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Review on Nanomaterial (Nms): Classification, Synthesis by Biological Methods, Sources of Toxic Nps and Health Effects, Toxicity, and Regulations

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Abstract

The recent past in the technological development evidenced has evolution in Nanotechnology and nanoscience is the key factor. Nanomaterials (NMs) have gained prominence in technological advancements due to their tunable physical, chemical and biological properties with enhanced performance over their bulk counterparts. NMs are categorized depending on their size, composition, shape, and origin. Due to increased production of NMs and their industrial applications, issues relating to toxicity are inevitable. The review presents an overview of the definitions for the scientific terms and classifications of NMs and gives an overview of the various sources of NPs (nanoparticles) and NMs, natural to synthetic, and their sources of toxic. Additionally, naturally produced nanomaterials with nano-organisms, the health effects and toxicity of nanomaterials were reviewed.

Keywords: Nanomaterials, sources of NMs, sources of toxic, health effects of NMs, Nanomaterial toxicity.

مراجعة للمواد النانوية (Nms) : التصنيف والتوليف بالطرق البيولوجية ومصادرNps السامة والآثار الصحية و الآثار السمية وغير السمية

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الخلاصة

اكتسبت المواد النانوية (NMs) مكانة بارزة في التقدم التكنولوجي بسبب خصائصها الفيزيائية والكيميائية والبيولوجية القابلة للضبط مع تحسين الأداء لها. يتم تصنيف NMs اعتمادًا على حجمها وتكوينها وشكلها وأصلها.. بسبب زيادة نمو إنتاج المواد النانوية وتطبيقاتها الصناعية، فإن القضايا المتعلقة بالسمية أمر لا مفر منه. تقدم المراجعة نظرة عامة على تعريفات المصطلحات العلمية وتصنيفات NMs وتعطي لمحة عامة عن المصادر المختلفة للجسيمات النانوية NPs و NMs ، من الطبيعية إلى الاصطناعية ، ومصادرها السامة. بالإضافة إلى ذلك، يتم إنتاج المواد النانوية بشكل طبيعي من الكائنات الحية الدقيقة وتمت دراسة الآثار الصحية وسمية المواد النانوية.

الكلمات المفتاحية: المواد النانوية، مصادر المواد النانوية، مصادر السمية، التأثيرات الصحية، سمية المواد النانوية.

Introduction

Materials such as nanostructured (NSMs) and nanoparticles (NPs) signify a dynamic area of research and a sector as a techno-economic with full enlargement in numerous domains of application [1]. The NM display various properties as physicochemical compared to bulk material that depends inherently on their shape and size. NMs might be of various shapes i.e., NPs, nano-rods, and nano-sheets that can be branded according to their dimensionality. Surprisingly the NMs yields an exclusive character of new capabilities and characteristics through modifying the size and shape at the level of nanoscale (NS) [2]. NPs and NSMs have added standing in technological progress because of their characteristics as tunable physicochemical i.e., wettability, point of melting, thermal and electrical conduct activity,

activity as catalytic, absorption of light, and scattering leading to enhancing act over their counterparts as bulk [1].

Also, (USFDA) denotes to NMs being "materials that have at least one dimension in the range of approximately 1 to 100 nm and exhibit dimension dependent phenomena" [3]. Likewise, the (ISO) has designated NMs as a "material with any external nano-scale dimension or having internal nano-scale surface structure" [4]. Nano-fibers, nano-plates, nanowires, dots of quantum and other related terms have been well-defined according to such definition of ISO [5]. Similarly, the word NMs is defined as "a manufactured or natural material that possesses unbound, aggregated or agglomerated particles whose external dimensions are in the 1–100 nm size range", as stated by the European Union Commission [6]. Lately, the Institution of British Standards [7] suggested the definitions as following for the scientific terms which have been utilized as show in table 1[1]:

Table 1: Definitions for the scientific terms according to the Institution of British Standards [1]

The scientific terms Definitions
• **NS**: Around range of 1 -1000 nm size. •**Nanoscience**: The matter study and science at the NS which compacts with thoughtful their size and structure-dependent properties and compare the individual molecules or atoms emergence or related differences of bulk materials. • **Nanotechnology**: matter control and Manipulation on the dimension of NS through utilizing scientific understanding of numerous applications as bio-medical and industrial. • **NMs**: Material with any structures as external or internal on the dimension of NS . • **Nano-object**: Materials which have 1 or additional peripheral NS dimensions. • **Nanoparticle**: Nano-object with 3 dimensions as external of NS. The terms Nano-plate or nano-rod are employed, in place of (NP) If the shortest and longest axes lengths of a nano-object are

various.

• **Nanofiber**: If 2 alike exterior dimensions of NS and a 3rd bigger dimension is existing in a nano-material, it is denoted as nano-fiber.

• **Nanocomposite**: Structure as multiphase with a minimum 1 phase on the NS dimension.

• **Nanostructure**: Interconnected composition of constituent portions in the NS region.

• **NSMs materials:** Material comprising surface nano-structure or internal.

NANOPARTICLE CLASSIFICATION

Generally, NPs are categorized according to their morphology, dimensionality, uniformity, composition, and agglomerations [8]. A significant extra distinction must be prepared between thin films of NSMs or other nano-meterscale fixed objects, and NPs being free. The free NPs motion is not controlled, and they are able to be freed easily into the environment, and exposed to human that might pose a severe health hazard.

Also, it is so significant to diagnose that not all the NPs are toxic; toxicity relies on a minimum shape and chemical structure besides to the simplicity aging and size of particle. Actually, numerous NPs types appear to be non-toxic, others might be considered as non-toxic, while others look to have effects being advantageous to health. We are about to learn a significant message from nano-science is that simple physical behavior categorizations (and, consequently, toxicity) are limiting overly and that we should investigate every material toxicology and every morphology, as well to particle aging for obtaining precise data to inform regulatory and policy processes [8].

As NPs morphology or shape plays a significant role in their toxicity, it is beneficial to categorize them according to their dimensions (Fig. 1.) Table 2 [2].

Table 2: According to the nano-scale dimensions (<100 nm) [2].

The dimensions Definitions
1- NM of 0-dimension (0-D): In 0-D, all the NM of 3 dimensions is in the range of NS. NPs will come into such ordering.
2- NM of 1-dimension (1-D): In 1-D, any 1 dimension will be in the range of NS and the remaining 2 dimensions are out of the range of NS. Nano-tubes or nano-wires nanorods are related to such class.
3- NM of 2-dimension (2-D): Any 2 dimensions are in the range of NS and the remaining 1 dimension is out of it. Such comprise nano-layers, nano-films, and nano-coatings.
4- Bulk NM or 3 dimension In whichever dimension, such NM are not in the range of NS. **(3-D):** .Such means in 3 dimensions as randomly they are scale of >100 nm. Such comprise core shells, nano-composites, Multi-nano-layers, nanowires bundles -, and nanotubes bundles [9].

Characteristics of morphology to be considered are sphericity, flatness, and ratio of aspect. A general ordering occurs between low- and high ratio of aspect- particles (Fig. 1). High ratio of aspect NPs is includes nano-wires and nano-tubes of several shapes e.g., zigzags, helices, belts, or maybe nano-wires whose diameter differs with length. A low ratio of aspect morphologies includes oval, spherical, prismatic, cubic, helical, or pillar shapes. Many particle collections exist as suspensions, powders, or colloids [8].

NPs can be collected from one component materials (Fig. 1) or numerous materials. In nature, NPs frequently fonud materials agglomerations of numerous compositions whereas single pure composition materials can be synthesized easily through variety method nowday[8].

According to their electromagnetic and chemistry properties, NPs can be present as dispersed aerosols ,colloids/suspensions, or agglomerate (Fig. 1), e.g., magnetic NPs have a tendency to cluster, creating state as agglomerate, except if the surfaces with a nonmagnetic materials are coated. In the state of being agglomerate, NPs might act as bigger particles, based on the agglomerate size [8].

Hence, it is obvious that nanoparticle size, agglomeration reactivity of surface, and shape, should be considered when considering new materials for environmental and health regulations.

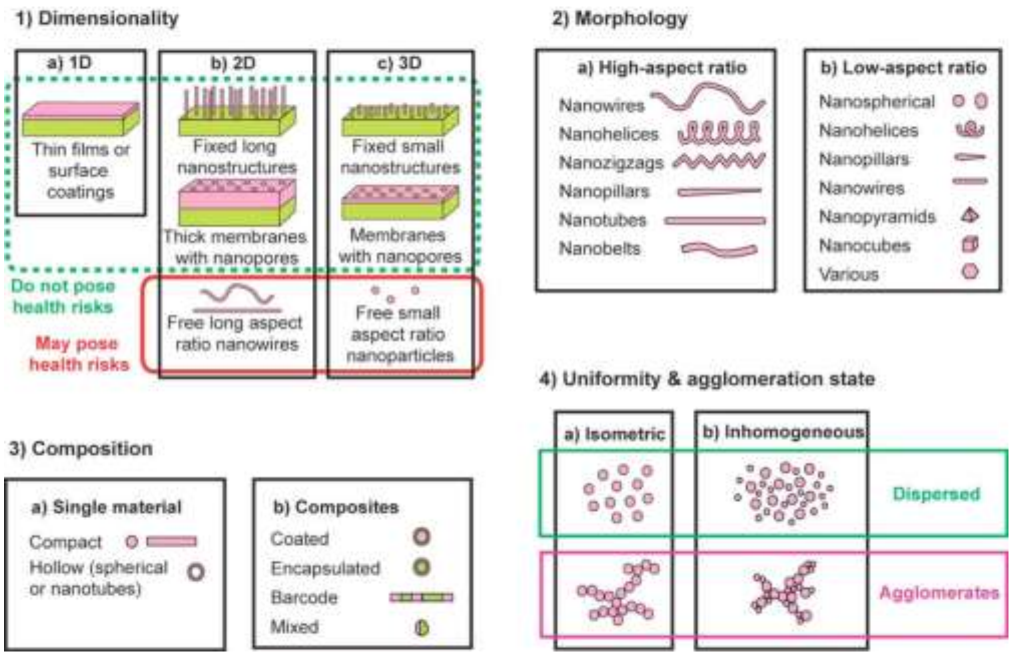

Figure 1: NSMs Classification materials from nano-structure dimensions point of view, composition, morphology, uniformity and state of agglomeration

NMs synthesis [2]

NPs synthesis can be performed via 3 numerous approaches as following:

(1) Biological Methods

(2) Physical Methods

(3) Chemical Methods

In this review, we will focus on the biological method, because this method is easy , simple general in a single step, and friendly for the environment. In such context, we are able to utilize micro-organisms besides different plant parts for NMs preparation [10].

NMs synthesis via microorganisms use [1]

Different micro-organisms (i.e., fungi, bacteria, and algae) might be utilized for various NMs preparation from the metal salts aqueous solution.

Bacterial use

In the process of bio-mineralization, the organisms alive will contribute to NPs synthesizing through utilizing a protein, e.g., bacteria being magneto tactic make the particles as magnetic as a compass to their preferred habitat path through the magneto static use that is protein-coated for the nano-sized magnetic crystals synthesis of iron oxide [11]. In conditions as *in vitro,* the 20–45 nm core diameters of particles being homogeneous might be formed [12-14]. Despite all such, in applications being medical magnetisms displays good properties as magnetic and might be hyperthermia [15, 16]. By utilizing bacteria being photosynthetic set at 10–20 nm size gold NPs extra-cellular. NADH-dependent reductase enzyme of bacteria has a main function in gold ions reduction to gold NPs. They witnessed in which growth medium pH controls NPs morphology and shape [17]. Extracellular palladium NPs production is through utilizing cells of Pseudomonas that are detected in the site of alpine [18].

Fungi use

Fungus of *Fusarium oxysporum* was utilized for extracellular silver NPs preparation. Such are stable long-term NPs because of the NADH-reductase activity. A higher protein secretion amount is noticed in cells of fungi compared to cells of bacteria [19]. Today in the animal feed, food, paper, medicines, and textile industry, *T. reesei* is used extensively.

Algae use

Achieved production (95%) suggested preparation of extracellular gold NPs from Sargassum wightii within 12 h (Singaravelu et al.) [20]. Nanoparticle preparation research via algae use is not further explored. Such processes have disadvantages because few fungi, algae, and bacteria are pathogenic, and thus safety measures want to prevent accumulation.

NMs synthesis by biological templates use

By utilizing the process as biological, the NMs synthesis within the organism might be attained. To attain such, templates being biological are the chief tools. Advanced and exclusive nano-structures are formed by utilizing templates being biological such as proteins and DNA. BioNEMS, bio-sensors [21], and bio-electronics systems [22] can be deliberated by such NPs. Proteins are the chief elements as constituents for nano-composite materials.

NPs tOXIC sources and their effects on health

Individuals are exposing to NPs (diameter <100 nm) from definite workplaces and air being ambient. There are two chief kinds of NPs [23]:

1- combustion-NPs-derived (e.g., matters being particulate, diesel particles exhaust, and welding fumes) are polydispersed, soluble, or poorly soluble with a chemically complex nature, and their toxicity might be because of physicochemical surfaces characteristics. Numerous epidemiological reports have confirmed that elevated particulate matter levels exposure in urban air is linked to the opposing effects of health in humans include an upsurge in mortality and morbidity correlated with diseases as cardiovascular and pulmonary in vulnerable people.

2- NPs engineered or manufactured (e.g., carbon black, titanium dioxide, carbon nano-tubes, copper oxide, zinc, and silver).

Current reports display various associations between numerous physicochemical NPs properties and the related effects on health, raising some doubts where the utmost significant parameters in determining their toxicity: number, mass, bulk, size, aggregation, or chemistry of surface or whole collected. As follow, we will highlight what we consider are the utmost significant nano-particle features related to their toxicity [8].

1. **Toxicity as dose-dependent**: Dose is well-defined as the substance quantity or amounts that will revelry a biological system. The dose is directly related to exposure or the concentration of substance in the relevant medium air, food, and water multiplied by the duration of contact.
2. **Toxicity as size-dependent**: In the former 10 years, studies of toxicology have confirmed that lesser NPs (100 nm) were causing opposing effects on respiratory health, classically cautilizing additional inflammation compared to bigger particles finished from the similar materials. Particles of titanium oxide with 2 sizes, 20 and 250 nm diameters having identical structure of crystalle show that smaller ones caused a persistently inflammatory of high reaction in the lungs in comparison to larger ones.
3. **Toxicity as surface-area-dependent**: For the similar mass of particles with the same crystalline structure and chemical composition, a superior toxicity was detected in NPs compared to their larger counterparts. Such made the conclusion that the inflammatory influence might be relied on the NPs surface area, signifying a necessity for changes in regulations and definitions related to limits of exposure and dose. Certainly, NPs being smaller are of greater area on surface and number of particles per unit mass in comparison to larger ones. Bodies are variously reacting to the similar mass dose having billions of NPs in comparison to numerous micro-particles. Larger area of surface contributes to reactivity enhancement and increased source of ROS, as confirmed by experiments performed *in vitro*.
4. **Toxicity as concentration-dependent**: There are numerous inconsistent findings connected to the effects of toxic NPs at various levels. Few reports display that definite materials are

not as toxic as were perceived by other reports. Through results comparing of numerous reports, one needs to consider the variances in the aggregation NPs properties in water and air, as it results in discrepancies being inherent between instillation and inhalation reports or experiments as *in vitro*. The aggregation might rely on many factors e.g., charge of surface, type of material, size, etc.

Naturally produced NM

NPs and nanostructures (NS) exist in organisms alive ranging from micro-organisms (i.e., algae, bacteria, and viruses), to complex organisms (i.e., insects, plants, animals, birds, and humans). Current equipment developed in for NMs visualizing aid in recognizing such naturally formed NMs morphology. The NS knowledge present in micro-organisms is significant for the further organisms utilize for advantageous bio-medical applications [1].

Insects: they have NS which are made through process as evolutionary which aids them to live in tough living circumstances.

Plants: they consume also the available nutrients in water and soil for the- growth that causes such bio-minerals accumulation in form as nano.

Small insects and animals: they use NS for their defense against organisms being predatory besides the wings as lightweight via coatings being of nano-wax.

Humans: they have organs that are constructed primarily by NS, i.e., bones. enzymes, antibodies, and different secretions which are extremely helpful for the correct function of humans are establish to be in the range of nanometer size. Also, it can be observed that (RNA or DNA) is significant for all living cells function and formation is NS, such shows clearly that NS are the elementary groundwork for all earth life systems. The sections as follow try to list the NS which are exist in organisms alive.

Nano-organisms and health effects:

NS organisms, normally are recognized as nano-organisms, they are established everywhere and even inside the bodies. The class “nano-organisms” are occurring as expected NMs which includes a huge organism’s range (i.e., viruses, nano-bacteria, fungi, yeast, and algae) which are able to yield NPs in thebodies. Many organisms are lesser than a small number of microns, including some bacteria (30 nm–700 µm) and viruses (10–400 nm). Nevertheless, we must make a perfect difference between “particles” (micro-particles or NPs) and nano-organisms or their constituents (including viruses, bacteria, cells and the organelles [1].

Viruses: they are the major structurally branded molecular gatherings known to date, which can be non-living crystal and living organisms inside host cells. Generally, they are considered to be harmful as they cause disease in bacteria [24], plants [25], animals [26], and humans [27]]. Advances in molecular biology have increased the possibility of genetically tailoring viruses for use as catalysts and bio-scaffolds. Nanosize, monodispersity, distinct shapes, selective permeability to smaller molecules, composition controllability by genome manipulation, self-assembly and polyvalence, rapid growth, and stability towards pH and temperature [28, 29], are properties that make viruses an unique category among NMs [30]. Plant viruses have been found to be non-toxic to human cells at required dosages for the effective administration of the drug load [31, 32].

Nano-bacteria and nano-tubes: In general, bacteria are banded to heavy toxic soluble metals and their precipitation on surface, generating metal NPs. These are called nanobacteria and are highly useful in the biosynthesis of low-toxicity NPs [33]. Many metal NPs, such as gold [34], alloy NPs [35], nonmagnetic oxide NPs [36-39], and metal sulfide quantum dots such as CdS [40,41] and ZnS [42], were synthesized utilizing various strains of bacteria. Other than bacteria, actinomycetes such as the *Rmomonospora sp.* and *Rhodococcus sp.* [43] are also used to produce NPs. This bacteria-mediated NP formation was found to be highly useful in a nanomedicine application as they were found to reduce potential cellular toxicity [44]. However, the major drawbacks of these NPs are that they require more time to synthesis, are challenging for filtering, and yield a low NPs harvest in comparison to synthesis as chemically [45].

Algae, yeast, fungi, and bacterial spores: Algae i.e., *Chlorella Vulgaris* support the formation of Ag NPs, phytochelatin-coated CdS by Phaeodactylum tricornutum [46], and nanocomposite and nanoporous structures via coccoliths and diatoms [47]. Since very limited studies are available, the possible mechanisms for algae-mediated nanoparticle formation are still unidentified [48]. Similarly, fungi are utilized for the synthesis of NPs and the literature suggested that they are excellent candidates for metal and metal sulfide nanoparticle synthesis [49]. Fungi contain a variety of enzymes and they are simple to handle, which gives the possibility of synthesizing NPs with various sizes and shapes. It is noted that Fusarium oxysporum and Verticillium sp. of fungi have been noted to aid in Au, Ag, and Au–Ag alloy NP synthesis [50-52]. Enzymes in Fusarium oxysporum fungi also help in the synthesis of CdS quantum dots [53] and serve as a source of sulfate reductases [53,54] and also in the formation of zirconium particles [55]. Moreover, yeasts namely Candida glabrata, Torulopsis sp., chizosaccharomyces pombe, and MKY3 (which is a yeast strain with a tolerance of Ag) were also used in the synthesis of NPs such as CdS quantum dots [56], PbS nanocrystals [57] and Ag NPs [58], respectively. Recently, it was found that the spores of bacteria such as Bacillus anthracis on the NS can cause food contamination and contagious diseases [59]. Similarly, a list of autotrophic plants and heterotrophic microbes that help in the Ag NPs formation besides probable mechanisms of nucleation are offered in latest review papers [60-63]. Such list helps in identifying the crucial factor that induces nanoparticle nucleation. This identification results in the preparation of nanometer-sized targeted drugs that can inhibit the growth of these harmful bacteria in their early stage.

Human body NPs and NS

The body of a human has NS Without it, the normal functions of is not possible. It is made through NS i.e., enzymes, bones, antibodies, proteins, and DNA. A NS list that exists in the body of a human is shown in Table 3. Although some reports classify bone as a nanomaterial comprised of organic collagen and hierarchical inorganic nanohydroxyapatite, [64]. Furthermore, microorganisms like bacteria and viruses are NS that able to cause humans diseases.

Table 3: NSMs list of particles related to the body of human [1]

Nanostructure Size
Glucose 1 nm
DNA 2.2–2.6 nm
Average protein size 3–6 nm
Haemoglobin 6.5 nm
Micelle 13 nm
Ribosomes 25 nm
Enzymes and antibodies 2–200 nm

Toxicity OF NMs

Individuals are exposing to NPs since they are formed by processes being natural [65]. Use, disposal, production, and waste products treatment comprising nano-products are the major environmental causes for the NPs release in their modified or original forms. In general, substances being foreign are impassable by skin, while organs vulnerable to substances being foreign including lungs and GT. NPs are analogous to size of viruses. For example, the (HIV) particle diameter is about 100 nm [65]. Inhaled NPs can effortlessly revery the blood-stream and further locations in the body of human including the heart, liver, or blood cells. It is noteworthy to remark that the NPs toxicity is contingents to their origin. Numerous of them appear to be non-toxic and others are of health positive effects [67]. The general toxic acute effects through NPs and NSMs materials exposure include ROS generation, denaturation of protein, disconcertion of mitochondria, and phagocytic functions perturbation. Based on toxicological information, the NMs toxicity is influenced by several factors [1]:

• Exposure time and dose effect. The NMs number which directly penetrates the cells be influenced by the molar NPs concentration in the nearby media multiplied by the time of exposure.

• Concentration and aggregation effect. Many inconsistent reports are there on the NPs toxicity at various concentrations. Elevating the concentration of NP encourages aggregation. Maximum NP aggregates are micro-meter in size, thus a noteworthy aggregated quantity of NPs might not enter cells thus losing the toxicity.

•Effect of size of particle. NPs reveal dependent toxicity of size.Ag NPs with diameter of ≈ 10 nm display a greater capacity for penetration and disturbing various organisms' cellular systems compared to greater diameters (20–100 nm) of Ag+ ions and Ag NPs [68].

• Effect of particle shape. NPs display toxicity as shape-dependent, in which several levels of toxicity at numerous aspect ratios. E.g., 10 μm length asbestos fibers able to cause cancer of lung, asbestos fibers being shorter (5–10 μm) able to cause mesothelioma, and fibers of 2 μm length able to cause asbestosis [69].

• Effect of surface area. Classically, the toxicological NPs affect upsurges with declining size of particles and elevating the area of surface. Also, it can be noticed that nano and micro-particles with the similar mass dose variously react with the cells of human.

• Effect of structure of crystal. According to the structure of crystal, NPs might display numerous cellular uptakes, mechanisms of oxidation, and localization as subcellular [288]. E.g., the 2 crystalline TiO_2polymorphs (anatase and rutile) display numerous toxicity. Rutile NPs (200 nm) in the dark cause damage toDNA through oxidation, whereas anatase NPs (200 nm) does not cause DNA damage in conditions being dark [70].

• Effect of functionalization of surface. The surface NPs properties of have revealed extreme effects linking to processes of translocation and sub-sequent oxidation [71,72].

Toxicity mechanism

NPs come in the body of humans mainly by [23]:

1- Dermal contact or inhalation.

2- Ingestion or injection (food or medicines).

NMs regulations

NMs have characteristics i.e., extraordinary chemical reactivity and bioactivity, penetration ability of cellular, tissue and organ, and greater bio-availability. Such unique NMs properties render them greater in applications asbiomedical [1]. The regulations through laws, legislation, and rules are implemented by a number of organizations of governments to decrease or escape dangers linked to NMs [73]. Nevertheless no precise international regulation is there, no internationally settled upon production legal definitions or protocols, labeling or handling, toxicity testing, and assessing the environmental NPs impact. Standards of medicine in relation to ethics, safety of environment, and governance as medical are modified for covering NMs introduction into the field of biomedical [74].

In USA, agencies regulation i.e., (FDA), (USEPA) and (IFAS) have established protocols for dealing with the possible NMs risks and nanoproducts. FDA has been searching since 2006 on identifying NMs sources, assessing the environmental NMs impact and their hazards on animals, people, and plants, and the way such hazards could be mitigated or avoided [75]. Such is encompassing a pre-cautionary basis for precise NMs regulations, transparency, health, and public and workers safety, participation of public, protection of environmente, in addition to the broader impacts inclusion and liability of manufacturer [76]

Likewise, the policy approvals report of NMs covers means to reduce or avoid the NMs risk in industries of food-related. Also, the current report guides companies for adopting a policy being detailed public for NMs utilize, publish safety NMs analyses, standards of issue supplier, labeling NPs below 500 nm and adopting an approach for hazard control for preventing exposure to NPs [77]. The Canadian general standards board and the Australian biological farmers [78] [79] already have banned the engineered NPs utilize in food. Manufacturers and researchers must be educated on the regulatory legislations and laws earlier to NMs production for avoiding such bans types against NMs. Currently, it is approved that NMs are not hazardous intrinsically per se and numerous of them appear to be non-toxic, though others have advantageous effects on health. Nevertheless, the assessment risk in the future will govern if the NMs and their products are risky or if any additional actions are required.

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