RISKS OF NANOTECHNOLOGY AND THE LACK OF SPECIFIC REGULATION

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Abstract
Nanotechnology has been rapidly and continuously advancing, creating a gap between innovation and appropriate regulation, including the potential risks associated with this technology. By raising questions and exploring different perspectives on the subject, this work aims to showcase various uses and implications (both positive and negative) and initiate a debate to arrive at possible and viable solutions. In this context, this study seeks to develop qualitative exploratory research using the analytical method to examine aspects of environmental legislation and nanotechnology. The inclusion criteria for this research involved selecting scientific articles published in the last 7 years (January 2015 to May 2022) using Scopus with the keywords "legislation" AND "environment" AND "nanotechnology," following Boolean Logic. From the results obtained, it is evident that nanotechnology and nanomaterials have significant potential to benefit society, such as in pollutant removal and the treatment of contaminated water. However, it is essential to facilitate a dialogue among stakeholders to analyze potential risks and implications. Therefore, creating a regulatory framework that addresses the needs brought about by innovations in nanotechnology is of paramount importance.

Keywords: Law, Nanoscience, Regulation.

1. Introduction

Nowadays, nanotechnology is an interdisciplinary field of science that operates on the nanoscale (around 10-9 nm) with significant growth in research and the commercial field in several areas such as medicine, energy, cosmetics, space exploration and the environment (Naqvi and Flora, 2020). Moreover, due to the attention of the industry and the consequent increase in the production of nanostructured systems, it ends up putting us in new unusual situations, where the influence that nanomaterials can have on the environment and living beings, through the nanotoxicity and ecotoxicity of these nanomaterials (Martínez et al., 2021). Accordingly, the development of nanosecurity is essential to lessen the impediment to the efficient deployment of emerging and promising technologies associated with nanotechnology, through regulatory and governance improvements (Soeteman-Hernández et al., 2021).

In this way, nanotechnology presents a strong potential and economic and technological opportunities for society, with opportunities and challenges, due to the existence of possible

damages to human and environmental safety, since there is a significant gap between technological advancement and the adequate development of regulatory frameworks, making it necessary for a proactive and interactive positioning by regulators (Soeteman- Hernández et al., 2019).

In parallel, ecotoxicological and citotoxicological studies are recent, being developed in silico, in vitro and to a lesser extent in vivo assay. The main studies involve in silico databases and online and real-time simulations, such as predictions performed in ProTox II, Molinspiration and Lazar, to mention a few. In vitro studies include assays recognized by NanoReg (e.g., MMT, MTS, phenol red and comet assay). Regarding the in vivo assays, studies with standard living organisms, such as Daphnia magna and zebrafish are reported to a higher extent (Fan et al., 2016; Wang et al., 2014). Also, ecotoxicological has been carried out, especially in vegetable seeds (Wu et al., 2017; Kumar et al., 2022).

Currently, Brazil faces a deficit in its legal system in the face of nanotechnology and nanomaterials, even though Brazilian Health Regulatory Agency (ANVISA) efforts are made to monitor the growth of this area in the national territory, however, this measure is still too inert (Melo et al., 2015).

In this context, the present work aims to present a global overview and Brazilian territory on nanotechnology and nanomaterials that may be regulated through a legal system that supports all the characters in the environment, that is, researchers, industry, regulators, and legislators, either through bases such as NanoReg and other documents already prepared in a global panorama. The novelty of this manuscript is the identification of the mechanism of action inside the living cells (nanotoxicological effects) of the nanomaterials used commercially and the legal validation of their commercialization as either an additive in the product chemical composition or bioactive compound in commercial formulations.

2. Nanomaterials: applications, cytotoxicity and nanoimpacts

Firstly, understanding the environmental impact of nanomaterials (metallic nanoparticles, nanoemulsion, lipid-based nanosystems and carbon-based nanomaterials) requires a thorough understanding of their characteristics, such as their properties, physicochemical qualities, and interaction with the environment, such as toxicity in living organisms, and the ability to reach and infiltrate different environmental compartments (land, water, air) (Martínez et al., 2021).

Nanotechnology can be used in an extremely positive way, as in the removal of persistent organic pollutants (POPs) using nanofilters with carbon nanotubes (CNTs) and/or metallic nanoparticles (MNPs), showing great effectiveness due to their small size (at least one dimension smaller than 100 nm), high surface: volume ratio, high chemical reactivity, and can be used in new hybrid materials, such as nanocomposites suitable for wastewater treatment (Negrete-Bolagay et al., 2021).

Moreover, MNPs and NTCs can be used to remove pollutants in water, through biosensors, being able to increase the electrode contact surface area in these electrochemical biosensors, due to the size of these nanomaterials and the techniques in which they can be applied to biosensors, to provide more efficient equipment, to automating the manufacturing process (Hernandez-Vargas et al., 2018).

Recent studies have brought the application of nanotechnology in the wastewater treatment of produced in oil fields through metallic nanoparticles, which ends up improving the water disposal rate and its recyclability, results that conventional additives do not achieve, therefore, depending on the situation, nanoparticles can be used as an oil repellent, due to their hydrophilic and hydrophobic qualities, in addition to having a good rejection of polymers and recyclable qualities, providing more economical and environmentally conscious disposal (Sudharsan et al., 2020; Siddiqui and Alrumman, 2021).

In addition, nanotechnology, through its use in nanoparticles, ends up being a possible solution for application in packaging materials, aiming to minimize food contamination in the external environment, thus, some nanoparticles (nanoemulsions, liposomes, titanium and silver nanoparticles) have important properties for this industry, including chemical and thermal stability, heat resistance and antimicrobial activity, still, the use of nanoparticles in food packaging could be beneficial in the idea of reducing the weight of these packages, reducing costs and generating less waste (Basavegowda et al, 2020).

In contrast, reports show that some nanomaterials (e.g., graphene and carbon nanotubes) can harm the function and behavior of aquatic flora and fauna, as well as soil and sediments, along with their environmental fate and durability (Gong et al., 2023). Moreover, the absorption process of microorganisms, unfavorable toxic effects on physiology, behavior, and bioaccumulation in living bodies are still unknown, and the scientific data on the effects of artificial nanomaterials on the environment is insufficient (Naqvi and Flora, 2020).

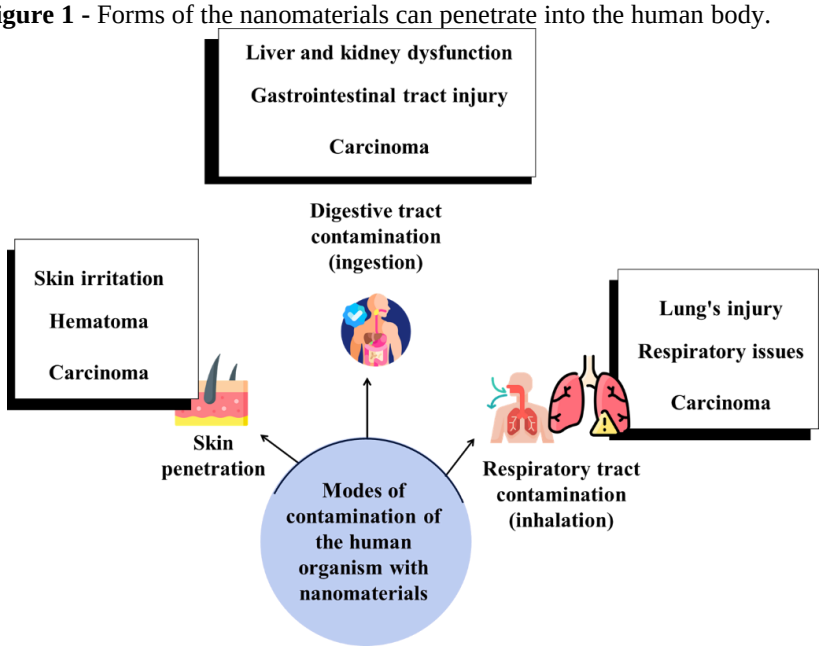
The problem also comes from the current gap in research related to how nanoparticles move through the soil and what role they play in the deterioration of soil ecosystems because the nanoparticles have greater migration capacity and greater bioavailability, so, a survey of these data on the extent of the environmental hazard with a long-term view is highly necessary, a fact that becomes more dangerous if we talk about illegal evictions (Tuktarova and Bolotov, 2021).

In this way, questions are raised about the fate, movement, and modification of nanoparticles discharged into the environment, requiring an assessment of this situation. For example, silver nanoparticles, for being one of the most used nanomaterials in consumer goods that are directly related to the daily life of society, being known to be dangerous to plants, fish and human cells, causing inflammatory processes inside the cell through reactive oxygen species

generation, cell membrane disruption and DNA damage. Thus, when these metallic nanoparticles are released into the environment, a careful eco and toxicological analysis are necessary to understand their real impact and evaluate the lethal dose responsible for 50% of animal deaths (LD50), associated mainly with the release of the metallic nanoparticles in form of ions (Llaver et al., 2021).

Therefore, the negative effects of nanoparticles on human health depend on unique circumstances, such as genetic predisposition, pre-existing disease, duration and intensity of exposure, which makes a comprehensive study of all possible effects of nanoparticles even more important, in addition, the hazards can also be influenced by the characteristics of nanoparticles, such as their dimensions, surface area, reactivity, solubility, structural composition, making it clear that exposure limits for nanoparticles will be different from those for chemicals in macro format (Kuka et al., 2016). Thus, Figure shows the main forms of contamination of the human organism with nanoparticles.

Figure 1 - Forms of the nanomaterials can penetrate into the human body.



Source: author's construction.

According to Figure 1, the main forms of contamination of the human organism by metallic and non-metallic nanoparticles are ingestion, inhalation and direct contact (cutaneous contamination). To the best of our knowledge, the following sections present a detailed description

of the main class of nanomaterials used commercially and their nanotoxicological effects generated in living organisms, as well as some reports about ecotoxicity studies.

2.1 Metallic Nanoparticles - MPNs

Metallic nanoparticles (e.g., TiNPs, ZnNPs, CuNPs, AgNPs) showed great applicability in industrial activities and commercial products, such as ultraviolet radiation blockers, antimicrobial agents, catalysts and chemicals for water treatment. Some of them (nanostructured ZnO and TiO^2 have been used commercially as fertilizers since that at low dose (~100 mg/kg) titanium and zinc nanoparticles can boost crop production and photosynthesis. However, some studies report that at high concentrations (~300-400 mg/kg), phytotoxicological and cytotoxicologial effects are observed (Gacía-Gómez et al., 2018; Babele 2019).

Furthermore, this toxicological effect was found to be due to the generation of high levels of reactive oxygen species (ROS) and membrane cell disruption, followed by an increased cell damage biomarkers content such as proline, catalase (CAT), guaiacol peroxidase (GPX) and superoxide dismutase (SOD) proline content and catalase, as well as guaiacol peroxidase, and superoxide dismutase activities (Zoufan et al., 2020).

Regarding cytotoxicity studies, it was reported cell death (evaluated by MMT assay) for TiNPs and Cr at concentrations range of from 0.1-1 µg mL-1, and at 10-100 µg mL-1 for CoNPS (Liu et al., 2023). It is worth mentioning that few studies in vitro showed considerable toxicological effects, as studies who search for a combined proteomics and metabolomics approach to assess the effects of gold nanoparticles in vitro, for example (Babele, 2019).

2.2 Labile and carbon-based nanomaterials nanoparticles

Drug delivery nanosystems (labile nanomaterials) are nanomaterials used to protect and preserve physically and chemically the bioactive compounds present in food formulations (additives), pharmaceuticals, and nutraceutical substances (Khursheed et al., 2022). The nanosystem consists of nanocapsule, nanoemulsion, and polymeric nanostructure drug-delivery systems, whose toxicological effects are mainly associated with the concentration of the tensoactive/surfactant used in their preparation.

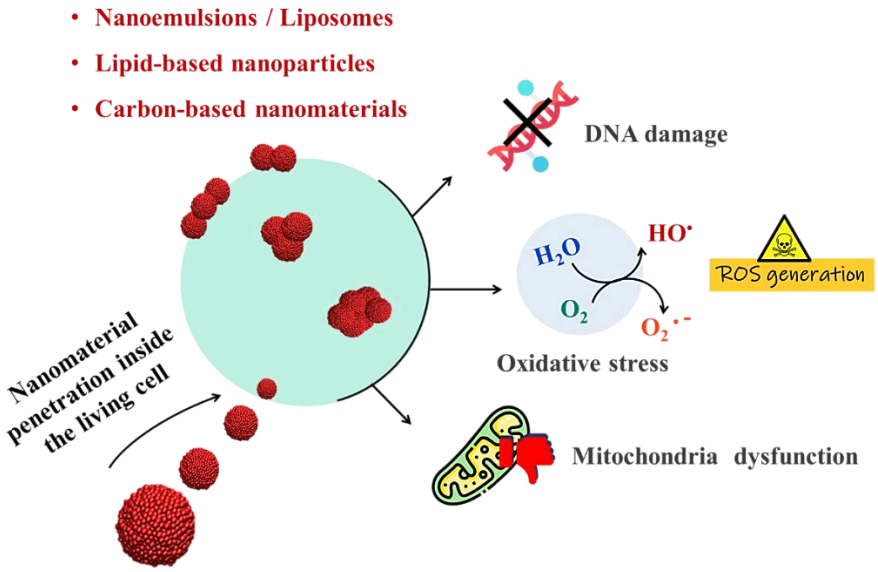
It is important to notice that higher concentration of the surfactant, higher the cell damage (Friedl et al., 2022). The latter class has been vastly used to develop commercial supplementary food products with antioxidant activities, administered by oral via (Khan et al., 2023). Also, thermogenic agents are included in these classes.

In parallel, depending on the concentration used, the carbon-based nanomaterials such as carbon nanotubes, graphene oxide and fullerenes has proved to present nanotoxicological effects to cells, in a similar manner of the MNPs (Monteiro-Riviere and Inman, 2006; Chen et al.,

2017; Rozhina et al., 2021). These nanomaterials have been used in nanotheranostics and some types of cancer (Gao et al., 2022; Jiao et al., 2022).

Thus, Figure 2 show the main mechanism of cytotoxicity observed when these nanosystems penetrate the inside of a living cell.

Figure 2 - Cytotoxicity of drug-delivery nanosystems and carbon-based nanomaterials.



Source: author's construction.

According to Figure 2, cellular damage caused by nanoemulsion, liposomes, lipid-based nanoparticles and carbon-based nanomaterials can be due to interactions of these nanomaterials with DNA (genotoxicity), tissue inflammation in response of ROS generation and mitochondrial activity dysfunction.

Furthermore, the cytotoxicity of the drug-delivery systems showed to be dependent on the particle size (Khan et al., 2022). Therefore, nanosystems with small diameters proved to be able to penetrate the barrier (hematoencephalic barrier) of the human body, which is hard for macro and microscopic substances, affecting the brain activity and the central nervous system (CNS) (Khursheed et al., 2022).

3. Legal aspects of nanotechnology

3.1 World view and regulation

Initially, to distinguish nanomaterials from other items, the European Commission (EC) produced a kind of recommendation on the definition of nanomaterial, that is, even though it is not legally applicable, it provides a guide that can be used in various regulatory contexts and being adapted to the legislation of each product, thus, the only defining attribute of the material is the size, between 1 and 100 nm, this definition includes all particulate nanomaterials, regardless of their source (Amenta et al., 2015).

For this reason, the European Union (EU) was the forerunner to implement a set of regulations regarding products developed with nanotechnology, through the EU Regulation 1223/2009, which is applied to the EU market for safety assessment of nanomaterials, with due process of approval to be applied to all cosmetic products with nanomaterials, because of these innovations, it would be necessary to create a product information file for a minimum period of ten years after the date on which the last batch was placed on the market (Auplat and Slimane, 2015).

Currently, a change in behavior by regulatory bodies would be ideal, to adopt a proactive behavior, seeking to be more agile and adaptable to the changes that new technologies bring, as regulations do not always cover all aspects of innovation safety, thus, there is a need for greater involvement on the part of regulators, together with innovators and policymakers in the field of innovation, adopting the use of new databases that have been created, aiming to unify a vision of nanoregulation (Soeteman-Hernández et al., 2021). Thus, Table 1 presents some of the main nanotechnology regulatory databases.

Table 1 - Nanotechnology regulatory databases.

Data base	Description
Safe-by-Design (SbD)	Created in response to findings that nanomaterial security would be more successful and cost-effective for companies if implemented earlier and throughout the innovation process.
Regulatory-Preparedness (RP)	Result of observations that regulators need to better anticipate and modify governance to keep up with the pace of knowledge generation and innovation of nanomaterials and nanoenabled products.
Safe Innovation Approach (SIA)	Developed in the Horizon 2020 NanoReg project, Combines Safe-by-Design and Regulatory Preparedness, addresses the need for proactiveness in the face of the safety demands of innovation.

Source: author's construction.

According to Table 1, there are already several specialized bodies focused on this regulatory field, such as the Organization for Economic Co-operation and Development (OECD), Scientific Committees and Agencies of the European Union, and the Food and Drug Administration (FDA) of the United States. In 2007, a Russian Nanotechnologies Corporation was created, seeking to assess risk and safety levels for nanomaterials, countries such as Japan and South Korea are also active and involved with the OECD, seeking regulation of nanomaterials in food products, as is the case of China and Brazil (Wacker et al., 2016; Basavegowda et al., 2020).

Moreover, the innovation and regulation of nanotechnology are of interest to various organizations in society, including governments, companies, workers and civil society, and these companies are seeking to employ specialists in areas such as innovation, legislation and assessment of risks and working conditions, in addition to other professionals who are more concerned with ensuring that materials are safe for both people and the environment (Larsson et al., 2019).

Furthermore, European countries are pioneers in implementing nanosafety assessment in their regulatory frameworks, demonstrating global efforts in regulating the characterization of nanomaterials. However, consumer safety is more important in Europe than the concerns of national industry, which could lead to a stifling of innovation in nanotechnology, a fact that is evidenced by the patent situation in Europe, being in third place after China and the United States (Wacker et al., 2016).

Consequently, given the lack of specific testing guidelines and methodologies to assess the safety of these nanomaterials, as well as legislation that specifically addresses the safety aspects of nanotechnology innovations and political motivation and appropriate resources to support regulatory preparation, were identified as barriers to Regulatory Preparedness (RP), thus the OECD test guidelines program and the Working Party on Manufactured Nanomaterials (WPMN) are now working to produce harmonized test rules and procedures (Soeteman-Hernández et al., 2019).

In view of this, countries such as the United States and China are not paying enough attention to the regulation of engineered nanomaterials, since most mandatory labeling programs do not recognize engineered nanomaterials, yet, some engineered nanomaterials may pass premarket assessments, in view that their macro-scale equivalents are categorized as non-toxic, as the opinion may not be a distinction between nano and macro materials, as substances can become more dangerous at the nanoscale (Lai et al., 2018).

In this way, the need for new regulatory actions is necessary in a European panorama, since health items, chemical and electrical are currently being governed by the same regulatory framework, which ends up being risky due to the fact that health products present a greater

safety risk to the consumer since they are directly exposed to the product that contains nanoparticles, as well as a possible solution, would be a regulation that focuses on the description of nanomaterials, to avoid conflicting interpretations between regulatory frameworks (Musazzi et al, 2017).

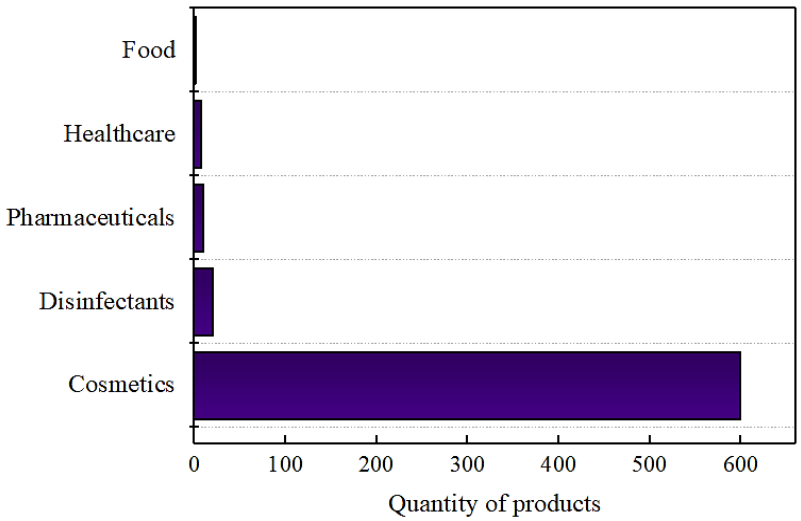
For this reason, an important step to be taken in the assessment of possible risks in a regulatory environment would be the creation of standardized tests for nanomaterials, to produce data that can be used in this assessment of risks and impacts of nanomaterials, as they can be reliable and comparable, as are the testing techniques brought in as part of the NANoREG project, offering this technology in a data management system that the entire nanosecurity community can adopt (Teunenbroek et al., 2017).

3.2 Brazilian vision and challenges

In the Brazilian scenario, the Brazilian Health Regulatory Agency (ANVISA) is the body that has been observing advances in the area of nanotechnology, through bill number 6741/2013 proposed by the Chamber of Deputies, proposing a national nanotechnology policy, furthermore, ANVISA is responsible for matters related to nanosafety, requiring manufacturers to submit information on products containing nanotechnology, by the multidisciplinary committee on nanotechnology, founded in 2014 for the ANVISA (Wacker et al., 2016).

Therefore, Ordinance number 993/2013 ANVISA instituted the Internal Nanotechnology Committee (CIN), aiming to verify the current understanding of nanotechnology, count items and information related to nanotechnology, develop documents containing regulatory activities and policies on nanotechnology that other governments have implemented, and make recommendations to the Agency on alternative guidelines and regulatory measures, later being published by CIN the “Institutional Diagnosis of Nanotechnology”, at the time being brought the existence of 608 industries that used nanotechnology and 637 products that referred to this technology (Melo et al., 2015). Figure 3 shows the main products that refer to nanotechnology in Brazil, according to the Institutional Diagnosis of Nanotechnology.

Figure 3 - Main products that refer to nanotechnology.



Source: author's construction.

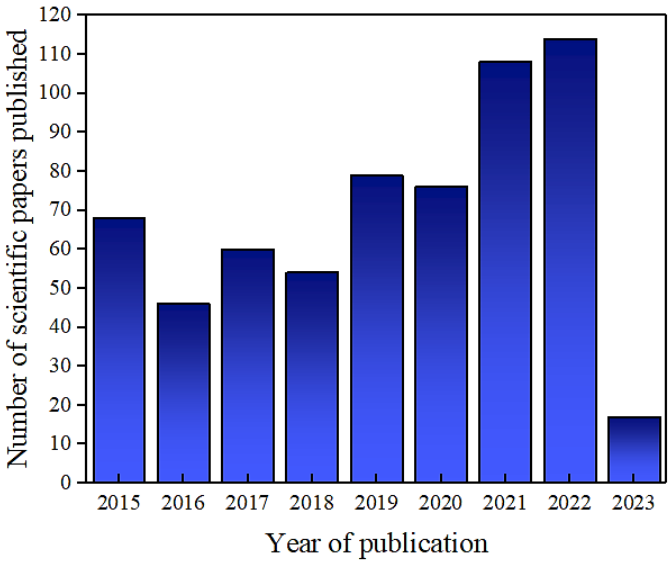
4. Methodological research

In this study, an exploratory review was carried out addressing the theme of law related to nanoscience, with a focus on environmental law, through exploratory qualitative research using the analytical method. In this context, we searched for scientific articles on the platform Scopus.com, using the following descriptors "legislation" AND "environment" AND "nanotechnology" by Boolean Logic, during the period 2015 to 2022 and only studies in English were found.

Exclusion criteria consisted of ongoing studies, book chapters, works that touch the theme, as well as those that were not directly related to the theme. Scopus platform was selected due to the greater number of scientific papers published in renowned scientific journals associated with interdisciplinary studies, which includes papers found in Science Direct and Web of Science.

According to Figure 4, 60 scientific papers were published in the period from 2015 to 2022 from the Scopus.com platform.

Figure 4 - Number of publications of scientific articles from January 2015 to January 2023.



Source: author's construction.

After applying the exclusion criteria, 39 articles were disregarded because they did not fit the objective of this research. Thus, 21 scientific articles were used for the construction of this work. In addition, it was observed that the theme has been addressed with a reasonable number of publications, that are recurrent during the years in which the research was delimited, demonstrating that it is a relevant and extremely important subject to maintain the debate between the entities involved.

5. Conclusões

From the present study, the extraordinary potential that can be explored with the use of nanotechnology and nanomaterials in their various spheres of applications is verified. However, as evidenced by the present research, a debate must be initiated between all entities interested in the field of nanotechnology and correlated areas, to glimpse the relationship and its implications in the case of possible risks to humans and health, to the environment, being first important to create a regulatory framework that can meet the needs of the innovations that the field of nanotechnology needs.

Therefore, it was observed that Brazilian legislation is currently totally unprepared to provide any kind of legal support to anyone who may need it, in terms of possible implications that nanotechnology may bring, leaving researchers, industry professionals, legal professionals helpless and even the final consumer of these products that contain this technology. This shows that Brazil is in the opposite direction of what was exposed in the present work, since European

countries are already well advanced in terms of laws and legal systems that support and seek a form of precaution regarding the treatment of products that contain nanotechnology, demonstrating the current unpreparedness that Brazil has in relation to new technologies, in terms of legal support.

In this way, this lack of regulation and legal order, ends up generating several insecurities and interfering in the development of nanotechnology in a negative way, since, when the State does not provide support and security for researchers, industry, commerce and users of these products, it generates uncertainty for everyone involved, whether due to the delay in research and technological development in our country, as well as the aforementioned risks to the environment and human health.

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