8

MAIN DIFFICULTIES IN THE REGULATION OF NANOMATERIALS[1]

Ruth Robles
ruthberumen@yahoo.com.mx

Abstract

This text identifies the main problems that hinder the regulation of nanomaterials, emphasizing key aspects mentioned in documents issued by the U.S. and the European Union; powers that guide the regulation of nanomaterials worldwide. The result indicates that they are materials in continuous evolution, they can be found as nanomaterials in themselves or as part of advanced materials and chemicals. Their great development is out of step with the ability of governments to regulate them. Basic elements of regulatory support such as their definition and the methods of analysis to characterize them are not yet fully developed. Determining the risk by conventional means is a complicated process because each nanomaterial behaves in a particular way, making it difficult to determine its toxicity and exposure pathways, in addition to the fact that these materials are susceptible to transformation throughout their life cycle. In general, the legislation on nanomaterials is complex in its very structure, because they are part of the R&D of several countries and of the productive base of several economic activities, so they

1 This text is part of the Science Frontier research project #304320 Funded by the National Council on Humanities, Science and Technology (CONAHCYT) of Mexico.

are found both in everyday goods and in highly specialized products, which has caused them to enter and accumulate in ecosystems.

Keywords: *nanomaterials; chemicals; risk; legislation; regulation.*

1. Introduction

This article mentions the main problems that have hindered the regulation of nanomaterials in the world.[2] For this purpose, documents promulgated by the United States Government and the European Union are analyzed; powers that lead the regulation of nanomaterials at a global level. In addition to reports from organizations such as the World Trade Organization (WTO) and the Organization for Economic Cooperation and Development (OECD). The regulation of nanomaterials is a topic under discussion at the international level for several reasons: first, there is scientific information that indicates that some of these manufactured materials can affect health and the environment (SCENIHR, 2009, p. 10); second, nanomaterials can be harmful to human health and the environment (SCENIHR, 2009, p. 10). 10); second, nanomaterials are in continuous evolution, it is not possible to focus only on these materials per se, many of them are part of what is known as advanced materials and chemicals, which possess or show a higher complexity, for example they bring with them a new or improved function and/or are made up of multiple components (OECD, 2022a, p. 5); third, nanomaterials are part of new areas of research and development (R&D) in regions such as Europe, which aim to generate commercially viable products and processes (CEC, 2004, p. 3); and finally, global institutions such as the OECD have stated that a gap is emerging between nanotechnology and the development of regulatory tools and frameworks, especially in terms of risk assessment (OECD, 2020, p. 8).

The European Commission (EC) identifies four important elements in the legislation of nanomaterials, the methods of analysis and risk assessment methods that support the implementation of the legislation, the decisions taken by the

2 "Nanomaterials cover a heterogeneous range of materials. In terms of market volume the main categories on the market include inorganic non-metallic nanomaterials (e.g. synthetic amorphous silica, aluminium oxide, titanium dioxide), carbon based nanomaterials (e.g. carbon black, carbon nanotubes), metal nanoparticles (e.g. nanosilver) and organic, macromolecular or polymeric particulate materials (e.g. dendrimers)" (EC, 2012, p. 10).

institutions in charge of formulating policies for these new technologies, and the obligations of those involved in the development of the nanomaterials cycle (CEC, 2008, p. 8). These elements and others are taken up in the following paragraphs to identify and discuss the main difficulties encountered in the regulation of nanomaterials.

2. Problems in the Regulation of Nanotechnologies

As a preamble, it is mentioned that the regulation of nanomaterials in the world is a legislation in gestation because although there is a lot of research on the nature and safety of these materials, there are still many aspects that are unknown. Besides that, most of the information present on these materials has not been possible to bring into the regulatory arena (Teunenbroek, Baker, & Dijkzeul, 2017, p. 3).

Normally, the regulation of nanomaterials has been building on the regulatory frameworks of conventional substances, since the generality of their definitions can encompass this type of materials. However, various institutions have insisted that legislation should be reviewed and reformed to regulate nanomaterials because they may exhibit different behaviors than conventional substances. The EC, in its 2008 and 2012 communications on regulatory aspects of nanomaterials, alludes to this need (CEC, 2012, p. 13, 2008, p. 4). [3] Currently one of their main regulations REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) includes specific provisions for nanomaterials (EC, 2018). Other countries have also made additions to their legislation mainly on risk management, such as Australia, Canada, Japan, South Korea and the United States (OECD, 2022b, pp. 14-18).

Table 1 below shows in summary the main difficulties that have been detected in regulating nanomaterials, then they are discussed more extensively in the following paragraphs.

3 "Overall the Commission remains convinced that REACH sets the best possible framework for the risk management of nanomaterials when they occur as substances or mixtures but more specific requirements for nanomaterials within the framework have proven necessary" (CEC, 2012, p. 11).

Table 1 Main difficulties in the regulation of nanomaterials

Characteristic	Difficulty
Speed	Nanomaterials are entering the market at a faster rate than governments are able to restrict them until their potential health and environmental risks are known. Today, it is no longer possible to speak of nanomaterials per se; many of them are part of what are known as advanced materials and chemicals.
Identity	The legislative basis for the regulation of nanomaterials is not fully developed, there is a struggle in the development of their definition and in the knowledge of their physicochemical, toxicological and eco-toxicological characteristics.
Security	There is a gap between the development of nanomaterials and the assessment of their risks. There are serious difficulties in the evaluation of toxicity and exposure for this type of materials, each nanomaterial is a specific case of study.
Stability	Nanomaterials can be transformed throughout their life cycle and their effects may also change. This aspect makes risk assessment more complex.
Complexity	It is a complex legislation that must protect both health and the environment, and must also consider other aspects such as labor, transportation, safety and commerce.
Disposition	The manufacture of nanomaterials is overtaking the natural disposal and degradation systems of nanomaterials; there is a notable imbalance that is allowing the accumulation of nanomaterials in ecosystems.

Source: own elaboration with own information and data from GAO (2008, p. 1), OECD (2020, p. 8, 2022a, p. 5), ANSES (2014, p. 3 and 7) and Teunenbroek et al. (2017, p. 3).

The first problem that hinders the regulation of nanomaterials is that they develop at "clock speed" (GAO, 2008, p. 1). Various agencies investigate the trends in the value of the production of these materials for the coming years, although it is possible to find differences, in general they all indicate an upward trend, for example, Allied Market Research mentions that the global value of the nanomaterials market for 2021 was 16.3 billion (US) and that this is expected to increase to 62.8 billion (US) by 2031, with a compound annual growth rate of 14.6 % from 2022 to 2031 (Allied Market Research, 2023).

Most legislations take for granted that all nanomaterials that are manufactured must enter the market, rarely is the need to suspend their production until their potential risks to health and the environment are known. The prevailing logic in the manufacture of nanomaterials is that their technical advantages are

investigated first and, ultimately and under pressure, their potential risks. This is because research is an investment that must yield returns in a short period of time.

This first difficulty is magnified by the fact that these materials are in continuous evolution; the U.S. Environmental Protection Agency (EPA) has identified four generations of these materials, many of which are probably already on the market.[4] In addition, many nanomaterials are part of new advanced materials and chemicals, which are being used in various areas such as renewable energy, electric mobility, digitization, healthcare or efficient use or saving of resources (OECD, 2022a, p. 5).

Nanomaterials can enter the market as materials themselves, as intermediates with nanoscale properties or incorporating nanomaterials, and as final products enabled with nanomaterials (GAO, 2011, pp. 10-11). These different presentations multiply the presence of nanomaterials in the market and quite possibly in the environment. The behavior of these materials in the environment is gradually becoming known, and it is known that certain nanomaterials can be toxic to many species of living beings, in addition to the fact that they can be transferred or bioaccumulate along food chains (SCENIHR, 2009, p. 4).

This first difficulty makes it clear that in order to regulate nanomaterials, greater national and international dialogue and greater collaboration of the stakeholders involved in the development of the life cycle of these materials is essential (Teunenbroek, Baker, & Dijkzeul, 2017, p. 5). Producers have the greatest responsibilities as they are the ones who must provide the necessary information to characterize and identify the risks of nanomaterials. In fact, this was an important aspect that underpinned the development of the European Union's REACH chemicals framework legislation; a regulation that basically encompasses the entire life cycle of nanomaterials (Teunenbroek, Baker, & Dijkzeul, 2017, p.

4 See Nanotechnology White Paper (EPA, 2007). "We may be nearing the end of basic research and development on the first generation of materials resulting from nanotechnologies that include coatings, polymers, more reactive catalysts, etc. The second generation, which we are beginning to enter, involves targeted drug delivery systems, adaptive structures and actuators, and has already provided some interesting examples. The third generation, anticipated within the next 10-15 years, is predicted to bring novel robotic devices, three-dimensional networks and guided assemblies. The fourth stage is predicted to result in molecule-by-molecule design and self-assembly capabilities" (EPA, 2007, p. 12).

16). However, sometimes, companies take refuge in the secrecy of confidentiality in order not to provide the information demanded by governments.

In addition, most of the legislation in developing countries based on Command and Control still keeps the burden of proof in the hands of the legislative authorities so that the lists of substances regulated for their hazardousness are rather limited.[5] In general, the development of legislation on nanomaterials has not been seen as a priority, so these materials enter the market in an uncontrolled manner.

The second difficulty is that there is still no fully consolidated definition of what nanomaterials are, and there are controversies in this regard. The legislative development of nanomaterials depends to a large extent on reaching agreements on how to define this type of materials and how to characterize them. The nature of these materials is gradually becoming known, but there are still gaps that prevent existing regulations from controlling all regulatory aspects of nanomaterials, such as risk management during their production, use and fate. The latest definition of what is a nanomaterial was published by the EC on June 10, 2022; a definition that replaces the one issued by this institution in 2011.[6] Recently, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) presented an analysis of the modifications made to this new definition. [7] Its most general conclusion was that "taken together, these amendments result in a more restrictive definition of nanomaterials" (ANSES,

5 These types of regulations set uniform performance standards for companies while giving some freedom to meet them, such as emissions per unit of output (Popp, Newell & Jaffe, 2009, p. 10).
6 "Nanomaterial means a natural, incidental or manufactured material consisting of solid particles that are present, either on their own or as identifiable constituent particles in aggregates or agglomerates, and where 50 % or more of these particles in the number-based size distribution fulfil at least one of the following conditions:a) one or more external dimensions of the particle are in the size range 1 nm to 100 nm; b) the particle has an elongated shape, such as a rod, fibre or tube, where two external dimensions are smaller than 1 nm and the other dimension is larger than 100 nm; c) the particle has a plate-like shape, where one external dimension is smaller than 1 nm and the other dimensions are larger than 100 nm. In the determination of the particle number-based size distribution, particles with at least two orthogonal external dimensions larger than 100 μm need not be considered. However, a material with a specific surface area by volume of < 6 m2/cm3 shall not be considered a nanomaterial" (EC, 2022, p. 4).
7 See Definition of nanomateriales: analysis, challenges and controversias (ANSES, 2023).

2023, p. 6).[8] This makes it easier for many materials with potential nanoscale properties to fall outside this definition and enter the market with fewer difficulties.

This new definition, like its predecessor, continues to encompass uncertainties that are often not taken into account in order to enact regulations on the subject. For example, the workbook that accompanied the formulation of the 2011 definition specified that in reality there is no scientific justification for saying that nanomaterials behave differently from conventional materials in the range from 1 nm to 100 nm; it may be that outside this range they also behave differently from conventional materials. Or, that within this range the particles do not show a specific behavior of nanomaterials (EC, 2012, p. 7). This observation leads to question whether the definition of a nanomaterial should be based on its size (up to 100 nm) or on the new functionality that the material shows.

Generally, this definition applies only to particulate materials, not to products and articles containing a fraction of nanomaterials unless the products are themselves particulate materials (Rauscher et al., 2023, p. 25). Other types of advanced materials or chemicals where nanomaterials are present are not considered, nor are products that during their life cycle emit nanomaterials; "even if a product is designed to release nanomaterials, or releases nanomaterials as wear debris during use or ageing, the original product does still not become a nanomaterial" (Rauscher, Kestens, Rasmussen, Linsinger, & Stefaniak, 2023, p. 25). These new advanced materials and chemicals open up a new field of regulatory action that has not been covered to date.

Adding to this second difficulty is the fact that there is a struggle to know the physicochemical, toxicological and eco-toxicological identity and characterization of nanomaterials (ANSES, 2014, p. 7). A recent OECD publication concluded that there are test guidelines (TGs) and guidance documents (GDs) for the characterization of conventional substances that are not considered suitable may be applicable to nanomaterials, while others may be applicable with minor adaptations (Heunisch, Cassee, Bleeker, Kuhlbusch, &

8 One of the most criticized aspects of this definition is that the following statement set forth in the 2011 definition, which reads: "In specific cases and where warranted by concerns for the environment, health, safety or competitiveness the number size distribution threshold of 50 % may be replaced by a threshold between 1 and 50 %" (EC, 2011, p. 3).

Gonzalez, 2022, pp. 4–5).[9] In order to assess the magnitude of this problem and direct research in this field, EPA formulates a series of questions, among which the following stand out: What are the unique chemical and physical characteristics of nanomaterials? How do these characteristics vary among different classes of materials (e.g., carbon based, metal based) and among the individual members of a class (e.g., fullerenes, nanotubes)? How do these properties affect the material's reactivity, toxicity and other attributes? Are there adequate measurement methods/technology available to fully characterize nanomaterials, to distinguish among different types of nanomaterials, and to distinguish intentionally produced nanomaterials from ultrafine particles or naturally occurring nanosized particles? (EPA, 2007, p. 72).[10]

The TGs/GDs used for the identification and characterization of nanomaterials is a field still under development without which adequate regulation cannot be consolidated since these tools are at the structural basis of regulatory systems. TGs/GDs in the first instance test whether or not a material falls within the sphere of nanomaterials and whether or not they have a hazardous character. In general, the development processes of TGs are exhausting because apart from the investments of time and money involved, they imply demonstrating that the methodology proposed to solve certain questions leads to relevant and reliable results (Heunisch, Cassee, Bleeker, Kuhlbusch, & Gonzalez, 2022, p. 81); independent of the controversies that may arise between different laboratories and methodological modifications.

On the other hand, alternative approaches have been proposed to minimize data gaps in the characterization of chemicals in general. Annex XI(1) of REACH gives a more general overview of these approaches (ECHA, 2020, p. 14).[11] In the case of nanomaterials, the grouping of nanoforms and their possible extrapolation

9 See Development of revisions of OECD Test Guideline (TGs) and Guidance Documents (GDs) for nanomaterials (Heunisch, Cassee, Bleeker, Kuhlbusch, & Gonzalez, 2022).
10 See Nanotechnology White Paper (EPA, 2007).
11 "REACH Annex XI(1) specifies the general rules for adaptation of the standard testing regime set out in annexes VII to X. It provides different options for deviating from the standard requirements and for using alternative approaches, provided they are duly justified and scientifically sound. These options are listed as possible adaptations in REACH Annex XI(1) and include: 1) use of existing data, including historical human data; 2) use of a weight-of-evidence approach; 3) information generated using quantitative structure activity relationships (QSARs); 4) in vitro test methods; and 5) grouping of substances and read-across" (ECHA, 2020, p. 14).

to identify their (eco)toxicological properties is discussed in appendix R.6-1 of the paper *Guidance on QSARs and Grouping Version 2.0 – December* (ECHA, 2019, pp. 7–8). It is still difficult to speak of the results of these new approaches, and it is possible that more evidence will be available in the coming years.

The third difficulty is the complexity of developing a risk assessment by the traditional route and, thus, determining whether a nanomaterial is safe or not for health and the environment. This paradigm is of great interest worldwide because it is the main support for risk management in most of the world's regulations on chemical substances, including nanomaterials, despite the contradictions that may arise during its development. In fact, due to its importance, there are currently many international regulatory projects on this subject that try to unify proposals for risk assessment in nanomaterials.[12]

A risk assessment is the evaluation of scientific information on the hazardous properties of environmental agents, the dose-response relationship, and the degree of exposure of humans or environmental receptors to those agents (EPA, 2007, p. 29). Risk assessment in nanomaterials is difficult to address in contrast to conventional materials, due to the presence of serious difficulties in the toxicity and exposure assessment stages. The fact is that it has been observed that nanomaterials may present different toxic effects compared to conventional substances with the same chemical composition but different physicochemical properties. Besides that, a nanomaterial may have different forms or rather nanoforms, depending on its size distribution, shape, surface treatment and functionalization and specific surface, in that sense, nanoforms of the same substance may have different hazard profiles (ECHA, 2019, p. 6). [13]

These aspects make the study of the toxicity of nanomaterials more complex than that of conventional substances. There is still a lack of elements to determine which physicochemical characteristics of nanomaterials are associated with certain hazards (OECD, 2022b, p. 67). In this context each nanomaterial is a

12 ProSafe, NANoREG, NanoReg2, GRACIOUS, SmartNanoTox, NanoFASE, caLIBRAte, DF4nanoGrouping, nanoGRAVUR , NanoMILE and ACEnano.

13 An example of how the shape of a nanomaterial can influence its toxicity is found in the comparison of carbon nanotubes and asbestos fibers; the similarity of these materials in relation to their shape has led scientists to believe that perhaps exposure to carbon nanotubes also generates mesothelioma, a disease characteristic of asbestos fibers (GAO, 2011, p. 25).

specific case study, its toxicity and ecotoxicity depending on properties such as solubility, zeta potential, aggregation/agglomeration, size, shape, etc. (ANSES, 2014, p. 3). "As there is not yet a generally applicable paradigm for nanomaterial hazard identification, a case-by-case approach for the risk assessment of nanomaterials is warranted" (SCENIHR, 2009, p. 4). Consequently, the risk assessment of nanomaterials involves the investment of large amounts of time and resources, and is a much slower process than the development of new materials; however, according to some researchers, in the context of current European regulations, it is a process that hinders the exploitation of the innovative potential of nanomaterials. (Teunenbroek et al., 2017, p. 3).

On the other hand, the OECD and the EC are promoting strategies for the development of safe nanomaterials such as Safe by Design (SbD). The OECD Working Party on Manufactured Nanomaterials (WPMN) presented an inventory of guidelines to promote SbD. This document shows the particularities of SbD in action where both new functionalities of materials and potential risks are combined. A difficult situation to face when the new function has a higher weighting over the risks that a new nanomaterial may bring.

The fourth difficulty is that nanomaterials can be transformed throughout their life cycle and possibly their effects also change (Teunenbroek, Baker, & Dijkzeul, 2017, p. 3). This aspect makes risk assessment for this type of materials more complex and increases the number of uncertainties. In addition, it forces manufacturers to characterize nanomaterials and assess their risks (either in humans or other living species) at each stage of their life cycle, especially when they are used or disposed in the environment. A complex situation considering the size and evolution of these materials.

On the other hand, there will always be the possibility that a harmless nanomaterial can become potentially dangerous once it interacts with its environment or within a biological body. In addition, there may be cases where a final product enhanced with nanomaterials may release such materials throughout its life cycle.

The fifth difficulty in regulating nanomaterials refers to the complexity of the legislation in its own structure due to the fact that these types of materials are part of various products and constitute part of the inputs of numerous productive

processes. These materials are found both in everyday goods and in highly specialized products in electronics or biomedicine (EC, 2012, p. 10). In this sense, it is a legislation that must consider diverse areas such as health, safety, transportation, environment, among others. In addition to the fact that they are materials that are part of the R&D of several countries whose rapid development has boosted the economy of various sectors, therefore, the legislation, apart from protecting the environment and health, should facilitate innovation.

In the case of European legislation, the REACH Regulation that regulates the manufacture, placing on the market and use of chemical substances on their own or in the form of preparations or products together with the Classification, Labeling and Packaging (CLP) Regulation form the base regulation for nanomaterials in this region; because together they manage the risks of these materials (OECD, 2022b, p. 16). In particular, the REACH regulation is of great significance because the data it generates can be used in other regulations (CEC, 2008, p. 5). In addition, substances subject to this regulation are subject to an environmental impact assessment (CEC, 2008, p. 6). In general, the REACH Regulation has been a model to follow not only for countries belonging to the European Union, but also for others outside it.

Added to this fifth difficulty is the fact that it has not been possible to bring the current scientific information in its entirety into the regulatory arena. *The Prosafe White Paper*, issued by the EU FP7 NANoREG and H2020 ProSafe projects, mentions that there has been a lot of research on the safety of nanomaterials during the last few years, although, these have been science-oriented and not oriented and not oriented towards the regulation of these materials (Teunenbroek, Baker, & Dijkzeul, 2017, p. 3).

The science used to regulate must develop measurement techniques, methodological tools and decision-making protocols for the standardization, authorization or control of technological goods. In addition, this type of science must generate knowledge for administrative, political or judicial action, but at the same time it must feedback to science itself so that it continues to develop specific knowledge in this area (Gaudillière, 2014, p. 72).

The development of scientific knowledge to regulate nanomaterials is a complex aspect considering the amount of information that must be systematized and

agreed upon. This has created the need to develop agreements for the management of regulation at the bilateral, regional or global level, which magnifies the latter difficulty. Global organizations such as the WTO and the OECD have tried to create the basis for the formulation of global regulatory frameworks of a voluntary, non-binding nature.[14] An example of these actions is the Mutual Data Recognition (MAD) system, which according to the latest OECD report on international regulatory cooperation has, among other things, reduced the duplication of testing procedures (OECD, 2021, p. 66). However, it has been criticized in the sense that the analysis methodologies used are influenced by chemical corporations and ignore those carried out by independent organizations.

International regulatory cooperation is an issue that has gained much importance in recent decades, however, despite the benefits it can bring, it is well known that the political responses on how to manage nanomaterials will not be the same in all nation states for various reasons, such as the way their own legislation is structured.

The sixth point that makes it difficult to regulate nanomaterials is that they are substances that are increasingly present in ecosystems. The pathways through which nanomaterials reach ecosystems are very varied and involve various regulatory instruments for their control. However, it is possible to mention that the manufacture of nanomaterials is overtaking the systems for their disposal and degradation; there is a notable imbalance that is allowing the accumulation of nanomaterials in ecosystems. Nano plastics are an example of this disaster.

The EC framework directive on integrated pollution prevention and control proposes the establishment of emission limit values for substances based on the application of best available techniques (CEC, 2008, p. 7). In the case of nanomaterials, it is currently possible to find state-of-the-art facilities that retain or remove these materials almost entirely, however, there is no information on existing industrial waste treatment systems or from years ago (OECD, 2016, p.

14 In this regard, the WTO has formulated multilateral agreements related to trade in goods that seek to regulate non-tariff measures, such as the Agreement on Technical Barriers to Trade (TBT Agreement) and the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement). Although these agreements do not directly regulate nanomaterials, they do cover aspects for substances in general, see the publication Technical Barriers to Trade (WTO, 2021).

11). Studies have been done in pilot wastewater treatment plants, where it has been identified that they can capture more than 80 % of some types of nanomaterials, while the rest would pass to surface water bodies (OECD, 2016, p. 12).

The latter difficulty is very difficult to address because the processes of transformation and degradation of ecosystems on wastes are largely unknown which prevents predicting their fate. In addition to the fact that the vast majority of legislations are based on the paradigm of risk analysis that allows the emission of certain limits of pollutants into the environment without considering the capacity of ecosystems to metabolize them.

3. Conclusions

The regulation of nanomaterials is a developing process in the world. This article shows that there are serious difficulties in its consolidation. The first of these is that nanomaterials are entering the market at a faster rate than the capacity of governments to restrict them until their possible risks to health and the environment are known. The prevailing logic in the manufacture of nanomaterials is that their technical advantages are investigated first and, ultimately and under pressure, their potential risks. The second difficulty is that the legislative basis for the regulation of nanomaterials is not fully developed, given that there is a struggle in the development of their definition and in the knowledge of their physicochemical, toxicological and eco-toxicological characteristics. The third difficulty identifies that there is a gap between the development of nanomaterials and the evaluation of their risks. There are serious difficulties in the evaluation of toxicity and exposure for this type of materials, each nanomaterial is a specific case of study. The fourth difficulty is that nanomaterials can be transformed throughout their life cycle and their effects may also change. This aspect makes risk assessment more complex. The fifth difficulty considers that the legislation on nanomaterials is complex in its own structure due to the fact that these types of materials are part of various products and constitute part of the inputs of numerous productive processes. In this sense, it is a legislation that must consider several areas such as health, safety, transportation, environment, among others. In addition, it has not been possible to bring all the current scientific information into the regulatory sphere. Finally, the last difficulty identified in this article is that the manufacture of nanomaterials

is overcoming the systems of disposal and natural degradation of nanomaterials; there is a notable imbalance that is allowing the accumulation of nanomaterials in ecosystems.

References

Allied Market Research. (2023). *Nanomaterials Market*. https://www.alliedmarketresearch.com/nano-materials-market

ANSES, (French Agency for Food, Environmental and Occupational Health and Safety). (2014). *Évaluation des risques liés aux nanomatériaux. Enjeux et mise à jour des connaissances*. ANSES. https://www.anses.fr/fr/system/files/AP2012sa0273Ra.pdf

ANSES, (French Agency for Food, Environmental and Occupational Health and Safety). (2023). *Definition of nanomaterials: Analysis, challenges and controversies. Anses opinion Collective expert appraisal report*. ANSES. https://www.anses.fr/en/system/files/AP2018SA0168RaEN.pdf

CEC, (Commission of European Communities). (2004). *Communication from the Commission. Towards a European strategy for nanotechnology*. European Commission. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52004DC0338

CEC, (Commission of European Communities). (2008). *Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee. Regulatory Aspects of Nanomaterials*. European Commission. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2008:0366:FIN:en:PDF

CEC, (Commission of European Communities). (2012). *Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee. Second Regulatory Review on Nanomaterials*. European Commission. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012DC0572

EC, (European Commission). (2011). *Commission Recommendation of 18 October 2011 on the definition of nanomaterial*. Official Journal of the European Union.

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011H0696

EC, (European Commission). (2012). *Commission Staff working paper. Types and uses of nanomaterials, including safety aspects Accompanying the Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee on the Second Regulatory Review on Nanomaterials*. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012SC0288

EC, (European Commission). (2018). *REGLAMENTO (UE) 2018/1881 DE LA COMISIÓN de 3 de diciembre de 2018 por el que se modifica el Reglamento (CE) n.o 1907/2006 del Parlamento Europeo y del Consejo, relativo al registro, la evaluación, la autorización y la restricción de las sustancias y mezclas químicas (REACH) en cuanto a sus anexos I, III, VI, VII, VIII, IX, X, XI y XII para tener en cuenta las nanoformas de sustancias*. Diario Oficial de la Unión Europea. https://eur-lex.europa.eu/legal-content/ES/TXT/PDF/?uri=CELEX:32018R1881&from=NL

EC, (European Commission). (2022). *Commission Recommendation of 10 June 2022 on the definition of nanomaterial*. Official Journal of the European Union. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022H0614(01)

ECHA, (Agency and European Chemicals). (2019). *Appendix for nanoforms applicable to the guidance on QSARs and Grouping of Chemicals – Guidance on information requirements and chemical safety assessment* (2 ed.). European Chemicals Agency. https://data.europa.eu/doi/10.2823/273911

ECHA, (Agency and European Chemicals). (2020). *The use of alternatives to testing on animals for the REACH Regulation*. European Chemicals Agency. https://doi.org/doi/10.2823/092305

EPA, (Environmental Protection Agency). (2007). *Nanotechnology White Paper* (p. 120). EPA. https://www.epa.gov/osa/nanotechnology-white-paper

GAO, (United States. Government Accountability Office). (2008). *Highway Safety: Foresight Issues Challenge DOT's Efforts to Assess and Respond to New Technology-Based Trends* (GAO-09-56; p. 107). United States. Government

Accountability Office.
https://digital.library.unt.edu/ark:/67531/metadc299456/

GAO, (United States. Government Accountability Office). (2011). Nanotechnology: Nanomaterials are Widely used in Commerce, but EPA Faces Challenges in Regulating Risk. In *Nanotechnology Considerations for the EPA and FDA* (pp. 1–58). Nova Science Publishers, Inc.

Gaudillière, J.-P. (Ed.). (2014). DES, Cancer, and Endocrine Disruptors. Ways of Regulating, Chemical Risks, and Public Expertise in the United States. In *Powerless science? Science and politics in a toxic world* (Vol. 2, pp. 65–94). Berghahn Books.

Heunisch, E., Cassee, F., Bleeker, E., Kuhlbusch, T., & Gonzalez, M. (2022). *Development of revisions of OECD Test Guideline (TGs) and Guidance Documents (GDs) for nanomaterials. July 2022*. OECD. https://www.oecd.org/chemicalsafety/nanomet/status-report-test-guidelines-guidance-documents-nanomaterials.pdf

OECD, (Organisation for Economic Co-operation and Development). (2016). *Nanomaterials in Waste Streams: Current Knowledge on Risks and Impacts*. OECD Publishing. https://doi.org/10.1787/9789264249752-en

OECD, (Organisation for Economic Co-operation and Development). (2020). *Moving Towards a Safe(r) Innovation Approach (SIA) for More Sustainable Nanomaterials and Nano-enabled Products*. OECD Environment, Health and Safety Publications. https://one.oecd.org/document/env/jm/mono(2020)36/REV1/en/pdf

OECD, (Organisation for Economic Co-operation and Development). (2021). *Cooperación Regulatoria Internacional*. OECD Publishing. https://doi.org/10.1787/e2233df7-es.

OECD, (Organisation for Economic Co-operation and Development). (2022a). *Advanced Materials: Working Description*. OECD Environment, Health and Safety Publications. https://one.oecd.org/document/ENV/CBC/MONO(2022)29/en/pdf

OECD, (Organisation for Economic Co-operation and Development). (2022b). *Important Issues on Risk Assessment of Manufactured Nanomaterials*. OECD

Environment, Health and Safety Publications. https://one.oecd.org/document/ENV/CBC/MONO(2022)3/en/pdf

Popp, D., Newell, R. G., & Jaffe, A. B. (2009). *Energy, the Environment, and Technological Change* (Working Paper 14832). National Bureau of Economic Research. https://doi.org/10.3386/w14832

Rauscher, H., Kestens, V., Rasmussen, K., Linsinger, T., & Stefaniak, E. (2023). *Guidance on the implementation of the Commission Recommendation 2022/C 229/01 on the definition of nanomaterial, EUR 31452 EN*. Publications Office of the European Union. https://publications.jrc.ec.europa.eu/repository/handle/JRC132102

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

Teunenbroek, T. V., Baker, J., & Dijkzeul, A. (2017). *Towards a more effective and efficient governance and regulation of nanomaterials. The Prosafe White Paper*. https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5b4091891&appId=PPGMS

WTO, (World Trade Organization). (2021). *Obstáculos Técnicos al Comercio* (3 ed.). WTO. https://www.wto.org/spanish/res_s/booksp_s/tbt3rd_s.pdf