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BACHELOR THESIS

Assessing potential risks of exposure to nanomaterials on human health – A bibliometric analysis

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Content

Abstract

Background

Due to quick development of nanotechnology, nanomaterials are now widely used in a variety of field, such as consumer goods, electronics, and medicine. Nonetheless, worries about their possible health hazards have surfaced, calling for a through comprehension of their effects on human health. The aim of the following research is to evaluate the state of research on nanomaterials and human health exposure by determining which health consequences are anticipated in the future and by examining the interlinkage between these two key concepts.

Methods

VOSviewer was used to perform a bibliographic analysis, taking into account 3007 papers, in order to accomplish the aim of this research. The information was obtained on the 16th of October 2024 from Scopus database. Bibliometric analysis used co-occurrence analysis and keywords to show emerging and important topic areas. Therefore, it is a suitable approach to achieve the stated research aims.

Results

The analysis revealed four different clusters, of which each represent a unique viewpoint on interlinkage. The main consequences of nanomaterial exposure on human health could be derived from different clusters, including widespread use in consumer product, medical applications, industrial applications, inhalation, dermal contact, lack of safety protocols in the laboratories, lack of awareness and environmental release of nanomaterials. Once released, they have the potential to contaminate soil, water, and air, which could expose humans indirectly through consuming contaminated resources.

Conclusion

The results highlights the importance of continued research on the health implications of nanomaterials. Although there has been a progress in understanding their risks, more research is necessary to fill in the knowledge gaps and guide regulatory policies. Besides that, further risk assessments are necessary to identify possible risks, inform regulatory frameworks, and guarantee that the advantages of nanomaterials are realized without endangering environment or human health. Overall, to ensure that nanotechnology is developed and applied safely for the benefit of human health and the environment, cooperation between researchers, legislators, and industry stakeholders will be essential.

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List of Abbreviations

WHO = World Health Organization

NM = Nanomaterial

NP = Nanoparticle

NNM = Natural Nanomaterial

ENM = Engineered Nanomaterial

MNM = Manufactured Nanomaterial

INM = Incidental Nanomaterial

AgNPs = Silver Nanoparticles

GIT = Gastrointestinal tract

ROS = Reactive Oxygen Species

DNA = Deoxyribonucleic acid

ZnO = Zinc oxide

TiO2 = Titanium oxide

Cu = Copper

1. Introduction

Nanotechnology development in recent years may have had a significant impact on industrial processes, medical research, and electronics manufacturing (Qamar et al., 2024, p. 1). Materials are classified as nanomaterial if at least one of their dimensions is in the range between 1 and 100 nm. Richard Adolf Zsigmondy was the first to use the term “nanometer” in 1914. In 1959 American physicist and Nobel Prize laureate Richard Feynman presented the particular idea of nanotechnology in a speech at the annual meeting of the American Physical Society. This may be regarded as the first scholarly discussion of nanotechnology. “There’s Plenty of Room at the Bottom” was the title of the lecture he gave (Baig et al., 2021, p. 1822). Nanomaterials are widely used in various fields, including pharmaceuticals, cosmetics, energy storage water treatment, air filtration, environmental remediation, chemical and biological processes. They are also used in military defenses, explosives, and variety of consumer devices. For example, nanomaterials can be used in the food industry to create functional foods, new taste and flavor, hygienic food processing and packaging, intelligent, lightweight, and robust packaging, longer shelf lives, and lower levels of agrochemicals, colors, flavors, and preservatives. Improved dispersion

Nanomaterials are widely used in various fields, including pharmaceuticals, cosmetics, energy storage water treatment, air filtration, environmental remediation, chemical and biological processes. They are also used in military defenses, explosives, and variety of consumer devices. For example, nanomaterials can be used in the food industry to create functional foods, new taste and flavor, hygienic food processing and packaging, intelligent, lightweight, and robust packaging, longer shelf lives, and lower levels of agrochemicals, colors, flavors, and preservatives. Improved dispersion and stability of formulations, less usage of chemicals components, and enhanced control over material qualifications. Once more, some take advantage of the improved absorption of nutrients and supplements or elevated levels of chemical and metabolic activity (WHO, 2013, p. 1). In the biomedical field, nanomaterials have gained a considerable attention in the past few decades. Nanomaterials, as novel imaging probes, may provides ultra-sensitive, high-resolution, and high-accuracy diagnostic tools for disease early detection, diagnosis, and management. Furthermore, nanomedicine may have a unique ability to improve drug-forming properties. Beside that, they may developed a new class of therapeutic tools, like photodynamic and photothermal therapy, for the direct treatment of diseases (Liu et al., 2024, p. 2). Apart from the numerous advantageous uses of nanomaterials in health and medicine, there are concerns about the potential negative effects of unintended human exposure to these materials on human health (WHO, 2013).

This aim of this thesis is to use a bibliometric analysis to evaluate the possible health risks related to nanomaterials exposure. This study will use the VOSviewer tool to organize and visualize the current literature into four different clusters: (1) Health Hazard and Heavy Metal, (2) Engineered Nanomaterial and Toxicity, (3) Environment and Nanomaterial, and (4) Food and Pesticide. Each cluster represents a critical area study that highlights the multifaceted nature of nanomaterial exposure and its implications.

In conclusion, analyzing potential health impacts requires an understanding of how nanomaterials impact human health. Therefore, by developing risk management strategies, this knowledge is strategically required to help mitigate health risks. This research aims to address these research gaps by providing answers to the following questions in order to acquire the previously mentioned knowledge:

(1) What is the current status of research on nanomaterials and human health in the literature?
(2) What health implications have been identified for the future of nanomaterial and human health interlinkage?
(3) How are the two key concepts related, based on the current state of the research in the literature?

To accomplish this, the following chapter discusses the theoretical background of the two key concepts: nanomaterials and human health. The methodology, including the data collection and analysis strategies, is then described, followed by the bibliometric analysis results. Thematic clusters are discussed at the end of document, providing additional information to the theoretical framework. Finally, the conclusion section summarizes the key results of this research and provides a forecast for the future.

2. Theoretical Background

2.1 Research in Nanomaterial Applications

The Greek word “nanos” which means “dwarf”, is the source of the prefix “nano” which may getting increasingly prevalent in scientific writing. Countless modern scientific concepts may be commonly referred to as “nano”, and dictionaries may have include terms like “nanometer”, “nanoscale”, “nanoscience”, “nanotechnology”, “nanostructure”, “nanotube”, “nanowire”, and “nanorobot”. Microelectronic fabrication, which uses lithography and thin film coating to produce micro- and nanosized features on computer chips, seems to be the one of most sophisticated nanotechnological fabrication process. On the other hand, the study and industrial application of nanostructured materials may have continued to grow due to development in synthesis and characterization techniques. The key words and ideas in the new vocabulary that has resulted by the research are defined in the following.

Materials with structural components smaller than 1µm in at least one dimension may be referred to as nanomaterials. Bulk crystals with a lattice spacing of nanometers but macroscopic dimensions overall are frequently excluded, even though the atomic and molecular building blocks of matter, which may have a ~ 0.2nm spacing may be regarded as nanomaterials. However, nanoparticles are defined as particles having at least one dimension less than one meter, and possibly as small as 0.2nm for atomic molecular length scales. The surface of nanoparticles, which may be either crystalline or amorphous, may carry gases or liquid droplets (Buzea et al., 2007, p. 22).

In our daily lives, thousand of distinct nanoparticles (NPs) come from a variety of sources, including food, cosmetics, medications, and even the inherent obstacles of living tissues and organs. It is claimed that downsizing materials to nanoscale levels could facilitate their undesirable adsorption. These NPs interaction with the biological environment interfere with cells normal processes and may lead to health problems (Vineet Kumar et al., 2022, p.1). Nanomaterials (NMs), both natural and manufactured, are generated, altered, and released into the environment on a regularly basis. Approximately 79% of all NMs are naturally accruing, and their yearly flow into the environment is far higher than that of synthesized NMs. Synthetic NMs, however, are thought to be harmful into the environment. Synthetic NMs are widely used in many industries, such as chemical, engineering, electronics, and medical, which puts them at a risks of being released into the atmosphere, diverse water sources, soil, and landfill debris. Understanding NMs activity in different environmental situations, their exposure pathway, and their consequences on human health is critical as more and more of them enter our environment and interact with the biota (Malakar et al., 2021, p.1).

In the following part the importance of the research field is shown trough an graphical presentation of data with the Scopus index (see Fig. 1).

Figure 1 shows the number of research publication on the themes of nanomaterial exposure and human health from 2014 – 2025, with Scopus index. the focus on nanomaterials exposure on human health. The data indicates a significant increase in the number of publications over the years, particularly from 2014 to 2023. This suggests a growing interest and research focus in the health implications of nanomaterials. The most notable jump occurs between 2020 and 2021, where the number of documents rose from 230 to 387, indicating a sudden increase in research activity. The number of 2024 and 2025 suggest an expectation of continued growth in this field, with 796 documents projected for 2024. The increasing number of documents reflects the rising awareness of the potential health risks associated with nanomaterials, including their exposure pathways, toxicity, regulatory aspects. This may be consistent with global trends in health and safety research. As more research is conducted, it may influence policy decisions and regulations regarding the use of nanomaterials in various industries, particularly in healthcare and consumer products.

Overall, this data highlights the expanding field of research on nanomaterials and their implications for human health, indicating both a growing concern and a commitment to understanding these complex interactions.

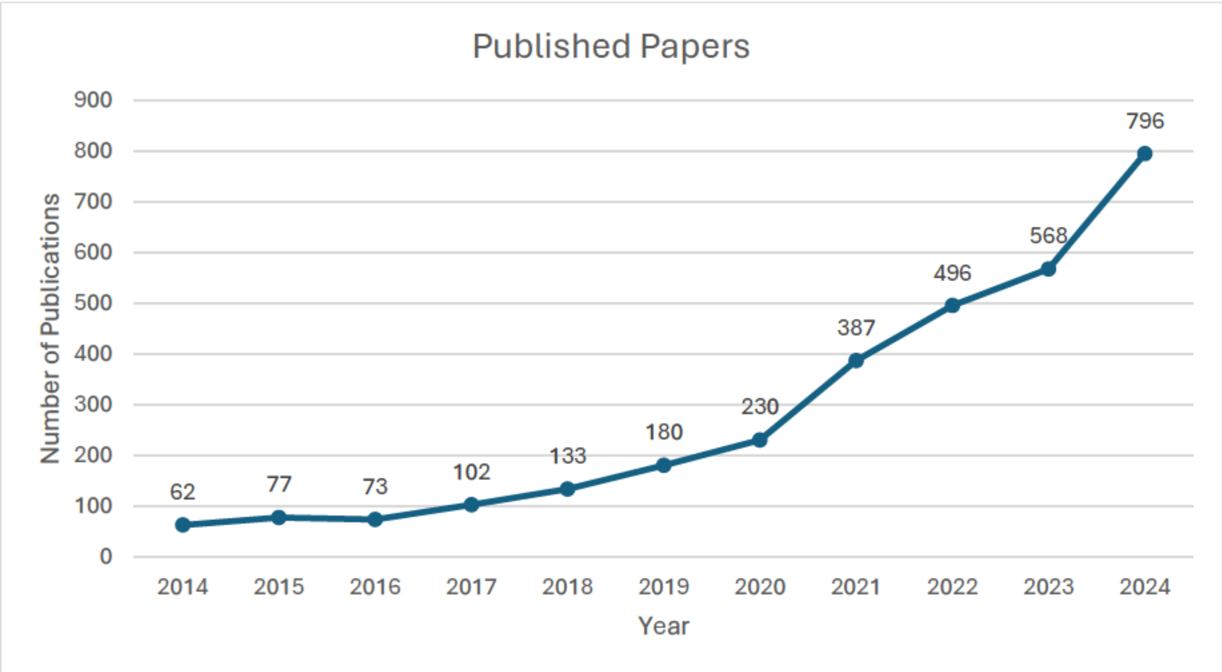

Figure 1: Analyze search results. Adapted from Scopus (2024), author's elaboration

2.2 Nanomaterials

The European Commission (EU) released a recommendation in October 2011 regarding the definition if nanomaterial (2011/696/EU), henceforth referred to as the EC Definition. The objective of this make it possible to determinate when a substance qualifies as a nanomaterial (NM) for within the European Union for regulatory purposes. The term encompasses natural, incidental and manufactured materials and is determined only by the size of a materials constituent particular risks or functional characteristics of hazards. The following definition of 'nanomaterial' is suggested by the European Commission:

"Nanomaterial means a natural, incidental or manufactured material containing particles, in an unbound state or as an agglomerate and where, for 50% or more of the particles, in the number size distribution, one or more extremal dimensions is in the size 1nm – 100 nm. 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%."

The *Recommendation* additionally identifies:

"By derogation […] fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimension below 1 nm should be considered as nanomaterials" (Rauscher et al., 2014, p. 15).

Materials classified as nanometer material may have at least one dimension in a three-dimension space that is nanoscale (1-100 mm) or are made of basic nanometer materials (Attarilar et al., 2020; Isodat et al., 2020, as cited in Cheng et al., 2021, p. 2). Because of their superior physiochemical characteristics, they may have been extensively utilized with great success in numerous fields, including materials, optoelectronics, aerospace, military, and biomedicine potential. Engineered nanomaterials (ENM) are useful because they regularly show up in commercial goods (Gubala et al., 2018b; Liu et al., 2020d; Zhang et al., 2020, as cited in Cheng et al., 2021, p. 2). Because of this, nanomaterials may be continuously added to the environment in addition to existing naturally. Due to human production and living activities, nanomaterials may be constantly being released into the environment (Cornu et al., 2020; Lojk et al., 2020; Missaoui et al., 2018, as cited in Cheng et al., 2021, p. 1). Nevertheless, the use of nanoparticles may have numerous advantages, including environmental. With a well-considered approach, the toxicity may be a concern. This could cause unforeseen risks to one's health or the environment, which is a source of concern (Saleh, 2020, as cited in Vineeth Kumar et al., 2020, p. 1). The main way of exposure to nanoparticles may be through the respiratory system and skin. Therefore, most toxicological studies may be based on inhalation, skin, and oral exposure; hence they focused on the lungs, liver and skin (Cao et al., 2018b; Liu et al., 2020d; Zhang et al., 2020 as cited in Cheng et al; 2021, p. 2).

Natural Nanomaterials

The naturally occurring nanomaterials found in the crust of the Earth's are categorized as Natural NM (NNMs). Typically, these are created by various biogeochemical process. Every year, a million megatons of NNMs with sizes ranging from one to a thousand nanometers may circle the Earth (Hochella et al., 2019; Tabasum et al., 2019; Malakar et al., 2021, p. 2).

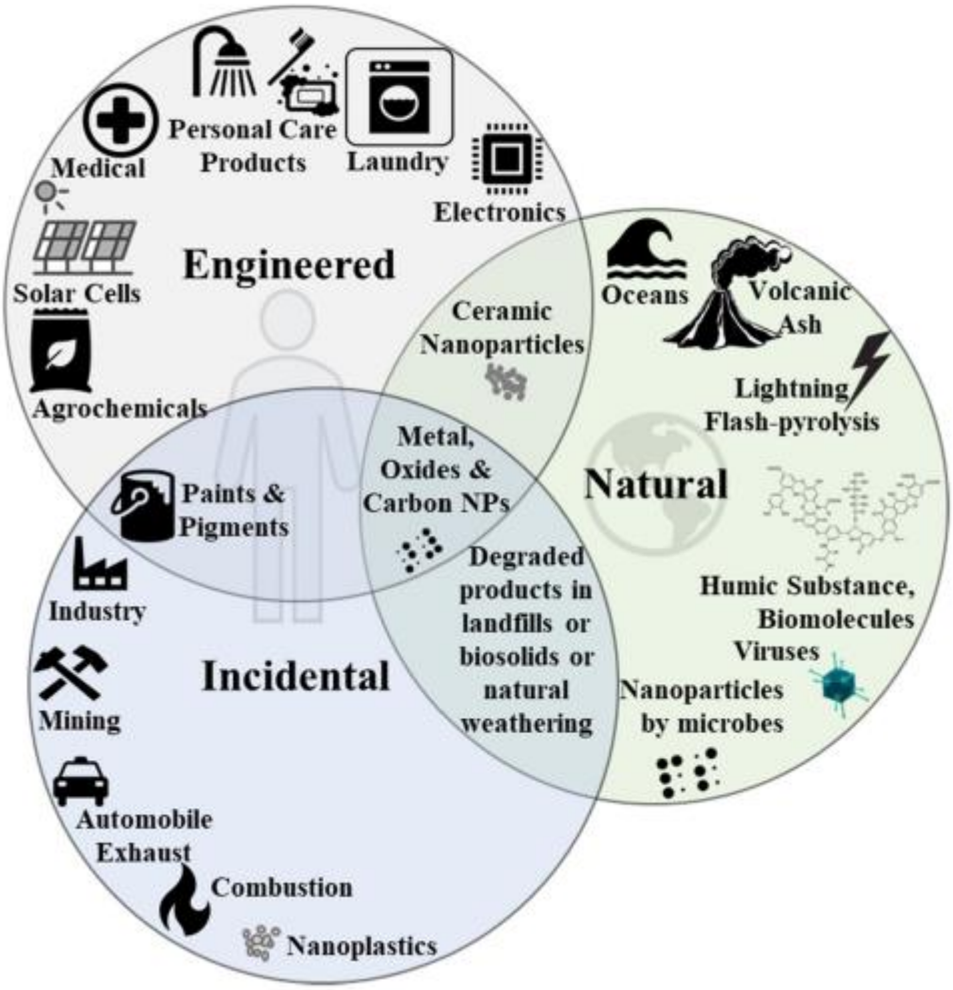

Figure 2: *Different classes of natural and anthropogenic nanomaterials. It shows how these various nanomaterials are formed are formed, where they are primarily present, and where the engineered, natural and incidental NM are major utilized. Adapted from Nanomaterials in the environment, human exposure pathway, and health effects: A review, Malakar et. al. (2021, p. 4).*

Incidental Nanomaterials

Incidental nanomaterials are created by human induced activities unintentionally producing nanomaterials (Baalousha et. al., 2016, as cited in Malakar et al., 2021, p. 4). Figure 1 illustrates multiple sources of accidental nanoparticles, including wear and corrosion processes, combustion processes, industrial and mining waste, and vehicle exhaust. It can be metal- or carbon-based, resulting from corrosion in tap water, or carbon-based, such as carbon soot from combustion or nanoplastics from plastic degradation, and may come into contact with humans (Kunhikrishnan et al., 2015; Lehner et al ., 2019; Maher et al., 2016; Venkatesan et al., 2018; Westerhoff et al., 2018, as cited in Malakar et al., 2021, p. 4). A case study for incidental NMs is presented in Figure 2, which is a reproduction of a work by Baalousha et al (2016). In this case study, PM2.5 air samples were collected in Shanghai, China, on a foggy day, and they were examined using X-ray energy dispersive spectroscopy (X-EDS) and transmission electron microscopy (TEM). The presence of incidental NMs of aluminum, iron, and lead is indicated by the bright-field TEM micrograph (a) and X-EDS maps (b-i), which also demonstrate the presence of NMs of calcium silicate (c, e, and g), galena (f and i), and iron oxide (c and h) (Baalousha et al., 2016, as cited in Malakar et al., 2021, p. 4).

Engineered nanomaterials

Engineered nanomaterials (ENMs) are defined as those that are created for commercial use (Baum et al., 2017; Singh, 2016, as cited in Malakar et al., 2021, p. 4). ENMs may be used in variety of industries, including computing, telecommunications, agrichemicals, and personal care goods. The use of ENMs may be growing daily, and more of them are finding their ways into different water sources (Malakar et al., 2019; Malakar and Snow, 2020; as cited in Malakar et al, 2021, p.4). ENMs may be utilized in a wide range of technologies, including quantum computing and agriculture (Kahle et al., 2018, as cited in Malakar et al., 2021, p. 4). Nanotechnology may be play a crucial role in various sectors nowadays. The morphology of ENMs, such as quantum dots, nanorods, graphene, or fullerene, as well as their composition, such as metal-or carbon nanomaterials, can be used to classify them into broad categories (Jeevanandam et al., 2018, as cited in Malakar, 2021, p. 5).

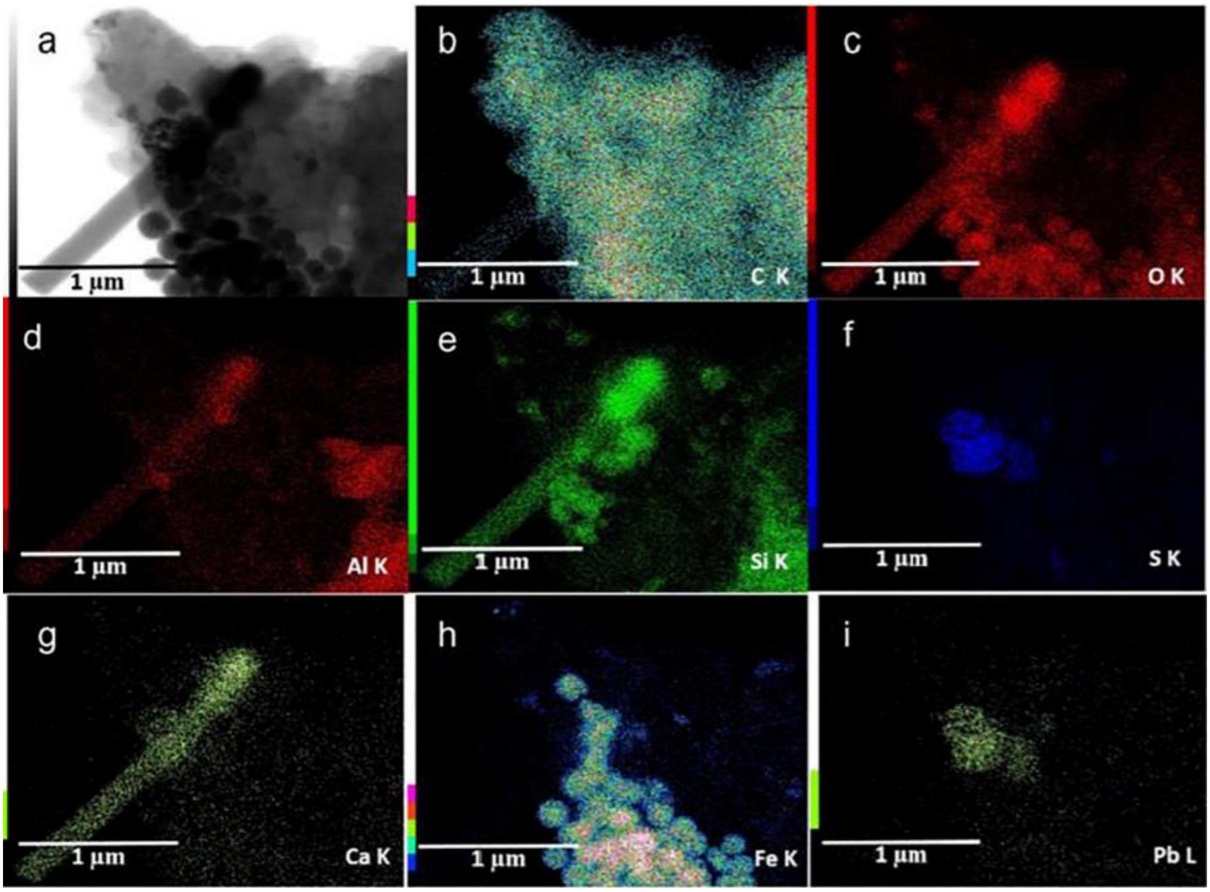

Figure 3: *Transmission electron microscopy (TEM) and X-ray energy dispersive spectroscopy (X-EDS) maps of a typical NM aggregate in a carbon matrix found in a PM2.5 sample collected during a hazy day in Shanghai, China: (a) bright field micrograph; and (b–i) elemental maps of O, Al, Si, S, Ca, Fe and Pb, respectively. These analyses indicate the occurrence of iron oxide (c and h), galena, PbS (f and i) and Ca2SiO4 (c, e and g) nanomaterials. Iron oxides were identified as magnetite NMs using their selective area electron diffraction (SAED) patterns (data not shown). Reproduced from Baalousha et al. (2016) with permission from Elsevier. Adapted from Nanomaterials in the environment, human exposure pathway, and health effects: A review, Malakar et. al. (2021, p. 5).*

Morphology-based classification of ENMs.

Figure 3 displays examples of NM classification based on morphology, as reproduced from Jeevandam et al. (2018). And it also illustrates (A) nonporous palladium nanoparticles with zero dimension (D) and (B) 2D graphene. Examples of 1D nanosheets include silver nanorods and polyethylene oxide nanofibers (C-D), whereas 3D examples include zinc oxide nanowires and tungsten oxide nanowire networks (E-F). Electrons are often enmeshed in dimensionless space in 0D NMs, unidirectional spaces in 1D NMs, and bi-directional or multi-directional space in 2D and 3D NMs, separately (Jeevanandam et al., 2018, as cited in Malakar et al., 2021, p.5). Both zero (0) and one (1) dimensional materials may be widely used and produced in large quantities for commercial use. Among the various nanomaterials, two-dimensional material (2D) nanomaterials may be a relatively new and appealing high member. One well-known example of 2D NM may be graphene. The considerably physical, chemical, optical, and electrical characteristics of 2D NMs and related, nanocomposites may have led their wide range of applications in energy, catalysis, bioimaging, antibacterial, drug delivery, and therapy (Su et al., 2019; Tan et al., 2017; Wang et al., 2012, as cited in Malakar, et al., 2021, p. 5). Graphene, the first two-dimensional atomic crystal, may lives up to its moniker as “miracle material” due to its physical and chemical properties (Fang et al., 2015, as cited in Malakar et al., 2021, p.5). A digital computer model may serves as the foundation for 3D printing, a technology that builds 3D structures using a “bottom-up” discrete-accumulative approach. Structures with carefully controlled geometry and size can be created using three-dimensional printing and used in the chemical, medical and electronical fields (Jiang et al., 2019, as cited in Malakar et al., 2021, p.5). According to a study, 3D macrostructures may have better adsorption capacities than both conventional and developing contaminants because they might be made of self-assembling 2D graphene oxide (GO) and 1D carbon nanotubes (CNTs) (Shen et al., 2017, as cited in Malakar et al., p. 5). When CNTs were evaluated for their ability to adsorb CIO4-, it may be was discovered that the order of increase in CI04- adsorption into various CNTs seemed to be multi-walled CNTs < single-walled CNTs < double-walled CNTs (DWCNTs) (Fang and Chen, 2012, as cited in Malakar et al., 2021, p.5).

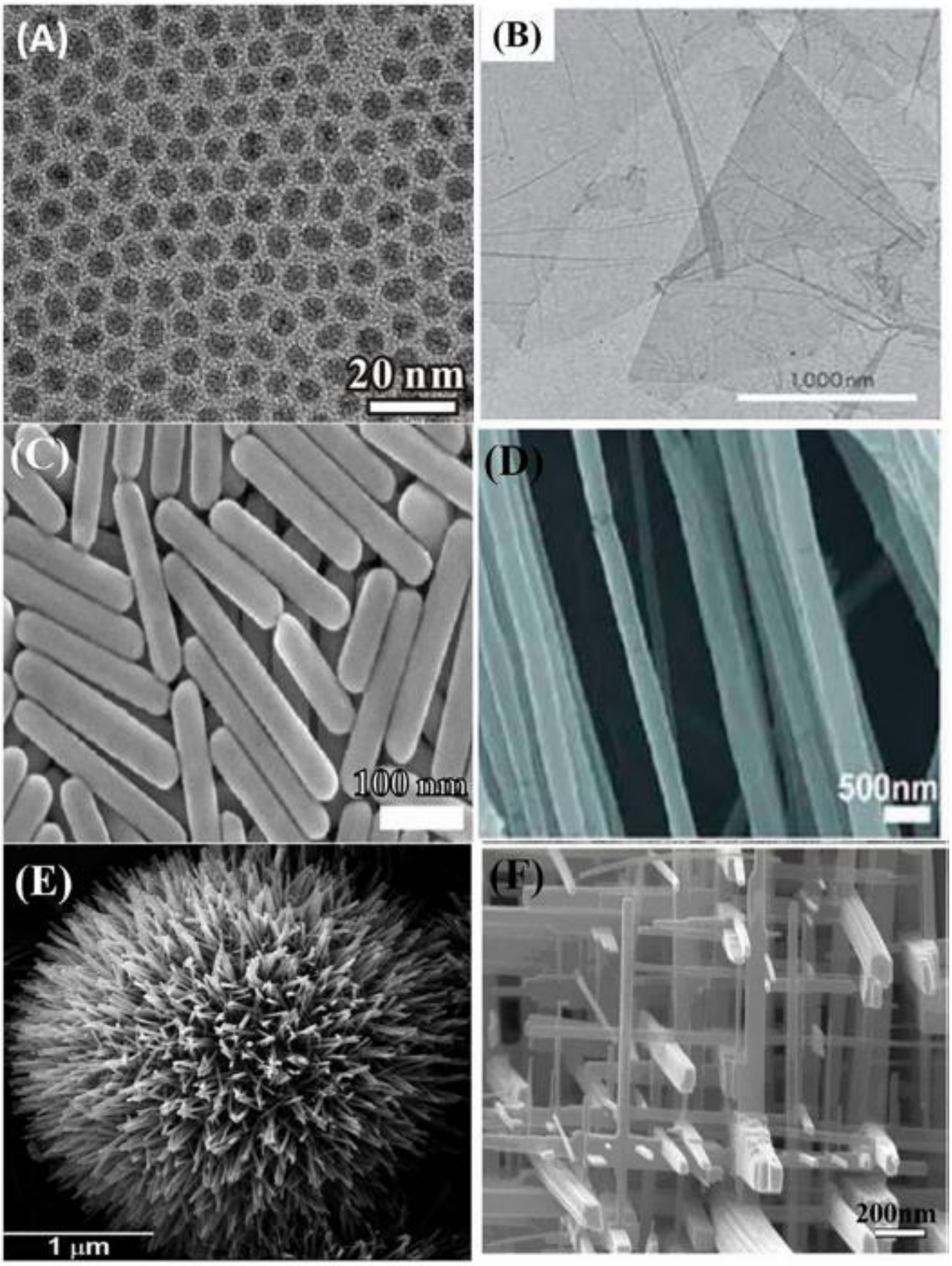

Figure 4: *Nanomaterials with different morphologies: (A) nonporous Pd NPs (0D) (B) Graphene nanosheets (2D) (C) Ag nanorods (1D) (D) polyethylene oxide nanofibers (1D) (E) urchin like ZnO nanowires (3D) (F) WO3 nanowire network (3D). Reproduced from Jeevanandam et al. (2018) with permission from Beilstein Journal of Nanothechology. Adapted from Nanomaterials in the environment, human exposure pathway, and health effects: A review, Malakar et. al. (2021, p. 6).*

2.3 Human health

Despite the widespread use oft the term “health“ in everyday discourse, its definition and meaning may be different. Human health can be defined in a variety of ways, including as a resource, a state of balance or well-being, or the antonym of disease. In a similar vein, different researchers and disciplines have different definition.

The definition provided by the World Health Organization (WHO) in its 1948 constitution may be perhaps the most often used one. It states that “health is a state of complete physical, mental, and social well being and not merely the absence of disease or infirmity” (WHO, 2024, p. 1).

Alternative definition of health may have attempted to balance the aspirational and absolute conceptions of health (McCartney et al., 2019, p. 23)

“Health is the experience of physical and psychological well-being. Good health and poor health do not occur as a dichotomy, but as a continuum. The absence of disease or disability is neither sufficient nor necessary to produce a state of good health” (Card, 2017, p. 131*).*

These definitions may avoid the WHO’s binary and supreme challenges, instead introducing a similar term (“the extent to which”) built on ambitious realization, need satisfaction, and ability to cope with a variety of settings. One potential advantage of this method may be that health is contextually defined by cultural norms about desire and necessity, and thus evolves over time. However, failure to identify potentially enormous disparities in mortality or morbidity between populations (e.g., Sierra Leon and Frane) or change in expectations over time based on contemporaneous and local morality and morbidity experience may be problematic. Recognizing the essentially relative nature of health assessment and the significance of the selection of comparator populations may be crucial since the interpretation of health includes some sort of comparison across populations or between points in time. This covers who may be included and omitted from the definition of a population, as well as the income level and development history of populations both inside and between countries (McCartney et al., 2019, p. 23 – 24). The term “human health” will be used in this research based on Last’s dictionary of public health (2007) which provides two definitions of health that have worthwhile quality:

“A sustainable state of equilibrium or harmony between humans and their physical, biological and social environments that enables them to coexist indefinitely”

“A structural, functional and emotional state that is compatible with effective life as an individual and as a member of family and community groups” (Last, 2007, as cited in McCartney et al., 2019, p. 24).

The first definition comes from an ecological viewpoint, according to which sustainability and interaction with the environment may be key components of health. And the latest definition given by Last may have the multidimensional components of the earlier WHO definition, as well as an experience element that many of the proposed definition lack, but avoids an absolutist view that health must be a ‘complete’ state. Additionally, this definition associates health with the ability to participate socially, which may be lacking in many definition of poverty, as well as to operate independently (Last, 2007, as cited in McCartney et al., 2019, p. 24).

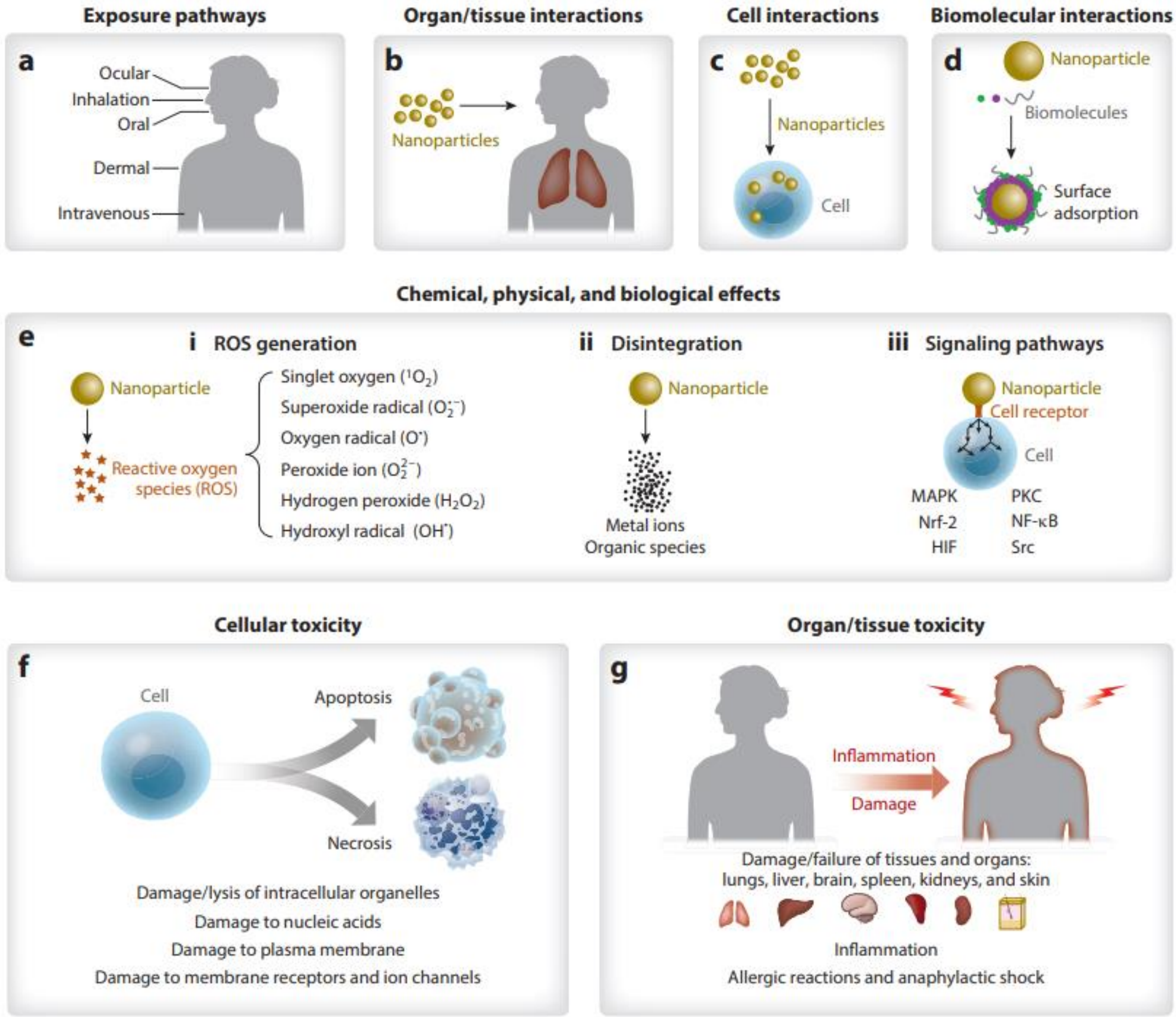

Figure 5: *Schematic representation of nanoparticle adverse effects and nanotoxicity. (a) Nanoparticle exposure pathways. Upon exposure, nanoparticles can interact with (b) organs/tissues, (c) cells, and (d) biomolecules. Major nanoparticle toxicity mechanisms include (e, i) the generation of reactive oxygen species (ROS), (e, ii) nanoparticle disintegration and release of metal ions and organic species, and (e, iii) nanoparticle-mediated activation of cell signaling pathways. Nanoparticle adverse effects and toxicity can lead to (f) cell apoptosis and necrosis and (g) tissue/organ damage, inflammation, and anaphylactic shock. Adapted from Nanoparticle Toxicology: Annual Review of Pharmacology and Toxicology, Yang et al. (2021, p. 272).*

2.4 Human Interaction with Nanomaterials

The main focus of nanotoxicology, a branch of nanomaterials toxicology, may be the harmful effects of nanomaterial exposure. Due to differences in the properties of materials at the nanoscale, change may result in an explosion of effects that are unique to a size-specific domain that may be completely absent from bulk materials (Laux et al., 2018; Mourdikoudis et al., 2018, as cited in Asmatulu et al., 2022, p. 2512) The majority of study may have been on nanomaterials, with little to no studies on the effects of natural nanoparticles on the human immune system were presented by Cronin et al. (Cronin et al., 2020, as cited in Asmatulu et al., 2022, p. 2512). Depending on how the physical and chemical characteristics of the nanomaterials may be exposed, there might be differences in the life cycle, residence periods, and eventual fate of the nanomaterials in different human organs (Gupta and Xie, 2018, as cited in Asamtulu et al., 2020, p. 2512). The production volume and required use of engineered nanomaterials may have led to a number of worries about their life cycle and potential harm to human health (Asmatulul et al., 2021, p. 2512).

<u>Exposure of engineered nanomaterials to humans</u>

Engineered nanomaterials (ENMs) may have become increasingly popular in industrialized applications because of their unique properties related to size. This may have raised concerns about their security and potential effects on human health (Asmatulul et al., 2021, p. 2512). ENMs may be in high demand for consumer and commercial applications, including food additives, water purification, soil cleaning, sunscreen, biocides, supplement, shampoos, agriculture, energy production, feed, veterinary drugs packaging and IT (Martirosyan and Schneider, 2014; Kaphle et al., 2018; Yata et al., 2018; Rai et al., 2019, as cited in Asmatulul et al., p. 2512). Common nanopesticides on the market may be larger than 100 nm, however as research into nanotechnology advances, it is possible that more goods may be related to agriculture will fail into the lower 100nm range of nanoscale size (Chhip, 2017, as cited in Asmatulul et al., 2021, p. 2512).

After identifying a source of ENMs, it may be important to evaluate the risks of exposure. Assessing possible exposures to ENMs might be challenging due to their various variations. It may be important to investigate not only the amount of nanomaterial present at a receptor, but also its specific shape at the point of exposure. Nanoscale materials may experience subtle and dramatic alterations as they pass through biological and environmental systems. Changes in size, surface chemistry, and reactivity may create various hazards (Committee to Develop a Research Strategy for Environmental, Health and Safety Aspects of Engineered Nanomaterials, 2012, p.77).

Manufactured nanomaterials (MNM) ingestion, skin absorption, or inhalation may all pose health risks. Because of their massive surface area, low epithelial barriers, and vast vasculature, the human lungs may be a prime entry point for MNMs. Although exposure through the skin and mouth is possible, inhalation is more likely to result in a higher systematic dose of MNMs. The largest recognized health risks at this time may be inhaling bio-persistent particles and fibers that resemble asbestos and may cause cancer and localized inflammation.

Even though people may have been exposed to accidentally produced nanomaterials, such as those from combusting processes, more research is necessary to determine the possible toxicity and negative health impacts of these materials after exposure given the recent rise in

MNM synthesis. It may be generally recommended to remain caution until test results are available because newly created MNMs may not be thoroughly studied for potential health risks. This implies that unless there is unambiguous evidence to the contrary, NMs should be regarded as harmful (WHO, 2017).

2.5 NMs impact on human health

Humans may be exposed to NM by a variety of routes, including injection, ingestion, skin penetration, and inhalation (Oberbeck et al., 2019, as cited in Malakar et al., 2021, p. 12). One of the main routes of exposure may be the inhalation of airborne nanoparticles which might enter and settle in lung tissues and alveolar region (Qiao et al., 2015, as cited in Yang et al., 2021, p. 276). Both acute and chronic lung inflammation by oxidative stress might result from the buildup of nanoparticles in the lungs (Zhang et al., 2012; Adamcakova-Dodd et al., 2014, as cited in Yang et al., 2021, p. 276). Nanoparticle buildup in the brain may also result from inhalation. According to Maher et al. (2016), the olfactory bulb allows airborne magnetite nanoparticles to penetrate the brain. Magnesium oxide (ROS) generation may be increased when magnetite nanoparticles, which may be prevalent in airborne particulate matter pollution, accumulate in the brain. This may be associated to the development of neurological illnesses like Alzheimer's disease (Maher et al., 2016; Lin et al., 2020, as cited in Yang et al., 2021, p. 276). Nanoparticles may interact with the primary organ or tissue they come into contact with once they have entered the body. In order to reach distant organs or tissues by systemic transport, nanoparticles may also subsequently translocate and enter the bloodstream (such as from the lungs to the capillary network to larger arteries) (Choi et al., 2010; Raftis & Miller, 2019, as cited in Yang et al., 2021, p. 276). Nanoparticles may interact with cells and intracellular organelles in organs, tissues, and blood to potentially induce toxicity at the cellular and subcellular levels. It may be crucial to note that nanoparticles may interact with a wide range of biomolecules once they enter the body, including lipids, proteins, carbohydrates, and nucleic acids. A surface corona of biomolecular nanoparticles, also called the protein corona, might be formed as a result of these interactions. The formation of protein corona, also known as biomolecular corona, may alter the surface chemistry of nanoparticles and significantly activate the complement system, which can eventually impact nanotoxicity and the effectiveness of nanomedicine (Moghimi & Simberg, 2017; Szebeni, 2014; Abu Lila et al., 2014, as cited in Yang et al., 2021, p. 276). Protein unfolding may also result from protein degradation to nanoparticles surfaces (Dominiguez-Medina et al., 2016; Deng et al., 2011, as cited in Yang et al., 2021, p. 276). This process may result in immunotoxicity and the loss of protein function (Saptarshi et al., 2013; Neagu et al., 2017, as cited in Yang et al., 2021, p. 276). Furthermore, the activation of cell signaling pathways (Deng et al., 2011, as cited in Yang et al., 2021, p. 276), loss of enzyme activity (Nel et al., 2006, as cited in Yang et al., 2021, p. 276), aggregation of nanoparticles (Dominiguez-Medina et al., 2016, as cited in Yang et al., 2021, p. 276), development of new antigenic sites (Cedervall et al., 2007, as cited in Yang et al., 2021, p. 276), and protein fibrillation (Linse et al., 2007, as cited in Yang et al., 2021, p. 276).

2.6 Risk management strategies for reducing the impact of NM

With the development of nanotechnology, advanced tools may have been available to develop novel materials (e.g., building from the atom upward or breaking down bulk materials). This technology may have not only made it easier to produce new products with novel applications of nanoscale properties in optics, electronic, photocatalysis, energy generation, enhanced material strength, lightweight composites, and conductivity, it also made it also possible to create synthetic materials that may interact with biological molecules and cellular processes – some of them may possess deep-seated nanoscale features or purposes (Roco, Mirkin, Hersam, 2010, as cited in Nel, 2013, p. 561). Although there may have been rapid gains in research and knowledge collection about ENM safety, nanotechnology may be based on innovative, scientific principles that should be considered when assessing hazards. Because of lack of information and uncertainty about how to deal with complicated three-dimensional ENM structures, the initial approach may have been to view there materials as 'novel' chemical materials and assess their safety using traditional chemical toxicity methodologies. Based on current experimental findings, it may be evident that safety assessment would have to be modified to account for the contribution of nanoscale characteristics and functions to the pathways of toxicity (POTs), and that descriptive animal studies that assess material at a time are not suitable for this purpose (Oberdorster et al., 2005; Nel et al., 2006; Meng et al.., 2009, as cited in Nel, 2013, p. 562).

Because of the complexity of omics platform, robotics, high adoption of high throughput screening (HTS), and requirement for computational analysis of large database, risk assessment expert usually may interpret risk assessment as primary a high-volume in vitro screening exercise with no obvious connection to traditional techniques. As a result, risk assessment may be will need adapt to accommodate predictive toxicological approaches and the development of alternative testing strategies (ATSs). However, the backlog produced by implementing standard safety assessment procedures, to deal with the vast quantity of untested chemicals may have raised significant concerns, potentially slowing efforts to bring new technology to market (Hartung, 2009, as cited in Nel, 2013, p. 570). As a result, regulators and companies around the world may appear to be becoming increasingly aware that the current status quo needs to change and that it may be the time to investigate the role of ATSs and predictive toxicological modeling (Gangwal et al., 2011; Oberdorster, 2012; Chen et al., 2012; Kuempel & Castranova, 2012; Kuempel & Geraci & Schulte, 2012; Kuempel & Castranova & Geraci, 2012, as cited in Nel, 2013, p. 570).

3. Methods

In order to achieve the aim of this research, a bibliometric analysis will be conducted. This will be done by using a data-collection strategy. A methodical approach to date collection will be used to in this analysis, which includes locating pertinent scholarly works, articles and publications that are relevant to the research topic. The data-collection strategy will include a number of key steps: The first step is to clearly define the kind of literature that is considered relevant, including time frames, keywords, and publication types (such as journal articles, books, book review, conference paper). The next step is the data selection. Scopus was chosen as a suitable academic database and repository in order to guarantee a diverse and representative sample of the literature. The bibliometric data, which may include publication counts, citation metrics, authorship details, and public trends over time, must then be extracted using the specified keywords and criteria. Lastly, in order to effectively communicate the conclusions and insights obtained from the bibliometric analysis, visual representation of the data, such as graphs will be created.

3.1 Data Collection Strategy

To conduct a bibliometric analysis, data must be collected from academic sources related to the research topic, which is in this case nanomaterials and its impact on human health. Consequently, in order to access a scientific database containing the relevant data, a search string is required. The search string (see Tabel 1) contains the most essential keywords relevant to the research which could be done by using narrative literature research targets. Various approaches were used to find the most appropriate search string with sources relevant to the research aims; however, a fractional search for each nanomaterials dimension revealed a large number of sources and was thus unused. The first part of the search string contains terms related to human health, and the second part focuses on nanomaterial exposure. In both cases, the TITLE operator was used to select data that was primarily focused on the keywords found in the search string. Furthermore, health-related keywords are included in the final part of the search string. As a result, the literature on nanomaterials exposure and human health was narrowed down to sources that used health-related keywords throughout the text, and no operator was used in the last part. The Scopus scientific database was chosen for its extensive coverage of various sources. The search was conducted on October 16th, 2024, yielding 3016 papers. This initial number was further reduced by using inclusion criteria to eliminate irrelevant sources. The exclusion criteria are shown in Table 1. After applying the inclusion criteria, a total of 3007 papers were chosen for downloading their bibliographic data.

Table 1: Search strategy

Search String	**Inclusion criteria**	**Number of documents**
TITLE ("human health" OR "health" OR "respiratory health" OR "health risk" OR "cardiovascular health" OR "long-term health" OR "mental health" OR "health impacts" OR "physical health" OR "healthcare" OR "health risks assessments" OR "health effects" OR "health impact" OR "health impact assessment" OR "health implications" OR "health hazard") AND ("exposure" AND ("nanomaterials*" OR "nanotechnology" OR "nanoparticle toxicity" OR "nanomaterials bioaccumulation" OR " nanomaterials risk" OR "nanomaterials pathway" OR "nanomaterials regulation" OR "engineered nanomaterials")) AND PUBYEAR > 2013 AND PUBYEAR < 2026 AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re") OR LIMIT-TO (DOCTYPE , "ch") OR LIMIT-TO (DOCTYPE , "cp")) AND (LIMIT-TO (LANGUAGE , "English"))	▪ English language ▪ Article, Book Chapter, Editorial, Conference Paper or Book ▪ Year	3007

3.2 Data Analysis Strategy

Bibliometric analysis are seen to be beneficial as supplementary tools for decision – making concerning, among many others, funding distribution, identifying areas of scientific excellence, tracking the advancements of science and technology, and prioritizing research. These techniques, which originated in the field of information and library science, may have5 rapidly expanded due to their adaptability. The spread of information may be partly caused by the volume of available data and its accessibility. Additionally, since processing and analytical tools may have become more advanced, current bibliometrics are now accessible to practitioners and scientist of any ability levels (Meija et al., 2021, p.1). Software with bibliometric analysis option can be used to process the data and display its different features. The bibliometric program VOSviewer was used to enter the previously collected data. The software tool called

VOSviewer is used to create maps from network data and to visualize and explore them. Using network data to create maps may be improved by it. An already existing network can be used as the basis for an map, but it is also necessary to first build a network. Networks of scientific publications, scientific journals, researchers, research organizations, countries, keywords, or terms can be created by using VOSviewer. Co-authorship, co-occurrence, citation, bibliographic coupling, or co-citation linkages are some of the ways that items in these network are related to one another. Data from Web of Science, Scopus, PubMed, RIS, or Crossref JSON files can be applied to built a network. Map exploration and visualization are also conducted with it. The network visualization, overlay visualization, and density visualization are the tree map visualization options offered by VOSviewer. The possibility to zoom and scroll on a map makes it possible to study it in complete detail, which is crucial when working with big maps that include thousands of items on them. VOSviewer can be used to develop, visualize, and analyze maps based on any kind of network data, even though it's primary purpose may be to analyze bibliometric networks (van Eck & Waltman, 2023, p. 3).

Items are shown in the network visualization by their labels and, by default, by a circle. The weight of the object may determine the size of the label and the circle. Both the label and the items circle enlarge with increasing weight. The label might not appear for some items. This process serves to prevent labels from overlapping. The cluster to which a certain item belongs determines its color. Links are shown by lines connecting items. The 1000 strongest linkages between items are represented by the largest number of 1000 lines that are shown by default (van Eck & Waltman, 2023, p. 9).

Figure 5 shows an illustration of the network visualization. The visualizations distance between two journals roughly represents how related the journals are to one another in terms of co-citation relationships. Typically, two journals are more related the closer they are to one another. The lines also show the strongest co-citation relationships between journals.

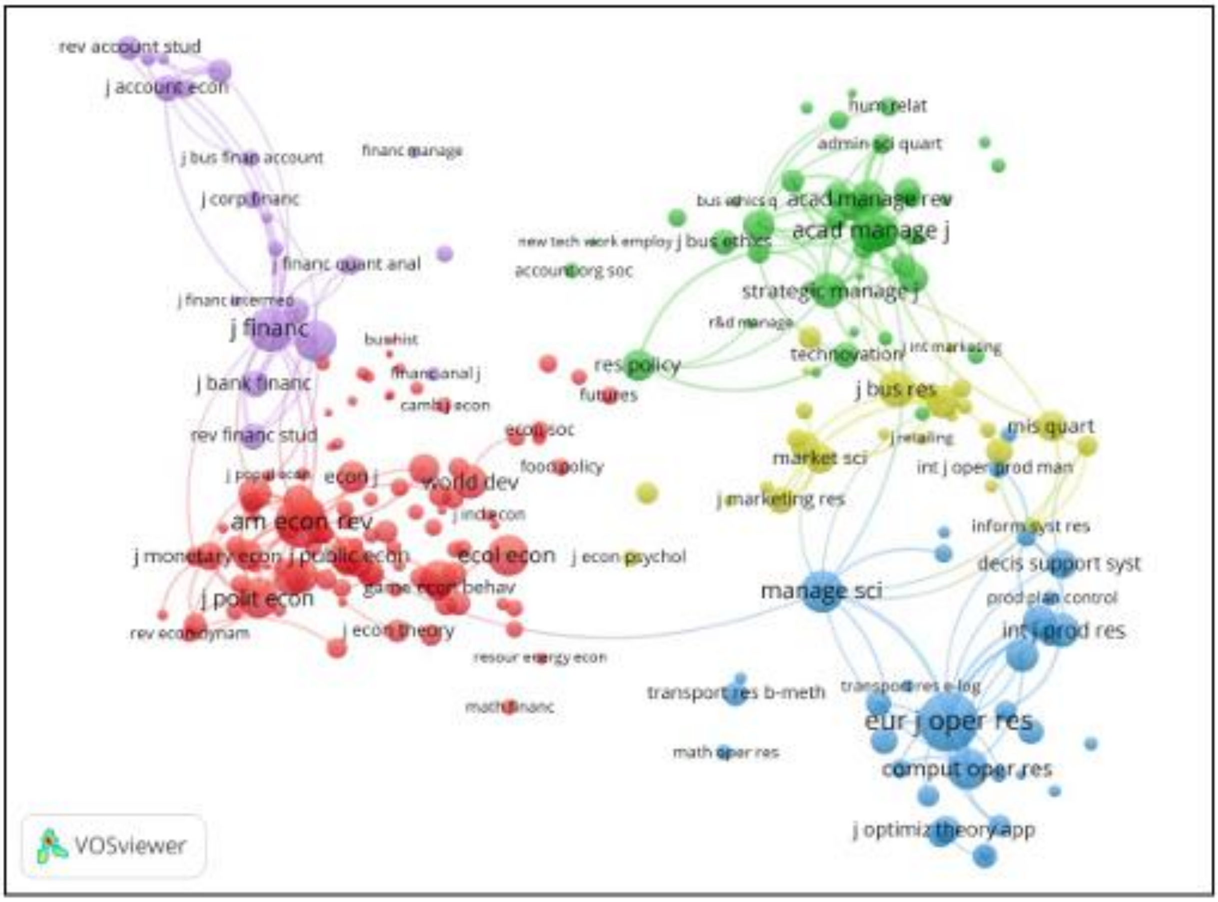

Figure 6: *Network visualization. Adapted from VOSviewer Manual: Manual for VOSviewer version 1.6.20. van Eck & Waltman. (2023, p.9)*

The only difference between the network visualization and the overlay visualization is the color scheme of the items. Items in the overlay visualization can be colored in two different ways. When an item has a score, it's color is also based on it's score; by default the colors range from blue (low score) to green (average score) to red (high score). However if an item has user definition colors, then the items color is determined by its user – defined color. Items without user – defined colors or scores are not eligible for overlay visualization. Figure 6 provides an illustration of the overlay visualization. The visualizations bottom – right concern shows a color bar. Only when colors are based on item scores is the color bar shown. The way scores are mapped is shown by the color bar. Colors in Figure 6 overlay illustration represent the journals impact factors. For instance, the impact factors of blue journals is less than 1 that of green journals is, approximately 2, and that of yellow journals is greater than 3 (van Eck & Waltman, 2023 p. 10).

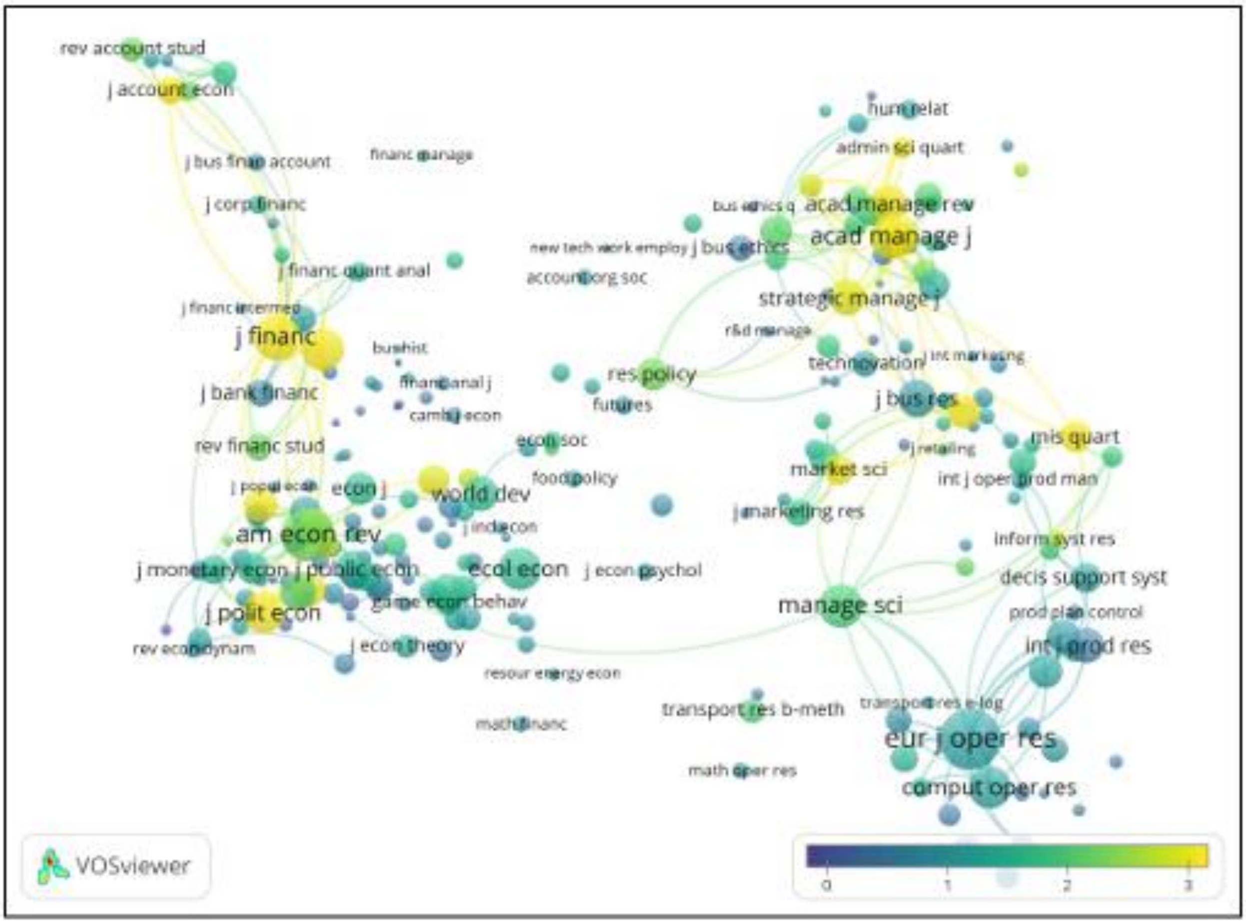

Figure 7: *Overlay visualization. Adapted from VOSviewer Manual: Manual for VOSviewer version 1.6.20, van Eck & Waltman. (2023, p. 10)*

Furthermore, a thesaurus file was produced following the initial analysis to improve the quality of the keywords and prevent term duplication, such as nanomaterial and nanomaterials. The final bibliographic map was then created by adding the thesaurus file to the analysis.

4. Results and Discussion

Figure 7 illustrates the final figure created with VOSviewer using the above described methodology. The graph is organized into four main clusters and has 58 keywords overall, 827 linkages, and a total link strength of 3569.

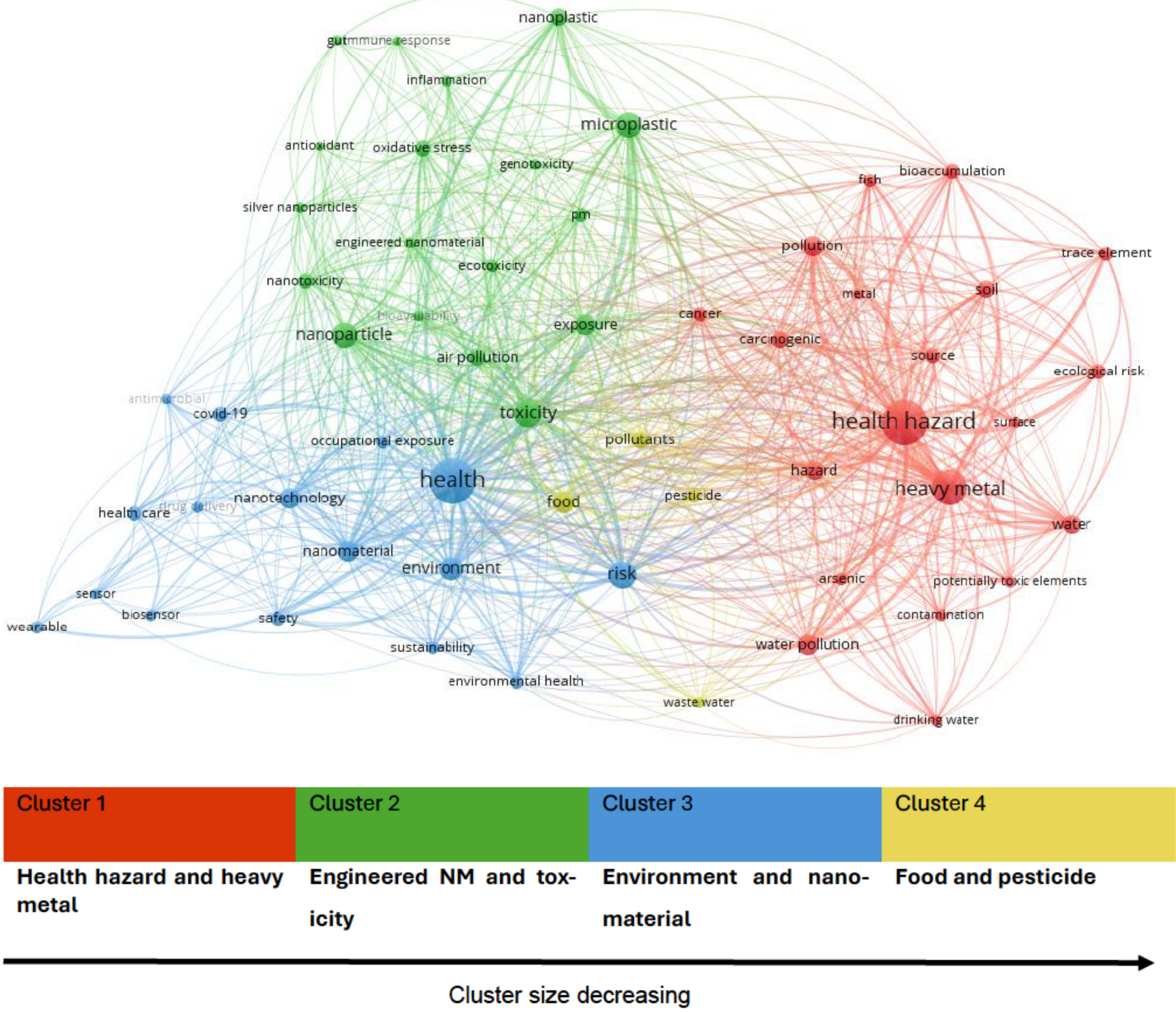

Figure 8*: Bibliometric analysis from VOSwiever, authors' elaboration (pm. = particulate matter)*

In the interest of understanding the Figure 7, it is essential to differentiate between the identified clusters and understand their relationship. Cluster 1: Health hazard and heavy metal has the most keywords associated with it and is therefore the largest cluster in the graph. The keywords here are primarily focused on two key concepts: health hazard and heavy metal. Cluster 2: Engineered nanomaterial and toxicity, is the second largest cluster in the graph, with keywords that highlight toxicity-related topics like air pollution, exposure, and nanoparticles. The keywords in cluster 3: Environment and nanomaterial are primarily associated with health, but there is also have a overlap with nanomaterial. The final one, cluster 4: Food and pesticide primarily contains keywords related to pollutants and waste water.

4.1 Cluster 1: Health Hazard and Heavy Metal

The two major concepts of health hazard and heavy metal are found in cluster 1, which is the largest. Because keywords related to the two concepts from two major sections of the used search string, the size of the of the corresponding nods was already predicted prior to the analysis. The closeness of both terms can be explained by the largest number of overview articles that examine the relationship between heavy metals and health hazards from a long term perspective in the literature related to this cluster. The work of Al-Tohamy et al. (2022) is among the most well-known in the field with approximately 1382 citations. The main goal of the scientific research is to assess the various methods for treating wastewater containing textiles dyes. The articles discusses the environmental and health risks faced by these dyes, as well as the potential remediations strategies for ensuring environmental safety. The connection between this article and nanomaterials is found in innovative wastewater treatment approaches that use nanotechnology. Nanomaterials, with their unique properties such as high surface area, reactivity and, the ability to absorb or catalyze reactions, may improve efficiency of dye removal processes. The article most likely discusses how specific nanomaterials can be used to treat dye-containing wastewater, emphasizing their efficacy in degrading or removing harmful dyes. The article also addresses negative effects that some of the nanomaterials used in dyes have on the environment and human health: Textile dyes released into aquatic environment as domestic sewage because they may not adhere to the fabric well. Therefore, when wastewater from various textile industries in continuously released without first being treated, it might have a negative impact on both the environment and human health (see Fig. 9). Aquatic organisms may be poisoned by textile dyes, which might contaminate aquatic habitats and make their way into the food chain (Al-Tohamy at al., 2022).

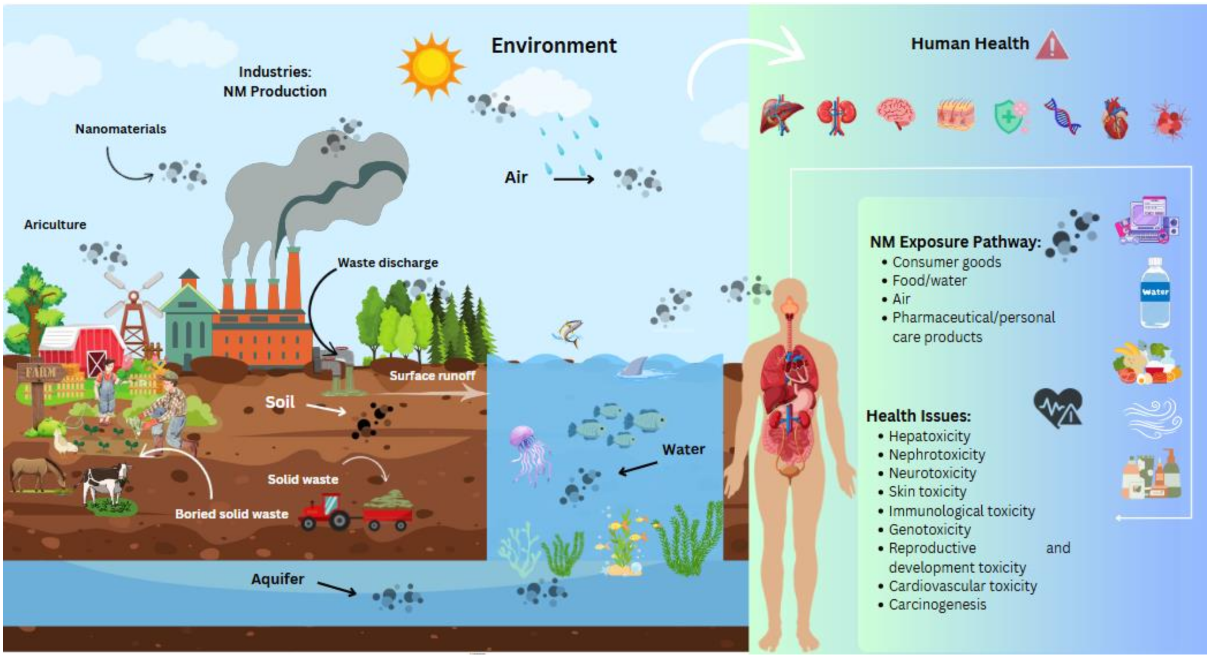

***Figure 9**: Environmental and human health exposure to nanomaterials, author's elaboration*

The textile industry produces a lot of wastewater that may be highly colored and contains a variety of persistent pollutants, making dye-containing wastewater a major environmental polluter that may also have an impact on human health (Carney Almroth et al., 2021; Ali et al., 2022). Approximately 7x107 tons of synthetic dyes may be produced globally each year, and the textile industry uses over 10,000 tons of these dyes (Chandanshive et al., 2020). Based on their structure, application, and place of origin, dyes may frequently be categorized into multiple groups (Holkar et al., 2016; Akpomie and Conradie, 2020). Textile industries primarily use synthetic dyes such as azo, direct, reactive, mordant, acid, basic, disperse, and sulfide (see Fig. 9). Wool, cotton, silk, polyester, polyamide, and acrylic are examples of natural and synthetic fibers may be commonly used in the textile industry (Deopura & Padaki, 2015; Silva et al., 2021).

Textile dyes may not stick well to fabric and are released untreated as wastewater into aquatic environments like lakes, rivers, streams, and ponds, posing major ecological and toxicological risks to living organisms (Parmar et al., 2020). Numerous hazardous dyes, heavy metals needed to produce textiles dye color pigments, including mercury, chromium, cadmium, lead, and arsenic as well as aromatic compounds, might have been discovered to be present in textile wastewater. In order to produce textile dye color pigments, heavy metals like arsenic, cadmium, chromium, mercury, and lead needed to be present (Singha et al., 2021). Along with the wastewater, these hazardous substances may be transported over great distances.

Afterwards, they might linger in the soil and water for extended periods of time, endangering the health of living organisms and decreasing soil fertility and aquatic plant photosynthetic activity, which may lead to the creation of anoxic conditions for aquatic flora and fauna (Dutta & Bhattacharjee, 2022). Furthermore, textile dyes may reduce the aesthetic quality of water bodies by raising the chemical and biochemical oxygen demand, which could hinder photosynthesis, prevents plant growth, makes plants in the food chain, causes recalcitrance and bioaccumulation, and may increase toxicity, mutagenicity, and carcinogenicity (Mudhoo et al., 2020; Patil et al., 2022). The production of fabric may use a lot of water, which could lead to an equal amount waste water with high concentrations of organics, metal salts, dissolved solids, and resistant dyes (Ismail & Sakai, 2022, p. 2). Azo dyes which structurally contains one or more groups, may be the most common type of textile dye used in the textile industry and make up the largest class (above 60%) of all textile dye groups (Ayed et al., 2011; Bhattacharya et al., 2018; Thangaraj et al., 2021). While some textile factories treat their wastewater to break down the free azo dyes that are released into the environment, other may release untreated industrial effluents straight into waterways, which could have harmful effects on living organisms and pose ecotoxicological risks.

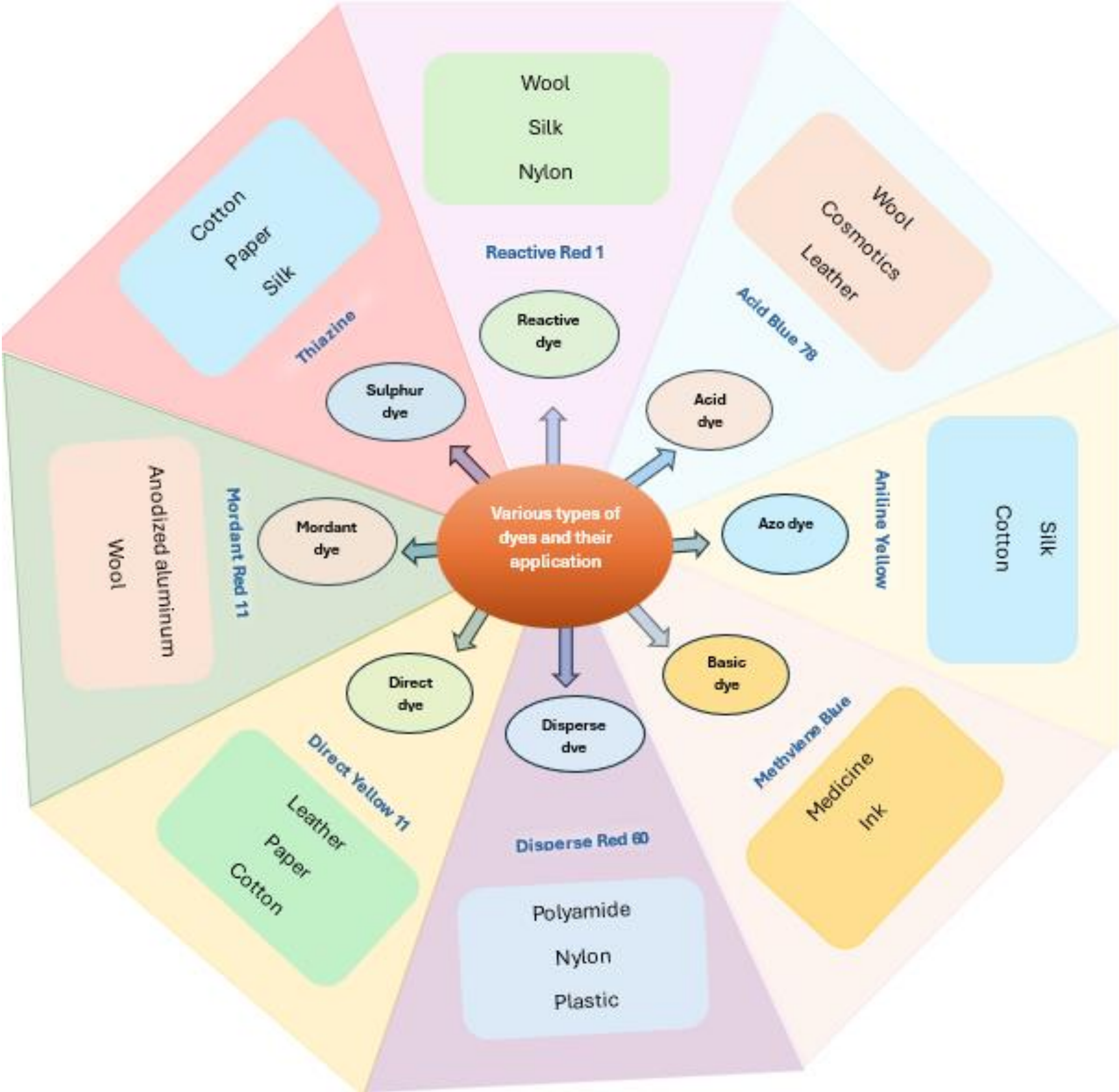

***Figure 10**: Various categories of dyes and their possible industrial applications. Adapted from A critical review on the treatment of dye-containing wastewater: Ecotoxicological and health concerns of textile dyes and possible remediation approaches for environmental safety, Al-Tohamy et al. (2022, p. 2), authors' elaboration*

The keyword heavy metal which is also the main topic of this cluster is also analyzed and thoroughly discussed by Rai et al. (2019). The primary goal of this article is to investigate the sources, behavior, and effects of heavy metals in agricultural systems, with specific focus on how these metals accumulate in food crops. It aims to educate readers about the health risks associated with consuming contaminated crops and to discuss management strategies for reducing these risks (Rai et al., 2019, p. 365). Around the world, heavy metal pollution may have become widespread, disturbing the ecosystem and potentially harming human health. Overall, the fast rate of urbanization, land use changes, and industrialization particularly in developing countries with large populations like China and India could be the main causes of this issue (UN-HABITAT, 2004; Rai et al., 2019, p. 365). A few metals and metalloids such as As, Pb, Cd, and Hg may be among the dangerous heavy metals and metalloids that are categorized as not being necessary for metabolic and other biological processes. These metals seems to be harmful in a number of ways (Gall et al., 2015, p. 12) and the US Environmental Protection Agency for Toxic Substances and Disease Registry may have consequently listed them among the top 20 hazardous substances[1] (Xiong et al., 2016a; Xiong et al., 2016b; Khalid et al., 2017; Rai, 2018, ASTDR, 2024). The metabolic function of biota may be strongly linked towards certain heavy metals, such as Cu, Fe, Zn, and even Cr (III), which are necessary for metabolic processes like cytochromes and enzymes. Although excessive amounts of nickel may be harmful to human health, they are essential part of urease (Zhuang et al., 2009; Marschner, 2012; as cited in Rai, et al., 2019, p. 365). Therefore, a classic example of antibiotic-biotic interaction in the environment could be found in soil-food crop/vegetables system. Heavy metals from point sources (such as energy-intensive industries like coal mines and thermal power plants, and chlor-alkali chemicals industries like goldmines, smelting, electroplating, textiles, leather, and e-waste processing) and non-point sources (such as soil/sediment erosion, agricultural runoff, and open disrupt soil), which is the basic substrates of food crops. Heavy metals could have negative effects on soil biota through microbial processes and soil-microbe interactions, in addition to their effects on human health (Gadd, 2010; Gall et al., 2015; Rai, 2018).

The majority of soil heavy metal may build up in crops, which may allows them to transfer the food chain to other media. The crop-soil interfaces bioconcentration factor (BCF) for a number of heavy metals, especially in important worldwide staple crops like wheat and corn, may have been recorded (Wang et al., 2017a, 2017b, 2017c, p. 180). Consuming heavy metal-contaminated vegetables[2] could lead to serious health issues, including gastrointestinal cancer, weakened immune systems, developmental delays, and malnutrition (Iyengar and Nair, 2000; Turkdogan et al., 2003; Carrizales et al., 2006; Khan et al., 2008b; Hu et al., 2013; Gress et al., 2015; Dickin et al., 2016; El-Kady & Abdel-Wahhab, 2018, as cited in Rai et al., 2019, p. 369). Consumption of food crops contaminated with metals may be closely associated with health risks to humans. Through dietary consumption, heavy metals could build up in human bones or fatty tissues, reducing vital nutrients and affecting immune system. A number of heavy metals, including Al, Cd, Mn, and Pd, may also be thought to contribute to intrauterine growth retardation (Iyengar and Nair, 2000; Turkdogan et al., 2003; Khan et al., 2010; Rai, 2018, as

[1] The exact design of the ASTRD 2024 can be found in annex 1
[2] The exact design oft the Table with heavy metal contamination from diverse source in global food crops can be found in annex 2

cited in Rai et al., 2019, p. 369). Lead exposure may have an negative impact on mental development an could cause neurological and cardiovascular disorders in people, particularly in young children (Navas-Acien et al., 2007; Zhou et al., 2016; Al-Saleh et al., 2017, p. 1255). In addition to their carcinogenic effects, certain heavy metals – particularly Pb and Cd may cause bone fractures and malformations, cardiovascular problems (Trichopoulos, 1997, as cited in Rai et al., 2019, p. 369), kidney dysfunction, hypertension, and other severe illnesses of the immune, liver, lung, and nervous system (Klassen et al, 1999; Jarup, 2003; Zhou et al., 2016; Zhuang et al., 2009; El-Kady & Abdel-Wahhab, 2018, as cited in Rai et al., 2019, p.368). Cancer, skin issues, respiratory complications and numerous other illnesses affecting the cardiovascular, gastrointestinal, hematological, hepatic, renal, neurological, developmental, reproductive, and immune systems may all be caused by high levels of As in soil, food crops, and groundwater (Chiou et al., 1995; Kapaj et al., 2006; Hartley & Lepp, 2008; Hu et al., 2013; Lin et al., 2013; Liu et al., 2013; Zhou et al., 2016; Islam et al., 2017; El-Kady & Abdel-Wahhab, 2018, as cited in Rai et al., 2019, p. 371). The effects of Cd contamination in food crops on human health may have also been widely documented (Yang et al., 2018, p. 268). High-density lipoprotein concentrations and the immune system could both be impacted by excessive Zn levels in the body (Zhou et al., 2016, p. 1) Similarly, humans who consume too much Cu may develop liver damage and other problems related to the abdomen (Gaetke & Chow, 2003; Rahman et al., 2014; Zhou et al., 2016, as cited in Rai et al., 2019, p. 371). Heavy metals such as Cr, Cu, and Zn in soil could lead to non-carcinogenic health risks like neurological complications, headaches, and liver disease (US EPA, 2000; Liu et al., 2013, p. 531). Cr(V) may be more unstable than Cr(III) and other ionic forms, making it a higher risk (Park et al., 2004; Liu et al., 2013, p. 537). The former concept thought to be more likely to may be lead to lung cancer than the latter one. Cd may be considered as a highly carcinogenic substance found in a contaminated food crops, particularly rice, and could lead to postmenopausal breast cancer (Hiro et al., 2014, p. 70). The absorption of soil and consumption of fruits, vegetables and crops contaminated with metals or metalloids could cause gastrointestinal cancer (Turkdogan et al., 2003, as cited in Rai at al., 2019, p. 371).

To characterize the translocation of heavy metals in soil and plant system (plant uptake factors) and to evaluate the degree of risk associated with dietary intake of vegetables and other food crops, indicators of soil-plant metal transfer and health risks may have been proposed (Yang et al., 2018, pp. 264 – 267).

Diverse health risk assessment indices

Numerous studies may have been conducted on the health risks associated with contaminants being transmitted from food crops to humans (Cui et al., 2004; Hough et al., 2004; Chary et al., 2008; Khan et al., 2008; Zhuang et al., 2009; Gall et al., 2015; El-Kady & Abdel-Wahhab, 2018, as cited in Rai et al., 2019, p. 371) using indices like HRI, hazard index (HI), hazard quotient (HQ), DIM, and daily dietary index (DDI).

$$HQ = [W_{plant}] + \frac{[M_{plant}]}{R_f D \ x \ B}$$

HQ < 1 is safe, where HQ ≥ 1 could be a health risk (Chary et al., 2008, p. 516, as cited in Rai et al., 2019, 371).

In the equation above, W*plant* represent the dry weight of the contaminated plant material that was consumed (mg/day), M*plant* represents the metal concentration in the vegetable(s) (mg/kg), RfD represents the food references does (mg/day), and B represents the mass of the human body (kg)

$$DDI = \frac{X \ x \ Y \ x \ Z}{B}$$

A person's daily consumption of metal is indicated by their DDI. Where *Z* is the approximate daily intake, *B* is the average body mass of consumers, *Y* is the dry weight of the vegetable, and *X* is the metal concentration of a particular vegetable.

$$DIM = \frac{C_{metal} \ \ X \ \ C_{factor} \ \ X \ \ D_{food}}{B_{average\ weight}}$$

Where D*food* is the daily intake of vegetables, B*average* is the average weight of the consumers, C*metal* is the concentration of heavy metals in plants (mg/kg), and C*factor* is the conversion factor (usually 0.085 to covert fresh vegetable weight to dry weight) (Rattan et al., 2005; Oves et al., 2012, as cited in Rai et al., 2019, p. 371).

$$HRI = \frac{DIM}{R_f D}$$

While HRI ≥ 1 may be harmful to health due to multiple metals, HRI < 1 could be safe (Oves et al., 2012, as cited in Rai et al., 2019, p. 371). DIM can be used to calculate HRI, where RfD stands for food references dose (Rai et al., 2019, p. 371).

4.2 Cluster 2: Engineered nanomaterial and toxicity

Cluster 2 is focused on the engineered nanomaterial (ENM) perspective within the interlinkage of toxicity on human health. Here, keywords such as silver nanoparticles, nanotoxicity, exposure, nanoparticle and ecotoxicity can be found.

In 1959, physicist Richard Feynman presented the concept of novel nanoscale technology in his lecture “There is plenty of room at the bottom,” which covered the significance of atomic scale manipulation and control. The American engineer Kim Eric Drexler popularized the idea of molecular nanotechnology by using it in his 1986 book Engines of Creation: “The coming Era of Nanotechnology”. Professor Norio, Taniguchi coined the term “nanotechnology”, in the 1974. However, the development of nanotechnology in the modern era was not stimulated until the development of tools for imaging surfaces at the atomic level, such as the atomic force microscope and the scanning tunneling microscope in 1981. The precise placement, design, and manipulation of atoms and molecules at the nanoscale level may be all part of the rapidly developing and expanding field of nanotechnology (Ferdous & Nemmar, 2020, p.1).

Nanotechnology may have made significant strides in the field of biotechnology, medicine, the environment, therapeutics, and drug development during the last 20 years. Engineered nanomaterials (ENMs) may be a key component of technology. A natural, incidental, or manufactured material that contains particles in an unprocessed form, aggerate or agglomerate and where 50% or more of the particles in the number size distribution, one or more external dimensions are the size range 1 – 100 nm is what European Commission defines as NMs (EU Commission, 2011). The health sector may have paid close attention to NMs harmful effects on humans (Korani et al., 2015; Li et al., 2018). The majority of exposure to airborne NMs may happens at work when these materials are manufactured, formulated into products, transported, or handled in storage facilities (Matteis, 2017, p.1). Furthermore, it may be likely that many consumers could be exposed through direct contact with ENM-containing products and oral inhalation (Matteis, 2017, pp. 3 – 9). The tiny size of this kind of particle then could make it easier for it to move past natural barriers like skin, lungs, or gastrointestinal tract (GIT), which could have both short term and long-term harmful effects (Jeevanandam et al., 2018, p. 1064). Despite the many benefits of nanoscale materials, their unchecked use, release into the environment, and possible toxic effects might make them unavoidable health risks. Therefore, in order to make the use of NMs more practical and environmental friendly, nanotoxicology demands extensive research studies. Fullerenes, carbon nanotubes (CNTs), silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), titanium oxide nanoparticles (TiO2) zinc oxide nanoparticles, iron oxide (FeO), and silica nanoparticles may be a few of the most frequently researched NMs (Vance et al., 2015, as cited in Ferdaous & Nemmar, 2020, p. 2).

Early reach on AgNPs may be primarily concerned with their synthesis and characterization through chemical methods (Ferdous & Nemmar, 2020, p. 2). Nonetheless, research may have focused more on their biological effects and application for a lot of different reasons. AgNPs are also recognized to possess special qualities in electrical resistance, surface plasmon resonance, and toxicity (Syafiuddin et al., 2017, p. 734). On the basis, these extensive research may have been done to examine their characteristics and possible uses as antimicrobial agents in wound dressings, water disinfectants, electronic devices, and anticancer agents, among other uses (Zhang et al., 2016; Syafiuddin et al., 2017, as cited in Ferdous & Nemmar, 2020, p. 2).

The purpose of the following section is to present information on the harmful effects of AgNPs after exposure through oral, inhaled, dermal, and intravenous routes.

Silver Nanoparticle (AgNPs)

Duo to their potential for use in commercial applications, AgNPs have taken a prominent place among all the ENMs that may have been developed and characterized this far though. With the highest electrical conductivity of any metal, silver, represented by the symbol Ag, is a “lustrous, soft, ductile, and malleable metal”, that may be finds extensive applications in electrical devices. This metal may be used to make coins, jewelry, and ornaments because it is chemically inactive, steady in water, and does not oxidize in air. Both pure deposits and silver ores, like argentite and horn silver, could be acquire silver. Along with deposits of ores containing lead, copper, and gold, the large portion of silver may be obtained as a by-product (Ferdous & Nemmar, 2020, p. 3). An estimated 26,000 metric tons of silver were produced worldwide on 2023 (Statista, 2024). Nearly 320 tons of silver nanoparticulate may be produced annually and utilized in food products, biosensing, and nanomedical imaging (Siddiqi et al., 2018, p. 1). The unique physiochemical properties of AgNPs, such as their small size, greater surface area, shape, particle morphology, composition, coating/ capping, agglomeration, rate of particle dissolution, particle reactivity in solution, efficiency of ion release, and type of reducing agents used for AgNP synthesis, might give them unique characteristics compared to their bulk components (Zivic et al., 2018, as cited in 2020, p. 3). Furthermore, AgNPs may be widely recognized for their optical, electrical, catalytic, and antimicrobial qualities (Syafuddin et al., 2017,

p. 744). Duo to their special qualities, AgNPs may be widely used in food storage, household utensils, the medical applications, and biomedical applications like disinfectants, surgical equipment, and wound dressings. Additionally, these NPs may have been employed in biosensors, electronics, and catalysis because of their optical properties (Zivic et al., 2018, as cited in 2020, p. 3).

AgNPs Synthesis and Characterization

The traditional physical synthesis process involves pyrolysis and spark discharged (Ferdous & Nemmar, 2020, p. 3). Three primary components may make up a chemical process that can be either top–down or bottom–up: stabilizing/capping agents, reducing agents, and metal precursors. Chemical reduction may be using organic or inorganic reducing agents, such as sodium citrate, ascorbate, sodium borohydride, elemental hydrogen, polyol process, Tollens reagent, N, N-dimethylformamide, and polyethylene glycol-block copolymer, may be the typical method. Additionally, processing consist thermal decomposition, sono-decomposition, electrochemical reduction, laser irradiation, lithography, laser ablation, and cryochemical synthesis (Zhang et al, 2016, p. 3). In contrast to the physical method may have a low yield, the chemical method may have a high yield, which is the main advantage. Nevertheless, the chemical approach might be far more costly, hazardous, and toxic than the physical approach (Ferdous & Nemmar, 2020, p. 3). Biological systems such as bacteria, fungi, plant extract, and small biomolecules like vitamins, amino acids, and enzymes are used in this simple, economical, and environmentally friendly method to synthesize AgNPs. Because of the abundance of biological resources, reduced time needed, high density, stability, and ready solubility of prepared NPs in water, the green approach might be generally be accepted (Gudikandula & Maringanti, 2016, p. 720).

An important step in assessing the functional impact of synthesized particles may be AgNP characterization (Zhang et al., 2016, p. 4). Numerous studies may have shown that the morphology, structure, size shape, charge, coating/capping, chemical composition, redox potential, particle dissociation, ion release, and degree of aggregation may all affect the biological activity of AgNPs (Gilga et al., 2014; Loza et al., 2014; Wei et al., 2015; Kim et al., 2017; Siddiqi et al., 2018, as cited in Ferdous & Nemmar, 2020, p. 3). Analytic methods like dynamic light scattering (DLS), zeta potential, and sophisticated microscopic methods like atomic force microscopy, scanning electron microscopy (SEM) and transmission electron microscopy (TEM), UV-vis spectroscopy, X-ray diffractometry (XRD), Fourier transform infrared spectroscopy (FITR), and X-ray photoelectron spectroscopy (XPS) may all be used to determinate these parameters, just like for all other NPs (Lin et al., 2014; Xhang et al., 2016, as cited in Ferdous & Nemmar, 2020, p. 3). It should be mentioned that research using comparable AgNps from the same manufacturer produced different findings from a toxicological standpoint. For instance, Vandebriels repeated exposure study AgNPs may be cytotoxic to a variety of cells, as demonstrated by RJ et al. (2014) in rats. However, using comparable particles, Boudreau M. Det al. (2016) demonstrated the dose-dependent accumulation of AgNPs in different rat tissues without causing appreciable cytotoxicity. Studies have reported particle characteristics using only manufactured data without having investigators verify their findings or using a single analytical their findings or using a single analytical tool that Usually it may be advised to exercise caution may be offers little insight into the type of particle under study (DeJong et al., 2013; Vandebriel et al., 2014; Cho et al., 2018; Gherkhbolagh et al., 2018, as cited in Ferdous & Nemmar, 2020, p. 4).

One crucial characteristic that affects NPs uptake and other effects may be the size. According to a review study, AgNPs typically range from 1 to 10 nm when used in general applications (Tolaymat et al., 2010, as cite in Ferdous & Nemmar, 2020, p. 4). Besides that, researchers may have effectively demonstrated the significance of different AgNPs formulations during synthesis in relation to biomedical applications (Vandebriel et al., 2014, as cited in Ferdous & Nemmar, 2020, p. 4). For instance, loading AgNPs into multiwalled carbon nanotubes may have shown that AgNPs may be more effectively target sperm cells and, consequently, the potential for advancement as diagnostic instruments for the treatment of infertility (Jha et al., 2017, as cited in Ferdous & Nermma, 2020, p. 5). Similarly, Bilal et al. (2017) may have created a chitosan-alginate construct loaded with AgNPs that, demonstrated both cytotoxicity to cancer cells (HeLa cells). Aziz et al. (2017) may have created albumin-coated AgNPs, to develop anticancer agents. It may demonstrated that the latter was selectively absorbed by tumor cells and caused apoptosis.

<u>AgNPs Application and Mechanism of Action</u>

AgNPs may stand out among the different metal salts and NMs that may be known to be effective in preventing the growth of numerous bacteria due to their potent inhibitory and bactericidal effects (Nam et al., 2016, p. 55). It may be known that AgNPs and Ag salts can be used to prevent infection in wounds, burns, cuts, and catheters (Ferdous & Nemmar, 2020, p. 5). Although the literature may have indicated that these particles may interact with bacterial membranes, the precise mechanism underlying AgNPs antimicrobial effects may still be unknown (Qing et al., 2018, p. 3311).

AgNPs may have shown effective inhibitory activities against a number of viruses, such as the plant pathogenic bean yellow mosaic virus, human immunodeficiency virus, hepatitis B virus, herpes simplex virus, human parainfluenza virus, and peste des petits ruminants virus (Lara et al., 2010; Gaikawad et al., 2013; Khandelwal et al., 2014; Elbeshehy et al., 2015, as cited in Ferdous & Nemmer, 2020, p. 5). AgNPs may have been identified as having significant anti-inflammatory properties. Inflammation is the body's initial immunological reaction to foreign particles. Research assessing AgNPs anti-inflammatory effect may have revealed a notable decrease in wound inflammation, apoptosis inflammatory cells, a modulation of fibrogenic cytokines, and a downregulation of inflammatory cytokines (Ferdous & Nemmar, 2020, p. 5).

The main ways that NPs may enter the body could be through ingestion, inhalation, skin contact, and intraperitoneal (i.p.) or intravenous (i.v.) injections (De Matteis, 2017, p. 2).

Respiratory Exposure

AgNPs might enter the human respiratory system through inhalation when they are released into the environment during product manufacturing, washing, or disposal (Ferdous & Nemmar, 2020, p. 5). One possible method for consuming, nanoscale silver may be by inhalation, particularly from consumer goods like disinfectant sprays (Rezvani et al., 2019, p. 152). Even for wet production process, an exposure assessment conducted in a manufacturing facility in New Mexico may revealed a notable release of AgNPs during processing as soon as the reactor, dryer, and grinder were opened, potentially posing a risk of occupational exposure (Ferdous & Nemmar, 2020, p. 6). According to comparable research assessing occupational exposure and health risks, concentrations of AgNPs during the production and incorporation of AgNPs into different consumers goods may reach 1.35 $\mu m/m^3$. A sub chronic rat inhalation toxicity study and consideration of the human equivalent concentration with kinetics may have led to the recent proposal of an occupational exposure limit of 0.19 $\mu m/m^3$ for AgNPs (Ferdous & Nemmar, 2020, p. 7). The transport and deposition of NPs after inhalation may be irregular and dependent on a number of variables, including age, pulmonary function, flow rate, airway structure, and above all particle size (Ferdous & Nemmar, 2020, p. 7). The lungs homeostasis is maintained by the alveolar-capillary barrier, which is made up of the capillaries endothelial cells, and the basement membrane separating the two cells. After damage to the two alveolar capillary membranes epithelia layer, NP penetrations may have been demonstrated (De Mattheis, 2017, p. 6).

Oral Exposure

AgNPs may be utilized in food industry packaging and storage to improve food quality and shelf life. Additionally, industrial and urban pollutants may enter aquatic environments and build up along trophic chains. Therefore, the possible sources of oral exposure might be the presence of AgNPs in food fish and other aquatic organism, dietary supplements, or contaminated water (Ferdous & Nemmar, 2020, p. 7). AgNPs included in research to migrate from packaging into food under a variety of usage circumstances (Choi et al., 2018, as cited in Ferdous & Nemmar, 2020, p.7). Inhalation exposure during manufacturing may also result in oral exposure because particles that are cleared by the mucociliary escalator are swallowed and eliminated through the gastrointestinal tract. Humans may be thought to consume between 20 and 80µg of silver per day trough ingestion (De Mattheis, 2017, p. 4). The GIT may acts as a mucosal barrier after ingestion, favoring the breakdown and absorption of nutrients like fats, peptides, and carbohydrates. NP can penetrate the epithelium, act on mucus layer, move into the bloodstream, and then reach every organ. According to reports, endocytosis in epithelial cells is the primary mechanism for the uptake of NPs with diameter less than 100 nm (Ferdous & Nemmar, 2020, p. 7). AgNPs may have the ability to cause inflammation, DNA damage, and oxidative stress in enterocytes (De Mattheis, 2017, p. 3). This part will be further elaborated in the corresponding in the chapter of cluster 4.

Skin and Parenteral Exposure

The skin, which is the largest organ in the body and the first barrier separating the internal and external environments, may also expose humans to AgNPs. Solid nanoparticles may have a well established capacity to enter human skin, both healthy and damaged, and to enter into underlying structures (Ferdous & Nemmar, 2020, p. 7). In this regard, it may have been estimated that up to 20% of cosmetics are made using AgNPs. Apart from cosmetics, there may have been a increase in AgNPs when skin comes into contact with antibacterial textiles and wound dressings (Alessandrini et al., 2017, p. 2). AgNPs could enter the systemic circulation directly in a laboratory setting through intravenous, intraperitoneal, and subcutaneous injection. Besides that, the creation of medications or drug carries based on AgNP may allow these particles to enter the human body circulation system directly. An essential measure of cumulative toxicity, after biodistribution, is the evaluation of NPs clearance behavior. The postexposure clearance kinetics after subacute inhalation, intravenous, and oral exposure to different sizes of AgNPs and Ag^{+} ions may have been examined in a number of studies in this context

(Ferdous & Nemmar, 2020, p. 7). According to these studies, silver may be eliminated from the majority of organs following the recovery period, which typically lasts between 17 days for months. Nonetheless, in long-term oral exposure studies, silver may have shown persistence in biologically barrier-containing tissues, like the brain and tests, indicating that the metal is difficult to remove from these organs. Besides that, the perseverance of silver in these organs may raises the possibility of elevated toxicity (Ferdous & Nemmar, 2020, p. 8).

Toxicity

Although silver nanoparticles may have many benefits and need to be taken into account for novel and challenging biomedical applications, deep research on their toxicity may have only lately been conducted. Inconsistent results have been found in studies on the detrimental effects that silver nanoparticles can have on biological systems, such as bacteria, viruses, and human cells. And according to general consensus, silver nanoparticles may be incredibly effective antibacterial agents that may not harm normal mammalian cell cultures. Nevertheless, several in vitro studies may have demonstrated that silver nanoparticles might cause toxicity in rat hepatocytes, neural cells, murine stem cells, and human lung epithelial cells (Eker et al., 2024, p. 31). In in vitro experiment, the primary mechanism by which silver nanoparticle dependent cytotoxicity may be accomplished might be ROS induction. The size, concentration, and exposure duration of silver nanoparticles may be the main factors that may determine their cytotoxicity and genotoxicity (Du et al., 2018, p. 235). Because silver nanoparticles may be so tiny, they can enter cells and pierce biological membranes, which might be toxic. It has been shown that the size of the particles may affect how toxic silver nanoparticles are (Cunningham et al., 2021, pp. 9–11). The tested NPs sizes ranged from 20 nm to 100 nm. Together with higher concentrations, the zebrafish model showed that small-sized NPs could have the highest mortality rates. Besides that, even at the maximum concentration of 12 mg/L, the largest silver nanoparticles, measuring 100 nm, may not exhibit mortality greater than 20%. The 20 nm and 40 nm sizes had the most detrimental effects on the model, whereas the 80 and 100 nm sizes hardly showed any. Although the exact mechanism may be still unknown, the toxicity may primarily be associated with the generation of ROS, which results in oxidative stress, cellular dysfunction, and inflammation in a range of tissues. Organ failure, DNA damage, and the emergence of chronic illnesses may be all consequences of this process, which disrupts cell function and may have a detrimental effect on health (Eker et al., 2024, p. 31). Furthermore, exposure to silver nanoparticles may cause lipid peroxidation, a decrease in glutathione levels, an increase in the expression of genes that respond to ROS, and a rise in their protein levels. In the end, these processes may lead to necrosis, apoptosis,, and DNA damage (Du et al., 2018, p. 235). More specifically, Patlolla et al. used a rat model to assess the *in vivo* toxicity of silver nanoparticles given orally. Their research showed that exposure to different concentrations of silver nanoparticles 5, 25, 50, and 100 mg/kg increased lipid hydroperoxide levels, liver enzyme activity, and ROS production while also altering the morphology of rat liver tissue. Furthermore, they observed a significant rise in these side effects, particularly at the highest dosage of 50 and 100 mg/kg. Kim et al. also sought to show how oxidative stress affects the harmful effects of silver nanoparticles in human normal bronchial epithelial cells (BEAS-2B). *In vitro* tests were used, such as comet and micronucleus (MN) assays, and may found that silver NPs significantly increased oxidative DNA damage by producing reactive oxygen species (ROS). Besides that, their results may demonstrated that silver nanoparticles dose-dependently promoted DNA breakage and MN formation in BEAS-2B cells (Eker et al., 2024, p. 31). Beyond demonstrating the positive properties of silver nanoparticles, like their antibacterial and antifungal properties, *in vitro* studies may have also revealed the negative effects of silver nanoparticles may harmful to variety of biological system (Vazquez-Muňoz et al., 2017, p. 15). Compared to *in vitro* research, the possible causes of silver toxicity from *in vivo* studies may be less well understood. *In vivo* studies on the cytotoxicity and genotoxicity of silver nanoparticles address the question of whether these particles actually pose a threat to a variety of species, including aquatic organisms, terrestrial invertebrates, vertebrates, and higher plants. As a result, organisms may easily be exposed to NPs through ingestion, skin, contact, and inhalation. It may be possible for silver nanoparticles to enter cells and move to other vital organs. Exposure to silver nanoparticles may led to a variety of toxicological reactions following local injections, including impacts on the skin, liver, circulatory system, central nervous system, and respiratory system (Erker et al., 2024, p. 32).

4.3 Cluster 3: Environment and nanomaterial

The third cluster focuses on environment and nanomaterial perspective with the interlinkage of health. Here, keywords such as environmental health, nanotechnology, risk and safety can be found. Although nanotechnology may help treat and prevent pollution in the environment from hazardous substances, it may also pose risks to the ecosystem if not managed appropriately. A real concern may be that the special qualities of nanomaterials, like their small size and high reactivity, may have unanticipated ecological effects. Nanomaterials like Ag NPs and TiO2 NPs may cause toxicity in both aquatic and terrestrial organisms, potentially upsetting regional ecosystems and biodiversity (Ma et al., 2024, p. 66).

Both synthetic and natural NMs may interact with various environmental compartments via a variety of pathways[3]. NMs do seem to be frequently found in the atmosphere, for example, incidental NMs (INMs) are probably more prevalent in urban areas. Within those environmental compartments, NMs might accumulate and find their way to various water sources, soil surrounding landfills, industrial discharges, municipal wastewater, or may be produced naturally (Malakar et al., 2021, p. 7). Figure 9 illustrates the possible rout that NMs may take to various aquatic habitats. High volume and easily accessible in nature and cosmos, NNMs can be found in rainfall and end up in surface water sources or replenished to groundwater. NNMs may linger in the atmosphere for a long time as dust and may be probably present in the soil microbial ecosystem (Ermolin et al., 2018, p. 17, 21). Similarly, sewage from landfills or wastewater facilities, car emissions or waste from factories may enter natural water bodies and soil through rainfall from airborne particles or point of discharge sources. NMs that are produced commercially may be released into the water during the production phase or as waste products at the end of their life cycle. These ENMs may either stay in soils and eventually be absorbed by plants or animal-based food products, or they can gradually move to surface and groundwater environments. One of the main ways that ENMs may be released into the environment may be through wastewater (Malakar et al., 2021, p. 7).

[3] The exact design of the transportation pathway of NM can be found in annex 4

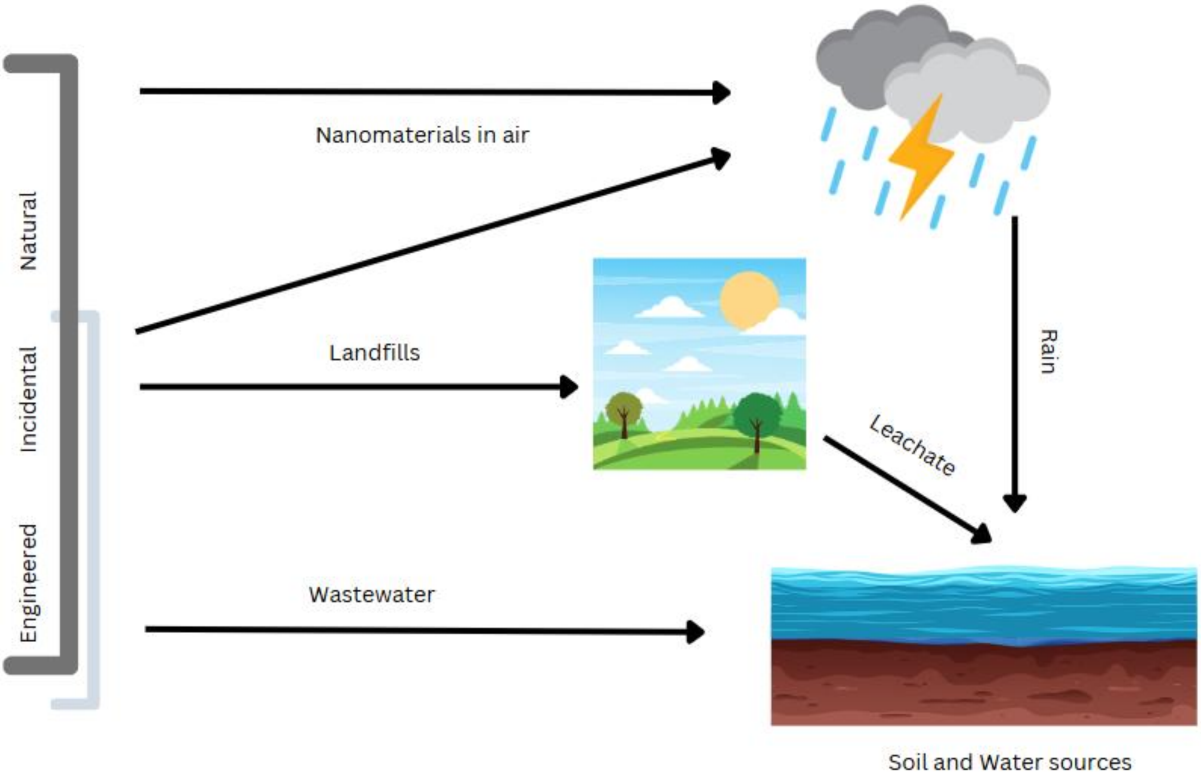

Figure 11:*Transportation pathways of natural and artificial (incidental and engineered) nanomaterials to soil and water sources. Adapted from Nanomaterials in the environment, human exposure pathway, and health effects: A review, Malakar et al. (2021, p. 8), author's elaboration*

Natural nanomaterials in the environment

According to Griffin et al. (2017), nature is an expert nanotechnologist, and a vast number of NNMs are found in nature. But typically, people may overlook their fate, transformation, and possible toxicity (Ermolin et al., 2018, p. 21). The main reason for NNMs have been disregarded might be the lack of appropriate analytical instruments to accurately and consistently measure them in a complex natural setting (Malakar & Snow, 2020, as cited from Malakar et al., 2021, p. 7). Another explanation for the lack of knowledge regarding NNMs effects on the environment might be that they were a part of the evolution of earth to its current state (Hochella et al., 2019, p. 1). The advanced of nanogeoscience may have produced sophisticated instruments to comprehend the fate, possible toxicity, and transportation of NNMs as well as their multifaceted ecological role. It may be simple for NNMs to exist in the atmosphere due to volcanic ash, forest fires, listening, or formations in space. There may be naturally occurring multiwalled carbon nanotube in the air that range from 15 to 70 nm and are produced from soot (Griffin et al., 2017, p. 3). Furthermore, volcanic eruptions may release silicon dioxide nanomaterials into the atmosphere where they may irritate the eyes (Malakar et al., 2021, p. 7). Other types of nanomaterials can also float in the atmosphere and travel the earth with the wind (Ermolin et al., 2018, p. 17). Naturally occurring mercury nanoparticles may also travel through the air and readily enter other natural resources like soil and water (Ghoshdastidar and Ariya, 2019, p. 1). By attaching to fungal spores and coming into contact with people, NMs – both natural and synthetic – could travel trough the air (Westmeier et al., 2018, p. 7091). NNMs may not pose a direct risk as contaminants, according to studies, but they may regulate trace elements like the levels of arsenic contamination in various water sources. A layer of organic material covers the majority of NNMs surfaces, providing a net negative surface charge and improving stabilization through double layer formation (Vindedahl et al., 2016, as cited in Malakar et al., 2021, p. 8). The mobility of bound trace elements onto the NNMs can be controlled by the enhanced colloidal stability, which could also dictate how NNMs are transported in various water sources. Size, surface charge, and the Stokes settling velocity may be the three important factors influencing NNM mobility (Kretschmar & Sticher, 1998; Wagner et al., 2014, as cited in Malakar et al, 2021, p. 8). The surface charge may largely regulate the aggregation processes, a gravitation force scan starts rainfall. Particles deposition, size exclusion, redox potential, pH, ionic strength of the bulk solution, and an NNMs surface charge all may affect how mobile NNMs might be in groundwater sources (Wagner et al., 2014, as cited in Malakar et al., 2021, p. 8).

At the interface of water, soil, and organisms, NNMs may be essential to other related processes (Hochella et al., 2019, p. 1). NNMs found in soil may affect rhizosphere functions and find their way into food items. However, research on the interaction of natural nanomaterials in the environment may be limited (Ermolin & Fedotov, 2016; Malakar et al., 2019, as cited in Malakar et al., 2021, p. 9). The development of analytical methods for measuring NMs may allow for a better understanding of the numerous environmental roles that NNMs might play in the microbial-soil-rhizosphere interfaces, climate change, and cycles. A considerable amount of information might be lacking about the chemical components of NNMs and how they evolve in natural systems (Malakar et al., 2021, p. 8).

Synthetical nanomaterials in the environment

Synthetical NMs may be released into the environment at the end of their life cycle. Tracing synthetic NMs in a different natural environment setting might be difficult and complex, much like NNMs. Nonetheless, tracking the life cycle in the natural environment may be made easier by the definitive source and sink of synthetic NMs. It is possible for synthetic NMs, including incidental NMs (INMs) and engineered NMS (ENMs), to be released into the atmosphere at the point of production and stay there for a long time. Road vehicles are thought to be the main source of synthetic NMs in the atmosphere, particularly in crowded urban areas (Baalousha et al., 2016, p. 743). The route for human exposure is thought to be trough atmospheric release of synthetic NMs, whether they are incidental or engineered (Baalousha et al., 2016, p. 744). Similar to NNMs, synthetic NMs in the air may travel through the different soil and water sources (Malakar & Snow, 2020, as cited in Malakar et al., 2021, p. 9). High level of synthetic NMs in urban runoff can be detected in stormwater and wind up in wastewater treatment plants, where they might further contaminate surface water and penetrate groundwater (Wang et al., 2020, p. 2). Different water bodies constituents interact with ENMs (Baalousha et al., 2016, p. 743). Besides that, waste and biosolids may contain ENMs, which readily leak out of landfills and enter surface water or groundwater. Synthetic NMs may enter the environmental directly through use or indirectly through wastewater leachate and landfills. During any of these release phases, ENMs may undergo transformations that alter their characteristics (Kaegi et al., 2015, p. 25; Gogos et al., 2019, p. 53). ENMs may enter the environment during the production, use, and post-dumping phases (Bundschuh et al., 2018, p. 8). In contrast to INMs, ENMs may be anticipated to be primarily responsible during the last two phases of the synthetic NM life cycle (Malakar et al., 2021, p. 9). During the production stage, incidental metals like silver may also be discharged into the environment. Landfills, biofilm reactors, and wastewater could all contain silver nanoparticles. Throughout laundry, silver nanoparticles (NMs) embedded in textiles – which make up 20% to 100% of the total particle content – are released and found in the wastewater stream. The main release pathway for ENMs is wastewater treatment plants. The redistribution of ENMs to various waterbodies is greatly aided by these treatment facilities. The fate, transformation, mobility and behavior of ENMs in the complicated wastewater matrix may still be largely unknown (Malakar et al., 2021, p. 9). The use of products based on nanotechnology in the environment is growing the moment. These applications, which include groundwater nano remediation, release ENMs directly into the environment for a variety of reasons. Groundwater remediation employs nanoscale zerovalent iron (nZVI)[4] particles (Soares et al., 2018, p. 935). For point decontamination of groundwater sources, nZVI is injected directly (Soares et al., 2018, p. 936). Unintended consequences may arise from direct injection into an aquifer as nZVI could interact with microorganisms (He et al., 2017, p. 32) and have the potential to negatively affect groundwater bacteria by altering the dominant subsurface biogeochemical cycle (Lei et al., 2016, p. 506). Following the last membrane filtration step, the frequently utilized ENMs in water treatment processes, such as TiO2, Ag, and ZnO ENMs, were discovered in dangerous concentrations (Sousa & Ribau Teixeira, 2020, p. 3). ENMs may acquire availability in water by interacting with NOMs[5], like humic matter (Malakar et al., 2021, p. 9). The soils synthetic NMs may be found in variety of agriculture goods. Recent reviews have gone into detail about how different crops absorb

[4] Nanoscale zerovalent iron = nZVI
[5] Natural Organic Matter = NOM

ENMs and how that affects irrigation water quality (Gupta & Xie, 2018; Malakar et al., 2019, as cited in Malakar et al., 2021, p. 11). The risks to human health posed by synthetic NMs in different environmental compartments may not be well understood. There might be some factors that restrict the knowledge of the effects of synthetic NMs as pollutants in various soils, water bodies, and the air, including their nanoscale size, temporary nature, and the availability of accurate monitoring tools. To understand the release and exposure pathway of synthetic NMs and their long-term effect on environment, these lack of knowledge have to be filled (Malakar et al., 2021, p. 11).

4.4 Cluster 4: Food and pesticide

The last and smallest cluster is cluster 4. This cluster is different to the other since it does not have a clear assemblage, spreading the four keywords it includes (food, pesticides, pollutants and wastewater) into the middle of the figure, closely intertwined with all the other clusters. Since nanomaterials may have a pathway through wastewater or contaminated soil which is explained in the other clusters, this keyword also appears in cluster 1. Additionally, this explains the overlapping with cluster 2, which focuses on engineered nanomaterials and toxicity aspects.

One of the main ways that's consumers may be exposed to inorganic nanoparticles (NPs) thought oral ingestion is through food (Tschiche et al., 2022, p. 4). The NPs that may be found in food come from either natural or man – made sources. Both are separated into incidental and engineered NPs. It is possible to purposefully add engineered nanoparticles to food. The European Food Safety Authority recently may assessed iron hydroxide adipate tartrate, which the first novel food in nanoparticles form, as safe, despite the fact that no engineered NPs may be currently authorized for use in food in Europe (EFSA , 2021, p. 22–23). Engineered nanoparticles (NPs) can be released from materials that may come into contact with food or can enter the food chain through the environment when they are used in other applications, like building and construction. It is possible for incidental NPs to form and be released during food production or preparation. A number of authorized food additives may also be available, including silver dyes (De Vos et al., 2020, as cited in Loeschner et al., 2023, p. 1) as well as titanium dioxide (TiO2) (Geiss et al., 2020, p. 251) may either be released or contain a portion of nanoscale particles. The direct effects of engineered nanomaterials (ENMs) on human health may be remain unclear, despite nearly three decades of research into their toxicology. With a typical translocation to distal organs of less than 1%, its is anticipated that the majority of ingested NPs may swiftly pass through the gastrointestinal tract and be lost via fecal matter after oral exposure. The toxicity of various NP types after oral exposure cannot yet be determined or even ranked due to a lack of appropriate studies (Loeschner et al., 2023, p. 2). There may still be a lot of unanswered questions, such as how NPs in food directly affect the microbiota and gastrointestinal issues (Bouwmeester et al., 2018, p. 6). For example, a broad range of US products that may use nanotechnology in their manufacturing or contain NMs are regulated by the US Food and Drug Administration (US FDA), including food, cosmetics, medications and drug formulations, devices, veterinary products, and tobacco products (FDA, 2024). More precisely, the Center for Food Safety and Applied Nutrition (CFSAN) regulates the use of NMs in food and cosmetics. The goal of this center is to enhance data on NM safety assessments so that regulatory decision-making can be better informed. The goal of this center is to enhance data on NM safety assessments so that regulatory decisions-making may be better informed. Research might been used to inform uses and restrictions, the allowable quantities of a given substance (in weight percent) when incorporated as a food additives, and labeling recommendation, even thought the US FDA is still gathering information to make regulatory decisions regarding safety. Under Titel 21 – Food and Drugs, all of this data is stored in a current database known as the Code of Federal Regulations (U.S. FDA, 2024). For example, the European Food Safety Authority (EFSA) has created particular guidelines for NM and small particle risk assessment that can be used in the food and feed chain (EFSA Scientific Committee, 2021a, p. 1; EFSA Committee, 2021b, p. 8). In the continuing reassessment and monitoring efforts concerning the safety of approved food additives by EFSA, the existence of tiny particles is taken into account, and if required, nano-specific considerations are added to the traditional risk analysis was carried out for the food additive titanium dioxide (E171). The EFSA Panel determined that E171 could no longer be regarded as safe when used as a food additive due to numerous uncertainties and the possibility of genotoxicity (EFSA FAV, 2021, p. 2). A number of initiatives to analyze E171 in foods may started by the above mentioned discussions and the later European ban. Nations around the world have looked at how well their legal systems handle nanotechnologies in food, feed, and agriculture industries. In 2015, Amenta et al. found that the European Union (EU) and Switzerland may be the only two countries in the world with nano-specific provision included in their current laws. Other regions primarily built on industry guidelines to regulate nanomaterials in a more implicit manner. For instance, the EU may required food labels to disclose the presence of NMs as ingredients since December 2014, in compliance with Regulation No. 1169/2011. For handling nanotechnologies in the food, feed, and agriculture industries. Regulation No. 1169/2011, for example, may made it mandatory in the EU since December 2014 to label food that contains NMs as an ingredient (Loeschner et al., 2023, p. 2). According to Regulation 1169/2011, all ingredients that are present in the form of engineered NMs may be identified in the ingredients list and their names may be followed by the word “nano” in parenthesis. If an engineered NM has not been used extensively for human consumption in the EU before May 15, 1997, it is deemed a novel food and is subject to the novel food regulation. Starting in 2018, specific guidelines for their safety evaluation on food authorization may be appropriate (Rauscher et al., 2017, p. 224). Reliable techniques for the detection and characterization of NPs in foods may be required in the context of risk assessment, food labeling, and the creation of novel foods. To evaluate consumer exposure, studies are needed to analyze the amount of NPs in food. Understanding whether purposefully added engineered NPs and food additives with small particles can be differentiated from the background levels of natural and incidental NPs is essential for food control purposes (Loeschner et al., 2023, p. 2). There may numerous analytical methods available for characterizing NPs in food. The three commonly used inductively coupled may be plasma-mass spectrometry (ICP-MS) in single particle mode (spICP-MS), and asymmetric flow field-flow fractionation (AF4) coupled to ICP-MS (Mattarozzi et al., 2017, Correia et al, 2019, as cited in Loeschner et al., 2023, p. 3). The gold standard for determining particles sizes may be electron microscopy, which also may offers details on particle shape, aggregation state, crystal structure, and, when paired with spectroscopy, chemical composition. It does, however, call for specialized equipment that may not commonly found in food control labs. AF4 requires skilled operators and may have reproducibility problems, primarily due to particle losses on the membrane (Mattarozzi et al., 2017; Correia et al., 2019, as cited in Loeschner et al., 2023, p. 3). Duo to its high sensitivity and elemental specific in providing information on particle size and number of concentration, single particle ICP-MS is a promising method for screening food sample for the screening food samples for the presence of metal-containing NPs. Fast analysis, comprehensively easy sample pre-treatment, and simple integration with cutting-edge ICP MS tools may otherwise be used for mental analysis and speciation, which may be additional benefits of spICP MS (Loeschner et al., 2023, p. 3).

The background level of natural and incidental NPs in food other than seafood, such as fruits and vegetables, generally may need to be determined by more screening studies. The best method for it may be single particle ICP-MS. Iron oxides and hydroxides (E172)[6] and aluminum (E173)[7] are two examples of food additives other than titanium dioxide and silver for which the suitability of spICP-MS should be studied. In order to examine the presence of inorganic nanoparticles in bread or vegetables oils, for example, sample preparation protocols for food with high starch and fat contents should be developed. Additionally, spICD-MS could be

[6] Iron oxide and hydroxide (E172)
[7] Aluminum (E173)

used to scan for NPs in feed and feed additives (Loeschner et al., 2023, p. 46). As with other techniques, NP analysis by spICP-MS should follow established sampling best practices that may take sample homogeneity and sample group representativeness into account. SiO2[8], a food additive is though to be less toxic, especially when used at the permitted limit of 2% by weight. It may be used as a stabilizer in the production of beer and as an anti-clumping agent in powdered food products (CFR, 2024) made available on June 12, 2023, (EFSA ANS, 2018, p. 50) made available on June 12, 2023). However, during the integration process, nanosized SiO2 may be produced, and the toxicological effects then become unclears (EFSA ANS, 2018, p. 4, 34; Lozano et al., 2022, p. 2). Therefore, research into SiO2s toxicological effects may be still ongoing. The multi-technique characterization of food additive/food grade SiO2 may have been the subject of recent research, with spICP-MS serving as a primary characterization avenue (Loeschner et al., 2023, p. 47). In order to ascertain the shape and composition of particles, spICP-MS investigations should ideally always be enhanced with other methods. If this isn't feasible, publications should make clearer the limitations of spICP-MS with regard to the assumptions used to calculate particle size. To demonstrate that the NP shape is either unknown or nonspherical, particle sizes could be displayed as mass-equivalent sizes. It may be necessary to discuss how the consistency and combination of NPs affect their size and mass concentration. It is important to note that there may be a noticeable widespread trend towards the use of traditional spICP-MS experimental setups for the analysis of inorganic NPs in food additives and food itself. This may be explained by the chosen publications prevailing in application focus in this arising field. Over the coming years, it is anticipated that other ICP -MS platform – aside from the single quadrupole tools that may currently hardly utilized in this field – will be gradually integrated. The trending use of time-of-flight ICP-MS may allow for the identification, quantification, and classification of NPs from unknown sources based on their multielement fingerprint (i.e., engineered, incidental, and natural NPs), while high sensitivity of double-focusing or sector field ICP-MS instruments may lower the size detection limits (Loeschner et al., 2023, p. 47).

Another keyword that emerges in that cluster is pesticide, which may also be an part of the discussion around nanomaterials exposure for several reasons. In every industrial sector, including pharmaceuticals, food, animal feed, cosmetics, electronics, and agriculture, nanomaterials may be widely used (Mazayen et al., 2022; Angelopoulou et al., 2022, as cited in Tripathi et al., 2023, p. 1). Providing food, textiles, wood materials for a variety of industries, agriculture boots the economies of developing countries. In order to solve the food crisis caused by the expanding human population, the Food and Agricultural Organization (FAQ)

[8] SiO2 = Siliciumdioxide (E551)

predicted in 2019 that the demand for agricultural production worldwide would may be need to rise by 23-70% by 2050. Agricultural productivity may be afflicted by a number of challenges, including soil contamination, climate change, the widespread use of chemical fertilizers, and the exhaustion and exploitation of soil and water resources. Precision farming and the development of agriculture may be being considerably impacted by recent developments in nanotechnology.

Application of Nanomaterials as Herbicides, Pesticides and Nano-fertilizers

The efficient delivery of macro-and micronutrients, plant growth regulators, pesticides, and fertilizers through smart nanoscale carries may be has made nanotechnology an effective approach to sustainable agriculture in recent years (Ahmed et al., 2018; Hassanisaadi et al., 2022, as cited in Tripathi et al., 2023, p. 8). By binding plant roots to the organic matter and soil structure in the ecosystem, nano-carriers may prevent chemical spills and address environmental problems. These may help reduce effort and waste product while increasing the plants bioavailability of active ingredients (Dasgupta et al., 2015, as cited in Tripathi et al., 2023, p. 9). The use of NPs to reduce the herbicides none-target toxicity may given more importance in herbicide research. De Oliveira et al. demonstrated that the target plant Raphanus raphanistrum may could be eradicated more effectively by pre-emergence application of solid lipid nanoparticles containing atrazine and simazine than by post-emergence application of the herbicide alone (de Oliveira et al., 2015, as cited in Tripathi et al., 2023, p. 9). Chidambaram et al. (2016) used 2,4 – dichlorophenoxyacetic acid (2,4-D) to analyze the load nano-sized rice husk waste particles. The target plant (Brassica sp.) was found to be more herbicidally affected by NPs loaded with 2,4-D herbicides than by 2,4-D alone. Herbicide loading at the rice husk may be also found to lessen the leaching effected in soil (Tripathi et al., 2023, p. 9). Dos Santos Silva et al. used paraquat loaded with chitosan or alginate instead of paraquat alone, which may decrease herbicide leaching in soil sorption tests (Silva et al., 2011, as cited in Tripathi et al., 2023, p. 9). The increased effectiveness of nanopesticide against a range of pests and their potential for tailored action, which may be reduces environmental toxicity, are making them a viable alternative to conventional pesticides, much like nanoherbicides. Chitosan loaded with permethrin and spinosad was tested for its anti-pest properties at different doses using Drosophila melanogaster as a model organism. Permethrin and spinosad together in chitosan were shown to be more effective than either substance alone, indicating the potential use of nanoformulations for pest control management (Sharma et al., 2019, as cited in Tripathi et al., 2023, p. 9). Moreover, the plants immunity is strengthened by the associated between chitosan and zinc. To improved disease control, Choudary et al. claim that the addition of zinc and chitosan nanoparticles boosts the amount of lignin and antioxidants in maize crops (Choudhary et al., 2019, as cited in Tripathi et al., 2023, p. 9). Silver nanoparticles made from red seaweed extract may have antibacterial and antifungal qualities that make them suitable for use in the creation of nanopesticide (Ghareeb et al., 2022, p. 10). Due to crop plants limited capacity to absorb 30-50% of chemical fertilizers, a significant amount of the input may be stays in the soil, resulting in ground water contamination and soil sterility. Over time, fertilizers efficiency may decreases as a result of saturation (Mózner et al., 2012, as cited in Tripathi et a., 2023, p. 9). Nonfertilizer may reduce the amount of fertilizer applied in the field because of their effectiveness in reducing the nutrient loss through controlled release (Huang et al., 2015, p. 385). The literature that is currently available may be indicates that nonfertilizers are increasing a number of crop yields (Huang et al., 2015; Sharma et al., 2022; Rady et al., 2023, as cited in Tripathi et al., 2023, p. 9). Various NPs may act as either nonfertilizers or as nanoencapsulating agents, which converts regular fertilizer into nonfertilizers (Kumari & Singh, 2020, p. 737). Copper nanoparticles (Cu NPs) and biofertilizer (Piriformospora indica, a fungus that promotes plant growth) applied to the leguminous crop Cajanus cajan showed that applying nano+ biofertilizer (nanobiofertilizer) together may be more efficiently stimulate plant growth and vitality (Tripathi et al., 2023, p. 9).[9]

Nanoparticle Uptake and Presence in Plants

Soil factors like organic matter, soil type, pH, and moisture content may influence the bioavailability, transport, fate, and toxicity of nanoparticles. These factors may cause changes in NP chemistry, including agglomeration, aggregation, dissolution, and biotransformation (Pachapur et al., 2016, p. 937). After being initially absorbed by the root system, nanoparticles may move to the aerial section and begin to accumulate in cellular or subcellular or organelles (Tripathi et al., 2017, p. 7, 9). The early phase of bioaccumulation is the absorption of nanoparticles by plant root surfaces. According to studies, the iron plaque in the plant root cap and the acidic environment of the root cap both enhance the uptake of silver nanoparticles in the root (Tripathi et al., 2023, p. 13). Size is a key factor in NP adsorption in plants, as it allows for entry through biological pores such as cell walls and stomata (Yusefi-Tanha et al., 2020; Pagano et al., 2023, as cited in Tripathi et al., 2023, p. 13). A study may found that absorption of 50 nm copper NPs in wheat roots altered root cell morphology and revealed the presence of Cu NPs adhering to the root surface through SEM-EDS analysis[10] (Adams et al., 2017, p. 110).

Soil Health and Biodiversity: ENMs in Soil

[9] The exact design oft the Table with manufactured and approved nanotechnology-enabled nano agro products/inputs can be found in annex 5
[10] SEM: Scanning Electron Microscopy, EDS: Energy Dispersive Spectrometry

Because of a lack of proper detection tools and analytical approaches, it may be impossible to determine the concentration of NMs pollution in the environment, so predicted environmental concentrations are used instead. A predicted model may have anticipated that carbon-based NMs have the highest concentration in aquatic systems, followed by titanium oxide NPs and copper NPs. In soil, CeO_2 and TiO_2 are assumed to have the highest concentration, followed by other NMs (Gottschalk et al., 2015, p. 5582). The data may suggest that NMs pollution has reached the soil by the end of the shelf life of nano-enabled products. ENMs may enter the soil either directly or through atmospheric deposition, sludge application, or agricultural irrigation (Usman et al., 2020, p. 9 – 10). Because of their low mobility, NM pollution may be much more concentrated in soil than in water or air (Qian et al., 2023, p. 14). As a result, soil might become the ultimate sink for NMs released into the environment. Once embedded in the soil matrix, NMs endangers the stability and function of the soil ecosystem. NMs may interact with both organic and inorganic soil components, undergoing a series of environmental transformations. Furthermore, NMs alter soil porosity, which may influence water and dynamics and soil aggregation properties. If NMs are released into the soil matrix without control, they may aggregate and not decompose in the soil, which could have negative consequences. The impact of NMs on soil microscopic characteristics was documented in studies by Cao et al. and Kolesnikov et al., in which high concentration of ENMs may adversely impacted the activity of the dehydrogenase enzyme (Kolesnikov et al., 2021, p. 11). Different nanoparticles may have different effects on soil enzymatic activity; for instance, different NPs (Cu-, Ni-, and Zn NPs) have different effects on enzymatic activity in a soil sample. When compared to Ni- and Cu NPs, the presence of Zn NPs may significantly impact catalase activity. The order of Cu = Zn > Ni indicates how sensitive the soil's overall enzyme activity may be to metal NPs (Kolesnikov et al., 2021, p. 7). Figure 12 explains the different mechanisms that regulate the reactivity, mobility, stability, and toxicity in soil.

The enzymatic activity may be also significantly impacted by the length of time that NPs are exposed. Following one hour and one week of treatment, the activity of phosphatase, arylsulfatase, glucosaminidase, and glucosidase decreased, as was seen in soil treated with silver (Eivazi et al., 2018, p. 210). The detrimental impact of NM application on soil microbial communities and soil nutrients cycle may be another very researched challenges. Multiwalled carbon nanotubes (MCNT) may have been shown to impact soil enzyme activity and rhizospheric microbial community diversity in a study by Chen et al. Under MCNT, it showed elevated urase, phosphatase, and sucrose activities; however, MCNT may had an impact on the taxonomic composition of soil microbes (Chen et al., 2022, p. 9).

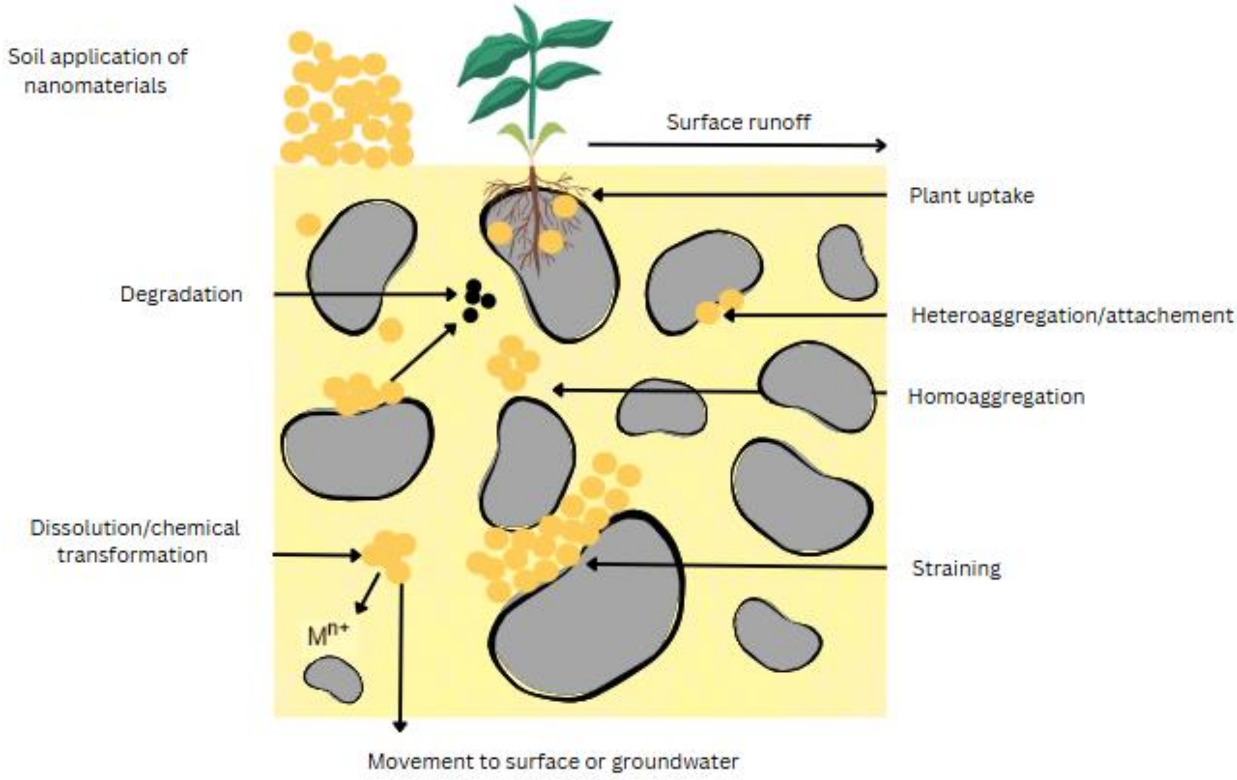

***Figure 12**:Fate of nanomaterials in soil system. Adapted from Nanotechnology in agriculture: Current status, challenges and future opportunities, Usaman et al. (2020, p. 9), author`s elaboration.*

Environmental Concern of NMs: Toxicological Aspects

Due to population's increasing demand for agricultural yields and more effective ways to balance environmentally harmful agricultural practices, the use of NMs in agroscience may be growing (Eivazi et al., 2018, p. 209). Nanotechnology may actually have a considerable influence on the development of sustainable agriculture on the development of sustainable agriculture and precision farming. The development of sustainable agriculture and precision farming may actually be influenced by nanotechnology. Increasing agricultural output, or crop yields, while reducing inputs, like fertilizers, pesticide, and herbicides, may be the goal of this approach. It keeps an eye on environmental factors and takes focused action to get the intended outcomes (Sampathkumar et al., 2020, p. 9).

As nanotechnology finds new uses in agriculture and other industries that may impact the global economy, researcher are considering the possible harm to human and environmental health (Tripathi et al., 2023, p. 18). Furthermore, there may be unanticipated health consequences if NMs are purposefully added to agricultural processes (Singh et al., 2019, p. 67). One exposure pathway that might contribute to an increased in uptake of nanomaterials residues by people and other environmental entitles is bioaccumulation in the environmental residues by people and other environment and food chain, according to this scenario. The environments soil, water and air are regularly contaminated by NPs, also referred to as nanostructured materials. Among others, lead and tin nanoparticles may have demonstrated remarkable stability, stiffness, and non-degradability. Additionally, these NPs may have toxicological effects when they enter the human, animal, and plant tissues and organs (Tripathi et al., 2023, p. 18). Moreover, the extensive use of silver nanoparticles (NPs) in consumer products may damage the aquatic systems environment by changing bacteria, fish, algae, and other aquatic organisms. The configuration, mass, and structure of nano-agrochemicals determine their hazardous significance. Even though the size of NPs and their adverse effects , may be related and reduce their size, crystal-structured nanocomposites may be more hazardous than amorphous ones. Additionally, it may has been found that, high concentrations of nanofertilizer could alter molecules in a number of ways and interfere with plant nutrition. Besides that, an excess of Cu NPs may decrease the levels of IAA and ABA in plant cells. In parallel, even though the same dose (100 ppm) of NFs[11] may found to be advantageous for first-generation maize, applying Fe_3O_4 NPs to second-generation maize crops may caused physiological harm because of a large accumulation of Fe (Tripathi et al., 2023, p. 18). The ecotoxicological risk assessment of nano-agrochemicals may be shouldn't be based only on the understanding of the "dose effect" at the organism level. A study of the lethal process, beginning at the level of the cell and its organelles, may should be part of it (211).

Even though NPs may have been widely used in sustainability applications, it is still unknown how prolonged exposure to them may harm the environment and human health. As a result, an evaluation of exposure and hazards using a present testing and monitoring procedure may be necessary, along with an integrated risk analysis based on the life cycle of NMs. Furthermore, carbon based NMs (such as graphene, CNTs, and fullerene) may be less harmful. As a substitute, NPs may be used to lessen NP toxicity (Yang et al., 2023, p. 11).

The applications of nanotechnology, including nanopesticides, nanoherbicides, and nanofertilizers, have improved agricultural productivity. Research on how nano-enabled tactics or goods produce the expected result may still be lacking. The size, shape, charge, and hydrophobicity of NMs may determine how they interact with living systems. Each species has a very different level of sensitivity to the NMs. Characteristics such as type, size, surface charge coating, and crystal chemistry, as well as exposure circumstances like concentrations, duration, and soil physicochemical properties, determine an ENMs ecotoxicological behaviors. Therefore, completing the toxicological effects may be requires a detailed characterization of

[11] NFs: Nano-Fertilizers

the NMs epitope. Additionally, a through assessment of MNMs impact on the physiochemical characteristics of soil is necessary. It may be important to thoroughly examine how various nanofabricated products change in soil and how they degrade in environmental matrices. NMs with variety of physical and chemical characteristics, including type, size, surface charge, coating, and crystal chemistry, may have been created, released into the environment, and deposited there in recent years. A functional understanding of NMs interactions with biological systems is necessary for the design of the future nanotechnology. It may be nearly impossible to fully understand all of the possible toxicological features of each NM. The evidence currently available indicates that different NMs commonly exhibit a range of toxicity tendencies in the environment and in numerous complex biological systems. A precise mechanists mechanism of NMs toxicity in complex systems may be needs to be comprehended in order to fill in the gaps in the future concerning environmental safety and nanotechnology (Tripathi et al., 2023, p. 19).

Example: “Heavy metal contamination and potential health risks in upland rice-producing soils in of rotational shifting cultivation in northern Thailand” by Arunrat et al. (2024)

4.5 Theoretical Framework

The clusters described provide an overview of the current research status of nanomaterials and human health. Through their analysis, it can be observed that the interlinkage between nanomaterials and various environmental and human health factors is complex and multifaced. Cluster 1 with the health hazard and heavy metal emphasizes the possible health hazards connected to heavy metal exposure, especially when it comes to nanomaterials. This field of study looks at how engineered nanomaterials can either lessen or increase the harmful effects of heavy metals. The textile sector contributes significantly to environmental pollution, especially through the release of wastewater that contains dyes and heavy metals. With an emphasis on the sources, effects on the environment, and related health risks, this cluster attempts to investigate the health risks connected to heavy metal contamination in wastewater. Heavy metals (such as chromium, lead, and cadmium) are among the chemicals used in textile industry dyeing, finishing, and printing procedures. Determining mitigation strategies requires an understanding of the precise process that lead to heavy metal contamination. The process of making textiles results in the creation of wastewater that contains dyeing. Heavy metals are among the complex mixtures of pollutants that are frequently present in this wastewater and can leak into environment if its not properly treated (Carney Almroth al., 2021; Ali et al., 2022). It also investigates how heavy metals from textile wastewater move through the environment, including soil and water systems. This includes examining adsorption, bioavailability, and potential accumulation in sediments and biota. Assessing the effects of heavy metal pollution on aquatic and terrestrial ecosystem. Along with analyzing the impacts on biodiversity, species composition, ecosystem health, and the possibility of bioaccumulation in food chains. Identifying the pathways by which humans can be exposed to heavy metals from textile wastewater, such as direct contact, ingestion of contaminated water or food, and inhalation of heavy metal-containing dust. The health risks connected with exposure to specific heavy metals found in textiles waste is also considered. Besides that, analyzing the presence of heavy metals in textiles end products such as dyed fabrics and garments is also part of it. As well as assessing the risk of heavy metal leaching during use and washing. Evaluating present regulations and standards for heavy metal content in textiles and wastewater discharge. Analyzing compliance with environmental laws and consumer safety is considered as well. For example, with diverse health risk assessment indices like HRI, hazard index (HI), hazard quotient (HQ), DIM, and daily dietary index (DDI) which have been conducted on the health risks associated with contaminants being transported from food to humans (Cui et al., 2004; Hough et al., 2004; Chary et al., 2008; Khan et al., 2008; Zhuang et al., 2009; Gall et al., 2015; El-Kady & Abdel-Wahhab, 2018, as cited in Rai et al., 2019, p. 371).

Trough wastewater treatment technologies investigation of advanced heavy metal removal methods from textile wastewater, such as physical treatment methods, filtration, chemical treatment methods, biological treatment method or advanced treatment technologies like membrane technologies (Okut et al., 2025, p. 2 ff.).

Cluster 2 with engineered nanomaterials and toxicity studies the psychotechnical characteristics, biological interactions, and mechanisms of actions of different engineered nanomaterials in order to determine their toxicity profiles. ENMs have particular features such increased surface area, quantum effects, and high reactivity, that distinguish them from their bulk counterparts. These properties may make them potentially useful in a variety of industrial, medical and technological applications, such as drug delivery, electronics, sensors, and environmental remediation. Among these nanomaterials, silver nanoparticles (AgNPs) have received attention because of their antibacterial, conductivity, and catalytic properties. Nevertheless, concerns may have been raised about the potential toxicity of these nanomaterials, particularly when AgNPs interact with biological systems at the molecular level. Understanding the toxicity of ENMs and their exposure pathways may be crucial to ensure their safety. Silver nanoparticles may be one noticeably studied and used engineered nanomaterials due to their broad antibacterial, antiviral, and antifungal properties. They may be commonly used in biomedical applications such as wound dressing, drug delivery systema, and diagnostic tools, as well as consumer goods such as textiles, cosmetics, and food packaging. However, the release of silver ions might contribute to the toxicity of these materials by interfering with cells, proteins, and DNA, potentially causing damage. ENMs such as AgNPs, may enter the body through a variety of routes, each with different health outcome. The main exposure pathways may be inhalation, ingestion, skin contact, Intraperitoneal (i.p.) and intravenous (i.v.) injections (De Matteis, 2017, p. 2). Nanomaterials primarily cause toxicity through the following mechanisms:

- Oxidative stress caused by ROS production disrupt normal cellular functions and cause inflammation, apoptosis (programmed cell death), and necrosis. AgNPs are known for their ability to release silver ions (Ag+), which can increase oxidative stress and contribute to toxicity of these materials. ROS generation can cause tissue damage and raise the risk of developing chronic diseases like cancer and cardiovascular disease.
- Genotoxicity is a substances ability to cause genetic damage, such as mutations, chromosomal aberrations, or cancer. AgNPs have been shown to cause genotoxicity effects, primarily by producing ROS, which can damage DNA. Nanoparticles interaction with cellular machinery may also intervene DNA repair mechanisms, increasing the risk of genetic mutations.
- Nanoparticles, particularly those with a high surface reactivity, may stimulate the immune system, resulting in the release of pro-inflammatory cytokines and other immune meditators. Chronic inflammation may been associated with numerous of health issues, which would include respiratory illnesses, cardiovascular disease, and cancer.
- Cellular Uptake and Accumulation: ENPs could be absorbed into by cells via endocytosis or membrane penetration due to their small size. Once inside the cell, nanoparticles may accumulate in organelles such as lysosomes, mitochondria, or the nucleus, causing cellular dysfunction.

Cluster 3 with environment and nanomaterials discusses the fate, transport and ecological transformation of nanomaterials as well as their impact on the environment. It focuses on the relationship between environmental health and nanomaterials, emphasizes both natural and synthetic nanomaterials (NNMs). This cluster investigates the dual role of nanotechnology in addressing environmental issues while also highlights potential risks associated with its use. NNMs are nanomaterials that exist naturally in the environment, such as soil, water, and air. NNMs can be released into the ecosystems through natural processes such as weathering and volcanic eruption. They can also be found in rainwater and contribute to the microbial ecosystem in soils. Synthetical nanomaterials also known as engineered nanomaterials (ENMs) are designed for specific applications, including environmental remediation. Examples include silver nanoparticles (AgNPs) and titanium dioxide nanoparticles (TiO2 NPs), which are used for their antimicrobial and photocatalytic properties. However, their introduction into the environment may cause toxicity in both aquatic and terrestrial organisms, potentially disrupting ecosystems and biodiversity. The link between nanomaterials and environmental health is complex. While nanotechnology can help with pollution control, it also poses risks if not handled properly. Nanomaterials unique properties, such as their small size and high reactivity, can have unintended environmental consequences. For example, the accumulation of NMs in aquatic and terrestrial ecosystems (air, water, and soil) may cause bioaccumulation and biomagnification, affecting food chains and human health. Industrial discharge, municipal wastewater, and landfill runoff all have the potential to introduce NMs into water. Once in the environment, they may accumulate in sediments and be absorbed by plants and animals, possibly causing toxicity. But to soil understand the release and exposure pathway of synthetic NMs and their long-term effect on environment, these lack of knowledge have to be filled (Malakar et al., 2021, p. 11)

Cluster 4 with food and pesticide investigates the effectiveness, safety, and possible health hazards of using nanomaterials in food production and pesticide application. NMs can be engineered to improve herbicide efficiency, allowing for more precise delivery and less chemical use. ENMs can improve pesticide effectiveness by increasing solubility, stability, and controlled release, reducing environmental impact. These are intended to provide nutrients to plants more efficiently, promoting growth while minimizing nutrient runoff and soil degradation. Plants can absorb nanoparticles through roots systems and foliar applications. Because of their small size, they can easily penetrate plant tissues, unlike conventional fertilizers and pesticides. The presence of ENMs in plants can affect physiological processes such as nutrient uptake, growth rates, and stress responses. Understanding these interactions is crucial for optimizing their agricultural applications. The introduction of engineered into soil may have both beneficial and considerable consequences. While they may increase nutrients availability and improve soil structure, there are concerns about their toxicity to soil microorganisms and invertebrates. ENMs impact on soil health may be closely related to their effects on microbial communities. Healthy soil microflora are necessary for nutrient cycling, organic matter decomposition, and overall soil fertility. The use of nanomaterials in agriculture involves a complex interplay between increasing food production and maintaining environmental health While ENMs can increase the efficacy of herbicides, pesticides, and fertilizers, their impact on plant uptake, soil health, and biodiversity must be thoroughly investigated. The potential risk associated with the use of ENMs in agriculture must be carefully evaluated. This includes determining the long-term impact on soil health, microbial communities, and overall ecosystem function. Developing guidelines and regulations for the safe use of nanomaterials in agriculture is critical to ensuring that their benefits are realized while maintaining environmental quality.

These clusters demonstrates the necessity of a comprehensive strategy to understand how nanomaterials impact the human health and environment. Through investigation the interlinkage between toxicity, environmental impact, and food safety, scientists may enhance the development of nanotechnology-related regulatory frameworks and public health initiatives. In conclusion, these clusters emphasize the necessity of a strategic framework to comprehend the effects of nanomaterials on the environment and human health.

It emphasizes the critical importance of understanding the sources, environmental impacts, and health risks associated with heavy metals in textiles industry wastewater. By addressing these issues through research and policy development, it can reduce the negative effects of heavy metal pollution on human health and environment. This integrated approach will help to develop safer industrial practices and improve public health outcome. Numerous factors influence the toxicity of nanomaterials, including silver nanoparticles, such as size, surface chemistry, and the release of reactive species. Understanding the exposure pathways and toxicity mechanisms associated with ENMs is critical for determining their safety and promoting responsible use. Research on the toxicity, biocompatibility, and regulatory aspects of engineered nanomaterials is crucial for minimizing health risks and optimizing their safe use in various industries. Research on the toxicity, biocompatibility, and regulatory of engineered nanomaterials is crucial for minimizing health risks and optimizing their safe use in various industries. Cluster 3 emphasizes the importance of a balanced approach to the use of a nanotechnology in environmental applications. While it offers promising solutions for pollution treatment and prevention, the risks associated with both natural and synthetic nanomaterials must be carefully considered. Ongoing research and risks assessment are essential for ensuring that benefits of nanotechnology's benefits do not impact environmental health and ecosystems honesty. Assessing the sustainability of nanotechnology and its long-term impacts on ecosystems requires an understand of these environmental interactions. It also demonstrates the potential of nanomaterials to transform agricultural practices by improving pesticides and nutrient distribution. Even so, it emphasizes the importance of understanding how their use impacts plant uptake, soil health, and biodiversity. Ongoing research and careful risk assessment are required to fully experience the benefits of nanotechnology in food production while protecting environmental health. Research can improve the way that nanotechnology-related regulatory frameworks and public health are informed by investigating the intersection of toxicity, environmental impact, and food safety.

4.6 Limitation

A bibliometric analysis has limitations that should be considered when interpreting the results, even though it is replicable and based on a great number of scholarly literature. The bibliometric analysis is also impacted by publication bias because it relies on academic literature (Donthu et al., 2021, p. 295). The selection of studies articles with positive results is known as publication bias, as a result, those with negative findings are unlikely to be published or shown up in the bibliometric analysis. The reliance on the literature also suggests that results interpretation must take into account the literatures limitations. For example, a knowledge gab that Hendricks et al. (2023) mentions is that while ENMs have been studied in various matrixes, there is still a gap for simple and affordable methods to assess their presences. More research is needed to better understand the fate and behavior of ENMs in the environment, as standard methods are lacking (Hendricks et al. 2023, p. 12949). Apart from that, research on nanomaterials impact on human health does not equal to how humans will be exposed to nanomaterials, but it needs to be observed in order to foresee the long-term nanomaterial implications on human health. Therefore, the studies discussed on various nanomaterials that may affect the human health especially on long-term through different pathways, which deliver results that are most trustworthy in terms of future implications, but are debatable in terms of the exact precision of the numbers. When it comes to measuring the impact of nanomaterials on human health, several variables can be quite challenging to assess: The behavior of nanomaterials in biological systems can be strongly influenced by their size and distribution. Accurately measuring these traits can be challenging. The way that nanoparticles interact with biological tissues can be influenced by their surface chemical characteristics, such as functional groups and coatings. It can be challenging to measure this variability. Apart from that, other variables such like exposure routes, biological interactions, long-term effects, individual variability, environmental factors are making it challenging to establish clear cause-and-effect relationships between nanomaterials and health outcomes. Therefore, these data collection challenges may result in the neglect of crucial information that could already show changes in nanomaterial pathways or production security and health may be missing due to these difficulties in data collation.

Moreover, since a section referring to health was added in the search string to retrieve literature that named at least one aspect connected to it, literature on solely the interlinkage of nanomaterials and human health was not considered that much. Additionally, the bibliometric analysis deliver quantitative results, hence the qualitative content analysis of the literature connected to the keywords underlies the subjective perspective of the person conducting it

(Donthu et al., 2021, p. 295). The individuals disciplinary history may have an impact on this. Further field studies that provide findings for various assessment of the toxicity of heavy metals and their byproducts can advance the understanding of the connection between nanomaterials, human health, and exposure pathways.

5. Conclusion

The bibliometric analysis showed that there is a strong interlinkage between human health and nanomaterials exposure, which will be an increasing concern to the society in the future due to the consequences stemming from it. This work contributes to theory by summarizing the status quo of the scholarly literature. The long-and short-term effects of nanomaterial influences all the dimensions of nanotechnology production and usage, posing a risks not only to the human health but also being a major concern for the environment. Nanomaterials have a great potential for a number of uses, such as electronics, environmental remediation, and medicine. Nevertheless, their distinct characteristics also give rise to worries about possible hazards and detrimental impacts on human health. While some nanomaterials may have therapeutic benefits, other nanomaterials may present risks, including cellular toxicity, respiratory problems, and unknown long-term health effects, according to current research. If nothing is done, this could have a negative impact on human health and lead to a higher number of disability-adjusted life years in the future. Accordingly, exposure to nanomaterials through a variety of pathways endangers human health, which is defined by author Last (2007) as a sustainable state that thrives in the balance with environment and permits humans to live actively in a community.

The analysis showed that the two main key concepts influence each other in various of ways, and that there are occasionally indirect pathways through mediators. For example, the body's natural barriers, like the skin, respiratory system, and gastrointestinal tract may influence the extent of which nanomaterials is absorbed into the body. These obstacles may restrict or help. The ability of nanomaterials to enter cells and tissues can be influenced by their size and shape. While certain shapes may affect how particles behave in biological systems, smaller particles may be more likely to enter cells. Furthermore, the bibliometric analysis has brought to light the various research directions that have prevailed so far in this field, including the overarching perspective on nanomaterials and human health, heavy metals, toxicity, food products, and environmental perspectives. Moreover the analysis has shown that while the heavy metal dimension has received much attention so far, more research is needed on other dimensions, as well as on different types of consumer sources. Although the main focus areas of each cluster under analysis are different, but they are all related in some way. The clusters are interconnected through pathways of exposure and the potential health impact with heavy metals and nanomaterials in the environment and food systems.

In terms of practical implications, the work has shown the importance of creating efficient risk assessments frameworks, because it is essential to comprehend the possible hazards associated with nanomaterials. By identifying the nanomaterials that present health risks, this research helps regulatory agencies in creating safety regulations and standards for their use in industrial processes, consumer goods, and medical applications. The research findings may help policymakers understand the need for nanomaterial specific regulations. In order to protect public health and promote nanotechnology innovation, this includes recommendations for safe production, handling, and disposal. Furthermore, research helps in the development of nanomaterials with enhanced safety profiles and lower toxicity. Manufactures can reduce potential health risks by developing safer consumer goods, such as food packaging, cosmetics, and medical devices, by comprehending how various nanomaterials interact with biological systems. Besides that, it can help guide public initiatives to limit exposure to dangerous nanomaterials. Campaigns to increase knowledge of possible hazards and safe handling procedures for good containing nanomaterials are part of this. And the safe use of nanomaterials in medical applications , like drug delivery systems and diagnostics tools, is also informed by research into the risks connected with these materials. This ensures that patient safety wont be compromised while the advantages of nanotechnology in healthcare are realized. Collaboration between scientists, engineers, medical professionals, and regulatory bodies is encouraged by nanomaterials research. This multidisciplinary approach is crucial for tackling the complicated problems related to nanotechnology and its effects on the environment and human health.

Lastly, this work demonstrates that the interlinkage between nanomaterials and human health would have a great impact on society in the future. In order to improve future policymaking, future studies should take into account the numerous variables that affect this interlinkage and, in addition to expanding the understanding of the ones that are already known, take into account those that have not yet been discovered. The need to understand the safety profiles of nanomaterials is growing as their use increases. Future studies should concentrate on long-term health consequences of being exposed to different nanomaterials, taking into account their possible toxicity and biological system interactions. This will help in developing comprehensive risk assessment frameworks. And in order to develop regulations that ensure the safe application of nanomaterials while encouraging innovation, scientists, legislator, and industry stakeholders will probably need to work together in the future. Despite developments, the field of nanotechnology still may have a lot of knowledge gaps. These include understanding the long-term effects of exposure, the mechanisms of toxicity, and the fate of nanomaterials in the environment. To ensure the safe development and use of nanotechnology, these gaps must be filled. Besides that, future studies should also be focused on efficient communication techniques to educate stakeholders and consumers about the safe use of nanomaterials. These are necessary to create a sustainable, prosperous future for everyone and to protect human health from the negative effects of exposure to nanomaterials.

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Appendix 1. Keywords of Clusters, listed

Cluster 1	Cluster 2	Cluster 3	Cluster 4
Health hazard and heavy metal	**Engineered NM and toxicity**	**Environment and nanomaterial**	**Food and pesticide**
Keywords:	**Keywords:**	**Keywords:**	**Keywords:**
arsenic	air pollution	antimicrobial	food
bio accumulation	antioxidant	biosensor	pesticide
cancer	bioavailability	covid-19	pollutants
carcinogenic	ecotoxicity	drug delivery	wastewater
contamination	engineered nanomaterials	environment	
drinking water	exposure	environmental health	
ecological risk	genotoxicity	health	
fish	gut	health care	
hazard	immune response	nanomaterial	
health hazard	inflammation	nanotechnology	
heavy metal	microplastic	occupational exposure	
pollution	nanoparticle	risk	
potentially toxic elements	nanoplastic	safety	
soil	nanotoxicity	sensor	
source	oxidative stress	sustainability	
surface	pm	wearable	
trace element	silver nanoparticles		
water	toxicity		
water pollution			

Annex 1

Table 2: The ATSDR 2022 Substance Priority List. Adapted from Agency for Toxic Substances and Disease Registry (2024), author's elaboration

2022 Rank	Substance Name	Total Points	CAS RN
1	ARSENIC	1675	7440-38-2
2	LEAD	1531	7439-92-1
3	MERCURY	1455	7439-97-6
4	VINLY CHLORIDE	1355	75-01-4
5	POLYCHLORINATED BIPHENYLS	1342	1336-36-3
6	BENZEN	1328	71-43-2
7	CADMIUM	1317	7440-43-9
8	BENZO(A)PYRENE	1306	50-32-8
9	POLYCYLIC AROMATIC HYDROCARBONS	1277	130498-29-2
10	BENO(B)FLUORANTGENE	1255	205-99-2
11	CHLOROFORM	1202	67-66-3
12	AROCLOR 1260	1191	11096-82-5
13	DDT,P,P'-	1182	50-29-3
14	AROCLOR 1254	1172	11097-69-1
15	DIEBENO(A,H)ANTHRACENE	1163	53-70-3
16	TRICHLOROETHYLENE	1153	79-01-6
17	CHROMIUN, HEXAVALENT	1151	18540-29-9
18	DIELDRIN	1142	60-57-1
19	PHOSPHORUS, WHITE	1142	7723-14-0
20	AROCLOR 1242	1126	53469-21-9

Annex 2

Table 3: Heavy metal contamination from diverse sources in global food crops. Adapted from Heavy metals in food from crops: Health , risks, fate, mechanisms, and management, Rai et al. (2019, p. 368 - 369), author's elaboration

NO.	Food crops (cereals, fruits, vegetables, etc.)	Country where investigated	Sources of heavy metal contaminants affecting food chains	Metal concentrations recorded in food crops (dry weight)	References
1	Brassica sp., Chenopdium sp., leafy and root vergetables, grains	India	Sewage effluent (inadequately treated)	Cu 1.7-12.9 mg/kg Pb 0.13 mg/kg Zn 7.25-24.6 mg/kg Cr 0.08-0.38mg/kg Pb 0.02-0.013mg/kg Cu 0.16-0.85mg/kg Zn	Rattan et al. (2005)
2	Rice, wheat soybean (*Glycine* max), corn Zea mays), potato	Brazil	Industrial/modern intensive urban agriculture	Below the standard limits hazardous to human health	Branco Courguinha et al. (2015)
3	Grain, maize (*Zea mays*), green cabbage, *Brassica juncea* L, radish (Raphanus sativus L), turnip, *Brassica napus*, spinach, cauliflower, and lettuce	China	Sewage effluent (indequateley treated using biological approach)	Cr 0.08-0.38 mg/kg Pb 0.02-0.013 mg/kg Cu 0.16-0.85 mg/kg Zn 0.16-0.53 mg/kg	Khan et al. (2018)
4	Lettuce (*Latuca sativa*); a leafy food crop/vegetable	Spain	Air (PM) from industries and vehicles	< 0.02 mg Ni/kg, < 0.008 mg Hg/kg <0.005 mg Cd/kg	Ercilla-Montserrat et al. (2018)
5	Brassica sp., food grains, and leafy vegetables	China	Both sewage and industrial waste (from smelter) drained into river waste used for irrigation	Cr.0.01-0.19 mg/kg Pb 0.12-0.23 mg/kg Cu 0.15-0.86 mg/kg Zn 0.42-0.95 mg/kg	Liu et al. (2005)
	Soybean	Argentina	Industrial (battery) waste in soil	Metals (Pb & Zn) well above permissble limits	Rodriguez et al. (2014) ; Blanco et al. (2017)
6	*Triticum aestivum* (wheat), *Lycopersicum esculentum* L. (tomato), radish, spinach, brinjal, carrot, *Capscium annum, Allium sativum* (garlic), *Coriandrum sativum* (conriander), and okra	Pakistan	Metal-contaminated groundwater	Cr > 0.18 mg/kg Pb 0.91-3.96 mg/kg	Khan et al. (2013)

No	Food crops (cereals, fruits, vegetables, etc.)	Country , where investigated	Sources of heavy metal contaminants effecting food chains	Metal concentration recorded in food crops (dry weight)	References
7	Rice and other paddy crops and vegetables	Australia (food crops imported from Bangladesh, India, Pakistan, Thailand, Italy, Canada and Egypt)	Arsenic-and metal-contaminated groundwater	Rice: Cr 15-465 µg/kg Pb 16-284 µg/kg Cu 1.0-9.4 mg/kg Zn 10.9-24.5 mg/kg Cd 8.7-17.1 µg/kg Co 7-42 µg/kg Mn 61-356 µg/kg Ni 61-356 µg/kg Pb 670-16,500 µg/kg Vegetables: Cr 27-774 µg/kg Pb 35-495 µg/kg Cu 1-29 mg/kg Zn 17-183 mg/kg Cd 3-370 µg/kg Mn 3-140 µg/kg Pb 35-495 µg/kg Cr 0.00078-0.049 mg/kg	Rahman et al. (2014) [see also Tripathi et al. (1997), Alam et al. (2003), Islam et al., 2018]
8	French beans (Phaseolus vulgaris) beetroot (*Beta vulgaris)* and kale (Brassic oleracea var. acephala)	Australia	Urban stormwater	Cr 0.00078-0.049 mg/kg Pb 0.001-0.11 mg/kg Cu 0.016-0.66 mg/kg Zn 0.038-0.145mg/kg	Tom et al. (2014)
9	Spinach	India	Sewage wastewater (inadequately treated)	Cu 0.09 mg/kg Cr 2.9 mg/kg Pb 3.1 mg/kg Cd 0.012 mg/kg Zn 2.48 mg/kg Ni 0.07 mg/kg	Chary et al. (2008)
10	Radish	China	Inadequately treated wastewater	Cu 0.34 mg/kg Cr 0.03 mg/kg Pb 0.07 mg/kg Cd 0.012 mg/kg Zn 2.48 mg/kg Ni 0.07 mg/kg	Song et al. (2009)

No	Food crops (cereals, fruit, vegetables, etc.)	Country where investigated	Sources of heavy metal contaminants affecting food chains	Metal concentration recorded in food crops (dry weight)	References
11	Industrially processed food stuffs (e.g. candy) and pharmaceuticals	United States of America (USA), Spain, Portugal, Belgium, England, and Chile	Industries/food processing industries/modern pesticides based agriculture	Cr (0.10-17.7 ppm), Ni (0.01-7.01 ppm), Cu (0.01-6.44 ppm), Zn (0.01-6.44 ppm), Pb (0.03-7.21 ppm)	Gonzalez-Martin et al. (2018)
12	Potato/ other foodstuffs	Egypt	Inadequately treated wastewater	Cu 0.83 mg/kg Cr nil Pb 0.08 mg/kg Cd 0.02 mg/kg Zn 7.16 mg/kg	Radwan and Salama (2006); El-Kady and Ab Wahhab (2018)
13	Potato	China	Inadequately treated urban wastewater	Cu 1.03 mg/kg Cr 0.03 mg/kg Pb 0.067 mg/kg Ni 0.054 mg/kg	Song et al. (2009)
14	Radish	India	Diverse contamination sources	Cu 5.96 mg/kg Cr nil Pb nil Cd nil Zn 22.5 mg/kg Ni nil	Arora et al. (2008)
15	Cauliflower	China	Urban wastewater	Cu 0.6 mg/kg Cr 0.02 mg/kg Pb 0.003 mg/kg Cd 0.014 mg/kg Zn 5.45 mg/kg Ni 0.68 mg/kg Cu 1.4 mg/kg Cr 2.4 mg/kg Pb 2.9 mg/kg Cd nil Zn 8 mg/kg Ni 3.1 mg/kg	Song et al. (2009)
16	Amaranthus	India	-	Cu 1.4 mg/kg Cr 2.4 mg/kg Pb 2.9 mg/kg Cd nil Zn 8 mg/kg Ni 3.1 mg/kg	Chary et al. (2008)
17	Chinese cabbage	China	Pot experiment with exogenous supply of Cd	Cd 0.12-1.70 mg/kg	Junhe et al. (2017)
18	Lettuce *(Lactuca sativa)*	United States (Florida)	-	As 27.3 mg/kg However, reduced by 21%	de Oliveira et al. (2017)

Annex 3

Table 4: Health risks from the dietary intake of foodstuffs contaminated with heavy metals and metalloids. Adapted from Heavy metals in food from crops: Health , risks, fate, mechanisms, and management, Rai et al. (2019, p. 370), author's elaboration

S. NO.	Heavy metals and metalloid	Sources of metallic contamination	Route/medium of exposure	Dose response details/toxicity limits	Health risks Acute, chronic, critical		References
1	Mercury	Non-surgical tools, chemical/chlor-alkali industries, energy-intensive industries such as thermal power plants	Methyl mercury enters the food chain through biomethylation; adversely affects the health of plants and humans	10µg/L (in whole blood); 20µg/L (in urine)	Inorganic Hg leads to lung damage; kidney damage, proteinuria, allergy, and amalgam disease Organic Hg perturbs central nervous system (CNS) coordination and the health of plants	Neuropsychological symptoms; hypersensitivity (pink disease), nephrotic syndrome, historical Minamata disease on sea coast of Japan & Iraq killed thousands of people	Jarup (2003); Heaton et al. (2003), Soghoian and Sinert (2008); Guzzi and La Porta (2008); Peralta-Videa et al. (2009); El-Kady and Abdel Wahhab (2018)
2	Cadmium	Soil amendments with fertilizer and sewage sludge, Ni-Cd batteries, alloys, cigarette smoking	Food crops in non-smoking population; smoking; Fe status also affects gastrointestinal absorption	NOAEL (food): 0.01mg/kg/day; RfD (mg/kg/day): 0.01 x 10^{-2}	Adversely affects kidney functioning through increased secretion of low molecular weight proteins (β2 macroglobulin & α1-macroglobulin) & enzymes (N-acetyl-β-D glucosaminidase), pneumonitis (oxide fumes), inhibition of sex hormones (progesterone & estradiol), endocrine disruption	Proteinuria in humans, kidney damage, human carcinogen (group I) causing lung & breast cancer, long-term exposure can result in itai-itai due to conjunction of osteomalacia & osteoporosis as evidenced in Japan	WHO (World Health Organization) (2001); Jarup (2003); Hough et al. (2004); Henson and Chedrese (2004); Brama et al. (2007); Zhang et al. (2008); Soghoian and Sinert (2008); Peralta-Videa et al. (2009)
3	Lead	Mining & smelting, paint, thermal power plants, crude petrol	Air/particulate deposition on food crops, occupational exposure	NOAEL:25µg/dL; RfD (mg/ kg/day): 0.35×10^{-3} [toxic limit] Pb≥70µ/dL	Encephalopathy, nausea & vomiting, adverse impact on CNS, circulatory, & cardiovascular systems, children are vulnerable to problems with learning and concentration	Accumulation of erythrocyte protoporphyrin through inhibition of ferrochelatase, anmia, abdominal pain, nephropathy, possible human carcinogen	Ma (1996); Jarup (2003); Hough et al. (2004); Soghoian and Sinert (2008); Peralta-Videa et al. (2009); El-Kady and Abdel Wahhab (2018)

S. NO.	Heavy metals and metalloid	Sources of metallic contamination	Route/medium of exposure	Dose response details/toxicity limits	Health risks Acute, chronic, critical		References
4	Copper	Irrigation with contaminated wastewater	Intake of contaminated food	LOAEL: 10mg/kg/day	Can affect renal & metabolic functions	Excess protein droplets in epithelial cells of the proximal convoluted tubules in rats	Hough et al. (2004)
5	Chromium	Electroplating/ chrome plating industries, dye industry, sewage wastewater/ sludge	Intake of food contaminated by wastewater & soil amendment with industrial sludge	Toxic limits in humans not specified clearly	Kidney/renal dysfunction/failure, Cr (VI) is more health hazardous than Cr (III) due to rapid absorption, hemolysis & gastrointestinal hemorrhage	Collapse/dysfunction of respiratory system through lung cancer & pulmonary fibrosis	Dong et al. (2007); Soghoian and Sinert (2008); Peralta-Videa et al. (2009)
6	Nickel	Ni-Cd batteries, wastewater	Intake of contaminated food	NOAEL: 5mg/kg/day; RfD: 0.05×10^{-1}	Can affect renal functioning, integral component of urease enzyme in kidney	Remarkable decrease in body & organ weights	Hough et al. (2004)
7	Arsenic (metalloid)	Inorganic As in contaminated groundwater, smelting of non ferrous elements, thermal power plants using fossil fuels (coal), particulate deposition, minor sources include arsenical pesticides & wood preservatives	Contaminated drinking water & foodstuffs	Dose-response: 100μg/L As can lead to cancer & 50–100 μg/L can lead to skin cancer [toxic limits] 24-h urine: ≥50μg/L, or 100μg/g creatinine	Multi-organ dysfunction, encephalopathy, bone marrow depression, hepatomegaly, melanosis, "rice-water" diarrhea, severe neuropathy, long QT syndrome, peripheral vascular disease (black foot disease of Taiwan)	Cancer in the lungs, kidney, bladder, and skin (hyperkeratosis & pigmentation); changes can occur from drinking As-contaminated water; diabetes & cardiovascular diseases	Jarup (2003); Soghoian and Sinert (2008); Peralta-Videa et al. (2009); Islam et al., 2017; El-Kady and Abdel-Wahhab, 2018
8	Zinc	Irrigation with contaminated wastewater (industrial & sewage)	Contaminated foodstuffs	LOAEL: 59.3mg/kg/day; RfD: 1.00×10 mg/kg/day	Respiratory problems	Significant decrease (47%) in erythrocyte superoxide dismutase concentration in adult females	Hough et al. (2004)

"Note/Abbreviations: No observed adverse effect level (NOAEL); lowest observed adverse effects level (LOAEL); RfD: reference dose (RfD, milligrams per kilogram per day) defined as the maximum tolerable daily intake of a specific metal that does not result in any deleterious health effects" (Rai et al., 2019, p. 370)

Annex 4

Table 5: : Summary of the presence of various natural and synthetic NMs in the natural environment. Adapted from Nanomaterial in the environment, human exposure pathway, and health effects: A review, Malekar et al. (2021, p. 7), author's elaboration

Nanomaterial type	Presence in the environment	References
Natural nanomaterials Silicon dioxide	Atmosphere, surface and groundwater	Lungu et al., 2015
Carbon nanotubes	Atmosphere, soot and fires	Griffin et al. 2018
Mercury nanoparticles	Saoil and water resources	Ghoshdastidar and Ariya, 2019
Ferrihydrite	Soil, surface and groundwater	Malakar and Snow, 2020
Iron oxyhydroxide	Oceans and seas	Hochella et al., 2019
Manganese based NMs	Oceans and seas	Hochella et al., 2019
Sulfur NMs	Mineral wells, springs	Griffin et al., 2018
Silver nanomaterials	Hydrothermal vents, surface water, wastewater	Sharma and Zboril, 2017
Polymeric nanomaterials	Atmosphere	Courty and Martinez, 2015
Nickel, zinc, cadmium, silver, tin, selenium, lead bismuth	Volcanic eruptions, atmosphere	Ermolin et al., 2018
Synthetic nanomaterials Platinum	Atmosphere	Baalousha et al., 2016;
Titanium dioxide	Wastewater, surface runoff, stormwater, surface and groundwater, landfills, atmos-phere	Bäuerlein et al., 2017 Baalousha et al., 2016; Bäuerlein et al., 2017; Pe-ters et al., 2018
Fullerenes (C_{60})	Air; sludge; wastewater	Bäuerlein et al., 2017
Iron oxide	Atmosphere, stormwater, surface water; tap wate	Baalousha et al., 2016; Malakar and Snow, 2020; Westerhoff et al., 2018
Cerium oxide	River water	Peters et al., 2018
Nanoplastics	Surface water, sea and ocean	Lehner et al., 2019
Zinc oxide	Soil, surface water, crops, landfills	Bundschuh et al., 2018; Du-renkamp et al., 2016; Sousa and Ribau Teixeira, 2020
Zinc sulfide	Stormwater	Baalousha et al., 2016
Lead sulfide	Atmosphere	Baalousha et al., 2016
Carbon nanotubes	Atmosphere, wastewater, surface water, landfills	Sun et al., 2016
Silver nanomaterials	Wastewater, landfills, sludge	Alizadeh et al., 2019; Bundschuh et al., 2018; Kunhikrishnan et al., 2015; Sousa and Ribau Teixeira, 2020

Annex 5

Table 6:Manufactured and approved nanotechnology-enabled nano agro products / inputs. Adapted from Recent Advances and Perspectives of Nanomaterials in Agricultural Management and Associated Environmental A Review, Tripathi et al. (2023, p.10), author's elaboration

Commercial Name of Product	Nanomaterial Compositions	Manufacturer	Current Status and Legislation Compliance	Nanomaterial Application	Country of Origin
Nano-Ag Answer®	Billions of microorganisms, sea kelp and mineral electrolytes	Urth Agriculture, Monterey, CA, USA	Commercialized	Nanofertilizer	United States (US)
Ready to Use Spray	Biohumus in size range 100-700 nm	GreenEarth-NanoPlant, Fort Myers, FL, USA	Commercialized US patents (U.S. 15/290, 257, U.S. 15/ 429, 380)	Nanofertilizer	US
NanoPro®	Silicon dioxide and humic acid	Aqua Yield Operations, LLC., Sandy, UT, USA	Commercialized comliance with OSHA HCS (29CFR 1910.1200) and WHMIS 2015 Regulations	Crop protection	US
NanoCS™	Nitrogen, phosphorus, potassium (NPK) and zinc	Same as above	Same as above	Nanofertilizer	US
NanoN+™	1% urea nitrogen	Same as above	Same as above	Nafertilizer (N-delivery)	US
NanoPhos®	NA	Same as above	Same as above	Controlled delivery of nutrient	US
NanoK®	NA	Same as above	Same as above	Controlled delivery of nutrient	US
NanoGro®	NA	Same as above	Same as above	Controlled delivery of nutrient	US
NanoStress®	NA	Same as above	Same as above	Controlled delivery of nutrient	US
NanoCalSi®	NA	Same as above	Same as above	Controlled delivery of nutrient	US

Commercial Name of Product	Nanomaterial Compositions	Manufacturer	Current Status and Legislation Compliance	Nano-material Application	Country of Origion
NanoFe™	NA	Aqua Yield Operations, LLC., Sandy, UT, USA	Commercialized comliance with OSHA HCS (29CFR 1910.1200) and WHMIS 2015 Regulations	Controlled delivery of nutrient	US
NovaLandNano	NA	LandGreen& Technology, Taipei,Taiwan	Commercialized	Plant growth stimulators	Taiwan
NANOCU®	Nano copper, 10%, adjuvants and cheating materials, 90%	Bio Nano Tech, Giza, Egypt	Commercialized	Plant protection (fungicide and bactericide)	Egypt
NanoUltra-Fertilizer	Organic matters, 5.5%; nitrogen, 10%; P_2O_5, 9%; K_2O_5, 8%; K_2O, 14%, P_2O_5, 8%; K_2O, 14%; MgO, 3%	SinoMyainTaiEco TechnologyCo., Ltd. (SMTET),Yangon, Myanmar	Commercialized	Nanofertilizer	Myanmar
Nano Calcium	$CaCO_3$ 77.9%; $MgCO_3$, 7,4%; SiO_2, 7.47%; K,0.2%; Na, ppm; Al_2O_3, 6.3 ppm; Sr, 804 ppm; sulfate, 278 ppm; Ba, 174 ppm; Mn, 172 ppm; Zn, 10 ppm	PAC International Network Co., Ltd., Koln, Germany	Commercialized	Nanofertilizer	Germany
PPC Nano	M protein, 19.6%; Na_2O, 0.3%; K_2O, 2.1%; $(NH_4)_2SO_4$, 1.7%; diluente, 76%	WAI International Developement Co., Ltd., Singapore/ Malaysia	Commercialized	Nafertilizer	Malaysia
Nano Green fertilizer	Extracts of grain, soybean, potatoes	Nano Green Sciences, Inc., Gwalior, India			India
Nano Urea	4% N as encapsulated nitrogen (20-50 nm)	Indian Farmers Fertilizer Cooperative Limited (IFFCO), Mumbai, India	Commercialized	Nanofertilizer	India

Tropical nano PHOS	Nano phosphorus	Geetharam Agencies Sole Proprietorship	Commerciali- zed	Controlled de- livery of nutrient	India
Geolife Nano Combi	16.6%Zinc+3.8% magnese +3.8% co- pper	Geolife Agritech India Pvt. Ltd., Mumbai, India	Commerciali- zed	Controlled de- livery of nutrient	India
Magic Root 4th Generation Nano Plant Growth Promoter	Mastermix of plant hormones	Infinite Biotech, Ahmedabad, In- dia	Commerciali- zed	Plant growth stimulators	India

Statutory Declaration

I herewith formally declare that I have written the submitted work independently. I did not use any outside support except for the quoted literature and other sources mentioned in the paper. I clearly marked and separately listed all the literature and all of the other sources which I employed when producing this academic work, either literally or in content. I am aware that the violation of this regulation will lead to the failure of the thesis.

[redacted]

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12.03.2025, Hamburg