs.

NMs as substances are covered by Regulation (EC) No 1907/2006 called Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) (European Parliament and Council 2006). Even if REACH does not specifically mention nanomaterials, they are covered by its substance definition, which addresses chemicals in whatever size, shape or physical form. The REACH guidance for the *'Information requirements and safety assessment'* in its update form from 2012 (ECHA 2012) is directly addressing NMs. In order to guarantee more clarity on how nanomaterials are addressed and safety is proved in registration dossiers, various activities are ongoing at European level to further develop the regulatory framework: e.g. revision of REACH annexes, review of the EC's nanomaterial definition and nanomaterials working groups at the European Chemicals Agency. Table 10 gives an overview of the current EU legislation and the status of the regulatory framework in dealing with nanomaterials in that legislation.

In EU, food additives/food contact materials/feed additives are regulated by several directives and regulations. Nanomaterials are specifically mentioned in the following, recently revised, regulations: EU Regulation 10/2011 on Plastic Materials Intended to Come into Contact with Food (European Commission 2011a), Active and Intelligent Materials and Articles Regulation 450/2009 (European Commission 2009) and the Regulation 1169/2011on the Provision of Food Information to Consumers (European Parliament and Council 2011). There are currently no provisions for nanomaterials in the legislation for pesticides or feed.

In December 2013, the European Commission has adopted a draft law on novel food which will provide legal certainty in this field (European Commission 2013). It refers to Regulation (EU) 1169/2011 as follows: "*Nanomaterials which are intended for food uses and covered by the definition of "engineered nanomaterials", as laid down in Regulation (EU) No 1169/2011 on Food Information to Consumers, shall be assessed and authorised under this Regulation before being placed on the EU market*". It also states that: "*Therefore, where a new production process has been applied to this food or where the food contains or consists of "engineered nanomaterials" as defined in Article 2(2)(t) of Regulation (EU) No 1169/2011, the food should not be considered to be traditional*".

4.2.1. Definition of a nanomaterial

Currently, only few European legislative pieces incorporate a definition of nanomaterial to enable specific provisions for nanomaterials. All of them include a provision that the European Commission shall adapt the definition of engineered nanomaterials referring to technical and scientific progress or to definitions agreed at international level.

Regulation (EC) No 1223/2009 for cosmetic products (European Parliament and Council 2009) was the first to include a definition of nanomaterials: "*nanomaterial means an insoluble or bio-persistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm''*.

Regulations on food information and food packaging materials followed with a different definition (European Commission 2011a; European Parliament and Council 2011): *''engineered nanomaterial 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''*. Properties that are characteristic of the nanoscale include ''*those related to the large specific surface area of the materials considered*'' and ''*specific physicochemical properties that are different from those of the non-nanoform of the same material*''.

The EC 'Recommendation on the definition of a nanomaterial' (European Commission 2011b) defines nanomaterials as *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 nm-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 %. By derogation […], fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.*

On 22 May 2012, a new regulation for biocidal products was adopted (European Commission, 2012) (European Parliament and Council 2012b). This regulation is the first to include a definition of nanomaterial which largely corresponds to the EC definition Recommendation. The current proposal of a revised Regulation on Medical devices (European Parliament and Council 2012a) also includes a definition of nanomaterial which is identical to the Recommendation of the EC.

Table 10: Overview of current EU legislation in the agri/feed/food sector and its reference to nanomaterials

Legislation	EU legislation	Definition[(a)]	Label[(b)]	Guidance
Products:				
Biocides	(EU) No 528/2013	Yes	Yes	No
Plant protection products	(EC) No 1107/2009	No	No	Yes

Cosmetics	(EC) No 1223/2009	Yes	Yes	Yes
Medical devices	COM (2012) 542 final 2012/0266 (COD)	Yes	Yes	No
Food/Feed:				
Food information to consumers	(EU) No 1169/2011	Yes	Yes	No
Novel foods/feeds	COM(2013) 894 final 2013/0435 (COD)	Yes	Yes[11]	Yes
Plastic food contact materials	(EU) No 10/2011	No	No	Yes
Active and Intelligent Materials and Articles	(EU) 450/2009	No	No	No
Food additives	(EC) 1333/2008	No	Yes[4]	Yes
Feed	(EC) No 767/2009	No	No	No
Chemicals:				
Registration, evaluation, authorisation and restriction of chemicals (REACH)	(EC) 1907/2006	No	No	Yes
Classification, labelling and packaging	(EC) 1272/2008	No	No	No
Occupational health and safety	89/391/EEC: 98/24/EC: 2004/37/EC: EC 1907/2006:	No	No	No

(a): In case the specific legislation includes a definition of nanomaterial, this is indicated by "Yes".
(b): In case the specific legislation requires that the use of nanomaterials is indicated on the product label, this is indicated by "Yes".

Some definitions include specification to discriminate natural, incidental and manufactured/engineered nanomaterials, or make a distinction between soluble and non-soluble nanomaterials and hard or soft nanomaterials. Such specifications are relevant in relation to the requirement of a specific risk assessment or legal labelling or reporting obligations (see below). Soluble nanomaterials dissolve quickly in media by changing into non-nanomaterials, whereas soft nanomaterials including micelles, emulsions and liposomes fall apart in the gastrointestinal tract. Both are expected to have limited nano-specific risks and consequently are considered of comparable risk to the bulk form. Some natural nanomaterials are already present in many food and feed products like for instance casein proteins in milk products. Furthermore, some nanomaterals materials containing a nanofraction may have a long history of use.

4.2.2. Risk assessment

A separate risk assessment or a case-by-case evaluation for nanomaterials is required under several frameworks (e.g. Food Additives or Biocidal Products Regulation) (European Parliament and Council 2008; European Parliament and Council 2012b). In this context, it is useful to note that EFSA has released in 2011 a guidance document entitled "*Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain*" (EFSA Scientific Committee 2011) providing a practical approach for assessing potential risks arising from applications of nanoscience and nanotechnologies in food additives, enzymes, flavourings, food contact materials, novel foods, feed additives and pesticides and testing approaches to identify and characterise hazards arising from the nanoproperties. Guidance is provided on the physico-chemical characterisation and testing

[11] Required through Regulation No 1169/2011 (Food information to consumers)

approaches to identify and characterise hazards arising from the nanoproperties. EFSA guidances, as any other EU guidances, are however not part of the EU legislation and thus not legally binding.

Some substances such as synthetic amorphous silica (E551), calcium carbonate (E170), titanium dioxide (E171) iron oxide (E172) or silver (174) in colloidal form have a history of (safe) use as food additives or in food contact materials but are not specified as nanomaterials. These substances may be considered nanomaterials applying the definition (e.g. SAS) or contain a fraction in the nanosized range (e.g. titanium dioxide). Such substances are currently re-evaulated to consider also potential nanospecific risks. For example calcium carbonate, titanium dioxide and iron oxide as food and feed additive are under evaluation by EFSA[12]. Concerning calcium carbonate (E170) EFSA concluded that "the available data are sufficient to conclude that the current levels of adventitious nanoscale material within macroscale calcium carbonate would not be an additional toxicological concern" (EFSA Panel on Food Additives and Nutrient Sources added to Food 2011). The re-evaluation of silicon dioxide (E551) is expected to be completed by 2016 (European Commission (DG SANCO) 2013).

Request for the safety evaluation of (new) nanomaterials have been submitted to EFSA[13] for

- nano-Hexadecyltrimethylammonium Bromide modified Montmorillonite Organoclay for use as additive in plastics.
- copolymer in Nanoform of methacrylic acid, ethyl acrylate, n-butyl acrylate, methyl acrylate, butadiene as additive in food contact materials
- Copolymer in nanoform of ethyl acrylate, methyl methacrylate, butadiene, styrene and either not crosslinked or crosslined with divinyl benzene or 1,3-butanediol dimethacrylate as additive in food contact materials.

4.2.3. Labelling of consumer products for their content of nanomaterials and nanomaterials registries

Cosmetic products, food and biocidal products have to be labelled for their nanomaterials content by adding the word "nano" in brackets after the substance name in the ingredient list. The labelling requirement entered into force for cosmetic and biocidal products in July and September 2013 respectively and will enter into force for food in December 2014. There is currently a discussion ongoing whether substances already included in the Union lists of food additives by EC Regulation 1129/2011 are excluded from the labelling requirement for "nano" in the list of ingredients.

Many EU countries are developing specific provisions to regulate nanotechnology-based products, which include also agri/feed/food products. A mandatory reporting system for nanomaterials has already been introduced in France. An interministerial Decree was published in 2012 (Ministère de l'Écologie du Développement durable et de l'Énergie 2012) on this issue and it applies to all companies and research laboratories producing, distributing or importing more than 100 gr a year of nano substances. This nanomaterials register is not publicly accessible due to confidentiality reasons. A first analysis based on public data was presented in November 2013 by the French Ministry of the Environment (Ministère de l'Écologie du Développement durable et de l'Énergie 2013). A total of 3,409 notifications referring to an estimated number between 243 and 422 different substances (nanomaterials) were received. 41% of the registrations did not provide a CAS number but the substances were identified by a chemical name. An aggregated amount of 504,104 tonnes (282,014 tonnes manufactured and 222,090 tonnes imported) of NM was reported with the highest tonnages for carbon black (274,837 tonnes), silicon dioxide (SAS) (155,072 tonnes), calcium carbonate (34,502 tonnes), titanium dioxide (14,321 tonnes), Aluminium oxide (2,193 tonnes) and copolymer of

[12] http://www.efsa.europa.eu/en/request/requests.htm
[13] http://www.efsa.europa.eu/en/request/requests.htm

vinylidene chloride (1,560 tonnes). Nanomaterials registers will also be implemented in Belgium[14] and Denmark (a Draft decree for the Belgian registry and a Draft order for the Danish registry have already been notified to the European Commission (BiPRO and Öko-Institut 2013; Miljoministeriet and Miljostyrelsen 2013)). The German Federal Environment Agency (UBA) supports the establishment of a central nanoproduct register at European level and has published a "Concept for a European Register of Products Containing Nanomaterials". Germany, as also some other member states, prefer a European register over national product registers as this would lead to a more uniform management of nanomaterials across EU (Umweltbundesamt 2014).

The EC has launched a "Study to assess the impact of possible legislation to increase transparency on nanomaterials on the market" to identify and develop the most adequate means to increase transparency and ensure regulatory oversight, including an in-depth analysis of the data gathering needs for such purpose (RPA and BiPRO 2014). The study will utilise (RPA and BiPRO 2014) experiences from already implemented transparency measures such as the French Notification Scheme and the Cosmetics Products Notification Portal. It should include those NMs currently falling outside existing notification, registration or authorisation schemes. The results of the impact assessment are expected by autumn 2014 (RPA and BiPRO 2014). In the UK, the Food Safety Authority (FSA) has published a list of nanomaterials that are allowed to be used in food/food contact materials. The list is short and comprised of fumed silica, nanoclay, titanium nitride and nanosilver (UK-FSA). The FSA has also published a call to interested parties to gather intelligence relating to nanotechnology-enabled foods/food contact materials that are being developed or near to being launched on the EU market (UK-FSA).

4.3. Legislation in non-EU OECD countries

The regulatory framework of nanomaterials in the agri/feed/food sector in non-EU OECD countries is presented hereunder and an overview is given in Table 11.

4.3.1. United States of America

The Food and Drug Administration (FDA) is the American Authority responsible for ensuring the safety of food additives/food contact materials/feed additives in USA. This is done under the *Federal Food, Drug, and Cosmetic Act* (FFDCA)(US-FDA), which is a set of laws giving authority to the FDA to oversee the safety of all food, drugs, and cosmetics. The FFDCA does not contain any specification for nanotechnology-based products and FDA has not yet adopted a regulatory definition of nanomaterials and has embraced a quite broadly comprehensive approach when dealing with nanotechnology-based products (Hamburg 2012). However, a Draft Guidance to Industry on considerations for evaluating whether an FDA-regulated product involves the application of nanotechnology was published in June 2011 (US-FDA 2011). As reported in the guidance: *"...when considering whether a FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, FDA will ask: "Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm)"; or "Whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer".* The guidance is intended to be broadly applicable to all FDA-regulated products, including food products.

More recently, in April 2012, FDA issued a Draft Guidance for Industry on *"Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives"* (US-FDA 2012). In the guidance FDA recommends a preliminary safety

[14] http://www.presscenter.org/nl/pressrelease/20140207/belgie-voert-een-nanomaterialenregister-in?lang=fr

assessment of Food Ingredients and Food Contact Substances produced at the nanoscale, which should be based on data relevant to the nanometer version of the food substance (Tyler 2012). FDA does not consider *a priori* all products containing nanomaterials as intrinsically hazardous but suggests a case-by-case approach when assessing the safety of the finished product and of its foreseen use. Regarding the safety of such products, FDA also states: "*at this time, we are not aware of any food ingredient or FCS (Food Contact Substance) intentionally engineered on the nanometer scale for which there are generally available safety data sufficient to serve as the foundation for a determination that the use of a food ingredient or FCS is GRAS (Generally Recognised As Safe).*" In the guidance FDA declares that: "*some Food Contact Notifications (FCNs) have included information describing the use of a food contact substance with particle sizes in a nanometer range. To date, we have not, to our knowledge, received food or color additive petitions, or GRAS affirmation petitions or notices, for any uses of food ingredients with a particle size distribution fully in the nanometer range."*

The Environmental Protection Agency (EPA) is responsible for regulating pesticides under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)(US-EPA). No specific provisions for nanomaterials are available at the moment under this regulation, however, in the US-EPA website the report 'Regulating Pesticides that use Nanotechnology' (US-EPA 2011) is available since July 2011. EPA is seeking for public comment regarding how nanotechnology-based pesticides should be regulated and incorporated into FIFRA. Companies intending to register nanotechnology-containing pesticides are recommended to contact 'EPA's pesticide registration Ombudsman'.

4.3.2. Canada

The Canadian Food Inspection Agency (CFIA) and Public Health Agency of Canada (PHAC), who have recently joined the Health Portfolio of Health Canada, are responsible for food regulation in Canada. As declared by one of the responders to our questionnaire on 'Regulation of nanomaterials in agri/feed/food applications' (and as can be found on a public website[15]), *"currently, there are no regulations specific to nanotechnology-based health and food products. Health Canada relies on authorities within existing legislative and regulatory frameworks, which require the assessment of potential risks and benefits of products to the health and safety of Canadians before they can be authorised for sale"*.

In October 2011 Health Canada published a "*Policy Statement on Health Canada's Working Definition for Nanomaterials*" (Health Canada 2011) which gives the following definition: "*Health Canada considers any manufactured substance or product and any component material, ingredient, device, or structure to be nanomaterial if: it is at or within the nanoscale in at least one external dimension, or has internal or surface structure at the nanoscale, or it is smaller or larger than the nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena*".

4.3.3. Australia and New Zealand

Food Standards Australia New Zealand (FSANZ) is the agency part of the Australian Government's Health portfolio and responsible for the regulation of food in Australia and New Zealand. All food marketed in Australia and New Zealand must be conform to the Australia New Zealand Food Standards Code (the Code) (FSANZ) and be safe for human consumption. As from the FSANZ website (FSANZ): *"using the best available scientific evidence, FSANZ has adopted a range of strategies to continually review and manage potential risks associated with nanotechnologies in foods to ensure the public are not exposed to any health or safety issues. These strategies include: amending the FSANZ Application Handbook to support new food regulations and ensure applicants provide all the necessary information to help FSANZ conduct a risk assessment advising the food industry about*

[15] http://www.hc-sc.gc.ca/sr-sr/pubs/nano/pol-eng.php

the amendments to the Application Handbook involving nanotechnology and asking industry for information about proposed nanotechnology applications engaging with other national regulatory agencies, industry and the public to outline FSANZ's regulatory responses". As stated in the recently published FAO/WHO technical report (FAO/WHO 2013), FSANZ has not yet received any applications to approve new or novel nanoscale particles for food use.

Regarding the general chemical regulation, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) introduced the first regulatory program for "industrial nanomaterials" (January 2011). On September 3, 2013, NICNAS posted an electronic copy of its Handbook for Notifiers (NICNAS 2013), which provides guidance for importers and manufacturers of industrial chemicals in Australia. Appendix H of that document includes guidance and requirements for notification of new chemicals that are industrial nanomaterials. Labelling of nanomaterials is encouraged in the Safe Work Australia's Code of Practice entitled *"Labelling of Workplace Hazardous Chemicals"* (Australia 2011), clause 3.10 *"Products Containing Nanomaterials"*. As stated in the Code *"for engineered or manufactured nanomaterials or chemicals containing engineered or manufactured nanomaterials, it is recommended that labels be prepared in accordance with this Code unless there is evidence that the nanomaterials are not hazardous. The following label statements are recommended for products containing nanomaterials when the hazards are not fully characterised: 'Contains engineered/manufactured nanomaterials. Caution: Hazards unknown' or 'Contains engineered/manufactured nanomaterials. Caution: Hazards not fully characterized".*

As reported in the Liason Report to ISO/TC 229 "Nanotechnologies" (ISO 2013), NICNAS has published information sheets on hazard reviews for nanoforms of TiO_2 and Ag, while the Tasmanian Institute of Agriculture has published a comprehensive review on Nanotechnology in Agricultural Products Logistics Management.

4.3.4. Japan

The Food Sanitation Law regulates the safety of food in Japan. The competent authority is the Ministry of Health, Labour, and Welfare. No nanomaterials-specific legislation is available to date in Japan but various research activities are ongoing in the nanotechnology field. A "Basic Survey Report on Safety Assessment Information on the Use of Nanotechnology in the Food Sector" was released in March 2010 (FSCJ 2010) and opinions on the current status of the use of nanotechnology in the food sector in Japan can be found in the document (English version available).

4.3.5. Korea

The Korean Food and Drug Administration (KFDA) is the main body responsible for food regulation and safety. However, no specifications for nanomaterials are available to date (FAO/WHO 2013). The Food Sanitation Act is the main piece of legislation and, as reported in the Agency website, *"covers the basic requirements and responsibilities for the hygienic and sanitary practices of the food manufacture, process, distribution and sales by establishing certain criteria and standards for foods, food additives, and food packaging materials sole in Korea".* KFDA also establishes food standards such as "Food Code", "Food Additives Code" and "Food Labelling Standards" (KFDA).

The Republic of South Korea has established a "National Nano-safety Strategic Plan (2012/2016)". The Ministry of Knowledge and Economy (MKE) and the Korean Agency for Technology and Standards, published in 2011 as a Korean standard the *'Guidance on safety Management of Nano-based products, Korean Agency for Technology and Science Public Notice No. 2011-0108 of 12 May 2011* (Park ; Mantovani *et al.* 2012), where nanomaterials are defined as follows: *"Nanomaterial means nano-objects and nano-structured materials (including materials having an internal nano-sized structure or materials with condensed nanoparticles), in a solid form, that are smaller than 100 nm in any dimensions".*

4.3.6. Switzerland

The safety of nanomaterials used in food products is ensured by existing regulations and procedures. "*The use of additives and ingredients in food is in part regulated with lists which provide information about whether a substance may or may not be used and whether quantitative restrictions apply. So far, the Federal Office of Public Health has not received any requests for approval of food additives containing nanomaterials. Possible future requests would be handled analogously to those for a new, as-yet unlisted additive. The same would apply to requests for packaging materials containing nanomaterials which come into contact with foodstuffs*" (FAO/WHO 2013).

Nanomaterials used in pesticide products submitted for registration must be declared. Specific information such as composition, shape, particle size, surface area, aggregation status, coatings, functionalization, are requested (Ordinance concerning the placing of plant protection products on the market; SR 817.091.6 (916.161) (FOPH 2005). No applications for nanotechnology-based pesticides have been submitted yet (Bucheli et al., 2013).

Regarding general chemical regulation and risk assessment in Switzerland, an action plan on the risk assessment and risk management of synthetic nanomaterials was launched in 2008. As part of the action plan, the Federal Office of Public Health (FOPH) and the Federal Office for the Environment (FOEN) published in 2008 a precautionary matrix for synthetic nanomaterials (Höck *et al.* 2008). "*This is a tool that has been designed to assist all stakeholders that are responsible for the safety of employees, consumers or the environment in the preliminary clarification of any need for action. The precautionary matrix is based on a limited number of evaluation parameters, including size of the particles, their reactivity and stability, their release potential, the amount of particles. These parameters are used to estimate the precautionary need for employees, consumers and the environment at each defined step in the life cycle.*"

The Swiss Secretariat for Economic Affairs (SECO) has published a guideline document for the compilation of safety data sheet for synthetic nanomaterials (SECO 2012). The guidance aims at giving assistance in identifying which information is necessary to gain to ensure the safe handling of nanomaterials and where and how this information has to be inserted in the SDS.

Table 11: Summary of food legislation in non-EU OECD countries

Country	Responsible Organization	Key legislation	Online resources
USA	US Food and Drug Administration (FDA) Environmental Protection Agency (EPA)	Federal Food, Drug, and Cosmetic Act (FFDCA) Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)	- http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactFDCAct/default.htm - http://www.fda.gov/Food/default.htm - http://www.epa.gov/oecaagct/lfra.html
Canada	Canadian Food Inspection Agency (CFIA) Public Health Agency of Canada (PHAC)	Food and Drugs Act	- http://www.hc-sc.gc.ca/dhp-mps/nano-eng.php - http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.%2C_c._870/
Australia and New Zealand	Food Standards Australia New Zealand (FSANZ)	Australia New Zealand Food Standards Code	- http://www.foodstandards.gov.au/code/Pages/default.aspx - http://www.nicnas.gov.au/communications/issues/nanomaterials-nanotechnology/nicnas-regulatory-activities-in-

			nanomaterials - http://www.foodstandards.gov.au/consumer/foodtech/nanotech/pages/default.aspx - http://www.nicnas.gov.au/regulation-and-compliance/nicnas-handbook/handbook-appendixes/guidance-and-requirements-for-notification-of-new-chemicals-that-are-industrial-nanomaterials
Japan	Ministry of Health, Labour and Welfare	Food Sanitation Law	- http://www.mhlw.go.jp/english/policy/health-medical/food/index.html - http://www.jetro.go.jp/en/reports/regulations/
Korea	Ministry of Food and Drug Safety (MFDS) Korean food and Drug Administration (KFDA) Korean Agency for Technology and Science (KATS)	Food Sanitation Act	- WHO/FAO report, 2013 - http://www.kfda.go.kr/eng/index.do?nMenuCode=61 - http://www.mfds.go.kr/eng/index.do - http://www.kats.go.kr/english/home/home.asp?OlapCode=ATSU15
Switzerland	Swiss Federal Office of Public Health (FOPH) Federal Office for the Environment (FOEN)		- http://www.bag.admin.ch/nanotechnologie/12171/12174/index.html?lang=en - http://www.bag.admin.ch/nanotechnologie/12171/12176/index.html?lang=en - http://www.bag.admin.ch/themen/lebensmittel/10380/index.html?lang=en

4.4. Other European countries including EU candidate countries (Balkan countries)

No specific information on nanomaterials legislation in agri/food/feed was found for Serbia, Bosnia Herzegovina, Montenegro, Macedonia and Albania.

4.5. Non-OECD countries covering other European countries, BRIC-countries and other countries

This chapter presents the regulatory framework of nanomaterials in the agri/feed/food sector in non-OECD contries; an overview is given in Table 12.

4.5.1. Brazil

The National Agency of Sanitary Surveillance (ANVISA), in cooperation with the Ministry of Agriculture, Livestock, and Food Supply (MAPA) and the Ministry of Health (MS), are the main responsible for regulation of food in Brazil. Food products are regulated under several legal documents issued by the Federal Government and, in order to be implemented must be published in Brazil’s Diario Oficial. (http://portal.anvisa.gov.br/wps/portal/anvisa-ingles). No nanomaterials specific legislation has been found for Brazil.

4.5.2. Russia

The legislation on food safety in Russia is articulated in sanitary and regulatory documents, such as the Sanitary Rules and Regulations (“SanPiN”), but also in national standards (known as “GOST”) and technical regulations (USDA, 2009). The Federal Service for the Protection of Consumer Rights and Human Well-Being of the Ministry of Health and Social Development, also known as Rospotrebnadzor, is responsible for food and foodstuff safety. As reported in the FAO/WHO report (FAO/WHO, 2013), 17 documents which deal with the risk assessment of nanomaterials in the food sector were released within a federal program that focused on the improvement of infrastructure of Nanoindustry in the Russian Federation for 2008-2010. Safe reference levels on nanoparticles impact on the human body were developed and implemented in the sanitary regulation for nanomaterials of silver, single wall carbon nanotubes and titanium dioxide (FAO/WHO, 2013).

4.5.3. India

The Food Safety Standard Authority of India (FSSAI), established in 2006, is the main Indian authority responsible for food safety and has been created for regulating manufacture, storage, distribution, sale and import of food articles and to ensure their safety. The Food Safety and Standards Act (2006) is the key piece of regulation for all matters relating to food safety and standards in India. The nation does not have a legislation that takes in consideration nanoparticles as a hazard (Sharma, 2009), "has a loose framework of legislation where nanotechnology risks can be addressed" (Jayanthi, 2012) and lacks of resources and expertise to handle nanotechnology risks (Barpujari, 2011). A good overview of the status of nanotechnology risk governance in India can be found in the review published by Jayanthi et al in 2012 (Jayanthi, 2012).

4.5.4. China

Food products are regulated under the Food Safety Law of China (2009) and the Ministry of Agriculture and the Ministry of Health are responsible for the risk assessment. No nanomaterials specifications are included in this law. One of the responders of our questionnaire declared that a national recommendation for a definition is available in China and mandatory labelling of nanomaterials in specific products is required, however this could not be followed up. The following definition of nanomaterial can be found in the "GB/T 19619-2004: 纳米材料术语 (Terminology for nano materials)" and it is effective since April 2005 (Park, 2012; ISO, 2013): “*material which has a structure in the three-dimensional space in at least one dimension in the nanometer scale (from 1 nm to 100 nm range of geometric dimensions), or constituted by the nano-structure unit and a material with special properties*”. Applications for nanominerals or nanomaterials to be used as food ingredients have been rejected so far by the Chinese regulatory authorities (FAO/WHO, 2013).

4.5.5. South Africa

The Republic of South Africa has several pieces of food-specific legislation, i.e the Foodstuff, Cosmetics and Disinfectant Amendment Act 2007; however, no specific legislation for nanomaterials in the food and agriculture sectors was found (FAO/WHO, 2013).

4.5.6. Malaysia

A National Nanotechnology Regulatory and Safety committee, placed under the National Nanotechnology Directorate, was established in Malaysia to monitor and review issues related to health, safety and environment. Regulations to ensure the health, safety and environmental aspects of nanotechnology include The Nanotechnology Industry Development Act and The Nanotechnology Safety-Related Act. The insertion of specifications relating to nanotechnology is foreseen, among others, in the Food Regulations 1985 and in The Food Act 1983 (ISO, 2013) (information taken from: Towards a Malaysian Regulatory Framework, Asia Nano Forum, Nanotech 2013, Japan 31st January, National Nanotechnology Directorate NanoMalaysia Ltd (power point presentation)).

4.5.7. *Taiwan*

A National Science and Technology Program for Nanoscience and Nanotechnology was launched in Taiwan in 2003. A system for certifying nanoproducts, called Nano Mark System, has been introduced in this context. 'Nanoingredients' are a category for which the Nano Mark Symbol is required in consumer products (http://www.taiwan.gov.tw/ct.asp?xItem=27511&ctNode=1906&mp=1001).

Table 12: Summary of food legislation in some non-OECD countries.

Country	Responsible Organization	Key legislation	Online resources
Brazil	National Agency of Sanitary Surveillance (ANVISA) Ministry of Agriculture, Livestock, and Food Supply (MAPA) Ministry of Health (MS)		- http://portal.anvisa.gov.br/wps/portal/anvisa-ingles - http://www.agricultura.gov.br/
Russia	The Federal Service for the Protection of Consumer Rights and Human Well-Being of the Ministry of Health and Social Development (Rospotrebnadzor)		- http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Food%20and%20Agricultural%20Import%20Regulations%20and%20Standards%20-%20Narrative_Moscow_Russian%20Federation_11.08.2009.pdf
India	Food Safety Standard Authority of India (FSSAI)	Food Safety and Standards Act, 2006	- http://www.fssai.gov.in/AboutFssai/Introduction.aspx?RequestID=kHte14K1h8e3hHK4iHe_doAction=True - WHO/FAO report, 2013
China	Ministry of Agriculture Ministry of Health National Institute of Metrology	Food Safety Law of China, 2009	- http://en.nim.ac.cn/ - http://en.nim.ac.cn/division/overview/924
South Africa		Foodstuffs, Cosmetics and Disinfectants Amendment Act, 2007	- WHO/FAO report, 2013
Malaysia	Ministry of Science Technology and Innovation	Food Regulations 1985 The Food Act 1983	- Towards a Malaysian Regulatory Framework, Asia Nano Forum Nanotech 2013, Japan 31st January: http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=2&ved=0CDUQFjAB&url=http%3A%2F%2Firannano.org%2Ffilereader.php%3Fp1%3Dmain_47e24b47020343c728d44a00681a79b5.pdf%26p2%3Dstatic_page%26p3%3D22%26p4%3D1&ei=KDanUu2lL8P9ygPMhIG4Dg&usg=AFQjCNFA69SOMsrseyu1NemcbZYc8Jxe1Q&sig2=G2r5yhfGlndIe3hvzAa4dA

4.6. Questionnaire on “Regulation and safety assessment of nanomaterials in agri/feed/food applications”

As described under 2.2 a questionnaire was prepared with the objective to collect information about the regulation of nanomaterials in EU and non-EU countries. The questionnaire was addressed to

persons having a good knowledge of legislation, reporting requirements (labelling and/or product register) and safety assessment of nanomaterials in EU and non-EU countries, including authorities, consultants, companies producing in or exporting to non-EU countries and researchers.
Questions were asked to retrieve information on the availability of a specific regulation for each different application field and of a definition for nanomaterials. Furthermore, questions addressed the presence of reporting requirements (labelling, product register) and of provisions to ensure the safety of nanomaterials. In addition, specific information about a maximum number of three nanomaterials either authorised/registered/notified or otherwise available on the market was asked (the final version of the questionnaire can be found in Appendix C).

4.6.1. Results from questionnaires

A total of 34 individual answers were received, the majority (24) from national authorities, 1 from an association and 9 from others, including 4 universities, a consultant, food industry association, non-profit organisation and regulator. The questions were answered mainly by researchers, department heads and other experts (since this was an open question there is no statistics available). 29 of the responders were from EU countries, 11 from Belgium, 3 from Croatia, 2 from Slovenia and the others from Ireland, Finland, Italy, Denmark, Bulgaria and Lituania. 5 responders were from outside the EU, specifically the USA, China, Korea, Switzerland and Norway. Most responders are active in the area of food (21), in novel food (12), food additives (12), food supplements (10), food contact materials (10), pesticides (10), genetically modified organisms (10) and chemicals (10). Half of the responders (17) said that they are dealing with nanomaterials (see figure 21).

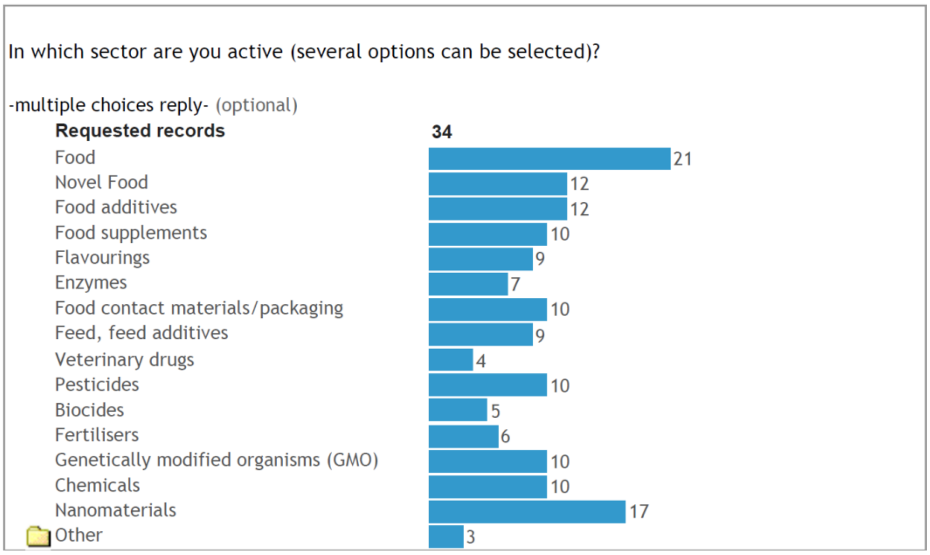

Figure 21: Statistics of activity of responders to the questionnaire on legislation

Most of the responders (14) stated that their knowledge of regulation of nanomaterials was good while 5 responders stated it was excellent. Respectively 3 and 8 responders stated their knowledge about regulation was fair and poor, while 3 responders indicated to have no knowledge about nanomaterials regulation.
Specific information on nanomaterials of their choice was provided by 6 experts. Most of the described nanomaterials are used as food contact materials (10) and food additives (11). Some information was provided for feed additives (2), pesticides (3), biocides (4), and fertilisers (1). The nanomaterials described (in addition to those already mentioned under 3.4.2) include:

- TiO_2 as pesticide

- Enamel as food contact material
- Polysysine as biocide
- Nanosilicon capsules
- Gold, nano-calcium and nano-silica as food supplement and food contact material

Translations of relevant laws, guidance and other documents are available from 11 responders, 10 responded that translations were not available, while 11 responders did not know whether they were available. It was positive to notice that most of the responders (24) were willing to be contacted to provide further information.

5. CONCLUSIONS

This study presents an inventory of currently used and reasonably foreseen applications of nanotechnology in the agri/feed/food sector and a review of nanomaterials legislation in EU and non EU-countries. Four sources of information were used to fill the Nano Inventory and carry out the regulatory review: 1) an extensive (structured) literature search resulted in the selection of 779 relevant references organised into the following categories: agriculture (and feed), food processing, food contact materials, mode-of-action, (eco-)toxicology, and legislation; 2) additional ad-hoc literature searches generated further 117 relevant references; 3) websites of companies involved in the production or use of nanomaterials which were identified on the internet and scrutinised; 4) two questionnaires were sent out to over 1000 experts in the respective field.

The Nano Inventory was implemented in a Microsoft Access environment and contains 633 records of nanotechnology applications describing physico-chemical characteristics of nanomaterials, reporting product names and related suppliers and providing information on (eco)toxicity testing, target species, exposure and risk assessment status. The inventory was used by the contractors to store, update and extract relevant information on nanomaterials in agri/feed/food applications. For the purposes of this contract, three types of inventory lists have been extracted from the Nano Inventory via dedicated queries: (i)"*Current and future application*", (ii) "*Toxicological data*" and (iii) "*Risk assessment status*". These inventory lists together cover all the relevant fields of the Nano Inventory in an easy-to-view and publishable format.

The results from the query "*Current and future application*" suggest that nano-encapsulates, silver and titanium dioxide have the highest number of records in the inventory and that food additives and food contact materials are the most indicated applications. Currently, 276 nanomaterials are confirmed to be available on the market, however, an exact distinction between those that are confirmed to be on the market and potential nanomaterisal applications cannot always be made. In total 633 nanotechnology applications were found and 55 types of nanomaterials for agri/feed/food were identified. The inorganic nanomaterials are very diverse, including metals, metal oxides, clay and full-carbon materials while the vast majority of organic nanomaterials consists of nano-encapsulates and nano-composites. Less than 20% of the different nanomaterials are involved in more than 80% of the applications and only a limited number of nanomaterials are involved in most of the applications. A comparison between current and future applications indicates a trend from inorganic materials like silver towards organic materials like nano-encapsulates and -composites. The results also indicate that applications in novel foods, feed additives, biocides and pesticides are currently mostly at a developmental stage. No information was found that would allow an extrapolation of nanotechnology applications from the food to the feed sector. However, some food applications may be expected to be used for feed as well.

The query on "*Toxicological data*" provides information about the type of toxicity tests performed with the different nanomaterials that were included in the inventory lists. Although, the inventory lists were not constructed as an exhaustive source of toxicity data of a particular material, still 691 nanomaterial-toxicological data combinations were found. The data included in the Nano Inventory mostly involve endpoints like cytotoxicity, genotoxicity and repeated-dose toxicity for silica, titanium dioxide and silver. In addition, it can be concluded that the lack of systematic reporting of the full set of physico-chemical properties reduces the usefulness and comparability of the toxicity data. Improvement of this aspect would facilitate the use of the studies in risk assessment processes. The potential toxicity of a few relevant nanomaterials (silver, titanium dioxide, zinc oxide, silica and carbon nanotubes) is presented. The effects of silver nanomaterials seems to be related with the release of silver ions from these materials. Studies also suggest the *in vivo* formation of silver nanoparticles following absorption of silver ions. Toxicity studies of titanium dioxide show that it may be bioavailable upon oral exposure, but that the translocation rate is unknown and that the genotoxicity shows conflicting results. From orally administered zinc oxide only minor amounts seem to be absorbed, most likely in ionic form. Absorbed zinc seems to be cleared from organs after 7 days. Synthetic amorphous silica is an important form of silica used in many food items and the most recent reviews suggest safety for consumers when exposed via food. *In vivo* studies with carbon nanotubes show no uptake while *in vitro* studies suggest the uptake in cells, however no ability to cross the intestinal wall. In all cases uncertainties and conflicting results remain and further studies are recommended to conclude on the possible uptake and toxicity of these nanomaterials.

The *"Risk assessment status"* query was retrieved from a very limited number of studies found in the literature search. A complete risk assessment of a specific nanotechnology application in the agri/feed/food sector including exposure and hazard assessment could only be retrieved for a few nanomaterials, e.g. on silica and titanium dioxide. Most studies reported in the literature focus either on hazard assessment (toxicity) or release (exposure) of nanoparticles. A complete risk assessment is available for only a few studies, one being SAS in food, the other titanium dioxide in packaging materials. Such risks assessments are made very carefully because of the uncertainties in both the hazard and the human exposure data. There is some risk assessment data on silver and zinc oxide but mostly incomplete which resembles the current situation on the risk assessment of nanomaterials. The main reason for carrying out a risk assessment was "self assessment", risk assessments because of regulatory requirements or as part of the submission of nanomaterials to the authorities were not found.

Legislation and regulation of nanomaterials were reviewed in EU as well as non-EU countries based on literature research and a questionnaire. Currently, only a few EU legal acts incorporate a nanomaterial definition: No 1169/2011 and 10/2011 on food information to consumers and plastic food contact materials, respectively, and No 1223/2009 and 528/2013 on cosmetic and biocidal products, respectively. Interestingly the definition in two former regulation is different from the one in the two latter definitions. In 2011 the European Commission published a Recommenation on the definition of a nanomaterial (2011/696/EU). A draft law on novel food (COM/2013/0435) also provides a legal basis to regulate nanomaterials or the application of nanotechnology in food products. The review of existing legislation in non-EU countries shows that other countries have limited nanomaterial specific legislation and no legally binding definition. They have rather adopted a broader approach which builds mainly on guidance for industry.

In conclusion, the results extracted from the Nano Inventory provide an overview on nanomaterials presently on the market for use in the agri/feed/food sector and their purpose. The comparison between products already on the market and products currently in research and development stage, suggest that in the near future nanotechnology applications in the agri/feed/food sector will include increasingly organic nanostructures such as emulsions and micelles in food processing, nano-encapsulates for the delivery of vitamins and nutrients, and encapsulation of pesticides and fertilizers in agriculture. Other foreseeable applications are in nano-sized adsorbents in feed for specific problems such as pathogens and mycotoxins. Beacause technological developments go fast, reports on new and potential applications of nanomaterials are not always accompanied by thorough/uniform physico-chemical characterisation of the nanomaterial, nor by safety tests representative for their ingestion. However, such information is vital to develop safe applications of existing nanomaterials or new nanomaterials safe by design.

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APPENDICES

Appendix A. List of additional literature references

A.1 List of relevant references retreived from additional literature searches used to fill the Nano Inventory

A.1.1 Peer-reviewed references

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A.1.2 Non peer-reviewed references

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A.2 List of relevant references retreived from additional literature searches used for the legislation review

A.2.1 Peer-reviewed references

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Villanueva T.	Europe unveils risk assessment guidance for engineered nanomaterials used in food chain	CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne	2011	EU
Sujit Bhattacharya, Koen Beumer, and A P Jayanthi	Nanotechnology: 'Risk Governance' in India	Economic & Political	2012	India
Barpujari I.	Attenuating risks through regulation: issues for nanotechnology in India	J Biomed Nanotechnol.	2011	India
Kanika Sharma and Archana Chugh	Legal Aspects on Nanobiotechnology Inventions: an Indian Perspective	Article presented at the SCRIPTed 'Governance of New Technologies'	2009	India

A.2.2 Non peer-reviewed references (in alphabetical order of countries)

Region	Name of International	Abbreviation	Document	Publication

	Organization			year
Australia	Safe Work Australia		Labelling of Workplace Hazardous Chemical Code of Practice	2011
Australia, EU, US	Friends of the Earth	FoE	Out of the laboratory and on our plates. Nanotechnologies in food and agriculture.	2008
Belgium	Beratungsgesellschaft für Integrierte Problemlösungen, Institute for Applied Ecology	BIPRO, Öko-Institut	Study of the scope of a Belgian national register for nanomaterials and products containing nanomaterials	2013
EU	European Food Safety Authority	EFSA	Guidance on the risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain.	2011
EU	European Commission	EC	Report on the European Commission’s public online consultation. Towards a strategic nanotechnology action plan (SNAP) 2010–2015.	2010
EU	Scientific Committee on Emerging and Newly Identified Health Risks	SCENIHR	Opinion on the scientific basis for the definition of the term 'nanomaterial'.	2010
EU	European Food Safety Authority Scientific Committee	EFSA	Scientific Opinion The Potential Risks Arising from Nanoscience and Nanotechnologies on Food and Feed Safety1	2009
Germany	Landesanstalt für Umwelt, Messungen und Naturschutz Baden-Württemberg	LUBW	Nanomaterialien: Regulierungen national – international	2012
Japan	Food Safety Commission of Japan	FSCJ	A basic survey report on safety assessment information on the use of nanotechnology in the food sector.	2010
Netherland	National Institute for Public Health and the Environment		Opinions in Netherland on European Registration of consumer products containing nanomaterials	2013
Russia	USDA Foreign Agricultural Service, Gain (Global Agriculture Information Network) Report	USDA	Russian Federation-Food and Agricultural Import Regulations and Standards – Narrative FAIRS Country Report	2009
South Africa	Department of Science and Technology of the Republic of South Africa		The national nanotechnology strategy. Pretoria: Department of Science and Technology	2011
Switzerland	State Secretariat for Economic Affairs, Chemicals and Occupational Health	SECO	Safety data Sheet (SDS): Guidelines for Synthetic Nanomaterials	2012

Switzerland	Federal Office for the Environment (FOEN) and by the Federal Office of Public Health (FOPH)	FOEN, FOPH	Synthetic Nanomaterials. Risk Assessment and Risk Management Basic report for the Swiss Action Plan	2007
UK	United Kingdom Parliament		Nanotechnologies and food. Volume I: Report.	2010
UK	Department for Environment Food and Rural Applications	DEFRA	UK Voluntary Reporting Scheme for engineered nanoscale materials. Department for Environment. London.	2008
UK	Food Standards Agency	FSA	A review of potential implications of nanotechnologies for regulations and risk assessment in relation to food.	2006
US	Food and Drug Administration	FDA	Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives	2012
US	Institute for Agriculture and Trade Policy	IATP	Racing Ahead U.S. Agri-Nanotechnology in the Absence of Regulation	2011
US	Food and Drug Administration	FDA	FDA opens dialogue on ‘Nano’ regulation.	2011
US	Food and Drug Administration	FDA	Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology - Guidance for Industry.	2011
US	Environmental Protection Agency	EPA	Nanomaterial research strategy. (EPA 620/K- 09/011)	2009
World	Organization for Economic Co-operation and Development	OECD	Regulatory frameworks for nanotechnology in food and medicinal products: summary results of a survey activity.	2013
World	International Organization for Standardization	ISO	External Liaison Report to ISO/TC 229 'Nanotechnologies', ISO/TC 229 N 1124	2013
World	World Health Organization, Food and Agriculture Organization of the United Nations	WHO/FAO	State of the art on initiatives and activities relevant to the risk assessment and risk management of nanotechnologies in the food and agriculture sectors.	2013
World	Observatory Nano		Developments in Nanotechnologies Regulation and Standards 2012 - Report of the Observatory Nano.	2012
World	Food and Agriculture Organization of the United Nations, World Health Organization	FAO/WHO	FAO/WHO expert meeting on the application of nanotechnologies in the food and agriculture sectors. Potential food safety implications. Meeting report. Rome: FAO and WHO	2010

World	International Organization for Standardization	ISO	ISO Nanotechnologies – Vocabulary Part 1: Core terms. International Organization for Standardization, DD ISO/TS 80004-1:2010.	2010
World	Joint FAO/WHO Expert Committee on Food Additives	JECFA	Evaluation of certain food additives and contaminants (Sixty-seventh report of the Joint FAO/ WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 940.	2007

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http://www.bdsi.com/ (assessed: 2013-10-31)
http://www.livonlabs.com/cgi-bin/htmlos.cgi/00958.1.827848976332598021/liposome-encapsulated/lypo-spheric-vitamin-c.html (assessed: 2013-11-04)
http://web.archive.org/web/20071217224829/http://www.369.com.cn/En/nanotea.htm (assessed: 2013-11-04)
https://www.rbclife.com/Corporate/products/product/1609 (assessed: 2013-11-04)
http://www.highvive.com/sunactiveiron.htm (assessed:2013-11-04)
http://jambajuicehawaii.com/boosts#/daily-vitamin-boost (assessed: 2013-11-04)
http://www.toddlerhealth.net/products-1.html (assessed:2013-11-04)
http://www.shemen.co.il/English/ (assessed: 2013-11-4)
http://lapostadelaguila.com.ar/home.html (assessed: 2013-11-04)
http://www.syngenta.com/country/au/SiteCollectionDocuments/Turf/FactSheet%20PrimoMAXX.pdf
http://www.syngenta.com/country/au/SiteCollectionDocuments/Turf/Fact%20Sheet%20BannerMAXX.pdf
http://www.syngenta.com/country/au/SiteCollectionDocuments/Turf/Fact%20Sheet%20SubdueMAXX.pdf
http://www.syngentafarm.ca/pdf/msds/Apron_Maxx_RTA_27577_en_msds.pdf
http://www.life-enhancement.com/shop/product/bjs-bionic-joint-support
http://www.ecosynthetix.com/biolatexr-technology/ecospherer/default.aspx
http://www.greencastonline.com/prodrender/index.aspx?prodid=747&prodnm=primo%20maxx (assessed: 26-11-2013)
http://www.syngentacropprotection.com/prodrender/index.aspx?prodid=420 (assessed: 26-11-2013)
http://www.solgar.com/pub/supplement/0916.pdf
http://www.solgar.com/pub/supplement/1823.pdf
http://www.aor.ca/wp-content/uploads/2012/11/Binder-Ortho-Iron.pdf
http://www.nanosilproducts.com/?wpfb_dl=6
www.fda.gov/food/ingredientspackaginglabeling/gras/noticeinventory/ucm153977.htm (assessed: 2013-12-06)
http://www.cabot-corp.com/wcm/download/en-us/fs/CAB-O-SIL%20Fumed%20Silica%20Food%20Appl.Guide.pdf (assessed: 2013-12-13)

http://www.gasbarriertechnologies.com/mxd6.html
http://www.rivm.nl/bibliotheek/rapporten/000200704.pdf (assessed on: 02-12-2013)

Appendix C. Questionnaires and cover letters

C.1 Cover letter: Survey on "Production, use, import, research and development of nanomaterials in agri-food-feed applications" (survey 1)

Dear *[Name]*,

I would like to invite you to the survey 'Survey on "Production, use, import, research and development of nanomaterials in agri-food-feed applications" (Survey 1)' which will be available at this url:

Access:
http://ec.europa.eu/yourvoice/ipm/forms/dispatch?invite=280102524131628313&UniqueAccessLink=358109530191628313

This survey aims to collect information on production, use, import, research and development of nanomaterials in agri-food-feed applications. It is addressed to

- companies (including their representatives, industrial or trade organisations) producing, importing or using materials < 1 µm in agri-food-feed applications and/or
- research institutes (private, public), research and development departments of industry, or others active in research and development of materials or products containing materials < 1 µm for application in agri-food-feed applications.

You are contacted as you or your organisation has been identified as expert in that field. This survey is carried out together with another survey on *"Regulation and safety assessment of nanomaterials in agri-food-feed applications" (Survey 2)* and we kindly ask you to fill one or both surveys according to your expertise. We appreciate if you forward this link also to other experts we may have missed or send us names and contact details of other experts to whom we can distribute the survey.

Deadline for submission of contributions is 3 November 2013

We thank you in advance for your participation in this survey and remain with

Best regards,

ASCHBERGER Karin (JRC-ISPRA)

If you have any notes or questions on the project and the content of the survey, please feel free to contact us at any time at the following email address: JRC-FOOD-NANOINVENTORY@ec.europa.eu

Additional information on the survey:
The European Commission - Joint Research Centre (EC-JRC) together with the Institute of Food Safety of the University of Wageningen (RIKILT) in The Netherlands are developing for the European Food Safety Authority (EFSA) an inventory of nanomaterials and nanotechnology in agri-food-feed applications worldwide. This work is performed in the frame of the contract CFT/EFSA/FEED/2012/01. This *inventory (*and background documents as prepared under the project) serves as a collection of the current knowledge of nanotechnologies used and/or reasonably foreseen to be used in agri-food-feed applications. It is intended to be used by EFSA's Panels for consideration

and potential update of specific guidance documents or allow the Scientific Committee and its Network to describe further best practices for safety assessment.

In order to support the preparation of this inventory, a set of surveys for industry, research bodies and competent authorities have been prepared with the aim to retrieve relevant information on:
- the current and potential future use of nanomaterials or nanotechnology in agri-food-feed applications and
- regulation, safety assessment and reporting of nanomaterials in different countries.
For the purpose of this survey

- all materials with a particle size in the range of 1 µm or below should be considered for answering to this survey and for reasons of simplification will be called *nanomaterials*. This size range was selected to increase the chance to receive more information on potential nanomaterials without strictly applying any existing definition. It is not intended to have any implication on the current discussion of a definition of nanomaterials in the EU nor does it trigger any regulatory requirement or consequence for the reported material.
- *agri-food-feed applications* include (novel)food, food additives, food supplements, flavourings, enzymes, food contact materials, feed, feed additives, veterinary drugs, pesticides, biocides, fertilisers
- *Novel food*: food with no "significant" consumption in EU prior to 15 May 1997 or comparable provisions in non-EU countries
- *Food contact material*: materials and articles (surface) intended to come into contact with foods such as packaging materials, cutlery and dishes, processing machines, containers, materials and articles in contact with water for human consumption.

Instructions for the respondents:
The survey needs to be filled in on-line and will take approximately 20 minutes (depending on the detail of information you provide). You can fill it anonymously and may choose only those questions that you can answer, except a few mandatory ones which are indicated.
The survey needs to be filled in one single session. Incomplete surveys cannot be saved. In order to examine the questions and elaborate the replies, the survey can be downloaded as pdf file (download PDF in the upper-right corner of the screen).
Please give concise answers. The space available for each answer is limited.
If you are willing to provide more information or in another format, you can directly attach files into the survey, give us your contact details or send relevant documents/web links to this topic to the email address: JRC-FOOD-NANOINVENTORY@ec.europa.eu

Any information provided through this survey will only be used for the purpose of the inventory for EFSA and published in aggregated form without reference to specific sources unless permission is explicitly given by the data owner.
This invitation has been sent through IPM (http://ec.europa.eu/yourvoice/ipm/forms/html/index.html) by aschbka

Survey on "Production, use, import, research and development of nanomaterials in agri-food-feed applications" (Survey 1)

Questions marked with an asterisk * require an answer to be given.

Introduction and instructions for the respondents

This survey aims to collect information on production, use, import, research and development of nanomaterials in agri-food-feed applications. It is addressed to

- companies (including their representatives, industrial or trade organisations) producing, importing or using materials less than 1 µm in agri-food-feed applications and/or
- research institutes (private, public), research and development departments of industry, or others that are active in research and development of materials or products containing materials less than 1 µm for application in agri-food-feed applications.

This survey is carried out together with another survey on "Regulation and safety assessment of nanomaterials in agri-food-feed applications" (Survey 2) and we kindly ask you to fill one or both surveys according to your expertise.

These surveys have been launched by the European Commission Joint Research Centre (EC-JRC) together with the Institute of Food Safety of the University of Wageningen (RIKILT) in The Netherlands for the purpose of developing an *inventory* of nanomaterials/nanotechnology in agri-food-feed applications worldwide for the European Food Safety Authority (EFSA). This *inventory* (and background documents as prepared under the project) serves as a collection of the current knowledge of nanotechnologies used and/or reasonably foreseen to be used in agri-food-feed applications. It is intended to be used by EFSA's Panels for consideration and potential update of specific guidance documents or allow the Scientific Committee and its Network to describe further best practices for safety assessment.

You or your organisation has been identified as expert in that field. We appreciate if you forward the links also to other experts we may have missed or send us names and contact details of other experts to whom we can distribute the survey.

Instructions for the respondents:

The survey needs to be filled in on-line and will take approximately 20 minutes (depending on the detail of information you provide). You can fill it anonymously and may choose only those questions that you can answer, except a few mandatory ones which are indicated.

The survey needs to be filled in one single session. Incomplete surveys cannot be saved. In order to examine the questions and elaborate the replies, the survey can be downloaded as pdf file (download PDF in the upper-right corner of the screen).

Please give concise answers. The space available for each answer is limited.

If you are willing to provide more information and/or in another format, you can directly attach files into the surveys, give us your contact details or send relevant documents/web links to this topic to the email address:

JRC-FOOD-NANOINVENTORY@ec.europa.eu

Any information provided through this survey will only be used for the purpose of the inventory for EFSA and published in aggregated form without reference to specific sources unless permission is explicitly given by the data owner.

For the purpose of this survey

- all materials with a particle size in the range of 1 µm or below should be considered for answering to this survey and will be called *nanomaterials*. This size range was selected to increase the chance to receive more information on potential nanomaterials without strictly applying any existing definition. It is not intended to have any implication on the current discussion of a definition of nanomaterial in the EU nor does it trigger any regulatory requirements or consequences for the reported materials.
- *agri-food-feed applications* include (novel)food, food additives, food supplements, flavourings, enzymes, food contact materials, feed, feed additives, veterinary drugs, pesticides, biocides, fertilisers.

If other selected please specify (between 1 and 250 characters)

Where your organisation is located?

- EU
- Non EU
- Both

Please specify the EU country (maximum 250 characters)

Please specify the non-EU country (maximum 250 characters)

If both selected please specify country/ies (maximum 250 characters)

Please specify the size of your organisation (worldwide). In case you are active in several different fields, please refer to the part of the company that is active in the agri-food-feed area. (one option to be chosen from the list below)

- up to 10 employees
- up to 50 employees
- up to 250 employees
- > 250 employees
- Other

If other selected please specify (maximum 250 characters)

Activity of your organisation

In which sector are you active (several options can be selected):
Manufacture and/or processing and/or import and/or research and development of:

- (Novel) food
- Food additives
- Food supplements
- Flavourings
- Enzymes
- Food contact materials/packaging
- Feed, feed additives
- Veterinary drugs
- Pesticides
- Biocides
- Fertilisers
- (Raw) material used for one of the applications above
- Other

If other selected please specify (maximum 250 characters)

Does your company/institution **PRODUCE/IMPORT** (raw) **materials** with constituents **less than 1 µm**, which are used (can be used) in agri-food-feed applications? (one option to be selected) *(NB: Use and R&D of nanomaterials will be asked below)*

- Yes
- Currently not, but envisaged or under development
- No and not planned
- I don't know
- Other

If 'yes' selected, please report number and name of that material(s).
More detailed information can be provided answering to the questions below. In addition, relevant documents can be attached or sent to us.

If 'under development', please report number and name of that material(s).
More detailed information can be provided answering to the questions below. In addition, relevant documents can be attached or sent to us.

If other selected please specify (maximum 250 characters)

Does your company/institution **USE materials** with constituents **less than 1 µm** to prepare agri-food-feed products or do you import any of these products? (one option to be selected) *(NB: R&D will be asked below)*

- Yes
- Currently not, but envisaged or under development
- No and not planned
- I don't know
- Other

If 'yes' selected, please report number and name of that material(s).
More detailed information can be provided answering to the questions below. In addition, relevant documents can be attached or sent to us.

If 'under development', please report number and name of that material(s).
More detailed information can be provided answering to the questions below. In addition, relevant documents can be attached or sent to us.

- *Novel food*: food with no "significant" consumption in the EU prior to 15 May 1997 or comparable provisions in non-EU countries
- *Food contact material:* materials and articles (surface) intended to come into contact with foods such as packaging materials, cutlery and dishes, processing machines, containers, materials and articles in contact with water for human consumption

Thank you for your participation in this survey!

General Information

Please specify the organisation you represent

*

- ◯ Private company (producer)
- ◯ Private research or control institute
- ◯ R&D department of industry/association
- ◯ Public research or control institute or university
- ◯ Industrial or trade association
- ◯ Consultant
- ◯ Other

If other selected please specify (between 1 and 250 characters)

What is your role within the organisation you are responding on behalf of?

*

- ◯ Manager
- ◯ Researcher/Scientist
- ◯ Administrator
- ◯ Representative of an industry or trade association
- ◯ Other

If other selected please specify (maximum 250 characters)

Does your **RESEARCH and DEVELOPMENT** deal with **materials** with constituents **less than 1 µm** which are used or can be used to prepare agri-food-feed products? (one option to be selected)

- Yes
- Currently not, but envisaged or under development
- No and not planned
- I don't know
- Other

If 'yes' selected, please report number and name of that material(s).
More detailed information can be provided answering to the questions below. In addition, relevant documents can be attached or sent to us.

If 'under development', please report number and name of that material(s).
More detailed information can be provided answering to the questions below. In addition, relevant documents can be attached or sent to us.

If other selected please specify (maximum 250 characters)

Specific information on nanomaterials

In the following we would like to ask you to describe briefly a maximum of three nanomaterials that your organisation is producing/using/importing or for which you perform research and development.

If possible please provide the following information:

- name of the substance
- composition
- trade name
- origin
- physicochemical properties
- application field
- purpose of the nanoform
- availability on the market
- other relevant information

If you are willing to provide more information and/or in another format, you can directly attach files into the survey, give us your contact details or send us relevant documents to this topic to the email address listed below. You can also give us URLs of websites.

If you cannot provide specific information to nanomaterials, please skip to the next (final) section (Additional Information).

Nanomaterial 1

Please describe briefly one nanomaterial your company is dealing with (production, use, import or, research & development). If possible please provide the following information:

Nanomaterials description: Chemical name, composition, CAS Number, origin (*e.g. manufactured, natural*)

Physicochemical properties: material: size, shape, type of nanoform (e.g. nanomicelles, nonocomposite)

Additional information

- on purpose of the nanoform: mechanism of action, new properties, efficacy, etc.
- availability on the market, volumes

What is the (expected) field of application of this nanomaterial?

☐ Novel food	☐ Enzyme	☐ Pesticide
☐ Food additive	☐ Food contact material	☐ Biocide
☐ Food supplement	☐ Feed additive	☐ Fertiliser
☐ Flavouring	☐ Veterinary drug	☐ Other

If other selected please specify (maximum 250 characters)

Is a safety/risk assessment of this nanomaterial available? *(one option to be selected)*

- Yes
- Currently not, but under development
- No
- I don't know
- Other

If yes please specify the motivation (e.g. self assesement, regulatory requirement)

If under development, please specify the motivation (e.g. self assesement, regulatory requirement)

If no, please specify the reason.

Nanomaterial 2

Please describe briefly a second nanomaterial your company is dealing with (production, use, import or, research & development). If possible please provide the following information:

Nanomaterials description: Chemical name, composition, CAS Number, origin (*e.g. manufactured, natural*)

Physicochemical properties: material: size, shape, type of nanoform (e.g. nanomicelles, nonocomposite)

Additional information

- on purpose of the nanoform: mechanism of action, new properties, efficacy, etc.
- availability on the market, volumes

What is the (expected) field of application of this nanomaterial?

☐ Novel food	☐ Enzyme	☐ Pesticide
☐ Food additive	☐ Food contact material	☐ Biocide
☐ Food supplement	☐ Feed additive	☐ Fertiliser
☐ Flavouring	☐ Veterinary drug	☐ Other

If other selected please specify (maximum 250 characters)

Is a safety/risk assessment of this nanomaterial available? *(one option to be selected)*

- Yes
- Currently not, but under development
- No
- I don't know
- Other

If yes please specify (i.e self assesement, regulatory requirement)

If under development, please specify the motivation (e.g. self assesement, regulatory requirement)

If no, please specify the reason.

If other selected please specify.

Nanomaterial 3

Please describe briefly a third nanomaterial your company is dealing with (production, use, import or, research & development). If possible please provide the following information:

Nanomaterials description: Chemical name, composition, CAS Number, origin (*e.g. manufactured, natural*)

Physicochemical properties: material: size, shape, type of nanoform (e.g. nanomicelles, nonocomposite)

Additional information

- on purpose of the nanoform: mechanism of action, new properties, efficacy, etc.
- availability on the market, volumes

What is the (expected) fuekd of application of this nanomaterial?

☐ Novel food	☐ Enzyme	☐ Pesticide
☐ Food additive	☐ Food contact material	☐ Biocide
☐ Food supplement	☐ Feed additive	☐ Fertiliser
☐ Flavouring	☐ Veterinary drug	☐ Other

If other selected please specify (maximum 250 characters)

Is a safety/risk assessment of this nanomaterial available? *(one option to be selected)*

- ○ Yes
- ○ Currently not, but under development
- ○ No
- ○ I don't know
- ○ Other

If yes please specify the motivation (e.g. self assesement, regulatory requirement)

If under development, please specify the motivation (e.g. self assesement, regulatory requirement)

If no, please specify the reason.

If other selected please specify.

Additional information

If you are willing to provide more information and/or in another format, you can directly attach files into the survey, give us your contact details or send us relevant documents/web links to this topic to the following email address JRC-FOOD-NANOINVENTORY@ec.europa.eu.

Please provide us with references or URLs of websites

You can up-load your files directly or send them to us on the address: JRC-FOOD-NANOINVENTORY@ec.europa.eu.

Are you willing in case we have any further question?

- Yes
- No

If yes, please provide us with your contact details

Background documents

Call for tender: Inventory of food additives and other food ingredients/food contact materials/feed additives applications in the area of nanotechnologies (CFT/EFSA/FEED/2012/01) :
http://www.efsa.europa.eu/en/tendersawarded/tender/cftefsafeed201201.htm

C.2 Cover letter: Survey on Regulation and safety assessment of nanomaterials in agri-food-feed applications (Survey 2)

Dear *[Name]*,

I would like to invite you to the survey 'Survey on "Regulation and safety assessment of nanomaterials in agri-food-feed applications" (Survey 2)' which will be available at this url:

Access:
http://ec.europa.eu/yourvoice/ipm/forms/dispatch?invite=482690451391628313&UniqueAccessLink=522955157421628313

This survey aims to collect information on the regulation of nanomaterials in agri-food-feed applications. It is addressed to persons having a good knowledge of legislation, reporting and safety assessment of nanomaterials in EU and non-EU countries, including authorities, consultants, companies producing in or exporting to non-EU countries and researchers. You are contacted as you or your organisation has been identified as expert in that field.
This survey is carried out together with another survey on "*Production, use, import, research and development of nanomaterials" (Survey 1)* and we kindly ask you to fill one or both surveys according to your expertise. We appreciate if you forward the links also to other experts we may have missed or send us names and contact details of other experts to whom we can distribute the survey.

Deadline for submission of contributions is 3 November 2013

We thank you in advance for your participation in this survey and remain with
best regards,

ASCHBERGER Karin (JRC-ISPRA)

If you have any notes or questions on the project and the content of the survey, please feel free to contact us at any time at the following email address: JRC-FOOD-NANOINVENTORY@ec.europa.eu

Additional information on the survey:
The European Commission - Joint Research Centre (EC-JRC) together with the Institute of Food Safety of the University of Wageningen (RIKILT) in The Netherlands are developing for the European Food Safety Authority (EFSA) an inventory of nanomaterials and nanotechnology in agri-food-feed applications worldwide. This work is performed in the frame of the contract CFT/EFSA/FEED/2012/01. This *inventory (*and background documents as prepared under the project) serves as a collection of the current knowledge of nanotechnologies used and/or reasonably foreseen to be used in agri-food-feed applications. It is intended to be used by EFSA's Panels for consideration and potential update of specific guidance documents or allow the Scientific Committee and its Network to describe further best practices for safety assessment.

In order to support the preparation of this inventory, a set of surveys for industry, research bodies and competent authorities have been prepared with the aim to retrieve relevant information on:
- the current and potential future use of nanomaterials or nanotechnology in agri-food-feed applications and
- regulation, safety assessment and reporting of nanomaterials in different countries.
For the purpose of this survey

- all materials with a particle size in the range of 1 µm or below should be considered for answering to this survey and for reasons of simplification will be called *nanomaterials*. This size range was selected to increase the chance to receive more information on potential nanomaterials without strictly applying any existing definition. It is not intended to have any implication on the current discussion of a definition of nanomaterials in the EU nor does it trigger any regulatory requirement or consequence for the reported material.
- *agri-food-feed applications* include (novel)food, food additives, food supplements, flavourings, enzymes, food contact materials, feed, feed additives, veterinary drugs, pesticides, biocides, fertilisers
- *Novel food*: food with no “significant” consumption in EU prior to 15 May 1997 or comparable provisions in non-EU countries
- *Food contact material*: materials and articles (surface) intended to come into contact with foods such as packaging materials, cutlery and dishes, processing machines, containers, materials and articles in contact with water for human consumption.

Instructions for the respondents:
The survey needs to be filled in on-line and will take approximately 20 minutes (depending on the detail of information you provide). You can fill it anonymously and may choose only those questions that you can answer, except a few mandatory ones which are indicated.
The survey needs to be filled in one single session. Incomplete surveys cannot be saved. In order to examine the questions and elaborate the replies, the survey can be downloaded as pdf file (download PDF in the upper-right corner of the screen).
Please give concise answers. The space available for each answer is limited.
If you are willing to provide more information and/or in another format, you can directly attach files into the survey, give us your contact details or send relevant documents/web links to this topic to the email address: JRC-FOOD-NANOINVENTORY@ec.europa.eu

Any information provided through this survey will only be used for the purpose of the inventory for EFSA and published in aggregated form without reference to specific sources unless permission is explicitly given by the data owner.

This invitation has been sent through IPM (http://ec.europa.eu/yourvoice/ipm/forms/html/index.html) by aschbka

Survey on "Regulation and Safety Assessment of Nanomaterials in Agri-Food-Feed Applications" (Survey 2)

Questions marked with an asterisk * require an answer to be given.

Introduction and instructions for the respondents

This survey aims to collect information on the regulation of nanomaterials in agri-food-feed applications. It is addressed to persons working for authorities or others having a good knowledge of legislation, reporting and safety assessment of nanomaterials in EU and non-EU countries (including consultants, company producing in or exporting to non-EU countries and researchers).
This survey is carried out together with another survey on *"Production, use, import, research and development of nanomaterials in agri-food-feed applications" (survey 1)* and we kindly ask you to fill one or both surveys according to your expertise.

These surveys have been launched by the European Commission Joint Research Centre (EC-JRC) together with the Institute of Food Safety of the University of Wageningen (RIKILT) in The Netherlands for the purpose of developing an *inventory* of nanomaterials/nanotechnology in agri-food-feed applications worldwide for the European Food Safety Authority (EFSA). This *inventory* (and background documents as prepared under the project) serves as a collection of the current knowledge of nanotechnologies used and/or reasonably foreseen to be used in agri-food-feed applications. It is intended to be used by EFSA's Panels for consideration and potential update of specific guidance documents or allow the Scientific Committee and its Network to describe further best practices for safety assessment.
You or your organisation has been identified as expert in that field. We appreciate if you forward the links also to other experts we may have missed or send us names and contact details of other experts to whom we can distribute the survey.

Instructions for the respondents:

The survey needs to be filled in on-line and will take approximately 20 minutes (depending on the detail of information you provide). You can fill it anonymously and may choose only those questions that you can answer, except a few mandatory ones which are indicated.
The survey needs to be filled in one single session. Incomplete surveys cannot be saved. In order to examine the questions and elaborate the replies, the survey can be downloaded as pdf file (download PDF in the upper-right corner of the screen).
Please give concise answers. The space available for each answer is limited.
If you are willing to provide more information or in another format, you can directly attach files into the surveys, give us your contact details or send relevant documents/web links to this topic to the email address: **JRC-FOOD-NANOINVENTORY@ec.europa.eu**

Any information provided through this survey will only be used for the purpose of the inventory for EFSA and published in aggregated form without reference to specific sources unless permission is explicitly given by the data owner.

For the purpose of this survey

- All materials with a particle size in the range of 1 µm or below should be considered for answering to this survey and will be called *nanomaterials*. This size range was selected to increase the chance to receive more information on potential nanomaterials without strictly applying any existing definition. It is not intended to have any implication on the current discussion of a definition of nanomaterial in the EU nor does it trigger any regulatory requirements or consequences for the reported materials.
- *Agri-food-feed applications* include (novel)food, food additives, food supplements, flavourings, enzymes, food contact materials, feed, feed additives, veterinary drugs, pesticides, biocides, fertilisers.
- *Novel food*: food with no "significant" consumption in the EU prior to 15 May 1997 or comparable provisions in non-EU countries
- *Food contact material:* materials and articles (surface) intended to come into contact with foods such as packaging materials, cutlery and dishes, processing machines, containers, materials and articles in contact with

water for human consumption

Thank you for your participation in this survey!

General Information

Please specify to which country/countries this questionnaire refers to. If countries are in an alliance/association/union with a comparable legislation you can fill one questionnaire covering several countries.

*

Please specify the organisation you represent

*

- National authority
- Union/Alliance/Federation/Association of countries (e.g. EU, EFTA, BRIC, ASEAN etc.)
- International organisation (e.g. OECD, WHO, FAO, WTO)
- Other

If other selected, please specify: (between 1 and 250 characters)

Please specify the institution/department you are working in:

Please specify your role within the authority/organisation you are responding on behalf of:

Application related information

In which sector are you active (several options can be selected)?

- [ ] Food
- [ ] Novel Food
- [ ] Food additives
- [ ] Food supplements
- [ ] Flavourings
- [ ] Enzymes
- [ ] Food contact materials/packaging
- [ ] Feed, feed additives
- [ ] Veterinary drugs
- [ ] Pesticides
- [ ] Biocides
- [ ] Fertilisers
- [ ] Genetically modified organisms (GMO)
- [ ] Chemicals
- [ ] Nanomaterials
- [ ] Other

If other selected, please specify: (maximum 250 characters)

Regulation of nanomaterials

How would you describe your knowledge of regulation of nanomaterials?

- Excellent
- Good
- Fair
- Little
- None at all

Specific legislation

Please indicate below, whether there is a specific legislation for the different applications in the country/ies for which you are filling this survey (one option to be selected). You can add additional information, explanations and links in the freetext field below.

a: Yes, specific legislation
b: No specific legislation
c: In preparation
d: Soft law
soft law includes action plans, codes of conduct, guidelines etc.
e: Voluntary actions
f: I don't know
g: other

	a	b	c	d	e	f	g
Food	○	○	○	○	○	○	○
Novel food	○	○	○	○	○	○	○
Food additives	○	○	○	○	○	○	○
Food supplements	○	○	○	○	○	○	○
Flavourings	○	○	○	○	○	○	○
Enzymes	○	○	○	○	○	○	○
Food contact materials	○	○	○	○	○	○	○
Feed/Feed additives	○	○	○	○	○	○	○
Veterinary drugs	○	○	○	○	○	○	○
Pesticides	○	○	○	○	○	○	○
Biocides	○	○	○	○	○	○	○
Fertilisers	○	○	○	○	○	○	○
Chemicals	○	○	○	○	○	○	○
Nanomaterials	○	○	○	○	○	○	○
Consumer Products	○	○	○	○	○	○	○

If other selected, please specify: (maximum 250 characters)

Please add additional information and explanation to the legislation in your country/ies. You can also provide us with URLs of websites or attach documents.

Definition

Is there a definition of 'nanomaterial' in the country/ies for which you are answering this survey?

- ☐ Legally binding definition
- ☐ (National) Recommendation for a definition
- ☐ Working definition
- ☐ Different definitions for different purposes
- ☐ No definition available
- ☐ Other

In case there is one or more definitions, please explain the criteria considered to define a nanomaterial. You can also provide us URLs for websites or attach documents. (maximum 250 characters)

If other selected, please specify: (maximum 250 characters)

Authorisation/Registration/Notification

In case authorisation, registration or notification is required, are there any nanomaterials authorised, registered or notified in the contry/ies for which you are answering this survey (several options can be selected and descibed below)?*

- ☐ Yes
- ☐ No, and no knowledge about intention
- ☐ Expected in near future
- ☐ Other

If yes selected, please report number and name(s) of nanomaterial(s).
More detailed information to individual nanomaterials can be provided by answering to the questions below (chapter on nanomaterials). In addition, relevant documents can be attached or sent to us.

If in future, please report number and name(s) of nanomaterial(s).
More detailed information to individual nanomaterials can be provided by answering to the questions below (chapter on nanomaterials). In addition, relevant documents can be attached or sent to us.

If not, please specify why

If other selected, please specify: (maximum 250 characters)

Nanomaterials without Authorisation/Registration/Notification

In case NO authorisation, registration or notification is required, do you know about nanomaterials used in agri-food-feed applications in the country/ies for which you are answering this survey?*

- ☐ Yes
- ☐ No, and no knowledge about intention
- ☐ Expected in future
- ☐ Other

If yes selected, please report number and name(s) of nanomaterial(s).
More detailed information to individual nanomaterials can be provided by answering to the questions below (chapter on nanomaterials). In addition, relevant documents can be attached or sent to us.

If in future, please report number and name(s) of nanomaterial(s).
More detailed information to individual nanomaterials can be provided by answering to the questions below (chapter on nanomaterials). In addition, relevant documents can be attached or sent to us.

If other selected, please specify: (maximum 250 characters)

Specific Information on Nanomaterials

In the following we ask you to provide more information on a maximum of 3 nanomaterials. More information or in a different format can be provided by attaching relevant documents to the survey, providing URLs of webistes or by sending them to the email address listed below. You can also give us your contact details.
If you cannot provide specific information to nanomaterials, please skip to the next section.

Nanomaterial 1

Please provide us with more information on one relevant nanomaterial used in agri-food-feed applications, including the following information:

- Name of the nanomaterial/s *(chemical name, trade name, composition, CAS No, etc.)*,
- Size, origin *(engineered, natural, incidental)*
- Form/type of the nanomaterial/s *(e.g. particle, micelle, encapsulation, emulsion, composite, nanocoating, polymer, clay)*
- Specific application field (e.g. *type of product*) (the general application field can be selected below)
- Availability on the market and estimated volume (*kg or tonnes*)

You can also provide us with an URL of a website, upload your files directly to this survey or send them to our address: ***JRC-FOOD-NANOINVENTORY@ec.europa.eu.***

What is the application field of this nanomaterial? (Several options can be selected)

☐ Novel food	☐ Enzyme	☐ Pesticide
☐ Food additive	☐ Food contact material	☐ Biocide
☐ Food supplement	☐ Feed additive	☐ Fertiliser
☐ Flavouring	☐ Veterinary drug	☐ Other

If other selected, please specify: (maximum 250 characters)

Nanomaterial 2

Please provide us with more information on one relevant nanomaterial used in agri-food-feed applications, including the following information:

- Name of the nanomaterial/s *(chemical name, trade name, composition, CAS No, etc.)*,
- Size, origin *(engineered, natural, incidental)*
- Form/type of the nanomaterial/s *(e.g. particle, micelle, encapsulation, emulsion, composite, nanocoating, polymer, clay)*
- Specific application field (e.g. *type of product*) (the general application field can be selected below)
- Availability on the market and estimated volume (*kg or tonnes*)

You can also provide us with an URL of a website, upload your files directly to this survey or send them to our address: ***JRC-FOOD-NANOINVENTORY@ec.europa.eu.***

What is the application field of this nanomaterial? (Several options can be selected)

☐ Novel food	☐ Enzyme	☐ Pesticide
☐ Food additive	☐ Food contact material	☐ Biocide
☐ Food supplement	☐ Feed additive	☐ Fertiliser
☐ Flavouring	☐ Veterinary drug	☐ Other

If other selected, please specify: (maximum 250 characters)

Nanomaterial 3

Please provide us with more information on one relevant nanomaterial used in agri-food-feed applications, including the following information:

- Name of the nanomaterial/s *(chemical name, trade name, composition, CAS No, etc.)*,
- Size, origin *(engineered, natural, incidental)*
- Form/type of the nanomaterial/s *(e.g. particle, micelle, encapsulation, emulsion, composite, nanocoating, polymer, clay)*
- Specific application field (e.g. *type of product*) (the general application field can be selected below)
- Availability on the market and estimated volume (*kg or tonnes*)

You can also provide us with an URL of a website, upload your files directly to this survey or send them to our address: ***JRC-FOOD-NANOINVENTORY@ec.europa.eu***.

What is the application field of this nanomaterial? (Several options can be selected)

- ☐ Novel food
- ☐ Food additive
- ☐ Food supplement
- ☐ Flavouring
- ☐ Enzyme
- ☐ Food contact material
- ☐ Feed additive
- ☐ Veterinary drug
- ☐ Pesticide
- ☐ Biocide
- ☐ Fertiliser
- ☐ Other

If other selected, please specify: (maximum 250 characters)

Reporting of Nanomaterials

Labelling

Are there any requirements to label the content of nanomaterials in agri-food-feed applications in the contry/ies for which you are answering this survey?*

- ☐ Mandatory labelling of nanomaterials in specific products
- ☐ Mandatory labelling planned
- ☐ Labelling of nanomaterials not required but encouraged in certain products
- ☐ No labelling required and not planned in near future
- ☐ Other

If mandatory labelling is required or planned, please specify:

If labelling encouraged, please specify:

If other selected, please specify: (maximum 250 characters)

Inventory/Register

Is there an inventory/register of nanomaterials or products containing them in the country/ies for which you answer this survey? *

- ☐ Mandatory reporting to authorities
- ☐ Mandatory reporting to authorities planned
- ☐ Voluntary reporting to authorities
- ☐ Voluntary reporting to authorities planned
- ☐ No currently and not planned in near future
- ☐ Collection of information on nanomaterials through other means
- ☐ No information on nanomaterials is collected
- ☐ I don't know
- ☐ Other

If mandatory or voluntary reporting to authorities is implemented or planned, please specify

Relevant documents can be attached or sent to us.

If collection of information on nanomaterials is implemented through other means, please specify:

If other selected, please specify: (maximum 250 characters)

In case information on nanomaterials is collected, how is it treated?

- ☐ Information is publicly available
- ☐ Information is partly publicly available
- ☐ No information is publicly available
- ☐ Other

If information is publicly available, please provide us with a link or attach a document.

If no information (or only part of it) is publicly available, please specify the reason for that.

If other selected, please specify: (maximum 250 characters)

Safety assessment of nanomaterials

How is the safety of nanomaterials used in agri-food-feed applications ensured in the contry/ies for which you answer the survey. For each of the answers, please specify in the fields below to which application it applies (several options can be selected).*

- ☐ A pre-market risk assessment is required
- ☐ No risk assessment of nanomaterials is required at all
- ☐ Currently no risk assessment required, but planned/under development
- ☐ Specific guidance for the risk assessment of nanomaterials in agri-food-feed applications is available
- ☐ No specific risk assessment required but certain standards have to be fulfilled
- ☐ No specific guidance but general guidance or recommendations for risk assessment are available
- ☐ The risk of nanomaterials is considered to be covered by the assessment of the bulk (non-nano) form
- ☐ I don't know
- ☐ No risk assessment for the nanomaterial is required, but risk is considered to be controlled by risk management measures (e.g. exposure control)
- ☐ Other

If a pre-market risk assessment is required, please specify for which application:
Food, Novel Food, Food additive, Food Supplement, Flavouring, Enzyme, Food contact material, Feed/ Feed additive, Pesticide, Biocide, Fertiliser, GMO, Chemical, Nanomaterial, Consumer product or other

If risk assessment is planned, please specify for which application:
Food, Novel Food, Food additive, Food Supplement, Flavouring, Enzyme, Food contact material, Feed/ Feed additive, Pesticide, Biocide, Fertiliser, GMO, Chemical, Nanomaterial, Consumer product or other

If no risk assessment is available but certain standards have to be fulfilled, please specify. You can also attach relevant documents.

If the risk of nanomaterials are considered to be covered by the assessment of the bulk (non-nano) form, please specify. You can also attach relevant documents.

If the risk of nanomaterials is controlled by risk management measures, please specify. You can also attach relevant documents.

If no risk assessment of nanomaterials is required, please explain the reason why.

If specific guidance is available, please specify. You can also attach relevant documents.

If general guidance or recommendations are available, please specify. You can also attach relevant documents.

If other selected, please specify: (maximum 250 characters)

Additional information

Are translations of relevant laws, guidance or other documents available (preferable in English)? *

- [ ] Yes
- [ ] No
- [ ] I don't know

If yes, please provide the URL of the website, attach the document or send it to **JRC-FOOD-NANOINVENTORY@ec.europa.eu**

In case you are willing to provide more information or in another format, you can directly attach files into the survey, give us your contact details or send us relevant documents/web links to this topic to the following email address JRC-FOOD-NANOINVENTORY@ec.europa.eu.

You can up-load your files directly or send them to us on the address: JRC-FOOD-NANOINVENTORY@ec.europa.eu.

Are you willing to be contacted in case we have any further question?

- Yes
- No

If yes, please provide us with your contact details

Background documents

Call for tender: Inventory of food additives and other food ingredients/food contact materials/feed additives applications in the area of nanotechnologies (CFT/EFSA/FEED/2012/01) : http://www.efsa.europa.eu/en/tendersawarded/tender/cftefsafeed201201.htm

Appendix D. Nano Inventory Structure

The structure of the Nano Inventory is illustrated below. It consists of three columns: the first column 'Group/field' contains the name of the group of fields and the name of each individual field; the second column 'Description' contains a short description of the meaning of each field; and the third column 'Value' contains an indication of the value to be inserted in each field based on the information retrieved from the literature. The yellow lines identify the 13 groups of fields. Each group can consist of one individual field or more fields. The first three groups of fields (i.e. 'Reference', 'Nanomaterial', and 'Application field') identify the source of information (e.g. a certain peer-reviewed publication), the nanomaterial that is used in the current and/or future application and the application field, respectively. The remaining groups of fields cover the possible information items that can be retrieved from the literature in order to better characterise the nanomaterial and its application, and they are: 'Application Info', 'Product Info', Use Info', 'Material Info', 'Legal context', 'Physico-chemical properties', 'Assessment', 'Hazard for HH', 'Kinetics HH', 'Hazard for ENV', 'Exposure' and 'Efficacy'. Some fields are more descriptive in nature (free-text) whereas other fields can be filled in choosing one among several given options. The free-text fields are associated with two font colours: blue means that the field is expected to store short pieces of information (i.e. up to 256 characters); red means that the field is expected to store long pieces of information (i.e. up to 2048 characters). Certain information blocks such as 'Physico-chemical properties', 'Hazard for HH', 'Kinetics HH', 'Hazard for ENV', and 'Exposure' are repeatable in case it is needed to list several properties or endpoints/scenarios for a certain nanomaterial.

GROUP/FIELD	DESCRIPTION	VALUE
Reference		
Year	Publication year of the source	Insert year
Type of reference	Type of source providing data and information to the inventory	One option to be chosen from the list: - *Peer reviewed literature* - *Non-peer reviewed literature* - *Direct information* - *Websites* - *Other*
Reference	Full name of the source	Insert reference
Comment	Personal comment on the source	Personal comment to be given
Quoted reference	Full name of the source	Insert reference
Nanomaterial		
Nanomaterial	Full name of the nanomaterial (generic and extended)	Insert name
Application field		
Application field	Field of application of the nanomaterial in the agri/food/feed sector	One option to be chosen from the list: - *Food additive* - *Food contact material* - *Novel food* - *Food ingredient (not specified)* - *Feed additive* - *Pesticide* - *Flavouring* - *Enzyme*

		- *Fertiliser*
GROUP/FIELD	**DESCRIPTION**	**VALUE**
Application Info		
Availability on the market	Availability of the application on the market (worldwide)	One option to be chosen from the list: - *Confirmed* - *In development* - *Not clear*
Detailed application purpose	Details on the application and its purpose	Description to be given if available
Potential application in feed	In case the nanomaterial is used in the food sector, comment on its potential application in the feed sector	Specification to be given if available
Mode/mechanism of action (incl. comparison to non-nanoform)	Short description of how the nanomaterial exerts its technical function in the application/product from a mechanistic perspective and comment on the differences between nanoform and non-nanoform.	Description to be given if available
Advantages of using nanoform	List of advantages of using the nanomaterial in the application	Description to be given if available
Disadvantages of using nanoform	List of disadvantages of using the nanomaterial in the application	Description to be given if available
Implications for efficacy	List of implications for efficacy due to the nanomaterial	Description to be given if available
Implication for safety	List of implications for safety due to the nanomaterial	Description to be given if available
Product Info		
Product name	Commercial name of the product(s) where the application is used	Name to be given if available
Supplier	Name of the company and its country	Name to be given if available
Type of product	Type of product(s) where the application is present or can be used (e.g. food, beverages, food and beverages, or more specific such as chocolate, fruit juices, meat)	Specification to be given if available
Tonnage	Production volume of the application/product	One option to be chosen from the list: - *< 1 tonne* - *1-10 tonnes* - *10-100 tonnes* - *100-1000 tonnes* - *>1000 tonnes*

Country of use (or territory)	Name of the country(ies) where the application/ product is used	Specification to be given if available
GROUP/FIELD	**DESCRIPTION**	**VALUE**
Use Info		
Target population	In case of food-related applications, details on the target population	One option to be chosen from the list: - *No target population* - *Specific age (e.g., infants, children, adults, seniors)* - *Specific health conditions (e.g., diabetes, allergies)* - *Not clear*
Target species (only for feed additives)	In case of feed-related applications, details on the target species	Specification to be given if available
Specific production system (only for feed additives)	In case of feed-related applications, details on the production system where the product can be used	Specification to be given if available
Period (use or production) (only for feed additives)	In case of feed-related applications, details on the period when the product can be used	Specification to be given if available
Other	Other relevant information	Information to be given if available
Material Info		
Appearance / physical state	Description of the appearance or physical state of the nanomaterial	One option to be chosen from the list – with possibility to add more options if needed: - *Solid particle* - *Micelle/Nanocapsule/Nanocarrier/Nanoemulsion* - *Nanocomposite/Nanolaminate/Nanopolymer* - *Not clear*
Chemical name	IUPAC name of the nanomaterial	Specification to be given if available
CAS number	CAS number of the nanomaterial	Specification to be given if available
Other identifiers: please specify (e.g., EINECS number, commercial name)	Other identifiers for the nanomaterial	Specification to be given if available
Composition	Details on the chemical composition of the nanomaterial including specification of the structure and physical state	Specification to be given if available
Origin	Origin of the nanomaterial	One option to be chosen from the list: - *Natural* - *Incidental* - *Manufactured* - *Not clear*

Description (specification) of Origin	Details on the origin of the nanomaterial (e.g. manufacturing process, extraction process)	Specification to be given if available
GROUP/FIELD	**DESCRIPTION**	**VALUE**
Nano justification: reason why it is considered nano	The reason why the substance is considered as a nanomaterial in the source. The reason may be related to definition provided by EC Recommendation or in EU food legislation or working definitions provided by e.g. ISO	One option to be chosen from the list: - *EC Recommendation for a definition of nanomaterial* - *Definition in EU food legislation* - *Claimed as nano without justification* - *Not clear*
Legal context		
Authorisation for the use in EU	Authorisation of the nanomaterial/product in EU	One option to be chosen from the list: - *Yes* - *No* - *Authorisation not required* - *Not clear*
Regulatory framework of the authorisation	Regulatory framework in EU under which the nanomaterial/product is authorised	Specification to be given if available
Restrictions (conditions) of authorized use	Restrictions in the use of the nanomaterial/product under the regulatory framework that gives authorisation	Specification to be given if available
Authorisation for the use in non-EU country	Authorisation of the nanomaterial/product in non-EU countries	One option to be chosen from the list: - *Yes* - *No* - *Authorisation not required* - *Not clear*
Country and regulatory framework of the authorisation (non-EU)	Regulatory framework in non-EU countries under which the nanomaterial/product is authorised	Specification to be given if available
Restrictions (conditions) of authorized use (non-EU)	Restrictions in the use of the nanomaterial/product under the regulatory framework that gives authorisation in non-EU countries	Specification to be given if available
Physico-chemical properties		
Parameter	Physico-chemical property that is measured/estimated	One option to be chosen from the list – with possibility to add more options if needed: - *Size range* - *Average particle size* - *Size distribution* - *Shape*

		- *Solubility in water* - *Surface area* - *Zeta potential* - *Surface chemistry*
GROUP/FIELD	**DESCRIPTION**	**VALUE**
Use stage	Physico-chemical properties of a certain nanomaterial vary according to the medium and conditions of use (e.g. size distribution of a nanomaterial added to the test medium during a toxicological study may be different from the pristine one). The use stage indicates the status at which the properties of the nanomaterial refer to	One option to be chosen from the list – with possibility to add more options if needed - *Pristine (as manufactured)* - *As delivered for application* - *As present in food/feed matrix* - *As used in toxicological tests* - *As present in biological sample (e.g. tissue)* - *Not clear*
Value/description	The value (qualitative and/or quantitative) associated to the parameter	Information to be given if available
Detection/characterisation method	Name of the characterisation method and/or detection method	Description to be given if available
Assessment		
Reason for the Assessment	If an assessment of the safety or efficiency of the nanomaterial/product is available, comment on the reason that triggered such an assessment	One option to be chosen from the list: - *Regulatory requirements* - *Self-assessment* - *Not clear*
Country	Name of the country that issued 'regulatory requirements' for an assessment	Specification to be given if available
Hazard for HH		
Endpoint	Name of the toxicological endpoint that is measured/estimated	Specification to be given if available
Study performed	Description of the study performed (e.g. in vivo/in vitro/in silico; chronic/acute; type of animal; exposure conditions)	Description to be given if available
Results	Main results and any comment on uncertainty	Description to be given if available
Hazard for ENV		
Endpoint	Name of the eco-toxicological endpoint that is measured/estimated	Specification to be given if available
Study performed	Description of the study	Description to be given if available

	performed (e.g. long-term/short-term; type of animal; exposure conditions)	
Results	Main results and any comment on uncertainty	Description to be given if available
GROUP/FIELD	**DESCRIPTION**	**VALUE**
Kinetics HH		
Endpoint	Name of the endpoint that is measured/estimated	Specification to be given if available
Study performed	Description of the study performed	Description to be given if available
Results	Main results and any comment on uncertainty	Description to be given if available
Exposure		
Scenario	Name of the exposure scenario that is investigated	Specification to be given if available
Study performed	Description of the study performed (e.g. experimental/modelling/monitoring; detection method; assumptions)	Description to be given if available
Results	Main results and any comment on uncertainty	Description to be given if available
Efficacy		
Assessment (efficacy)	Description of the study performed. Main results and any comment on uncertainty	Description to be given if available

GLOSSARY AND ABBREVIATIONS

ANVISA	Agência Nacional de Vigilância Sanitária
BRIC	Brazil, Russia, India and China
CAS	Chemical Abstracts Service
CFIA	Canadian Food Inspection Agency
CH	Switzerland
CMAJ	Canadian Medical Association Journal
EC	European Commission
ECHA	European Chemicals Agency
EEC	European Economic Community
EFTA	European Free Trade Association
EINECS	European Inventory of Existing Commercial Chemical Substances
ELC	Federation of European Specialty Food Ingredients Industries
ENM	Engineered nanomaterial
ENV	Environment
EPA	Environmental Protection Agency
ETAD	Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FCM	Food contact material
FCN	Food Contact Notification
FCS	Food Contact Substance
FDA	Food and Drug Administration
FEFAC	The European Feed Manufacturers' Federation
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FOEN	Federal Office for the Environment
FOPH	Federal Office of Public Health
FSA	Food Safety Authority
FSANZ	Food Standards Australia New Zealand
FSCJ	Food Safety Commission of Japan
FSSAI	Food Safety Standard Authority of India
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GMO	Genetically modified organism
GOST	Standards and technical specifications
GRAS	Generally Recognised As Safe
HH	Human health
IMA	Industrial Minerals Association
IPM	Interactive Policy Making
ISO	International Organization for Standardization
IUCLID	International Uniform Chemical Information Database
KATS	Korean Agency for Technology and Science
KFDA	Korean Food and Drug Administration
MAPA	Ministry of Agriculture, Livestock, and Food Supply
MFDS	Ministry of Food and Drug Safety
MKE	Ministry of Knowledge and Economy
MS	Ministry of Health
NIA	Nanotechnology Industries Association
NICNAS	National Industrial Chemicals Notification and Assessment Scheme

NL	Netherlands
NM	Nanomaterial
OECD	Organisation for Economic Co-Operation and Development
PHAC	Public Health Agency of Canada
R&D	Research and Development
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	National Institute for Public Health and the Environment
SanPiN	Sanitary Rules and Regulations
SAS	Synthetic Amorphous Silica
SECO	Swiss Secretariat for Economic Affairs
USDA	United States Department of Agriculture
UV	Ultraviolet
WHO	World Health Organization