EU Regulations and Nanotechnology Innovation

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Abstract The first EU Regulation that mentioned nanomaterials was published in 2008 (EC) No 1333/2008) on Food Additives), and since then several Regulations have been adopted that requires specific information for nanomaterials that are put on the EU market. In 2011 the European Commission adopted a recommendation for a nanomaterial definition (1–100 nm), that has been implemented e.g. in the Biocidal Product Regulation. The main EU chemical Regulation, REACH, was updated in 2018 with modification of several of its Annexes to require information on nanoforms of chemical substances. Many regulations in the food area have nano-specific provisions as well as in cosmetics and medical devices. Several EU Member States, France, Belgium, Denmark and Sweden require specific registration of nanomaterials that are put on their national markets. Responsible research and innovation and safe(r) by design concepts are being developed to bring nanotechnology products to the market by optimising resources.

Keywords Nanotechnology · Regulation · Legislation · EU · REACH · Nanoform · Nanomaterial · Safe(r) by design

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J. R. Lead et al. (eds.), *Nanotoxicology in Humans and the Environment*, Molecular and Integrative Toxicology, https://doi.org/10.1007/978-3-030-79808-6_8

EU Regulations: An Introduction

Laws within the European Union are based on core principles of human dignity and human rights, freedom, democracy, equality and the rule of law, enshrined in the Treaty of the European Union (TEU) and in the Treaty on the Functioning of the European Union (TFEU) (European Union 2020). The TEU was first signed in 1992 in Maastricht, thus often still referred to as the Maastricht Treaty and the last amendment was agreed in Lisbon in 2007, when the TFEU was also signed. Both were unanimously agreed, at the time, by all the Members States of the EU and they set out the four freedoms which are movement for goods, services, capital and people. The core principles and the four freedoms in the EU are implemented through legislative instruments. There are three main legally binding instruments in the EU; Regulations, Directives and Decisions, as presented in article 288 of the TFEU.

EU Regulations are directly applicable in all EU Member States whereas **Directives** have to be implemented into national laws to become legally binding. Finally, a **Decision** is directed to an individual or a company. An example of a Decision would be where the European Commission would directly intervene to insist that a specific company or an individual perform a specific measure. Such specific measures could include instruction to withdraw a product from the market.

As described in the TEU and TFEU EU law such as Regulations, Directives and Decisions takes precedence over national laws. A Directive can be considered to set out an aim of what should be achieved, whereas the practical route to achieve this aim can be performed differently in Member States. An adopted Directive therefore also sets out deadlines when Member States should have implemented the Directive in its national regulations.

The EU has slowly transitioned to creating more and more legislation in the form of Regulations. The advantage of Regulations are that they are applicable throughout the union and thus allow for a harmonised system, more easily managed by industries as well as by regulators and thus facilitating an understanding of the regulatory framework in EU. Nowadays, the EU approves on average 80 directives, 1200 regulations and 700 decisions per year (Toshkov 2014).

The European Commission, which is the EU Executive body, shape the EU's overall strategy, proposes new EU laws and policies, monitors their implementation and manages the EU budget. The European Commission is the only EU body that has the authority to initiate a legislative process of creating a new Regulation, a Directive or a Decisions. A legislative proposal from the EC can be vetoed or amended during the legislative process by the European Council or by the European Parliament. The European Council is made of governmental representatives of all EU Member States, and the European Parliament is composed of parliamentarians elected every five year in European wide national elections (see Fig. 1 for the EU institutional triangle). The process put in place by the EC to present a legislative proposal follows a process that usually starts with the publication of a White Paper. A White Papers contain proposals for European Union action in a specific area. The purpose of a White Paper is to launch a debate with the public, stakeholders, the European Parliament and the Council in order to arrive at a political consensus. A

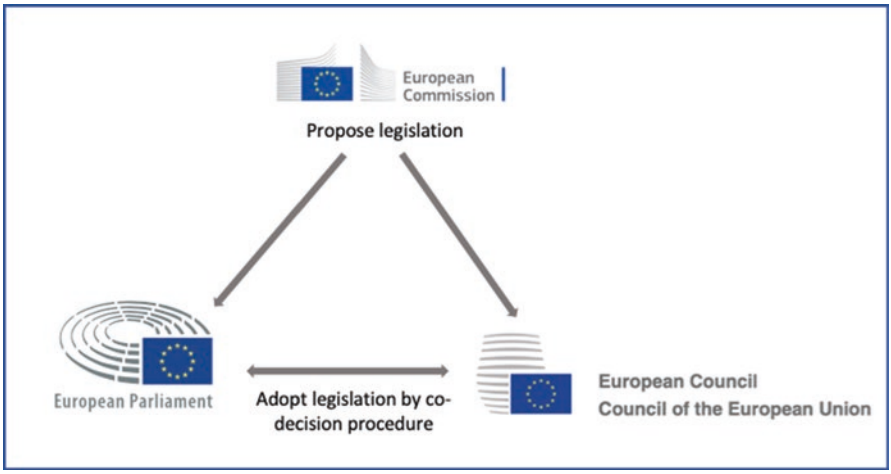

Fig. 1 The EU institutional triangle

White Paper can outline several types of possible issues that the EU should tackle, e.g. with regulatory actions, that could be developed over a longer timeframe, usually 5–10 years. Members States are consulted about the White paper, and comments are invited from the public which includes interested stakeholders such as industries, as well as individual citizens. The White Paper often outlines indicative time frames for when the EC is planning to present a legislative proposal to the European Council and the European Parliament. Before a legislative proposal is presented, a substantive amount of preparatory work takes place, including the EC asking for reports to be drafted by e.g. EU agencies in the sector in question, or by tendering out the drafting to consultants. The EC also has to prepare an impact assessment evaluating different scenarios that could arise depending on various possible regulatory measures.

Once the regulatory proposal is finalised by the EC, it is being officially presented to the European Council (2020) and to the European Parliament (2020), where discussions will then take place in relevant Committees. After amendments and agreement, the proposal, is adopted and published as a new legislative act in the Official Journal of the EU (2020). Once the legislation is published, it usually enters into force 20 days after publication as it is then an official EU regulatory act that must be complied with.

Introduction to the EU REACH Legislation

The main legislation in the EU for chemicals is the REACH Regulation, published in 2006. The acronym REACH stands for Registration, Evaluation, Authorisation and Restriction of Chemicals (EC no 1970/2006) (Juncker 2018). The Regulation is

made up of 141 Articles followed by 17 Annexes and applies to manufacturing and import of chemical substances, mixtures and articles as well as certain substances used research and development purposes. REACH provides a definition of a substance in Article 3 as 'a chemical element and its compounds in the natural state or obtained by any manufacturing process'.

The Regulation was negotiated for many years between the European Commission, the Council and the Parliament and was adopted following the procedure outlined above. REACH places the burden on industry to provide dossiers with information on the substances used on the EU market under the 'no data – no market' notion. The Regulation is managed by the European Chemicals Agency (ECHA) based in Helsinki, Finland (European Commission 2020a).

The REACH Regulation is closely connected to another Regulation from 2008 on Classification, Labelling and Packaging of Substances and Mixtures EC no 1272/20089 abbreviated as CLP (Pöttering and Le Maire 2008). The CLP Regulation classifies substances as hazardous when they meet classification criteria in CLP. Hazards of a substance are identified by assigning a certain hazard class and category. The hazard classes in CLP cover physical, health, environmental and additional hazards. Once a hazard is classified it consequently needs specific labelling and packaging. The CLP provides requirements to apply classification specifications for substances and how hazard labels should be presented on labels and the packaging. The CLP incorporates the Global Harmonised System by the UN into European legislation which harmonises hazard classification of substances.

Figure 2 provides an overview of EU regulations dealing with nanomaterials, in one way or another, where REACH and CLP are horizontal regulations dealing with chemicals in general, and where vertical regulations are dealing with specific areas or sectors.

The requirement to register a substance, mixture or an article under REACH and provide a dossier with information is based on annual tonnage produced in, or imported into, the EU market. The general rule is that all substances with an annual production over 1 tonne (1000 kg) should be registered. The tonnages are based on a potential exposure, where larger production volumes would consequently mean a

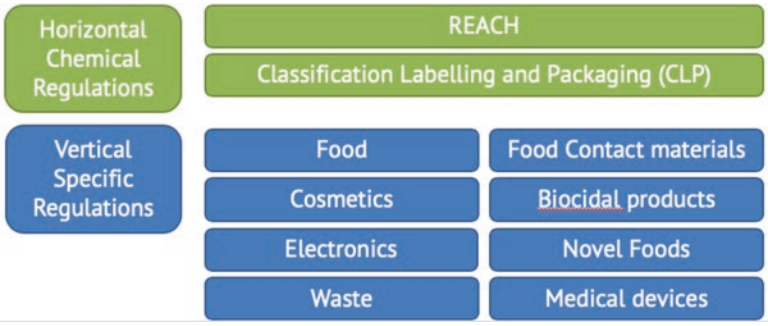

Fig. 2 Overview of EU Regulations dealing with nanomaterials. Each regulation is detailed further in the chapter

larger exposure thus with higher tonnage, more information needs be provided in the dossier. There are 4 tonnage bands; above 1 tonne, 10 tonnes, 100 tonnes and 1000 tonnes. Above 10 tonnes, the dossier should be also accompanied by a chemical safety report (CSR) following Annex I of the Regulation.

The requirement on when to register a substance was staggered over three phases to enable applicants to manage the transition to such a significant new legislative framework. The initial deadline was 2010 for substances over the 1000 tonnes annual production threshold, followed by 2013 for above 100 tonnes and finally May 2018 was the last registration deadline, for substances over 1 tonne.

In addition to substances, REACH also has provisions for mixtures (compositions of two or more substances) as well as articles (i.e. an object which during production is given a special shape, surface or design which determines its function to a greater degree than does its chemical composition).

The information to be provided in a dossier for a substance is provided in the Annexes VII (above 1 tonne) to × (above 1000 tonnes) of the Regulation. Information requirements include information on physico-chemical properties (e.g. melting point, water solubility etc) and toxicological information (e.g. skin irritation/corrosion, acute toxicity etc) and ecotoxicological information (e.g. aquatic toxicity, biodegradability etc). For the higher tonnage bands, more comprehensive information is required, sometimes involving testing on animals.

EU Regulatory History for Nanomaterials

Since publication of the 2004 UK Royal Society of Science (The Royal Society 2004) report, there has been an ongoing discussion among policy makers, including EU Member States, and stakeholders how best to ensure that the specific characteristics of nanomaterials are appropriately covered within EU legislation. This discussion not only focused on how to regulate nanomaterials, but also how do define a nanomaterial.

A Recommended EU Definition of Nanomaterial

Following discussions with stakeholders, policy makers and a public consultation, the European Commission published a Commission Recommendation in October 2011 on the definition of nanomaterial (2011/696/EU) (Potocnik 2011). As it is a recommendation (and not a Regulation), it is not legally binding and has to be transferred into a Regulation (or a Directive) to become legally applicable. However, a recommendation from the European Commission creates a strong message and can be referred to in court. The EC definition is also often referenced in activities outside the EU, possibly due to the comprehensive nature of EU regulatory frameworks

that are often regarded internationally to set the minimum requirements for countries outside EU to trade with EU.

The definition provides guidance how the regulator (i.e. the European Commission) intends to manage the complex issue of how to define nanomaterials in a legally binding manner. The 2011 recommendation states that a 'nanomaterial means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm.' It further states that 'By derogation […] fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nano materials.'

For the purpose of the recommendation, it also clarifies that 'particle' means a minute piece of matter with defined physical boundaries; 'agglomerate' means a collection of weakly bound particles or aggregates where the resulting external surface area is similar to the sum of the surface areas of the individual components and 'aggregate' means a particle comprising of strongly bound or fused particles.'

What is interesting to note in the recommendation is that it is solely based on size, as this is a property that can be measured, and thus should the need arise, hold up in court. It is also noteworthy that it also includes natural materials containing particles (Rauscher et al. 2019). The argumentation put forward by the European Commission for this inclusion is that a nanomaterial is based on size, and there could be instances where it could be appropriate to refer and describe natural materials as nanomaterials.

In practice, the accurate measurement of nanomaterial size is often challenging and depends on the size of the nanomaterial to be measured and the method applied, as well as on other aspects (e.g. matrix, elemental composition etc) (Miernicki et al. 2019).

The REACH Regulation and Nanomaterials

The REACH Regulation covers chemical substances (with some agreed exemptions), and consequently also nanomaterials. This was first agreed among EU Members States in 2008 communication from a meeting of CARACAL, a decision-making group of the EU Member States Competent Authorise for REACH (2008) and CLP (European Commission 2020a). However, as industries were registering their substances, the REACH Regulation did not specifically mention nanomaterials, nor place a requirement to provide detailed information on size or other properties. Therefore there was a concern that authorities, including ECHA, would not receive enough information to understand if a substance could have a nanoform, and if the properties of the nanoform would be different from the bulk or soluble form of the registered substance, and if this would impact the safety of the substance.

The European Commission have over the years performed two regulatory reviews on nanomaterials in EU legislation. The first one was performed in 2008 (European

Commission 2008) and the latest one was performed in 2012, where it again was reinforced that the European Commission considers the REACH Regulation to be an appropriate legal act to regulate nanomaterials (European Commission 2012). The second regulatory review stated that '…nanomaterials are similar to normal chemicals/substances in that some may be toxic and some may not. Possible risks are related to specific nanomaterials and specific uses. Therefore, nanomaterials require a risk assessment, which should be performed on a case-by-case basis, using pertinent information. Current risk assessment methods are applicable, even if work on particular aspects of risk assessment is still required.'

The perceived lack of information on nanomaterials in REACH substance dossiers initiated a long, and sometimes heated, discussion between the European Commission, Members States and stakeholders (including industry and civil society organisation) how to best ensure information on nanomaterials are to be provided to authorities. The discussions were initiated after the second regulatory review and continued until the REACH Annexes were adopted in 2018.

After several assessments (European Commission 2019) the European Commission, as the EU policy maker came to the conclusion that nanomaterials are substances and therefore already fall under REACH, that a nanospecific Regulation was not required, and that a modification of the REACH Annexes would be sufficient to request information on nanomaterials.

Amendment of REACH Annexes to Include Nanomaterials and Nanoforms

After many years of internal deliberations and discussions with Member States and stakeholders, the European Commission announced its proposal for a revision of several Annexes of the REACH Regulation in the Autumn of 2017. The proposal, in the form of a European Commission Regulation, was discussed and voted upon in the REACH Committee composed of representatives from the EU Members States. The European Commission then adopted the Regulation and it was published in December 2018 as Commission Regulation EU) 2018/1881 (KEMI 2020). This Regulation is in itself only composed of 3 Articles, but has an Annex setting out changes to 9 (Annex I, III, VI. VII, VIII, IX, X, XI and VII) of the 17 REACH Annexes.

The most profound change is that REACH Annex VI now includes a legally binding definition of nanomaterial, referred to as nanoform in the Annex, that, in turn, is based on the 2011 European Commission recommendation. The term used in Annex VI is not nanomaterial, but nanoform, as a nanomaterial can be considered as another form of a substance. Thus, a substance (as defined in REACH) can have several forms, including nanoforms. Further, an important aspect is that under REACH the concept of 'set of similar nanoforms' can be applied during the registration process. By using sets, a registrant can, for instance, provide a justification

that information from one nanoform can be applied to a wider group of similar nanoforms, thus reducing the amount of information to be provided. How sets will be used in practice will be interesting to find out once applicants are updating, revising or applying for registration under REACH.

Another notable modification of the REACH Annexes is that physicochemical description of nanoforms now has to include information on number-based particle size distribution, specific surface area by volume, morphology and surface functionalisation. The REACH Annexes related to information requirements for tonnages are also modified to include specific considerations, test methods and modifications for when nanomaterials are part of the dossier (Clausen and Hansen 2018).

To facilitate the registration of substances according to the REACH requirements, ECHA has published many guidance documents. As of summer 2019, ECHA is in the process of finalising a guidance document that describes the information to be provided to describe and characterise a nanoform. A draft of the 'Appendix for nanoforms applicable to the Guidance on Registration and substance identification' from June 2019 is available (European Chemicals Agency 2019). ECHA also has specific Annexes to their main guidance document on information requirements and chemical safety testing related to nanomaterials (ECHA 2020).

Vertical Regulations Within the European Union

Although REACH is a Regulation that, in principle, covers almost all chemical substances, there are several sector specific Regulations that can take precedence of REACH. These Regulations are prominent in food, cosmetics, biocides, medical devices, and other areas. The nanospecific aspects of EU sector specific Regulations are discussed below.

Nanomaterials Within Cosmetics

The EU regulates cosmetics in a Regulation from 2009 (EC No 1223/2009 on cosmetic products) (Buzek and Ask 2009) that establishes rules to be complied with by any cosmetic product made available on the EU market. This Regulation was the first EU Regulation that provided a definition of nanomaterials. Article 2(k) defines a 'nanomaterial' as an 'insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm'. This definition is, in many ways, different from the definition used in REACH and in the Biocidal Regulations, as well as the one used in the food area for engineered nanomaterials. The cosmetic definition uses the same size range (1–100 nm) as REACH and in Biocides, but also requires the nanomaterial to be intentionally manufactured and importantly also requires insolubility and biopersistence as its requirements. As a consequence, a substance that is used in several

sectors can be defined as a nanomaterial in one regulation, but not in another regulation. This can of course cause administrative burdens for producers who need to be aware where their product will be used.

To help industries submit a dossier for a nanomaterial to be used in cosmetics, the European Commission Scientific Committee on Consumer Safety (SCCS) published in 2012 a Guidance on the Safety Assessment of Nanomaterials in Cosmetics' (Scientific Committee on Consumer Safety SCCS 2012). This guidance provides information on what an applicant should provide in order for fulfil the requirements in the Regulation and for the SCCS to perform a risk assessment and provide an opinion. As of autumn 2019, the SCCS is in final phases of updating its guidance.

Nanomaterials Within Food Production

Within the EU, there are many Regulations that cover the food sector, ranging from Regulations on plant protection products, genetically modified organisms, hygiene aspects and specific Regulations on e.g. food additives, flavourings, enzymes, novel foods, as well as on food contact materials (i.e. food packaging) and labelling of foods. Many of the food Regulations have been revised to include specifics related to nanomaterials.

In the EU, there is a general food law from 2002 (EC) No 178/2002 (Cox and Piqué i Camps 2002) that, among other things, defines in general terms food as 'any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans.' The general food law also established the European Food Safety Authority (EFSA, based in Italy) to provide scientific opinions on risk assessment issues related to food.

EFSA has published several opinions related to nanomaterials, and in 2018 they published a new 'Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health' (Hardy et al. 2018). The EFSA nanomaterials guidance covers nanospecific aspects and considerations of all types of dossiers that EFSA covers. In this regard, the EFSA guidance focus on aspects that should be considered in addition to the normal guidance document EFSA publishes. E.g. a nanomaterial used as a food contact material should consider the nanospecific guidance in addition to the normal food contact material guidance.

Food Information and Labelling

Labelling of foods and its packaging is regulated in the Food Information to Consumers Regulation from 2011, Regulation (EU) No 1169/2011 on the provision on food information to consumers (Buzek and Dowgielewicz 2011) With respect to nanomaterials this Regulation uses the definition of engineered nanomaterials as found in the Novel Food Regulation (EU) 2015/2283 (Schulz and Schmit 2015). For

the list of ingredients to be used on the food label, the Regulation states that 'all ingredients present in the form of engineered nanomaterials shall be clearly indicated in the list of ingredients. The names of such ingredients shall be followed by the word 'nano' in brackets'. Currently, there are no known labelled nano food products on the European market.

Novel Foods

Novel Food is defined as food that had not been consumed to a significant degree by humans in the EU before 15 May 1997, when the first Regulation on novel food came into force. The current Regulation on novel foods (EU 2015/2283) provides a definition of engineered nanomaterials that is different from the 2011 EC recommendation (Schulz and Schmit 2015). Article 3 in this Regulation specifically sets out that food 'consisting of engineered nanomaterials is to be defined as novel food, and this is also applicable to vitamins and minerals if they 'they contain or consist of engineered nanomaterials' (Schulz and Schmit 2015).

The same Article provides a regulatory definition of 'engineered nanomaterial' to mean 'any intentionally produced material that has one or more dimensions of the order of 100 nm or less or that is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic of the nanoscale (Schulz and Schmit 2015). Properties that are characteristic of the nanoscale include: (i) those related to the large specific surface area of the materials considered; and/or (ii) specific physico-chemical properties that are different from those of the non-nanoform of the same material.'

As can be noted, the regulatory definition in the novel foods Regulation refers to engineered nanomaterials, and there are several differences compared to the 2011 recommendation as well as to the regulatory definition in the 2018 adopted REACH definition of nanomaterial.

Notably, the novel food definition talks about one or more dimensions 'in the order of 100 nm' which is imprecise compared with the 1–100 nm in REACH. Furthermore, an engineered nanomaterial needs to be intentionally produced, so natural nanomaterials are outside this definition. This is logical, as many constituents within foods are naturally in the nano size range and are thus excluded from the engineered nanomaterial definition.

The novel food definition is unfortunately also imprecise in that it references aspects that are difficult to objectively measure and define, including materials that 'retain properties that are characteristic of the nanoscale'. These characteristics are difficult to describe and agree upon in a regulatory precise manner.

Food Additives

The food additives Regulation from 2008 ((EC) No 1331/2008) (Pottering and Le Maire 2008) is the first EU legislation that specifically mentions nanotechnology, and states in Article 12 concerning changes in the production process of a food additive that '…or there is a change in particle size, for example through the use of nanotechnology…'. This means that in practice that an applicant submitting a dossier for a food additive authorisation needs to provide information on these changes in particle size. The EFSA guidance document for nanomaterials should therefore be followed by food additive applicants.

Food Contact Materials

There is a Regulation from 2004 in EU (EC No 1935/2004 on materials and articles intended to come into contact with food (Borrell Fontelles and Nicolai 2004) that provides an overall framework for all materials intended to come into contact with food. As this Regulation was adopted before the main nano discussions took place, there is no specific mention of nanomaterials or nanotechnology within the text. However, as it is a framework Regulation, it applies to all types of food contact materials, and therefore also nanomaterials are covered under this Regulation, even if they are not specifically mentioned.

In 2011, the Commission published a Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food (Barroso 2011) that specifically includes provisions for nanomaterials. Article 9 states that 'Substances in nanoform shall only be used if explicitly authorised and mentioned in the specifications in Annex I.' Since 2011, several food contact material substances in nanoform have been authorised, based on performed EFSA opinions, to be used in plastic packaging. Such materials include e.g. carbon black, titanium nitride and silicon dioxide. There is no definition of nanomaterials in this Regulation, rather the authorised substances in Annex I have specifications of the substance in question that needs to be fulfilled, e.g. that an authorised material needs to be within a specific size range.

Active and Intelligent Food Contact Materials

The Regulation on active and intelligent food contact materials (EC) No 450/2009 (Vassiliou 2009) apply to food contact materials that have been manufactured to have specific properties to inform about the food, or to release or absorb substances from the food e.g. to increase shelf life. With regard to nanomaterials, as it also an early Regulation, it is rather vague and refers to 'New technologies that engineer substances in particle size that exhibit chemical and physical properties that significantly differ from those at a larger scale, for example, nanoparticles, should be

assessed on a case-by-case basis as regards their risk until more information is known about such new technology' (Vassiliou 2009).

Nanomaterials and Biocides

The EU Regulation No 528/2012 concerning the making available on the market and use of biocidal products (Schulz and Wammen 2012) is the first Regulation with a definition based on the 2011 recommendation. However, as a biocide always has an intent, the word 'natural' is removed from the nanomaterial definition provide in Article 3(z). The Regulation requires that approval of an active substance shall not cover nanomaterials except where explicitly mentioned. The Regulation also requires that where nanomaterials are used in that product, the risk to human health, animal health and the environment has been assessed separately. The Regulation requires additional considerations for nanomaterials, as the simplified authorisation procedure allowed for conventional biocides is not allowed for biocidal products containing nanomaterials. Article 58 of the Regulation requires labelling of all articles treated with biocides. For nanomaterials this obliges the name of all nanomaterials contained in the biocidal products, followed by the word 'nano' in brackets to be on the label.

Organic Production and Labelling of Organic Products

Organic farming and food production have a specific Regulation that was most recently updated and published in 2018 (Miernicki et al. 2019). The Regulation (EU) 2018/848 on organic production and labelling of organic products defines 'engineered nanomaterials' (Tajani and Pavlova 2018) by referring to the definition in the Regulation on novel foods (EU 2015/2283) (Schulz and Schmit 2015).

Article 7 of the Regulation outlines specific principles applicable to the processing of organic food and states (in 7(e)) that the production of processed organic food shall be based, among others, on the exclusion of food containing, or consisting of, engineered nanomaterials. Thus, food products cannot legally be labelled as organic, if they contain engineered nanomaterials.

Nanomaterials Within Medicinal Products (Pharmaceuticals)

The basis for regulating medicinal products in EU is found in a Directive 2001/83/EC on Community code relating to medicinal products for human use (Fontaine and Reynders 2001). This Directive, due to its age, does not mention nanomaterials however, during the second regulatory review of nanomaterials in 2012 (European

Commission 2012), 'The Commission took the view that current legislation on medicinal products allows an appropriate risk/benefit analysis and risk management of nanomaterials.' This was also mentioned in the 2011 definition recommendation which noted the 'special circumstances prevailing in the pharmaceutical sector' and stated that the recommendation should 'not prejudice the use of the term "nano" when defining certain pharmaceuticals and medical devices'. Thus, there is no definition of nanomaterials or nanomedicines in the EU. However, European Medicines Agency (EMA, based in Amsterdam, The Netherlands, since it recent move from London in 2019) does apply a working definition of nanomedicines which outlines the following considerations:

- Purposely designed systems for clinical applications
- At least one component at nano-scale size resulting in definable specific properties and characteristics
  - related to the specific nanotechnology application and characteristics for the intended use (route of administration, dose)
  - associated with the expected clinical advantages of the nano-engineering (e.g. preferential organ/tissue distribution)
- Needs to meet definition as a **medicinal product** according to European legislation.

The EMA produces most of the scientific assessment of medicinal products and as such has produced a number of guidelines related to the use of nanomaterials and nanotechnologies in the sector (European Medicines Agency 2020).

Nanomaterials and Medical Devices

The EU Regulation on Medical Devices, (EU) 2017/746 (Tajani and Borg 2017), provides a definition of nanomaterials (in Article 2(18–21) that is based on the 2011 recommendation. Interestingly, this definition includes 'natural', which potentially could give rise to measurement issues of abrasion from medical devices not intentionally made of nanomaterials, thus giving rise to incidental nanomaterials. Chapter II of Annex I of the Regulation discusses requirements regarding design and manufacture of medical devices. This states that medical 'devices shall be designed and manufactured in such a way as to reduce as far as possible the risks linked to the size and the properties of particles which are or can be released into the patient's or user's body, unless they come into contact with intact skin only. Special attention shall be given to nanomaterials.'

The issue of nanomaterials is then further specified in Chapter III of Annex I where a number of specific rules have to be considered with regards to classification. For nanomaterials, Rule 19, which is based on potential exposure outlines the following for classification:

All devices incorporating or consisting of nanomaterial are classified as:

- class III if they present a high or medium potential for internal exposure;
- class IIb if they present a low potential for internal exposure; and
- class IIa if they present a negligible potential for internal exposure.

The separation into the three classes means that more information will need to be provided where internal human exposure is elevated. A guidance document on how to interpret Rule 19 is currently (autumn 2019) being drafted. It is foreseen to be published later in 2019.

Nanomaterials and Electrical Equipment

The EU has a number of specific sectoral legislations, e.g. on electrical equipment. Two important directives in this area are the RoHS and WEEE Directives, i.e. 'Restriction of the use of certain hazardous substances in electrical and electronic equipment' (European Commission 2020b) and 'Waste Electrical and Electronic Equipment Directive' (European Commission 2020c).

The RoHS directive lays down rules on the restriction of the use of hazardous substances in electrical and electronic equipment. The directive currently in force is referred to as RoHS2 as the first RoHS directive was repealed in 2013. Nanomaterials are mentioned in RoHS2; in the absence of scientific evidence concerning nanomaterials hazardous properties, the European institutions are monitoring them during the process of reviewing Annex II – List of Restricted Substances. The EC monitoring is a constantly ongoing process. The list of restricted substances does not include nanomaterials but upcoming reviews could target them in the future.

The WEEE Directive includes specific mentions of nanomaterials. However, the directive has currently no nano-specific provision. As in the ROHS2 directive, the European Commission reserves the right to amend Annex VII of this Directive to eventually apply selective treatment to nanomaterials contained in Electrical and Electronic Equipment.

Country Specific Registers for Nanomaterials

Mandatory reporting of nanomaterials are required in several EU Members States (EUON 2020). Demands for formalised reporting schemes originate from a number of reasons, ranging from governments' wishes to know what is on their national market to calls for 'the consumer's right to know' made by NGOs and consumer organisations, to market analysts' and policy makers' interest in the extent of innovation through and commercialisation of nanomaterials.

Diverse concepts for information gathering schemes have emerged. Some regulatory authorities sought simple notification of raw materials on the nanoscale as

part of an existing substance- or chemical authorisation process (e.g. Norway and Sweden), while others have set up traceability schemes that are applicable throughout a supply chain and enable the registration of nanomaterials in both raw material form and in final consumer products and waste disposal contexts (e.g. France, Belgium and Denmark).

In 2013 France launched a mandatory declaration for nanomaterials (Anses 2020). Prior to April 30 each year, importers or manufactures of nanomaterials in France must make a declaration for each nanomaterial produced, imported or distributed for the previous calendar year in quantities larger than 100 g.

Denmark, set up its registration of nanomaterials (Virk Indberet 2020a, b) in 2015, Belgium in 2016 (FPS Public Health 2020) and Sweden in 2018 (KEMI 2020). The four schemes are similar in the sense that they all base their definitions of nanomaterial on the 2011 EC recommendation. However, there are also considerable differences between the schemes as they cover different aspects and require different information. Notably, the Danish scheme focuses on substances that are marketed to consumer, and exclude professional use whereas the French, Belgian and Swedish schemes covers professional uses and consumer uses are excluded. In Europe, Norway also has a register where information on nanomaterials should be included (Norwegian Environment Agency 2020).

Innovation to Bring Safe Nanomaterials to the Market: Responsible Research and Innovation (RRI) and Safe(r) by Design (SbD)

The concepts of responsible research and innovation (RRI) and Safe(r) by Design (SbD) have been developed over time to support industries to take an early and active approach to develop new products and innovations that fulfil regulatory requirements for environmental health and safety aspects. It should be recalled that the terms research and innovation are two different processes where research is about generating knowledge, and innovation is about generating new benefits, or (economic) value. Applying RRI means engaging all societal actors early and with the aim of inclusiveness while also addressing mandatory legal aspects and societal relevance and acceptability of research and innovation outcomes (Dreyer et al. 2017). Both RRI and SbD approaches focus on the early stages of innovation and product development where considerations of environmental, health and safety as well as social aspects can have a profound influence of the progressive innovation steps.

Both RRI and SbD in the nanomaterials sphere reflect efforts by policy, research, NGOs and industrial communities to create a framework for the development of novel nanomaterials and nano-enabled products that builds confidence for consumers and industry as well as other communities e.g. public in general, NGOs, workers, along with governments (Rose et al. 2019).

The fast pace at which nanotechnology is currently evolving challenges the regulators' response time for amending legislation and providing a certain pathway for nanomaterials innovation. Ways to minimize this information gap include: (a) industry to reduce uncertainties and risks to humans and the environment from the upstream, early phases of the innovation process (SbD); and (b) regulators to improve anticipation in order that they can facilitate the development of adaptable (safety) regulations that can keep up with the pace of knowledge generation and innovation of MNMs and MNM-enabled products. The underlying fundamental principles in the field to reduce uncertainties are filled by academic research efforts, and by active screening and monitoring of early signs of emerging fields and risks. Regulators should shift from a reactive to a proactive way of working, meaning that it is more efficient to take a proactive approach to ensure that regulations already cover new developments and products than to regulate when products and possible damages have already occurred.

Regulators need to stay up to date regarding innovations and engage in dialogue with academics, innovators, industry and society at large, while recognizing that industry has the main responsibility and legal liability for the safety of their products. Such dialogue serves to share knowledge and insight on how nano-specific characteristics influence exposure and toxicity, and to translate scientific knowledge into action in an efficient manner. A key element of obtaining information and knowledge is dialogue with industry and to obtain willingness of industry to share information early in the innovation process by ensuring confidentiality and protection of commercial interests. This trust forming dialogue and sharing of information needs to be balanced with the potential benefits for society in getting access to innovative products and the public's right to know and in turn, the public's trust of governments. This dialogue and co-creation between Regulators and industry is essential for SbD implementation. Two approaches are discussed here, developed in the EU ProSafe project, which can support the risk management of nanomaterials (Teunenbroek et al. 2017).

The first approach is to change the current risk assessment process to shift it towards a concern-based testing approach. A concern-based approach, for example, put more emphasis on exposure assessments, where a limited exposure (e.g. only under occupational settings) could allow for a simplified risk assessment and risk management as when exposure is low the risk is consequently the risk is reduced. The second approach is the application of SbD). The SbD 'looks at ways to identify, and thus to avoid, potential adverse effects of NMs from the earliest stages of the innovation process onwards' and 'it also holds the potential to create a closer collaboration between product developers and safety scientists as well as among scientists, innovators and regulators who all work together to further the common aims of technology development that will be safe for human health and the environment' (ProSafe Project Office 2017). The basis for SbD for nanomaterials is to create a streamlined innovation process and support industries and academia in a structured manner while still retaining a high protection for human health and the environment. The SbD is also a core part of the Safe Innovation Approach (SIA) which encourages industries to an early integration of safety aspects in the innovation

process as well as applying a regulatory preparedness approach which aim to improve anticipation of regulators so that they are prepared to develop appropriate regulations (Soeteman-Hernandez et al. 2019). SIA aims to be a responsible approach to be used by industry when developing nanomaterials and products while stimulating a proactive dialogue with policymakers and regulators to reduce the gap between appearance and approval of innovative products.

SbD is still a somewhat academic concept and uptake of industries is still in progress, although especially larger companies are sometimes applying the concepts of SbD. The use in small to medium sized companies is still not widespread (Sørensen et al. 2019). For a transition into use by industry Safe by Design must be accessible, robust, effective for achieving required level of protection and cost-effective, tied to guidelines and standards and with a regulatory context. Adoption of RRI and SbD approaches both academia and industry will encourage early and continued assessment of product characteristics from a regulatory health and safety perspective, through the innovation and product development process. This would support efficient use of resources and allow for nanotechnology-enabled products reaching the market faster while retaining a high level of protection for human health and the environment.

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