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Regulatory aspects of nanotechnology in the agri/feed/food sector in EU and non-EU countries☆

Valeria Amenta [a, 1], Karin Aschberger [a, *], Maria Arena [a, 2], Hans Bouwmeester [b], Filipa Botelho Moniz [a], Puck Brandhoff [b], Stefania Gottardo [a], Hans J.P. Marvin [b], Agnieszka Mech [a], Laia Quiros Pesudo [a], Hubert Rauscher [a], Reinhilde Schoonjans [c], Maria Vittoria Vettori [c], Stefan Weigel [b], Ruud J. Peters [b]

[a] JRC, Nanobiosciences Unit, Institute for Health and Consumer Protection, Ispra, Italy
[b] RIKILT, Wageningen UR, Wageningen, The Netherlands
[c] EFSA, Scientific Committee and FEED Additives Unit, Parma, Italy

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ABSTRACT

Nanotechnology has the potential to innovate the agricultural, feed and food sectors (hereinafter referred to as agri/feed/food). Applications that are marketed already include nano-encapsulated agrochemicals or nutrients, antimicrobial nanoparticles and active and intelligent food packaging. Many nano-enabled products are currently under research and development, and may enter the market in the near future. As for any other regulated product, applicants applying for market approval have to demonstrate the safe use of such new products without posing undue safety risks to the consumer and the environment. Several countries all over the world have been active in examining the appropriateness of their regulatory frameworks for dealing with nanotechnologies. As a consequence of this, different approaches have been taken in regulating nano-based products in agri/feed/food. The EU, along with Switzerland, were identified to be the only world region where nano-specific provisions have been incorporated in existing legislation, while in other regions nanomaterials are regulated more implicitly by mainly building on guidance for industry. This paper presents an overview and discusses the state of the art of different regulatory measures for nanomaterials in agri/feed/food, including legislation and guidance for safety assessment in EU and non-EU countries.

1. Introduction

The rapid development of nanotechnology has opened the door for innovation in many industrial sectors, including agricultural production, animal feed and treatment, food processing, and food contact materials (hereinafter referred to as agri/feed/food). Some applications (Fig. 1) are already merchandised while many more are currently under research and development (Chaudhry et al. 2008; Parisi, 2014; RIKILT and JRC, 2014). Expected benefits of nanotechnology-enabled products in these sectors include increased efficacy of agrochemicals, enhanced bioavailability of nutrients or more secure packaging material. Such new products or ingredients may, however, also pose a risk to human health and the environment due to their specific properties and to the potential widespread use and exposure.

There are efforts worldwide to address and regulate the production and safe handling/use of nanomaterials (NMs) and nanotechnology either by legislation or by (non-binding) recommendations and guidances (van der Meulen et al. 2014). There is currently no piece of legislation entirely dedicated to regulation of NMs, neither in the EU nor in any other country (Arts et al. 2014). Current legislation is considered by many countries sufficient and specific enough to regulate NMs and nanotechnology (European Commission, 2012; OECD, 2013b); however, amendments have been suggested by several stakeholders, including the European Parliament (European Parliament, 2009) and non-

☆ The opinions expressed in this publication are those of the authors only and do not represent JRC's, EFSA's or RIKILT-Wageningen UR's official position.

* Corresponding author. JRC-IHCP, Via Fermi 2749, 21027, Ispra, Italy.
E-mail address: karin.aschberger@ec.europa.eu (K. Aschberger).
[1] Present address: ECHA, Substance Identity & Data Sharing Unit, Helsinki, Finland.
[2] Present address: EFSA, Pesticides Unit, Parma, Italy.

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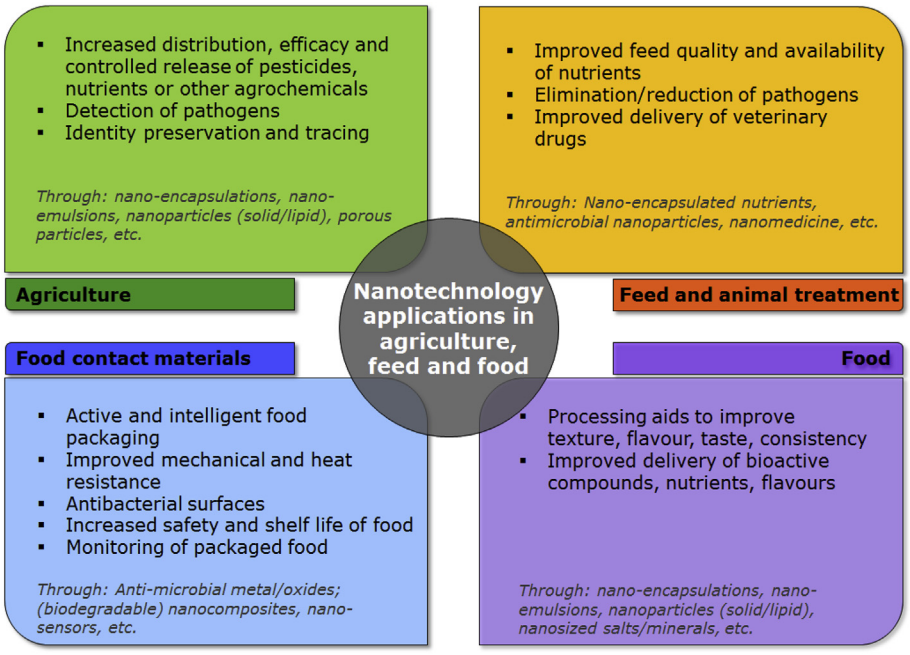

Fig. 1. Applications of Nanotechnology and nanomaterials in the agriculture, feed and food sector.

governmental organisations (NGOs) (BEUC et al. 2014). The need for additional guidance to assess the potential risk and for recommendations to ensure the safe use of NMs has been identified, and several expert bodies are active in this field, such as the EU Scientific Committees and Agencies, the Organisation for Economic Cooperation and Development (OECD), the International Standard Organization (ISO) or the US Food and Drug Administration (FDA). Relevant regulatory issues to be considered for NMs include a definition of the term "nanomaterial", registration or authorisation procedures, specific information requirements for risk assessment, risk management and provisions to increase the transparency and traceability on the commercial use, by e.g. labelling or by notifying to a register for products containing NMs (Falkner and Jaspers, 2012; Aschberger et al. 2014).

In this review we aim to provide an overview of existing legislation, and guidances for risk assessment as well as other relevant documents with regard to NMs and nanotechnology in agri/feed/food in EU and non-EU countries. Relevant information was gathered from peer-reviewed publications through a dedicated search in on-line bibliographic databases, websites of the European Commission, European Agencies/Authorities, the Official Journal of the European Union, national governments, national and international organisations and institutions during the period April to August 2013. Additional information was collected through a questionnaire on "Regulation and safety assessment of nanomaterials in agri/feed/food applications" issued in October 2013 (RIKILT and JRC, 2014). Information on non-EU legislation was mainly retrieved from recent reports, such as those published by WHO/FAO (FAO/WHO, 2013) or OECD (OECD, 2013b) and from other relevant sources. Here we present and discuss the results by taking into account also the latest developments (until May 2015) in the area of regulation and safety assessment of nanomaterials in the agri/feed/food sector. Furthermore, we will discuss some of the properties of nanomaterials used in agri/feed/food and the impact of such properties on environmental safety in agricultural applications and on consumer safety for food and food contact materials (FCMs). Issues surrounding the safe use of nanomaterials in the workplace are not within the scope of this paper.

2. Nanotechnology applications in agri/feed/food and potential impacts on safety

Nanotechnology in the agri/feed/food sector enables the development and production of products or ingredients at the nanometre scale with new beneficial properties (RIKILT and JRC, 2014) (as summarised in Fig. 1). The same properties that are beneficial for certain applications may, however, also have an impact on health and environmental safety (Chaudhry and Castle, 2011; Cushen et al. 2012).

In agriculture, nanotechnology can contribute to improved pest management and crop protection through better efficacy of pesticides and other agrochemicals such as fertilisers, hormones or growth agents (Chaudhry and Castle, 2011; Bucheli et al., 2013; Kah and Hofmann, 2014). Other agricultural applications include genetic engineering, identity preservation, sensors to monitor soil conditions as well as veterinary medicine (Gogos et al. 2012), which are, however, not the focus of this review. Enhanced efficacy of pesticides and other agrochemicals can be achieved by different ways (Kah et al., 2012). One way is decreasing the size of poorly soluble active ingredients, consequently increasing their solubility and (bio)availability. The other way is mixing/encapsulating active substances in micro or nano-emulsions and nano-dispersions, therefore allowing a slow/targeted release of the active ingredients and/or prevention of premature degradation. Both strategies enable reducing the dose while achieving comparable or even better performance. Any manipulation intended to improve efficacy and release, however, is also likely to impact the environmental fate and behaviour of pesticides or agrochemicals. Slow release of active ingredients may imply higher persistence and consequently higher risk for non-target organisms and potentially greater numbers of residues on harvest. The increased concentration of solvents and surfactants required for "nanoemulsions" many influence the fate of pesticides or have a direct effect due to soil sorption (Bucheli et al., 2013; Kah and Hofmann, 2014). On the other hand a reduced concentration of active ingredients in pesticide products may result in a better environmental safety profile due to lower environmental exposure and lower traces of residues

in treated food products.

In food production, most nanotechnology applications involve food additives which improve the stability of foods during processing and storage, enhance product characteristics, or increase the potency and/or bioavailability of nutrients in the food product (Chaudhry et al. 2010). Some of these applications may also be employed in animal feed where expected benefits include reduced use of feed additives, improved bioavailability, less environmental impact and removal of toxins in feed (Chaudhry and Castle, 2011; RIKILT and JRC, 2014).

Three major classes of NMs in food applications have been identified in the literature depending on their occurrence, their solubility and their metabolisation/excretion (Morris, 2011):

1) Natural food structures include naturally occurring biopolymers (carbohydrates, proteins or lipids) that have at least one dimension in the nanometre range or nanostructures introduced by processing or cooking (e.g. emulsions such as mayonnaise) (Morris, 2011). These biopolymers can also be used to design new food structures, e.g. fat reduced emulsions.
2) Engineered particulate NMs whose components are completely metabolised within the body or excreted (Morris, 2011) such as nanoemulsions or nanoencapsulations of nutrients (e.g. vitamins). The risk assessment has to consider that the biokinetics and toxicity profile in target tissues may be different from non-nano counterparts (EFSA Scientific Committee, 2011; Landsiedel et al., 2012).
3) Persistent or slowly soluble engineered particulate NMs (Morris, 2011) such as synthetic amorphous silicon (SAS; E551; anti-caking agent), nano-silver (antimicrobial agent), and titanium dioxide (food additive). Some of these materials are often not intentionally produced in the nanosized range, but may contain a fraction in that size range, as for example titanium dioxide (TiO_2) as white pigment (Peters et al., 2014). They are only weakly soluble and their components are not or slowly dissolved during digestion (Chaudhry and Castle, 2011; Cushen et al., 2012). Hence these NMs may be absorbed, retained and accumulated within the body (Morris, 2011).

In food packaging applications nano polymer composites offer new lightweight properties and at the same time stronger materials that can keep food products secure during transportation, fresh during long storage and safe from microbial pathogens (Chaudhry et al. 2010; Chaudhry and Castle, 2011). Metal/metal oxide nanoparticles such as nano-silver or nano zinc oxide in “active” packaging and nanocoatings on food contact surfaces serve to prevent microbial growth and keep food fresher over relatively longer periods. “Smart” packaging can either slowly release food preservatives and/or incorporate nano-sized (bio)sensors to monitor the condition of food. The main concern about (any) food contact materials, is their (potential) migration into foodstuffs which is addressed by specific legislation (e.g. (European Commission, 2011) (see also 3.4).

The safe use of all these applications is ensured by specific legislation and/or dedicated guidance, which are presented hereunder.

3. Regulatory aspects of NMs in agri/feed/food in the EU

In the EU, horizontal and sector specific legislation provides a binding framework for manufacturers, importers and users to ensure the safety of substances and products on the market. This framework covers NMs and nano-enabled products too. The need of adapting existing legislative provisions to NMs and nano-enabled products, however, has been recognised in some cases and this has led to amendments to the legal text of certain regulations. Table 1 gives an overview of the current EU legislation and to what extent NMs are explicitly addressed in that legislation for each type of agri/feed/food application. EU legislation is accessible and searchable on-line at http://EUR-LEX.europa.eu/.

NMs are either implicitly or explicitly covered by different pieces of legislation. Currently, EU legislation explicitly addressing NMs includes the Regulation on the Provision of Food Information to Consumers (1169/20119), the Regulation on Plastic Food Contact Materials and Articles (10/2011), the Regulation on Active and Intelligent Materials and Articles (450/2009), the Biocidal Products Regulation (528/2012) and the Cosmetic Products Regulation (1223/2009). Other pieces of legislation are currently under revision to better address NMs, e.g. Novel Food Regulation (258/97) (European Commission, 2013), or the Annexes to the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation (1907/2006) (European Commission, 2012).

3.1. Definition of “nanomaterial”

Legislative provisions that explicitly address NMs need to refer to a definition to identify and distinguish them from other materials (for definitions of a nanomaterial in the EU see Annex I). The European Commission (EC) published a “Recommendation on the definition of nanomaterial” to promote consistency in the interpretation of the term “nanomaterial” for legislative and policy purposes in the EU (European Parliament and Council, 2011). This definition is not legally binding but serves as a reference that is broadly applicable across different regulatory sectors and can be adapted to specific product legislation. The EC definition uses size (i.e., size range 1–100 nm) as the only defining property of the material. The size refers to the external dimensions of the constituent particles of a material which can be unbound but may also be in form of agglomerates and/or aggregates. The EC definition applies to all particulate NMs irrespective of their origin, i.e. natural, incidental or manufactured. A material is a nanomaterial if 50% or more of its constituent particles, regardless whether they are unbound or part of agglomerates or aggregates, in the number-based particle size distribution have one or more external dimensions between 1 nm and 100 nm. In specific cases that threshold of 50% can be lowered to values between 1 and 50%. The EC definition is under review in 2015 (Rauscher et al., 2014; Roebben et al., 2014).

Prior to the publication of the EC Recommendation, definitions of a nanomaterial were already adopted in certain sector-specific regulations. Those definitions are legally binding and differ in some aspects from the EC Recommendation. The definition of “engineered nanomaterial” in the Provision of Food Information to Consumers (FIC) Regulation refers to a size range consistent with the EC Recommendation, i.e. external dimensions in the order of 100 nm or less, however without clear size boundaries, and it covers only intentionally produced NMs, i.e., NMs that are manufactured to perform a specific function in the food matrix. The FIC definition currently does not include a threshold value. The EC intends to amend the definition of engineered NMs in the FIC Regulation and to harmonise it with the EC Recommendation, but this process is still ongoing. The European Parliament in November 2014 voted to adopt a 10% threshold of particles in the nanorange to be applied in the definition of NM in food. Such a threshold would pose a major challenge for detection, quantification and thus implementation (Roebben et al. 2014) of the definition. The proposal for a revision of the Novel Food Regulation (European Commission, 2013) does not include its own definition of “nanomaterial” but makes reference to the FIC Regulation and its definition of “engineered nanomaterial”. Any change of the definition in the FIC Regulation would therefore automatically apply to novel food.

Table 1
Overview of EU legal frameworks governing authorisation procedures and nanomaterial provisions in agri/feed/food applications.

Application	Authorisation[a]	Nano-definition	Nano-label	Guidance
Agriculture – Pesticides				
Plant protection products	(EC) No 1107/2009	No	No	EFSA guidance (for oral intake via food) (EFSA Scientific Committee, 2011)
Food/Feed				
Novel food/feed	(EC) 258/97	COM(2013) 894 final 2013/0435 (COD) reference to (EU) No 1169/2011	(EU) No 1169/2011	EFSA guidance
Food additives	(EC) 1333/2008	No	(EU) No 1169/2011	EFSA guidance
Enzymes	(EC) 1332/2008	No		
Flavourings	(EC) 1334/2008	No		
Food supplements	Dir 2002/46/EC	No	No	No
Feed ((EC) 767/2009)	Not required	No	No	EFSA guidance
Feed additives	(EC) 1831/2003 (EC) 429/2008			
Food contact materials				
Food contact materials	(EC) 1935/2004	No	No	EFSA guidance
Plastic food contact materials	(EC) 20/2011	No	No	EFSA guidance
Active and Intelligent Materials and Articles	(EC) 450/2009	No	No	EFSA guidance
Biocides/Chemicals				
Biocides	(EU) No 528/2013	(EU) No 528/2013	(EU) No 528/2013	Pending (information requirements)
Chemical substances	(EC) 1907/2006 (REACH) (authorisation required for certain hazardous substances)	No	No	ECHA guidance (ECHA, 2012)

[a] Authorisation required means that substances/products have to undergo pre-market approval.

The NM definition included in the Biocidal Products Regulation (European Parliament and Council, 2012) incorporates most of the EC Recommendation criteria; however, it does not mention the criteria referring to the specific surface area (>60 m^2/cm^3) which, according to the EC Recommendation, can also be used to define NMs if technically feasible and required in specific legislation. Neither does this definition include the possibility to reduce the size distribution threshold to values lower than 50%. Other regulations concerning agri/feed/food do not contain a "nanomaterial" definition (see overview in Table 1).

The use of different definitions allows addressing NMs in a way that is tailored to the needs of specific application areas (e.g. food or industrial applications); however, it can also lead to confusion and regulatory inconsistency as the same substance could be regarded as NM by one legislation but not by another. An alignment of these sector-specific definitions with the EC Recommendation is still being discussed in 2015. Possible changes include for example the alignment for the number-based particle size distribution for NMs in food applications as defining feature or the alignment of the specific threshold (see above).

The implementation of any definition based on quantitative criteria requires validated and harmonised measurement methods to correctly classify a material. The use of a multi-method approach is recommended (Linsinger et al. 2012), since at the moment no single method is able to cover the whole size range and all the different types of NMs. An important issue to implement a definition is the specification of the life cycle stage at which a nanomaterial should be identified, as pointed out by EFSA Scientific Committee (EFSA Scientific Committee, 2011), because the NM can change at each of these steps, e. g. in terms of size, agglomeration/aggregation state or surface properties. There are challenges in the choice of equipment (technique), metric for defining properties, protocols for sample preparation, protocols for the measurements and possibly protocols for conversions of the test result into a parameter of the definition. For these reasons, existing methods need to be further developed and improved, especially if they are to be applied in complex matrices such as food (Calzolai et al., 2012; Peters et al., 2014).

3.2. Legal acts for pesticides risk assessment

Pesticides are chemical compounds that are mainly applied to kill, repel or control pests and weeds, to protect crops before and after harvest or to influence the life processes of plants. Pesticides are regulated by the Plant Protection Products (PPP) Regulation (EC) 1107/2009 (European Parliament and Council, 2009a), which requires a pre-market authorisation procedure at EU level for active substances and at Member State (MS) level for plant protection products. Active substances and products are assessed on a case-by-case basis, which provides the possibility to assess the risk of ENMs as active substances even if they are not explicitly mentioned in the legislation (RIVM, 2012). Environmental fate studies are usually only undertaken with the active ingredient or a representative formulation but not with each formulation. The potential interaction between active substances and formulants and the influence on long term processes such as degradation and distribution, however, have to be addressed (Kah and Hofmann, 2014). Authorisation of plant protection products is only granted under the conditions that not only the active substance, but also safeners (added to eliminate or reduce phytotoxic effects) and synergists (to enhance the activity of the active ingredient) included in the product have been approved; co-formulants must not be included in a negative list (Annex III PPP Regulation). Pesticides containing nanoforms or nano-encapsulations of approved active substances could be considered as a different pesticidal product and as such would require a separate risk assessment and authorisation.

3.3. Legal acts for food and feed risk assessment

The basis for assurance of high level of protection of human health and consumers' interest in relation to food, is provided by Regulation 178/2002 (European Parliament and Council, 2002b) which lays down the "General Principles and Requirements of Food Law". There are separate directives/regulations for novel foods and novel foods ingredients, food additives, feed additives, food supplements, vitamins, minerals and food contact materials. In addition, a regulation on the provision of food information to

consumers exists and is described below (3.7). Depending on the type of nanomaterial or the purpose of its use as food/feed or part of food/feed, it would fall under its respective legislation. Definitions for the different terms and their sources are given in the supplementary information (Annex II). Although not explicitly mentioned, the use of nanotechnology in food production is currently covered by EC Regulation No 258/97 concerning "novel foods" and "novel food ingredients" (European Parliament and Council, 1997). "Novel food" is food not consumed to any significant degree in the EU prior to May 1997 and comprises newly developed, innovative food, or food produced using new technologies and production processes. This Regulation is currently under revision and the proposal for the revised Novel Food Regulation (European Commission, 2013) should provide a firmer basis for covering foods modified by new production processes such as nanotechnology and nanoscience as well as food, vitamins, minerals and other substances containing or consisting of "engineered nanomaterials".

Substances added to food for a technological purpose (e.g. synthetic amorphous silica (E551) and TiO_2 (E171)) or to improve solubility, flavour or bioavailability, are covered by the "Food Improvement Agent Package". It includes: Regulation (EC) 1332/2008 on food enzymes (European Parliament and Council, 2008b), Regulation (EC) 1333/2008 on food additives (European Parliament and Council, 2008c) and Regulation (EC) 1334/2008 on flavourings and certain food ingredients with flavouring properties (European Parliament and Council, 2008e). Minerals or vitamins are regulated by Directive 2002/46/EC on food supplements (European Parliament and Council, 2002a) and only those listed in its Annex I (vitamins and minerals) or Annex II (vitamin and mineral substances) can be used. Nanoforms of minerals or vitamins (e.g. encapsulations) require a safety evaluation under the Novel Food Regulation, due to the differences in production, potential differences in nutritional value and bioavailability when compared to macro-scale counterparts (European Commission, 2013). Feed for food-producing (e.g. cattle, species normally used for human consumption) and non-food producing (e.g. pet, zoo or fur) animals is regulated by Regulation 767/2009 on feed marketing (European Parliament and Council, 2009b). Substances added to feed (feed additives) for technological, nutritional, organoleptic or zootechnical purposes (e.g. animals performance) or as coccidiostats and histomonostats are regulated by Regulation (EC) No 1831/2003 on additives for use in animal nutrition (European Parliament and Council, 2003) and Regulation (EC) No 429/2008 describes the detailed rules for the implementation of this regulation (European Parliament and Council, 2008d).

Food additives, enzymes and flavourings must undergo a common (EU-wide) assessment and authorisation prior marketing, for which Regulation (EC) 1331/2008 (European Parliament and Council, 2008c) (see Table 1) lays down the common procedure. Pre-market approval is also required for feed additives, novel food and food supplements. The authorisation procedure based on a scientific risk assessment should ensure that only safe ingredients are contained in food and feed. Changes in the starting material used in the production method of an additive (e.g. change of particle size) are not covered by existing authorisation and must undergo a new safety evaluation (European Parliament and Council, 2008c). All food additives that were permitted before 2009 are currently under re-evaluation (European Commission, 2010). This includes also some of the common particulate food/feed additives, which have been in use for years, such as anti-caking/free-flow powders, pigments and others (e.g. SiO_2 – E551, TiO_2 – E171, $CaCO_3$ – E170, vegetable carbon – E153, silver – E174, gold – E175 and iron oxide – E172) (European Commission, 2010). Some of these materials may meet the criteria of the NM definition (e.g. E551 having the constituent particle size in the nanorange) (Dekkers et al. 2011) or contain a fraction in the size range below 100 nm (e.g. titanium dioxide) (Weir et al. 2012; Peters et al. 2014). Evaluations finalised so far did not point to health concerns for calcium carbonate (E170) as food additive (EFSA Panel on Food Additives and Nutrient Sources added to Food, 2011) or silicon dioxide silanated in FCMs (EFSA Panel on Food Contact Materials, 2014). The re-evaluation of SAS (E551) as a food additive is expected to be completed in 2016 (European Commission (DG SANCO) 2013). Recently, a risk assessment on SAS (E551) attempted to integrate the potential risks of the nanoparticle fraction (van Kesteren et al. 2014). Some results suggest that SAS in food may pose a health risk; however, the authors also conclude that the assumptions made can induce several sources of uncertainty which make it difficult to draw firm conclusions. Also for nano-silver knowledge gaps have been identified (Wijnhoven et al. 2009). It is intended that these studies are taken into account by EFSA as the responsible regulatory body for scientific safety re-evaluation, in order to be delivered to the EC for decision making.

3.4. Legal acts for food contact materials risk assessment

Regulation (EC) No. 1935/2004 is a framework regulation that covers all materials and articles intended to come into contact with food (= food contact materials). Specific measures for groups of materials and articles exist (e.g. active/intelligent materials and articles, adhesives, ceramics, plastics). So far only two legislative pieces explicitly refer to NMs in the legal text, although they do not contain a definition of the term "nanomaterial". While Regulation (EC) 450/2009 (European Commission, 2009) on "Active and Intelligent Materials and Articles" is rather general with regard to NMs and requires a case-by-case risk assessment of nanoparticles in intelligent packaging systems until more information is known, the revised "Plastic Food Contact Materials" Regulation (EU) 10/2011 (European Parliament and Council, 2011) is more specific. It states that substances in nanoform shall only be used if the nanoform is explicitly authorised and mentioned in the specifications of Annex I of the regulation. So far there is only one material named as "nanoparticle" in Annex I: "Titanium nitride for use as additive or polymer production aid". In addition, carbon black and amorphous silicon dioxide are listed without being specifically named as "nanoparticle", but with size ranges specified, which are below or around 100 nm. An important issue to consider is that nanoparticles in food contact materials are excluded from the functional barrier concept. The functional barrier consists of one or more layers within food contact materials or articles preventing the migration of substances from behind that barrier into the food. Behind a functional barrier, non-authorised substances may be used, provided they fulfil certain criteria (e.g. not being carcinogenic, mutagenic or reprotoxic) and their migration remains below a given detection limit (European Commission, 2011). Nanoparticles have to be assessed on a case-by-case basis with regard to their risk and can only be used in food contact material if explicitly authorised.

Substances released from active food contact materials (e.g. nano-silver as antimicrobial) into the food matrix are considered intentionally added to food. Thus for these applications, the conditions set out in the relevant Community or national provisions for their use in food apply, i.e. an authorisation as food additive may be required (European Commission, 2009). Other European legislative acts for food contact materials (e.g. Directive 84/500/EEC on ceramic articles) currently do not contain provisions for NMs.

3.5. Legal acts for Biocides and Chemical Substances Risk Assessment

The Biocidal Products Regulation (BPR) (EU) No 528/2012

(European Parliament and Council, 2012) specifies the provisions for the use of non-agricultural pesticides by both professional users and consumers. The 22 different biocidal product types (as described in Annex V of the BPR) cover uses such as insect repellents, disinfectants or industrial chemicals like anti-fouling paints for ships and material preservatives. The most common biocidal NM is nano-silver, which is largely used for its antimicrobial properties. The antimicrobial activity of silver (also the bulk form) is caused by the release of silver ions, which increases, when the particle size decreases. Comparable to pesticides, biocidal active substances and biocidal products have to undergo an authorisation procedure (European Parliament and Council, 2009a) at EU and MS level respectively. The BPR includes a definition (see Section 3.1 and supplementary information in Annex I) and specific provisions for NMs. The approval of an active substance for biocidal use does not cover NMs, except where explicitly mentioned. Biocidal products containing NMs are not eligible for a simplified authorisation procedure. To approve NMs as active substances and for subsequent product authorisation, the test methods applied to the NMs shall be accompanied by an explanation addressing their scientific appropriateness taking into consideration the specific characteristics of each NM.

Regulation (EC) No 1907/2006 called Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (European Parliament and Council, 2006) has the aim to improve the protection of human health and the environment from the risks that can be posed by chemicals and applies horizontally to all chemical substances. Substances used in food or feedingstuffs are exempted from registration under REACH for these applications. Substances used as plant protection products or biocides are regarded as registered under REACH. NMs that are applied as e.g. food contact materials (e.g. SAS, TiO_2, nano-silver etc.) or in industrial sectors (e.g. TiO_2 in paints), are not exempted from registration under REACH, and therefore the REACH provisions apply to them. REACH currently does not explicitly address NMs in the legal text; however, it addresses chemicals in whatever size, shape or physical form and therefore its provisions also apply to NMs. The Annexes of REACH Regulation are currently under revision to more explicitly address NMs (European Commission, 2012).

NMs, as any other substance, have to be classified for hazardous properties if they show the corresponding properties according to the Regulation on Classification, Labelling and Packaging (CLP) (European Parliament and Council, 2008a). Products containing hazardous substances or NMs have to be labelled (depending on the concentration and concentration limit). The responsible body to manage all REACH, Biocides and CLP tasks is the European Chemicals Agency (ECHA). The European Commission plays an important role in taking decisions in a number of REACH processes, in particular authorisation and restriction processes.

3.6. Available guidances for risk assessment of nanomaterials

Existing risk assessment methods and test methods are to a large extent considered applicable to NMs; however, some aspects, including sample preparation, characterisation, dosimetry, effect endpoints, exposure data and models require further development of standardised and validated methods (SCENIHR, 2007; OECD, 2013a). The EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) has recommended a case-by-case approach for the risk assessment of NMs (SCENIHR, 2009).

Guidance for risk assessment focussing on NMs' specific properties has been released from official bodies. EFSA published in 2011 a “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. It includes guidance for data generation by applicants on the physico-chemical characterisation and on testing approaches to identify and characterise hazards arising from the properties of nanomaterials. Furthermore, it presents 6 exposure scenarios and corresponding testing approaches to identify and characterise hazards arising from the properties of NMs. These 6 scenarios depend on the possible transformations of the NM before and after ingestion of the food/feed. For each scenario the type of data needed to conduct a risk assessment is specified. The guidance provides for reduced information requirements when no exposure to NMs is verified by data indicating no migration from food contact materials or when complete degradation/dissolution is demonstrated with no possible absorption of NMs as such. The guidance specifies that NMs used in food or feed which are transformed to non-nanoforms in a food/feed matrix and before ingestion can be treated as and follow the guidance for non-nanoforms. For NMs completely transformed into non-nanoforms in the gastrointestinal tract, local effects and possible absorption before transformation should be considered. Otherwise existing information should be used or guidance for non-nanoforms should be followed. A comparison should indicate whether the nanoform has increased, less or similar hazard as compared to the non-nanoform. An expert group organised by the International Life Science Institute (ILSI) (Cockburn et al. 2012) prepared a systematic, tiered approach for the safety assessment of NMs in food based on a comparison to the non-nano counterpart. The comparison is based on the dissolution rate of both the bulk and the nano form of the same material in water or under gastric conditions. These guidances, as any other guidance, even if published by EU bodies, are not part of the EU legislation and thus not legally binding. EFSA has also established a Network for Risk Assessment of Nanotechnologies in Food and Feed (EFSA Nanonetwork) with the overall goals to facilitate harmonisation of assessment practices and methodologies, to enhance exchange of information and data between EFSA and EU Member States; and to achieve synergies in risk assessment activities.[3] In 2012 the EFSA Nanonetwork asked for an “Inventory of Nanotechnology applications in the agricultural, feed and food sector” to receive more up-to-date information on the state of the art of nanotechnology applications, which was generated by RIKILT and JRC (RIKILT and JRC, 2014) and has become available on the EFSA website since July 2014. It is the basis for the current paper.

ECHA has addressed NM specific requirements in its “Guidance on Information Requirements and Chemical Safety Assessment” (IR & CSA) (ECHA, 2012). ECHA has also established a specific Nanomaterials Working Group to discuss scientific and technical questions and to give advice in relation to NMs under REACH and CLP. No specific guidance for NMs is yet available for biocides. The guidance on information requirements for biocides is pending the ongoing review by OECD of all existing methodologies in order to identify and implement the necessary changes needed for their application to NMs (ECHA, 2013).

3.7. Labelling and reporting schemes for NMs

Several stakeholders including the European Parliament, EU Member States, and NGOs have called for more transparency, traceability and information regarding the use and possible exposure to NMs by either labelling of products containing NMs or making use of nanotechnology and/or by the introduction of

[3] http://www.efsa.europa.eu/it/supporting/pub/531e.htm.

registers for such products (Aschberger et al. 2014). Mandatory labelling for the content of NMs (in an ingredients list) is already part of EU legislation on food, cosmetics and biocides (see Table 1). All ingredients present in food and biocidal products in the form of NMs have to be clearly indicated in the list of ingredients with the names of such ingredients followed by the word "nano" in brackets since December 2014 (European Parliament and Council, 2011) and September 2013 (European Parliament and Council, 2012), respectively. Voluntary nanoclaims have been observed for some product types, e.g. for biocidal claims on products containing nano-silver. Labelling provides information to consumers at the time of purchase and allows them to make an informed choice. On the other hand consumers may become overstrained by too much information, considering all the other information provided on a label. Moreover, ingredient labelling for nanomaterials could easily be confused with hazard labelling. In addition to a label which is placed directly on the product, information about NMs used in products or products containing NMs can be collected in a product register. Such register or inventory can give a better overview of the overall application of NMs and potential exposure of humans and the environment. In the UK, the Food Safety Authority (FSA) has published a list of NMs that are allowed to be used in food/food contact materials. The list is short and comprised of fumed silica, nanoclay, titanium nitride and nano-silver (UK-FSA).[4] Mandatory reporting systems for NMs or products containing NMs have so far been introduced in three EU MS, including France, Belgium and Denmark.

4. Regulatory aspects concerning NMs in agri/food/feed in non-EU countries

Several countries around the world are active in examining the appropriateness of their regulatory frameworks for dealing with nanotechnologies and are applying different approaches to ensure the safety of nano products in agri/feed/food. This section of the paper gives an overview on how NMs in agri/feed/food are regulated in non-EU countries. An overview on responsible organisations, key legislation and relevant online sources is provided in Table 2. Those countries, for which sufficient information in English was found, are presented in the paragraphs below.

4.1. United States of America

In the USA, the Food and Drug Administration (FDA) is responsible to ensure safety of food additives/food contact materials/feed additives that are placed on the market under the authority of the *Federal Food, Drug, and Cosmetic Act* (FFDCA) (US-FDA).[5] Substances used as food and colour additives are always subject to pre-market authorisation by the FDA, while for some other food substances, such as food ingredients that are generally recognised as safe (GRAS), pre-market authorisation by the FDA is not required. The FFDCA does not contain any specification for nanotechnology-based products and FDA has not yet adopted a regulatory definition of NMs. It has rather embraced a quite broadly comprehensive approach when dealing with nanotechnology-based products (Hamburg, 2012). To support industry, FDA has published several guidance documents addressing the issues of nanotechnology e.g.: "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology" (US-FDA, 2014a). As reported in that guidance, when considering whether a product contains NMs, FDA looks at the material's size (around 1 nm–100 nm), or properties or phenomena that are attributable to the material's external dimension(s), even if these dimensions are not in the nanoscale range, but instead up to 1 μm (see Annex I). This approach is meant to be broadly applicable to all FDA-regulated products, including food products.

The FDA issued also specific guidance for food related applications of nanomaterials/nanotechnology. FDA recommends a preliminary safety assessment of "Food Ingredients and Food Contact Substances produced at nanoscale", which should be based on data relevant to the nanometer version of a food substance (Tyler, 2012). FDA does not consider a priori all products containing NMs as intrinsically hazardous but suggests a case-by-case approach when assessing the safety of the finished product and its foreseen use. Regarding the safety of such products, FDA also states that there are no food substances intentionally engineered at the nanometer scale for which there are at the moment enough safety data so that their use can be considered as GRAS. In the guidance FDA declares to have not received food or colour additive petitions, or GRAS affirmation petitions, for any uses of food substances with a particle size distribution fully in the nanometer range. Similar considerations have been drawn by FDA in the recently published "Draft Guidance for Industry on Use of Nanomaterials in Food for Animals" (US-FDA, 2014b).

The US Environmental Protection Agency (US-EPA) is responsible for regulating pesticides under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (US-EPA).[6] No specific provisions for NMs are available at the moment under this regulation, the US-EPA webpage "Regulating Pesticides that use Nanotechnology" (US-EPA, 2011) is available since July 2011. Here it is reported that US-EPA is seeking for public comments regarding how nanotechnology-based pesticides should be regulated and incorporated into FIFRA. Companies intending to register nanotechnology-containing pesticides are recommended to contact the "US-EPA's pesticide registration Ombudsmen". US-EPA has recently conditionally registered a pesticide product containing nano-silver as a new active ingredient under FIFRA. The antimicrobial pesticide is a silver-based product, and as a condition of registration, US-EPA is requiring additional data on the product to confirm it will not cause unexpected adverse effects on human health or the environment.[7] US-EPA has also taken actions against a company producing and illegally selling on the market food containers with an unregistered nano-silver pesticide.[8] The agency is also responsible for evaluating new and existing chemicals and their risks under the Toxic Substances Control Act (TSCA).[9] Since 2005 US-EPA has received over 100 chemical notices for nanoscale materials and is actively participating in international activities aimed at increasing the actual knowledge and expertise in the nanotechnology field.[10] In order to have a more comprehensive view on the NMs that are already on the market, US-EPA has proposed in April 2015 a one-time reporting and recordkeeping requirements under TSCA section 8(a). Under the new proposed rule companies that manufacture certain chemical substances already in commerce as nanoscale materials shall notify EPA and provide information such as production volume, methods of manufacture and processing, exposure and release information, and available

[4] http://www.food.gov.uk/science/novel/nano/monitoring/
[5] http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactFDCAct/default.htm.
[6] http://www.epa.gov/agriculture/lfra.html.
[7] http://www.epa.gov/oppfead1/cb/csb_page/updates/2011/nanosilver.html.
[8] http://yosemite.epa.gov/opa/admpress.nsf/0/6469952cdbc19a4585257cac0053e637.
[9] http://www.epa.gov/agriculture/lsca.html.
[10] http://www.epa.gov/oppt/nano/.

Table 2
Summary of food legislation in some non-EU countries.

Country	Responsible organisation	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
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
Russia	The Federal Service for the Protection of Consumer Rights and Human Well-Being of the Ministry of Health and Social Development (Rospotrebnadzor)	Sanitary Rules and Regulations ("SanPiN")	http://www.rospotrebnadzor.ru/en/deyatelnost/bilateral.php
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	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
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
Malaysia	Ministry of Science Technology and Innovation	Food Regulations 1985 The Food Act 1983	http://www.mosti.gov.my/index.php?option=com_content&view=frontpage&Itemid=27&lang=en
Iran	Nanotechnology Committee of Food and Drug Organisation Iran Nanotechnology Initiative Council (INIC)		http://nanohealth.ir/pages/static_page.php?id=9&site=1&lang=2 http://irannano.org/nano/index.php?ctrl=section&actn=get_section&lang=2&id=22
Thailand	Food and Drug Administration of the Ministry of Public Health	Food Act B.E.2522	http://eng.moph.go.th/index.php/safety
South Africa		Foodstuffs, Cosmetics and Disinfectants Amendment Act, 2007	http://www.sani.org.za/
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/

health and safety data. The aim of such reporting rule would be to use the information gathered to decide if further actions, such as additional information collection, is needed under TSCA (US-EPA, 2015). In order to develop efficient testing strategies for engineered nanomaterials (ENM) US-EPA is studying several NMs: nano-silver, carbon nanotubes, cerium dioxide, titanium dioxide, iron and micronised copper. It has published case studies focussing on the specific examples which are organised around a comprehensive environmental assessment (CEA) framework, combining a product life-cycle perspective with the risk assessment paradigm, however, without drawing conclusions about potential risks. Instead, they are intended to be used as part of a process to identify what is known and unknown about these materials in a selected application and can be used as a starting point to identify and prioritise possible research directions to support future assessments of NMs. Such case studies include for example "Nanoscale Silver in Disinfectant Spray" (US-EPA, 2012).

4.2. 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. No specific regulation for nanotechnology-based food products is available but such products are regulated under the existing legislative and regulatory frameworks.[11] In October 2011 Health Canada published a "Policy Statement on Health Canada's Working Definition for Nanomaterials" (Health Canada, 2011), the document provides a (working) definition of NM which is focused, similarly to the US definition, on *the nanoscale dimensions, or on the nanoscale properties/phenomena of the material* (see Annex I). For what concerns general chemicals regulation in Canada, the New Substances (NS) program must ensure that new substances,

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

including substances that are at the nano-scale (i.e. NMs), are assessed in order to determine their toxicological profile (Environment Canada, 2014). The approach applied involves a pre-manufacture and pre-import notification and assessment process. In 2014, the New Substances program published a guidance aimed at increasing clarity on which NMs are subject to assessment in Canada (Environment Canada, 2014).

Canadian and US regulatory agencies are working towards harmonising the regulatory approaches for NMs under the US-Canada Regulatory Cooperation Council (RCC) Nanotechnology Initiative.[12] Canada and the US recently published a Joint Forward Plan where findings and lessons learnt from the RCC Nanotechnology Initiative are discussed (Canada–United States Regulatory Cooperation Council (RCC) 2014).

4.3. Australia and New Zealand

All food products marketed in Australia and New Zealand must fulfil the requirements set under the Australia New Zealand Food Standards Code (the Code) and be assessed as safe for human consumption. Food Standards Australia New Zealand (FSANZ), the agency responsible for regulation of food products in both countries, has adopted a range of strategies to manage potential risks for human health associated with use of nanotechnology in food. One of these strategies includes the amendment of the FSANZ Application Handbook to support new food regulations (Bartholomaeus, 2011). FSANZ has not yet received any applications to approve new or novel nanoscale particles for food use.[13] The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) introduced the first regulatory program for "industrial nanomaterials" (January 2011). In that context also a working definition has been adopted (see Annex I). In 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 NMs. 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 (Bowles and Jianjun 2012; ISO, 2013).

4.4. Non-EU European countries

From non-EU European countries we found several nano-related activities in Switzerland, Turkey and Russia.

In Switzerland the safety of NMs is ensured by existing regulations and procedures dealing with traditional chemicals. NMs used in pesticide products submitted for registration must be reported together with specific information on their composition, shape, particle size, surface area, aggregation state, coatings and functionalisation, as requested by a Swiss Ordinance of 2010 (Schweizerischer Bundesrat, 2010). Until 2013 the Federal Office of Public Health (FOPH) did not receive any requests for approval of food additives containing NMs (FAO/WHO, 2013), nor have applications for nanotechnology-based pesticides been reported (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 NMs was launched in 2008. As part of the action plan, FOPH and the Federal Office for the Environment (FOEN) published in 2008 a precautionary matrix for synthetic NMs ((Höck et al. 2008). The precautionary matrix is not legally binding and it can be used on a voluntary basis as an evaluation tool for the safe handling of NMs. It should always be employed in parallel to the existing non nano-specific assessment methods. Aim of this matrix is to estimate the risk management measures required for employees, consumers and the environment at each stage of the life cycle. The precautionary matrix is built up on a series of evaluation parameters, including particle's size, reactivity, stability, release potential, concentration of particles[14] (Höck et al. 2008). A NM definition is available from a guideline document for the compilation of safety data sheet for synthetic NMs as published by the Swiss Secretariat for Economic Affairs (SECO, 2012) (see Annex I).

In Turkey a national or regional policy for the responsible development of nanotechnology is under development (OECD, 2013b). Nanotechnology is considered as a strategic technological field and at present 32 nanotechnology research centres are working in this field. Turkey participates as an observer in the EFSA Nano Network (Section 3.6) along with other EU candidate countries Former Yugoslav Republic of Macedonia, and Montenegro (EFSA, 2012). The Inventory and Control of Chemicals Regulation entered into force in Turkey in 2008, which represents a scale-down version of the REACH Regulation (Bergeson et al. 2010). Moreover, the Ministry of Environment and Urban Planning published a Turkish version of CLP Regulation (known as SEA in Turkish) to enter into force as of 1st June 2016 (Intertek).

The Russian legislation on food safety is based on regulatory documents such as the Sanitary Rules and Regulations ("SanPiN"), but also on national standards (known as "GOST") and technical regulations (Office of Agricultural Affairs of the USDA, 2009). The Russian policy on nanotechnology in the industrial sector has been defined in some national programmes (e.g. Nanotechnology Industry Development Program) and a Russian Corporation of Nanotechnologies was established in 2007.[15] As reported by FAO/WHO (FAO/WHO, 2013), 17 documents which deal with the risk assessment of NMs in the food sector were released within such federal programs. Safe reference levels on nanoparticles impact on the human body were developed and implemented in the sanitary regulation for the nanoforms of silver and titanium dioxide and, single wall carbon nanotubes (FAO/WHO, 2013).

4.5. Asia

Some Asian countries are quite active in the production and regulation of NMs. Beside national regulations, several countries have established standards and certification systems for nano-enabled products and Japan and Korea are actively participating to the OECD Working Party on Manufactured Nanomaterials (WPMN). An overview of the responsible organisations and key legislation is provided in Table 2.

In Japan, the safety of food products is regulated by the Food Sanitation Law. No NMs-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 that document (English version available).

For the Republic of South Korea the main piece of legislation for

[12] http://nanoportal.gc.ca/default.asp?lang=En&n=5a56cb00-1.

[13] http://www.foodstandards.gov.au/consumer/foodtech/nanotech/Pages/default.aspx.

[14] http://www.bag.admin.ch/nanotechnologie/12171/12174/index.html?lang=en.

[15] http://en.rusnano.com/upload/images/documents/RUSNANO_Strategy_2020.pdf.

foods, food additives, and food packaging is the Food Sanitation Act. No specifications for NMs are available to date (FAO/WHO, 2013). As reported in their website, the Korean Food and Drug Administration (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", (Mantovani et al. 2012; Park, 2012), where nanomaterials are defined as nano-objects and nanostructured materials in a solid form, that are smaller than 100 nm.

In India the key piece of regulation for food safety is the Food Safety and Standards Act (2006). The Government had launched in October 2001 a programme called the Nano Science and Technology Initiative (NSTI), followed by the programme "Nano Mission" in 2007.[16] A series of research activities have been undertaken under this program and only recently some initiatives have started to address risk issues. Standardisation remains an area of concern, as India has only taken initial steps in addressing standardisation issues. As reported in some publications specifically addressing the topic of nanotechnology risk management in India, the nation does not have a legislation that takes in consideration nanoparticles as a hazard (Chugh, 2009), has a loose framework of legislation where nanotechnology risks can be addressed (Jayanthi et al. 2012) and lacks resources and expertise to handle nanotechnology risks (Barpujari, 2011).

In China food safety is regulated under the Food Safety Law, which does not include any NM specifications. The National Centre for Nanoscience and Technology (NCNST) and the Commission on Nanotechnology Standardisation are responsible for developing national standards in the nanotechnology area. One of these standards contains a definition for nano materials (GB/T 19619-2004) (see Annex I) (Park, 2012; ISO, 2013). Applications of nanominerals or NMs to be used as food ingredients have been rejected so far by the Chinese regulatory authorities (FAO/WHO, 2013).

In Malaysia a National Nanotechnology Regulatory and Safety Committee, placed under the National Nanotechnology Directorate, was established to monitor and review issues related to health, safety and environment. Regulations to ensure health, safety and environmental aspects of nanotechnology include "The Nanotechnology Industry Development Act" and "The Nanotechnology Safety-Related Act". Revisions of "The Food Regulations 1985" and "The Food Act 1983" are expected to include among others specifications relating to nanotechnology (NanoMalaysia, 2013).

In Taiwan a National Science and Technology Program for Nanoscience and Nanotechnology and "Nano Technology Industrialisation Promotion Plan" were initiated. In cooperation with the Standards Committee of TANIDA (Taiwan Nanotechnology Industry Development Association) a system for certifying nanoproducts, called nanoMark System (Fig. 2A) was established with the aim to enhance the quality and image of nanotechnology products, protect consumer's rights, and promote the development of a national nanotechnology industry.[17] The Asia Nano Forum NEWSLETTER (Issue No. 24) reported that from 2004 to 2014, 39 companies and 1490 products passed the NanoMark certification.[18] A definition of the term nanomaterial is available from the Council of Labor Affairs of Taiwan, within the context of Chemical Substance Nomination & Notification (David et al. 2013).

In Iran the Iran Nanotechnology Initiative Council (INIC) was established in 2003 to define the general policies for the development and access to the market of nanotechnology in the country. The main body responsible for the approval of food products is the Food and Drug Organisation (FDO) which established a specific Nanotechnology Committee to develop specific guidelines for the assessment and approval of nanotechnology-based pharmaceuticals, medical equipment, cosmetics, food, beverages and pharmaceutical supplements. A flowchart on approval procedures for nano-health products is available on the website as well as checklists with specification and safety aspects to be considered and reported for the approval of nanotechnology-based food packaging, food additives, supplements raw materials and supplements product.[19] A list of approved nano-health products is also available and product applications such as supplements, packaging for fruit maintenance and disinfectants are mentioned among others.[20] Iran has also introduced a nano symbol as industrial standard certification[21] which applies to "products pertaining to pharmacy, medical equipment, beauty and healthcare, food and beverages, and dietary supplements". Accreditation is obtained through a "nanotechnology committee" associated to the FDO; twelve products have so far received the certification.[22]

In Thailand the Food & Drug Administration of the Ministry of Public Health is responsible for controlling food products. The National Nanotechnology Centre (NANOTEC) has identified 10 flagship programmes of national priority, including industrial standards for nano-products in Thailand, called NANO-MARKS, and "Food Quality" aimed at improving and monitoring the quality for Thai Food prepared by applying nanotechnology. The "NanoQ label" (Fig. 2B) has been introduced for nano products that are certified by the Nanotechnology Association of Thailand[23,24,25]. The NanoQ label has been so far used in the paint, ceramics, textile, and household plastics industries with the aim to eliminate fake nano products on the market and increase people's trust on the products they are buying. No information was found on the application of such a nano label on food/feed products.

4.6. Africa and South America

The South African Nanotechnology Initiative (SANi) was established in the year 2002 (Leskey M. Cele, 2009) and a South African nanotechnology strategy with a 10-year plan for nanotechnology has been created in this context.[26] No specific legislation for NMs is, however, currently available and the regulation of nanotechnology-based food products falls under the several pieces of food-specific legislation, i.e. the Foodstuff, Cosmetics and Disinfectant Amendment Act 2007.

In Brazil food products are regulated under several legal documents issued by the Federal Government. Brazil is one of the leading countries in nanotechnology research and development in Latin America (Guillermo Foladori, 2007). Several programmes and considerable investments have in fact been undertaken in the nanotechnology sector; however, no specific regulation has yet been introduced in the country. A proposal aiming at introducing labelling of food, drugs and cosmetics

[16] http://nanomission.gov.in/.
[17] http://www.taiwan.gov.tw/ct.asp?xItem=27511&ctNode=1906&mp=1001.
[18] http://www.asia-anf.org/admin/upload/files/general/News432_1.pdf.
[19] http://nanohealth.ir/pages/static_page.php?id=14&site=1&lang=2.
[20] http://nanohealth.ir/contents/content_Nanohealth%20product%20list.pdf.
[21] http://www.nano.ir/index.php?ctrl=news&actn=news_view&id=42433&lang=2.
[22] http://www.nanotechia.org/news/news-articles/iran-introduces-certification-nano-foods-and-health-products.
[23] http://www.who.int/ifcs/documents/forums/forum6/ppt_nano_thailand.pdf.
[24] http://nanotech.apctt.org/countryreports/Thailand%20Country%20Report.pdf.
[25] http://www.oecd.org/science/nanosafety/47556610.pdf.
[26] http://www.sani.org.za/pdf/Nanotechnology_10-Year_plan.pdf.

Fig. 2. Nanoproducts certification system as introduced by industrial standards committees in A) Taiwan (∞Nano)[27] and B) Thailand (NanoQ).[28]

containing NMs was presented to the Congress's Senate in May 2010 but was rejected.

5. Comparison of EU and non-EU regulatory approaches

The overview presented in this work shows that several countries or regions all over the world are active in managing the marketing and use of nano-based products in agri/feed/food sectors and nanotechnology. The approaches applied to regulate them and to ensure their safe use are, however, different.

The EU, along with Switzerland, were identified to be the only world region where nano-specific provisions have been incorporated in legislation for agri/feed/food, which include specific information requirements for NMs risk assessment and/or legally binding definitions of the term "nanomaterial", and/or the obligation to label or report the presence of NMs in products. Furthermore, in the EU a recommendation for a broadly applicable definition of "nanomaterial" is available. All EU definitions of the term "nanomaterial" intended for regulatory purposes use size as main identifier. The definition in the Cosmetics Regulation No 1223/2009 considers only insoluble and biopersistent materials as NMs. For all other applications, further specific properties, like solubility or degradation are addressed in specific guidance for information requirements and risk assessment.

As presented in a recent study by the Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament (European Parliament, 2014), EU legislation is in general considered more stringent than US legislation and more open to consumer opinions. For example REACH requires that all chemicals, thus also NMs, must be registered, which includes the submission of safety data. According to TSCA in US, the submission of safety data is required only in particular cases, although US-EPA recently (April 2015) has proposed to use TSCA also for one-time reporting and record-keeping of existing exposure and health and safety information on chemicals currently in the marketplace, when they are manufactured or processed as nanoscale materials (US-EPA, 2015). Concerning food legislation, the study concluded that the "farm to fork" approach of the EU includes all stages of food production from manufacturing and processing to distribution (European Parliament, 2014). Monitoring in the US focuses only on "registered facilities" in the manufacturing and processing part of the supply chain with the aim of preventing and intercepting contaminated food. The precautionary approach as followed in the EU takes account of scientific uncertainty to implement measures addressing risks, beside other factors such as economic costs and benefits and consumer opinions. The US approach strictly relies on science-based assessments to prove risks and consequently take regulatory actions (European Parliament, 2014).

Several countries outside the EU have rather adopted a broad approach when dealing with regulation of NMs in agri/feed/food. Some of them have introduced non-mandatory frameworks and consider existing regulatory frameworks able to adapt to and cover the particularities of NMs (e.g. US, Australia and New Zealand, Canada). Some countries (e.g. Malaysia) are adapting their existing regulatory frameworks for agri/feed/food to include specifications for nanotechnology (OECD, 2013b).

No legally binding definitions could be identified outside the EU and rather working definitions of NMs are applied. Beside size, some countries (e.g. US, Canada) consider also other properties or phenomena to define NMs or nanotechnology. This points the focus to NMs which potentially have a different hazard profile and which may be of higher priority for risk assessment. Some non-EU countries such as Iran, Taiwan and Thailand have introduced systems for tracking and labelling consumer products containing NMs (e.g. NanoMark system), which are, however, substantially different from the labelling requirement in the EU.

As applications of nanotechnology are evolving and more advanced new generation nanotechnology products are expected to enter the market, the existence of a proper safety net and adequate regulatory frameworks adapted to products of nanotechnology are of high priority. A case-by-case risk assessment of each NM or nanoform – as currently recommended and practised in certain countries – is not the most efficient long term approach to ensure the safety of nanoproduct since it would require too many resources and could be impedimental to innovation. Several activities are ongoing in research but also by governmental and non-governmental international organisations and industry to identify common determinants of NM risks, which would allow applying more efficient approaches, including grouping of NMs and reading across of hazard or exposure data (Gebel et al. 2014; Arts et al. 2015). In addition, risk management measures to limit exposure to NMs are recommended. Exposure limitation may, however, not be the goal for certain products, e.g. when the nanoform should enable increased bioavailability of nutrients or active substances.

Considering that nanotechnology-based agri/feed/food products may enter the international trade and such products may be obtained via the internet, harmonised approaches addressing NMs marketing and their safe use would be beneficial. Guidance and standards on e.g. appropriate (test) methods for risk assessment can be harmonised at international level and periodically adapted to technical progress. Several activities are already ongoing under the umbrella of e.g. OECD and ISO. FAO and WHO have jointly created the Codex Alimentarius Commission, an intergovernmental agency that aims at creating international food standards, guidelines, codes of practice and advisory texts, which could also cover nanotechnology-based products. The development of a solid system for sharing information and experience gained on the use of NMs in agri/feed/food around the globe is also highly desirable in the present era of globalisation.

6. Conclusions

Applications of nanotechnologies and incorporation of NMs in agri/feed/food are growing and several novel products, currently in development are expected to enter the market in the near future. Therefore, it is becoming increasingly important to have regulatory frameworks that properly address and specifically manage the potential risks of nanotechnology. Several countries over the world have been active in examining the appropriateness of their regulatory frameworks for dealing with nanotechnologies. The overview presented in this work shows that countries within the EU

[27] http://www.tanida.org.tw/Eng/Mark/.
[28] http://www.nanotec.or.th/en/?p=1625.

and outside EU follow different approaches in regulating nano-based products in agri/feed/food and nanotechnology in general.

The EU, along with Switzerland, were identified to be the only world region where nano-specific provisions have been incorporated in legislation for agri/feed/food. In other regions nano-specific provisions are more implicit, building mainly upon guidance for industry.

Collaboration among countries around the world is required in order to exchange information and to ensure a high level of protection for humans and the environment, while not hampering the development of new beneficial products and their global marketing.

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Appendix A. Supplementary data

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Transparency document

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References

Arts, J.H.E., Hadi, M., Keene, A.M., Kreiling, R., Lyon, D., Maier, M., Michel, K., Petry, T., Sauer, U.G., Warheit, D., Wiench, K., Landsiedel, R., 2014. A critical appraisal of existing concepts for the grouping of nanomaterials. Regul. Toxicol. Pharmacol. 70 (2), 492–506.

Arts, J.H.E., Hadi, M., Irfan, M.-A., Keene, A.M., Kreiling, R., Lyon, D., Maier, M., Michel, K., Petry, T., Sauer, U.G., Warheit, D., Wiench, K., Wohlleben, W., Landsiedel, R., 2015. A decision-making framework for the grouping and testing of nanomaterials (DF4nanoGrouping). Regul. Toxicol. Pharmacol. 70 (2), S1–S27.

Aschberger, K., Rauscher, H., Crutzen, H., Christensen, F.M., Rasmussen, K., Sokull-Kluettgen, B., Stamm, H., 2014. Considerations on Information Needs for Nanomaterials in Consumer Products – Discussion of a Labelling and Reporting Scheme for Nanomaterials in Consumer Products in the EU. Ispra from. https://ec.europa.eu/jrc/sites/default/files/reqno_jrc88931_considerations_information_needs_nm_consumer_products_online.pdf.

Barpujari, I., 2011. Attenuating risks through regulation: issues for nanotechnology in India. J. Biomed. Nanotechnol. 7 (1), 85–86.

Bartholomaeus, N.F.A.A., 2011. Regulation of nanotechnologies in food in Australia and New Zealand. Int. Food Risk Anal. J. 1 (2), 33–40.

Bergeson, L.L., MacDougall, L.S., Navin-Jones, M., 2010. Turkey Enacts REACH-like Chemical Program: what Stakeholders Need to Know. Chemical Regulation Reporter. International Issues Turkey. Bureau of National Affairs, Inc. ISS 0148-7973from. http://www.lawbc.com/uploads/docs/00056427_1.pdf.

BEUC, EEB, CIEL, Client Earth, ECOS, ANEC, Health Care without Harm, 2014. European NGOs Position Paper on the Regulation of Nanomaterials. B.-T. E. C. Organisation, Bruxelles. David Azoulay, Managing Attorney, CIEL dazoulay@ciel.org; Vito A. Buonsante, Law & policy advisor, ClientEarth, vbuonsante@clientearth.org.

Bowles, M., Jianjun, L., 2012. Review on nanotechnology in agricultural products logistics management. In: International Conference on Computing and Networking Technology (ICCNT). http://ieeexplore.ieee.org/Xplore/defdeny.jsp?url=http%3A%2F%2Fieeexplore.ieee.org%2Fstamp%2Fstamp.jsp%3Ftp%3D%26arnumber%3D6418696%26userType%3Dinst&denyReason=-134&arnumber=6418696&productsMatched=null&userType=inst.

Bucheli, T.D., K, K., Gogos, A., 2013. Overview of Agricultural Applications of Nanotechnology; Nanotechnology for the Agricultural Sector: from Research to the Field. Workshop Organized by JRC IPTS Agrilife Unit, Seville. https://ec.europa.eu/jrc/sites/default/files/ipts_jrc_89736_(online)__final.pdf.

Calzolai, L., Gilliland, D., Rossi, F., 2012. Measuring nanoparticles size distribution in food and consumer products: a review. Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess. 29 (8), 1183–1193.

Chaudhry, Q., Castle, L., 2011. Food applications of nanotechnologies: an overview of opportunities and challenges for developing countries. Trends Food Sci. Technol. 22 (11), 595–603.

Chaudhry, Q., Scotter, M., Blackburn, J., Ross, B., Boxall, A., Castle, L., Aitken, R., Watkins, R., 2008. Applications and implications of nanotechnologies for the food sector. Food Addit. Contam. – Part A Chem. Anal. Control Expo. Risk Assess. 25 (3), 241–258.

Chaudhry, Q., Castle, L., Watkins, R., 2010. Nanotechnologies in Food. Royal Society of Chemistry, Cambridge.

Chugh, K.S. a. A., 2009. Legal Aspects of Nanobiotechnology Inventions: an Indian Perspective, 6:2 SCRIPTed 433. http://www.law.ed.ac.uk/ahrc/script-ed/vol6–2/sharma.asp.

Cockburn, A., Bradford, R., Buck, N., Constable, A., Edwards, G., Haber, B., Hepburn, P., Howlett, J., Kampers, F., Klein, C., Radomski, M., Stamm, H., Wijnhoven, S., Wildemann, T., 2012. Approaches to the safety assessment of engineered nanomaterials (ENM) in food. Food Chem. Toxicol. 50 (0), 2224–2242.

Canada-United States Regulatory Cooperation Council (RCC), 2014. Joint Forward Plan. Washington from. https://www.whitehouse.gov/sites/default/files/omb/oira/irc/us-canada-rcc-joint-forward-plan.pdf.

Cushen, M., Kerry, J., Morris, M., Cruz-Romero, M., Cummins, E., 2012. Nanotechnologies in the food industry – recent developments, risks and regulation. Trends Food Sci. Technol. 24 (1), 30–46.

David, R.M., Boverhof, D.R., Butala, J.H., Clancy, S., Lafranconi, M., Bramante, C.M., West, W.J., 2013. Comparative assessment of nanomaterial definitions and considerations for implementation. In: Society of Toxicology, American Chemistry Council – Nanotechnology Panel. http://nanotechnology.americanchemistry.com/Nanotechnology/Panel-Activities/Nanotechnology-Definitions/Nanotechnology-Panel-Presents-at-Society-of-Toxicology.pdf.

Dekkers, S., Krystek, P., Peters, R.J.B., Lankveld, D.P.K., Bokkers, B.G.H., van Hoeven-Arentzen, P.H., Bouwmeester, H., Oomen, A.G., 2011. Presence and risks of nanosilica in food products. Nanotoxicology 5 (3), 393–405.

European Commission (DG SANCO), 2013. Assessment of nanomaterials in food, health and consumer products. In: Workshop on the Second Regulatory Review on Nanomaterials. DG Health and Consumers, Brussels.

ECHA, 2012. Updated Guidance on Information Requirements and Chemical Safety Assessment for Nanomaterials from. http://echa.europa.eu/en/view-article/-/journal_content/3df5b7b9-a36d-4e74-811b-3aeee23366f8.

ECHA, 2013. Guidance on Information Requirements; Guidance on Regulation (EU) No 528/2012 Concerning the Making Available on the Market and Use of Biocidal Products (BPR). Helsinki from. http://www.echa.europa.eu/documents/10162/15623299/biocides_guidance_information_requirements_en.pdf.

EFSA, 2012. Annual Report of the EFSA Scientific Network of Risk Assessment of Nanotechnologies in Food and Feed for 2012 from. http://www.efsa.europa.eu/en/search/doc/362e.pdf.

EFSA Panel on Food Additives and Nutrient Sources added to Food, 2011. Scientific Opinion on Re-evaluation of Calcium Carbonate (E 170) as a Food Additive from. http://www.efsa.europa.eu/en/efsajournal/doc/2318.pdf.

EFSA Panel on Food Contact Materials, E., Flavourings and Processing Aids (CEF), 2014. Statement on the safety assessment of the substance silicon dioxide, silanated, FCM Substance No 87 for use in food contact materials. EFSA J. 2014. Parma EFSA 12, 3712. http://www.efsa.europa.eu/en/efsajournal/doc/3712.pdf.

EFSA Scientific Committee, 2011. Guidance on the Risk Assessment of the Application of Nanoscience and Nanotechnologies in the Food and Feed Chain from. http://www.efsa.europa.eu/en/efsajournal/doc/2140.pdf.

Environment Canada, 2014. Assessment of Nanomaterials under the New Substances Notification Regulations (Chemicals and Polymers). Ottawa from. https://www.ec.gc.ca/subsnouvelles-newsubs/default.asp?lang=En&n=53527-F9D-1.

European Commission, 2009. Commission Regulation (EC) No 450/2009 of 29 May 2009 on active and intelligent materials and articles intended to come into contact with food. Off. J. Eur. Union L135, 3–11.

European Commission, 2010. Commission Regulation (EC) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. Off. J. Eur. Union L80, 19–27.

European Commission, 2011. Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. Off. J. Eur. Union L328, 20–29.

European Commission, 2012. Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee: Second Regulatory Review on Nanomaterials from. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2012:0572:FIN:en:PDF.

European Commission, 2013. Proposal for a Regulation of the European Parliament and of the Council on Novel Foods. COM(2013) 894 final, from. http://ec.europa.eu/food/food/biotechnology/novelfood/documents/novel-cloning_com2013-894_final_en.pdf.

European Parliament, 2009. European Parliament Resolution of 24 April 2009 on Regulatory Aspects of Nanomaterials. Brussels and Strassbourg from. http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P6-TA-2009-0328+0+DOC+XML+V0//EN.

European Parliament, 2014. ENVI Relevant Legislative Areas of the EU – US Trade and Investment Partnership Negotiations (TTIP). European Parliament, Brussels from. http://www.europarl.europa.eu/RegData/etudes/STUD/2014/536293/IPOL_STU(2014)536293_EN.pdf.

European Parliament and Council, 1997. Regulation (EC) No. 258/97 of the European

Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. Off. J. Eur. Commun. Eur. Union L43, 1–6.
European Parliament and Council, 2002a. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the member states relating to food supplements. Off. J. Eur. Union L 183, 7.
European Parliament and Council, 2002b. Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Off. J. Eur. Union. E. Union Publ. Office Eur. Union L 31, 1–24.
European Parliament and Council, 2003. Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. Off. J. Eur. Union L268, 29–43.
European Parliament and Council, 2006. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the REGISTRATION, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. Off. J. Eur. Union L396 (1), 1–849.
European Parliament and Council, 2008a. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures. Off. J. Eur. Union L353, 1–1355.
European Parliament and Council, 2008b. Regulation (EC) No 1332/2008 of the European Parliament and of the Council of 16 December 2008 on food enzymes. Off. J. Eur. Union L354, 7–15.
European Parliament and Council, 2008c. Regulation (EC) No 1331/2008 of the European Parliament and of the Council of 16 December 2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings. Off. J. Eur. Union 354, 16–33.
European Parliament and Council, 2008d. Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. Off. J. Eur. Union L133, 1–65.
European Parliament and Council, 2008e. Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods. Off. J. Eur. Union L354, 34–50.
European Parliament and Council, 2009a. Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. Off. J. Eur. Union. Luxemb. Publ. Office Eur. Union L 309, 1–50.
European Parliament and Council, 2009b. Regulation (EC) No 767/2009 of the European Parliament and of the Council of 13 July 2009 on the placing on the market and use of feed. Off. J. Eur. Union L 229, 1–28.
European Parliament and Council, 2011. Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers. Off. J. Eur. Union L 304, 18–63.
European Parliament and Council, 2012. Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products. Off. J. Eur. Union L 167, 1–123.
Falkner, R., Jaspers, N., 2012. Regulating nanotechnologies: risk, uncertainty and the global governance gap. Glob. Environ. Polit. 12 (1), 30–55.
FAO/WHO, 2013. State of the Art on the Initiatives and Activities Relevant to Risk Assessment and Risk Management of Nanotechnologies in the Food and Agriculture Sectors. FAO/WHO from. http://www.fao.org/docrep/018/i3281e/i3281e.pdf.
FSCJ, 2010. A Basic Survey Report on Safety Assessment Information on the Use of Nanotechnology in the Food Sector, Conducted by the Toray Research Certer as 'A comprehensive study for ensuring food safety under the Cabinet Office Food Safety Commission (FY 2009)' for the Food Safety Commission of Japan from. http://www.fsc.go.jp/english/survey_programs/use_nanotechnology.pdf.
Gebel, T., Foth, H., Damm, G., Freyberger, A., Kramer, P.-J., Lilienblum, W., Röhl, C., Schupp, T., Weiss, C., Wollin, K.-M., Hengstler, J., 2014. Manufactured nanomaterials: categorization and approaches to hazard assessment. Arch. Toxicol. 88 (12), 2191–2211.
Gogos, A., Knauer, K., Bucheli, T.D., 2012. Nanomaterials in plant protection and fertilization: current state, foreseen applications, and research priorities. J. Agric. Food Chem. 60 (39), 9781–9792.
Guillermo Foladori, N.I., 2007. Nanotechnologies in Latin America. R. M. Rosa-Luxemburg-Stiftung, 81. Karl Dietz Verlag Berlin GmbH, 2008.
Hamburg, M.A., 2012. Science and regulation. FDA's approach to regulation of products of nanotechnology. Science 336 (6079), 299–300.
Health Canada, 2011. Policy Statement on Health Canada's Working Definition for Nanomaterial from. http://www.hc-sc.gc.ca/sr-sr/pubs/nano/pol-eng.php.
Höck, J., Hofmann, H., Krug, H., Lorenz, C., Limbach, L., Nowack, B., Riediker, M., Schirmer, K., Som, C., Stark, W., Studer, C., von Götz, N., Wengert, S., W, P., 2008. Precautionary Matrix for Synthetic Nanomaterials Bern from. http://www.bag.admin.ch/themen/chemikalien/00228/00510/05626/index.html?lang=en.
Intertek, 2014. Turkey Classification, Labeling, and Notification Regulation Services. Retrieved 03/12/2014. from. http://www.intertek.com/regulatory/turkey-clp/.
ISO, 2013. External Liaison Report Asia Nano Forum to ISO/TC 229.
Jayanthi, A.P., Beumer, K., Bhattacharya, S., 2012. Nanotechnology: 'Risk Governance' in India. Econ. 34 Political Wkly. XLVII (4).
Kah, M., Hofmann, T., 2014. Nanopesticide research: current trends and future priorities. Environ. Int. 63 (0), 224–235.
Kah, M., Beulke, S., Tiede, K., Hofmann, T., 2012. Nanopesticides: state of knowledge, environmental fate, and exposure modeling. Crit. Rev. Environ. Sci. Technol. 43 (16), 1823–1867.
KFDA, 2013. Ensuring Food Safety from. http://www.kfda.go.kr/eng/index.do?nMenuCode=61.
Landsiedel, R., Fabian, E., Ma-Hock, L., Wohlleben, W., Wiench, K., Oesch, F., van Ravenzwaay, B., 2012. Toxico-/biokinetics of nanomaterials. Arch. Toxicol. 86 (7), 1021–1060.
Leskey, M., Cele, S.S.R., Coville, Neil J., 2009. Nanoscience and Nanotechnology in South Africa (July/August 2009).
Linsinger, T.P.J., Roebben, G., Gilliland, D., Calzolai, L., Rossi, F., Gibson, N., Klein, C., 2012. Requirements on Measurements for the Implementation of the European Commission Definition of the Term "nanomaterial". European Commission Joint Research Centre, Luxembourg from. http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/26399/2/irmm_nanomaterials%20%28online%29.pdf.
Mantovani, E., Porcari, A., Morrison, M.D., Geertsma, R.E., 2012. Developments in Nanotechnologies Regulation and Standards 2021-Report of the Observatory Nano. Brussels, Observatory Nano from. http://www.observatorynano.eu/project/filesystem/files/ObservatoryNano_Nanotechnologies_RegulationAndStandards_2012.pdf.
Morris, V.J., 2011. Emerging roles of engineered nanomaterials in the food industry. Trends Biotechnol. 29 (10), 509–516.
NanoMalaysia, N.N.D., 2013. Towards a Malaysian Regulatory Framework, Asia Nano Forum, Nanotech 2013, Japan 31st January (power point presentation) ", from. http://www.google.com/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=1&ved=0CB8QFjAA&url=http%3A%2F%2Firannano.org%2Ffilereader.php%3Fp1%3Dmain_47e24b47020343c728d44a00681a79b5.pdf%26p2%3Dstatic_page%26p3%3D22%26p4%3D1&ei=QbAFVNT8PMriatPlgsAF&usg=AFQjCNFA69SOMsrseyu1NemcbZYc8Jxe1Q&sig2=9UloR7UCc4DmKnrRw_hDUw&bvm=bv.74115972,d.d2s.
NICNAS, 2013. NICNAS Handbook for Notifiers – Guide for Importers and Manufacturers of Industrial Chemicals in Australia CANBERRA Australian Capital Territory 2600 from. http://www.nicnas.gov.au/regulation-and-compliance/nicnas-handbook.
OECD, 2013a. Current Developments/Activities on the Safety of Manufactured Nanomaterials; Series on the Safety of Manufactured Nanomaterials No. 37. Paris from. http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2013. http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2013)2&doclanguage=en.
OECD, 2013b. Regulatory Frameworks for Nanotechnology in Foods and Medical Products. Summary Results of a Survey Activity. Paris from. http://search.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=DSTI/STP/NANO(2012)22/FINAL&docLanguage=En.
Office of Agricultural Affairs of the USDA, 2009. Russian Federation – Food and Agricultural Import Regulations and Standards – FAIRS Country Report. Moscow from. http://gain.fas.usda.gov/Recent%20GAIN%20Publications/Food%20and%20Agricultural%20Import%20Regulations%20and%20Standards%20-%20Narrative_Moscow_Russian%20Federation_11.08.2009.pdf.
Parisi, C., M, V., Rodríguez-Cerezo, E., 2014. In: . Proceedings of a Workshop on "Nanotechnology for the Agricultural Sector: from Research to the Field". Publications Office of the European Union, Luxembourg, 2014, from. http://publications.jrc.ec.europa.eu/repository/bitstream/111111111/31846/1/ipts%20jrc%2089736%20(online)%20%20final.pdf.
Park, Y., 2012. Nano-regulation in China, Japan, Korea, USA and EU from. http://www.egg2012.de/tl_files/pdf/Paper/EGG2012_C6_1_Park_presentation_slides.pdf.
Peters, R.J.B., van Bemmel, G., Herrera-Rivera, Z., Helsper, H.P.F.G., Marvin, H.J.P., Weigel, S., Tromp, P.C., Oomen, A.G., Rietveld, A.G., Bouwmeester, H., 2014. Characterization of titanium dioxide nanoparticles in food products: analytical methods to define nanoparticles. J. Agric. Food Chem. 62 (27), 6285–6293.
Rauscher, H., Roebben, G., Amenta, V., Boix Sanfeliu, A., Calzolai, L., Emons, H., Gaillard, C., Gibson, N., Linsinger, T., Mech, A., Quiros Pesudo, L., Rasmussen, K., Riego Sintes, J., Sokull-Klüttgen, B., Stamm, H., 2014. Towards a Review of the EC Recommendation for a Definition of the Term "nanomaterial"; Part 1: Compilation of Information Concerning the Experience with the Definition. European Commission Joint Research Centre from. https://ec.europa.eu/jrc/sites/default/files/lbna26567enn.pdf.
RIKILT and JRC, 2014. Inventory of Nanotechnology Applications in the Agricultural, Feed and Food Sector. Parma, RIKILT. European Commission Joint Research Centre from. http://www.efsa.europa.eu/en/supporting/doc/621e.pdf.
RIVM, 2012. Interpretation and Implications of the European Commission Recommendation on the Definition of Nanomaterial. Bilthoven from. http://www.rivm.nl/dsresource?objectid=rivmp:181801&type=org&disposition=inline.
Roebben, G., Rauscher, H., Amenta, V., Aschberger, K., Boix Sanfeliu, A., Calzolai, L., Emons, H., Gaillard, C., Gibson, N., Holzwarth, U., Linsinger, T., Rasmussen, K., Riego Sintes, J., Sokull-Klüttgen, B., Stamm, H., 2014. Towards a Review of the EC Recommendation for a Definition of the Term "nanomaterial"; Part 2: Assessment of Collected Information Concerning the Experience with the Definition.

European Commission Joint Research Centre from. https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/towards-review-ec-recommendation-definition-term-nanomaterial-part-2-assessment-collected.

SCENIHR, 2007. Opinion in the Appropriateness of the Risk Assessment Methodology in Accordance with the Technical Guidance Documents for New and Existing Substances for Assessing the Risks of Nanomaterials. Scientific Committee on Emerging and Newly Identified Health Risks, Brussels from. http://ec.europa.eu/health/archive/ph_risk/committees/04_scenihr/docs/scenihr_o_010.pdf.

SCENIHR, 2009. Risk Assessment of Products of Nanotechnologies. Scientific Committee on Emerging and Newly Identified Health Risks, Brussels from. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf.

Schweizerischer Bundesrat, 2010. Verordnung über das Inverkehrbringen von Pflanzenschutzmitteln (Pflanzenschutzmittelverordnung, PSMV), 916.161. F. O. o. P. Health.

SECO, S. S. f. E. A, 2012. Safety Data Sheet (SDS): Guidelines for Synthetic Nanomaterials.

Tyler, L.C., 2012. FDA Issues Draft Guidance on Use of Nanotechnology in Food and Food Packaging. Nanotechnol. Law Bus. 9, 149–155.

US-EPA, 2011. Regulating Pesticides that Use Nanotechnology. Retrieved 12/12/2013, 2013, from. http://www.epa.gov/pesticides/regulating/nanotechnology.html.

US-EPA, 2012. Nanomaterial Case Study: Nanoscale Silver in Disinfectant Spray (Final Report). Washington DC from. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=226723.

US-EPA, 2015. Chemical Substances when Manufactured or Processed as Nanoscale Materials: TSCA Reporting and Recordkeeping Requirements. Washington DC from. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2010-0572-0001.

US-FDA, 2014a. Guidance for Industry – Considering whether an FDA-regulated Product Involves the Application of Nanotechnology, 20993. US-FDA, Silver Spring, MD. from. http://www.fda.gov/regulatoryinformation/guidances/ucm257698.htm.

US-FDA, 2014b. Guidance for Industry on Use of Nanomaterials in Food for Animals. Draft Guidance, 20852. US-FDA, Rockville MD.

van der Meulen, B., Bremmers, H., Purnhagen, K., Gupta, N., Bouwmeester, H., Geyer, L.L., 2014. Governing Nano Foods: Principles-based Responsive Regulation: EFFoST Critical Reviews# 3. Academic Press.

van Kesteren, P.C.E., Cubadda, F., Bouwmeester, H., van Eijkeren, J.C.H., Dekkers, S., de Jong, W.H., Oomen, A.G., 2014. Novel insights into the risk assessment of the nanomaterial synthetic amorphous silica, additive E551, in food. Nanotoxicology 0 (0), 1–10.

Weir, A., Westerhoff, P., Fabricius, L., Hristovski, K., von Goetz, N., 2012. Titanium dioxide nanoparticles in food and personal care products. Environ. Sci. Technol. 46 (4), 2242–2250.

Wijnhoven, S.W.P., Peijnenburg, W.J.G.M., Herberts, C.A., Hagens, W.I., Oomen, A.G., Heugens, E.H.W., Roszek, B., Bisschops, J., Gosens, I., Van De Meent, D., Dekkers, S., De Jong, W.H., Van Zijverden, M., Sips, A.J.A.M., Geertsma, R.E., 2009. Nano-silver – a review of available data and knowledge gaps in human and environmental risk assessment. Nanotoxicology 3 (2), 109–138.