Risk Assessment and Risk Management of Nano-Material Toxicity

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Abstract

Increasing applications of nano materials in medicine, construction, textiles, computers, and other consumer goods have lead to increasing concerns of their effect on human health and ecology during synthesis, manufacturing, use, and disposal of nano-materials. Though much scientific progress has been made in nano material synthesis, manufacturing, and application in consumer goods and other sectors such as medicine, textiles and more, not much progress has been made in understanding the adverse effects of nano materials on human health and the environment. Physical, chemical, toxicological characteristics of these nano materials and their fate in the environment are important in understanding their adverse effects on the environmental and human health. This study is aimed at developing a preliminary framework for risk assessment (RA) and risk management (RM) of nano materials based on fundamental principles of chemistry, physics, toxicology, and other related disciplines.

Keywords: toxicity, nano, green, RA, RM
Chapter 1

1-1 Introduction

The expanded growth of nano-material applications requires continuous monitoring of their toxicity and exposure in various predominant conditions. Scientific methodology (chemical, physical, and biological approaches) with respect to engineering practices (environmental engineering and nano-engineering) is one of the applicable practices to properly assign the mechanism of nano-material toxicity, along with evaluating and extrapolating to formulate risk assessment and a management model. The comprehensive description of a nano-material toxicity mechanism also needs to include some essential factors: properties, characteristics, structure, chemical composition, sources, as well as consideration of nano-chemistry, nano-engineering, and understanding the harmful effects on natural environment and human health. Finally, design of a proper combined model of risk assessment and management in order to make certain decisions from possible outcomes is necessary.

To identify a systematic model of nano-particles toxicity, information and experimental data need to be collected that could lead to the building of a hypnotized system. This object might function as a valuable guideline to design the required and relevant modules, mental modeling, and diagrams. This study presents an appropriate outline to evaluate the toxicity of nano-materials, assess potential risk, and design an acceptable framework for risk management that would derive a practical method to challenge the harmful impacts of toxic nano-materials applications.
Consideration of the extraordinary and unusual properties of nano-materials, their relevant variables, uncertain events, contribution of new information, value of outcomes, characterization of nano-particle systems, and potential hazards of toxic nano-particles are essential parameters with which to design and build ideal modules and preferred modeling. The presented modules and models could be an exclusive back-up to organize and accumulate knowledge and experiences to reach successful procedures and applicable methods for risk assessment of nano-material toxicity. The preliminary and preferred factors in this research focus on a combination of nano-science characteristics and nano-engineering techniques. Three prominent and chosen nano-materials contain [Fullerenes (Bucky Balls & CNTs), ZNO, and TiO2] and their toxicity evaluations lead to the attainment of a general understanding and improved realization of some unique and unusual properties of nano-materials. Furthermore, these objects may assist to predict and recognize toxicity and exposure as two most significant factors in risk assessment.

The design modules and drawing models in this research are based on a fundamental description of the mechanism for nominated toxic nano-particles and their harmful effects. The most important functions have focused on eco-toxic impacts on natural environment and human health, their processing, and primary variables in both relevant branches of nano-chemistry and nano-engineering. Toxicity modules may occur explicitly from in vitro and in vivo studies, toxicokinetic, acute toxicity and toxicity dosage, carcinogenicity, and instillation versus inhalation. In addition, the focus is on three items: bioavailability, bioconcentration, and bioaccumulation, which are required to accurately estimate toxicity. Sketches of nano-chemistry and nano-engineering modules can be the proper experimental tools to enhance the controlling method. The benefits of
designed models of risk assessment and management in this study might help to complete the framework of research in scientific–engineering areas in two ways: first, by deriving certain outline of toxicity and exposure estimation, second, advantage leads toward an accurate guideline of potential risk assessment of nano-material toxicity to reach a regulation pathway.

1-2 Scope of work

The overall scope of the work is to understand the nano-material toxicity and propose risk assessment (RA) and risk management (RM) methodology which will minimize adverse impacts on human health and deterioration of the environment. The specific objectives of this research are listed below:

- Conduct a critical review of nano-material toxicity on human health and the environment
- Develop an integrated RA and RM methodology for nano-materials using the fundamental principles of chemistry, physics, biology, toxicology, and other related disciplines
- Propose nano-engineering and nano-chemistry for control measures to minimize the impact of various nano-material toxicity on human health and environment

1-3 Significance

The most important objective of this study is to provide critical reviews of the effect of nano-material toxicity on human health and the environment. In addition, approaches in chemistry, physics, and biology are needed to develop the RA methodology pathway in this area. A review of relevant studies and reports concerning
toxicity evaluation may lead to worldwide data and information that are fundamental to
the risk assessment of nano-material toxicity. [Fig-1]

Today, many studies and research have focused on nano-material toxicity
assessment, providing new and required data. Table 1 introduces some of the most
important studies for selected nano-scale materials in which some toxicity singes have
been observed in different fields based on proper experimental testing methods. (Table-1)

<table>
<thead>
<tr>
<th>Nano-Materials</th>
<th>Number of Citations on Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon Nanotubes</td>
<td>9</td>
</tr>
<tr>
<td>Dendrimer</td>
<td>29</td>
</tr>
<tr>
<td>Ceramic Nanoparticles</td>
<td>0</td>
</tr>
<tr>
<td>Nano (ultrafine)-ZnO</td>
<td>11</td>
</tr>
<tr>
<td>Nano-Cerium Dioxide</td>
<td>0</td>
</tr>
<tr>
<td>Nano-Zero Valent Iron</td>
<td>0</td>
</tr>
<tr>
<td>Nano (ultrafine)-TiO2</td>
<td>16</td>
</tr>
<tr>
<td>Fullerenes</td>
<td>37</td>
</tr>
</tbody>
</table>

The most significant purpose in this study is emphasis on an evaluation of human
health risks. However, because of a lack of sufficient data from human health analysis,
using animal data is preferred. In vivo and in vitro studies may support and be used
essentially to provide evidence missing from human studies and to help attain required
data from the natural environment due to toxic impacts of NM and NP actions.
Designing the appropriate models and modules may assist in making risk assessment
principles and subsequent risk management decisions. These options could be
extrapolated in various sites and fields with respect to predominant conditions.
they may be used to make proper regulation and/or standard settings.

Figure 1: Toxicity Evaluation Pathway

The principles in this study that support and develop the methodology of risk assessment and risk management associated with toxic nano-scale substances impacts either in the natural environment or in human health system include:

- Identification of physical and chemical properties, and analytical methods,
- Nano-engineering and nano-chemistry studies,
- Application of science and engineering approaches in methodology,
- Sources of exposure,
- Environmental transport, distribution, and transformation,
• Environmental levels and human exposure,
• Kinetics and metabolism in laboratory animals and humans,
• In vivo and in vitro studies and test systems,
• Estimation of adverse effects on the human health system and the natural environment,
• Effects on other organisms in the laboratory and field.
• Evaluation of human health risks and effects on the environment.
• Proper procedures to protect human health and the environment.
• Further plans to develop a research pathway.

The principles and methods in this study, as the essential objects, might have some beneficial effects with which to classify human analysis data and quantitative requirements for toxicity evaluation of NM and NP. The necessity to develop an accurate methodology for assessing the toxicity of nano-materials is to estimate the acceptable intake in different fields, the illustration of potential risk of toxicity, the application of uncertainty factors, and the determination of hazard and adverse disease endpoints, etc.

Chapter 2 General preface to nano scale materials

2-1 Concept of Nano-Materials and Nano-Particles

The concept of nano-material refers to structural components of substances in sizing range of 1 - 100 nano-meters in one dimension and/or more than one dimension. Also, the atomic and molecular building blocks with a size equal to [~0.2 nm] of matter may be considered in the nano-materials family. The other significant description in this
area relates to the concept of nano-particles which have at least one dimension and smaller than 1 micron. They are commonly as small as atomic and molecular length scales, about [0.2 nm].

The most important forms of nano-particles are amorphous or crystalline. Two familiar examples of materials in crystalline form are fullerenes and carbon nano-tubes, in addition to nano-particulate matter. This refers to a collection of Nan particles, emphasizing their collective behavior [23]. Therefore, based on these descriptions, nano-technology could be recognized as a new science that considers design, synthesis, and application of materials. Furthermore, there are some particular approaches to obtain the desired size and shape in nano-scale that might be processed via nano-engineering procedures. Undoubtedly, these materials have unique chemical, physical, electrical, and mechanical properties with a wide range of applications in various fields, such as the industrial and medical activities, etc. In spite of benefits and wide range of applications (Table 2) of nano-materials, the focus on nano-toxicology issues is necessary. In nano-

<table>
<thead>
<tr>
<th>Table 2. Application of NMs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application Area</strong></td>
</tr>
<tr>
<td>Industry</td>
</tr>
<tr>
<td>Science</td>
</tr>
<tr>
<td>Engineering</td>
</tr>
</tbody>
</table>

toxicology and nano-material toxicity evaluation as a novel portion of toxicology science, the harmful impacts produced by nano-materials may be subjected. Nano-toxicology science would be extended not only for investigation of the adverse effects of manufactured nano-materials, but it also encompasses the toxic impacts of natural nano-particles such as atmospheric particles. This critical viewpoint attains a comprehensive
assessment of nano-material toxicity and also leads to practical procedures in order to reduce and/or remove toxicity effects due to the application of NM and NP.

2-2 Classification of nano-particle sources

The three major groups of NM: natural NP, manufactured NM, and Anthropogenic NM.

In addition nano-particles are commonly classified according to their specific structural features, namely, dimensionality, morphology, composition, uniformity, and agglomeration.

2-2-1 Natural and manufactured nano-materials and their health effects:

The majority of nano-particles in nature could originate from many natural processes, which include: photochemical reactions, volcanic eruptions, forest fires, and simple erosion, in addition to being produced by plants and animals. Although we usually associate air pollution as being caused by human activities such as automobiles, industry, and charcoal burning, natural events such as dust storms, volcanic eruptions, and forest fires can produce such vast quantities of nano-particulate matter that they profoundly affect air quality worldwide [23]. One of the considerable examples of natural NM is an aerosol that is generated by human activities, which consists of about 10% of the total; the remaining 90% is due to natural processing. The most mass abundance of mineral aerosols primarily originates from soil deflation (wind erosion) with a minor component from volcanoes, sea salt, natural and anthropogenic sulfates, and products of biomass burning, excluding soot [23].
Terrestrial dust storms and extrarrestrial dust are other natural sources of NM in the environment. Long-range migration of both mineral dust and anthropogenic pollutants from the major continents has recently been the subject of intense investigation. Approximately 50% of troposphere atmospheric aerosol particles are minerals originating from deserts [61].

Terrestrial airborne dust particles produce some health problems, especially for people with asthma and emphysema.

Volcanic eruptions, as an important source, may eject an enormous mass of ash into the atmosphere. Ash as a NP with nano-scale size could reach to the different layers of the atmosphere, such as the troposphere and the stratosphere. This processing could impact the harmful radiation from the sun to all areas of the earth. Heavy metals (trace elements) are toxic NM for human health as they originate from volcanic eruptions as well. The most important effect of ejected ash on the health system occurs in the respiratory system (nose and throat irritations, bronchitic symptoms), and eye and skin irritations.

2-2-2 Anthropogenic nano-materials and health effects

In a second category to be considered, anthropogenic nano-materials also have critical impacts on the natural environment and human health.

Chemical manufacturing, welding, ore refining and smelting, combustion in vehicle and airplane engines, combustion of coal and fuel oil for power generation, diesel and engine exhaust are known as anthropogenic NM which have adverse health effects in various media. Diesel and automobile exhaust are the primary sources of
atmospheric nano- and micro-particles in urban areas [62]. The composition mixture of engine exhaust is the most serious reason for the magnitude of harmful health effects. Air pollution in some particular cases might be due to automobile exhaust and emission of toxic PM into the atmosphere, which influences mortality. However, this issue is associated with specific locations and fields.

2-2-3 Manufactured nano-materials and health effects

The manufactured nano-materials are synthesized by many applicable methods such as: gas phase processes, vapor deposition synthesis (electron, thermal, and laser beam evaporation); colloidal or liquid phase methods in which chemical reactions in solvents lead to the formation of colloids; and mechanical processes including grinding, milling, and alloying. Using these methods can obtain the desired NM with various applications.

In spite of this wide range of applications of engineered NM, the focus on potential health risk issues is required. This main consideration is due to the adverse health effects of fabricated NM that today is the critical issue in scientific and engineering investigations. The subject of research must be directed in finding solutions to decrease and/or remove these adverse impacts.

2 2-4 Introduction to nano-material toxicity

Today, toxicity and the adverse effects of nano-materials action are a critical issue. Many significant aspects of NP, such as their small size, can be translocated from entry portals into the circulatory and lymphatic systems, and ultimately to body tissues and organs. Furthermore, based on several investigations of the natural environment,
some insensible effects of toxic NM have been observed. These harmful impacts could
destroy ecological balances in different media. Some nano-particles, depending on their
composition and size, can produce irreversible damage to cells by oxidative stress and/or
organelle injury.

In spite of a number of benefits and valuable applications of nano-materials,
several reports have suggested negative and harmful effects of NM on living cells, the
natural environment, and ecological balances. The most important parameters which are
responsible for potential NP toxicity include: particle size, surface area, surface
chemistry, surface charge, and zeta potential. These factors are essential to provide the
uptake mechanism, persistence, and biological toxicity of nano-particles inside living
cells. Additionally, consideration of these significant factors could predict the
sustainability/mobility and reaction of materials inside the human body in terms of toxic
evaluation. Therefore, a focus on dependent toxicity parameters would recognize the
mechanistic details of their actions and might be an appropriate pathway to obtain a
complete analysis of toxicity assessment.

2-3 Dependent toxicity parameters

There are many factors that influence toxicity of nano-scale materials and
possibly its distribution in the natural environment and human health system as well.
These important aspects directly or indirectly have a critical role in toxicity generation
for nano-particles because of the specific properties that would be involved in various
mechanisms and processing. Also, different impacts may predict outcomes in many
fields. Some of these parameters are described in the following sections.
2-3-1 Physico-chemical characteristics

The toxicity of NM involves a number of parameters and predominant conditions. Studies show the most essential parameters that influence the health system consist of dose, dimension, and durability. Furthermore, today there is a belief that these parameters have direct and possibly indirect associations with the different physico-chemical properties of NP, including related health effects. On the other hand, there are some uncertainties about the range of alteration of NM properties relating to toxicity. Some of these optional parameters include: mass, number, size, bulk or surface chemistry, aggregation, or all together.

2-3-2 Dose-response

Dose is recognized as the amount or quantity of a substance that will reach a biological system. The dose is directly associated to exposure or the concentration of a substance in the relevant media (air, food, water) multiplied by the duration of contact.

Generally, the negative health effects of nano-particles do not correlate with nano-particle mass dose [23].

2-3-3 Sizes

Current investigation in toxicological studies have revealed small nano-particles (<100 nm) may cause harmful impacts on the respiratory health system, and normally causing more inflammation than larger particles made from the same material. In addition, some experiments on the crystalline structure of some nano-scale particles have demonstrated that smaller particles lead to a persistently high inflammatory reaction in the lungs compared to larger particles. Furthermore, investigation of an exposure period
(up to 1 year) has shown that the smaller particles had a significantly prolonged retention, and increased translocation to the pulmonary interstitium and pulmonary persistence of nano-particles [23].

2-3-4 Surface area

For the same mass of particles with the same chemical composition and crystalline structure, a greater toxicity was found from NP than from their larger counterparts. This led to the conclusion that the inflammatory effect may be dependent on the surface area of NM, suggesting a need for changes in definitions and regulations related to dose and exposure limits. Indeed, smaller NP has a higher surface area and particle number per unit mass compared to larger particles [23]. The body will react differently to the same mass dose consisting of billions of NP compared to several micro-particles. A larger surface area leads to increased reactivity [63] and is an increased source of reactive oxygen species, as demonstrated by in vitro experiments [65]. The higher surface area of nano-particles causes a dose dependent increase in oxidation [65] and DNA damage [64], much higher than larger particles with the same mass dose [65].

2-3-5 Concentrations

In toxicity evaluation, some studies show the different toxic effects of NP at the various concentrations. A comparison between the consequences of different studies on different concentrations of NM as a dependent parameter in toxicity is correlated to aggregation properties of nano-particles in air and water, resulting in inherent discrepancies between inhalation studies and instillation or in vitro experiments. Furthermore, aggregation may depend on surface charge, material type, and size, among others. One must stress the fact that aggregation of NM is essential in determining their
toxicity, due to a more effective macrophage clearance for larger particles compared to smaller ones. Therefore, experiments performed with high concentrations of nano-particles will lead to the formation of nano-particle aggregates that may not be as toxic as lower concentrations of the same nano-particles [23].

2-3-6 Particle chemistry and crystalline structure

Although there have been suggestions that size may be more important than chemical composition in deciding nano-particles toxicity [64], one cannot generally extrapolate the results of studies showing a similar extent of inflammation for the chemistry of different nano-particles. Particle chemistry is critical in determining nano-particles toxicity. Particle chemistry is especially relevant from the point of view of cell molecular chemistry and oxidative stress. Namely, depending on their chemistry, nano-particles can show different cellular uptake, sub-cellular localization, and the ability to catalyze the production of reactive oxygen species [67]. One must make the distinction between composition and chemistry. Though particles may have the same composition, they may have a different chemical or crystalline structure. The toxicity of a material depends on its type of crystalline form [66].

2-3-7 Surface coating and functionalization:

Due to the possibility of chemical interactions, the combined effects of inhalation, ingestion, or dermal application of NM with other NP, chemicals, and gases are largely unknown. The estimated risk of two or more pollutants is not a simple additive process. Particle surface plays a critical role in toxicity as it makes contact with cells and biological material.
Surfactants can drastically change the physicochemical properties of nanoparticles, such as magnetic, electric, optical properties, and chemical reactivity [23], and are affecting their cyto-toxicity. To follow and develop investigations with regard to NMs toxicity, the most significant results and observed impacts related to cyto-toxicity of NMs (selected some nano scale substances) are summarized in Table 3. These data are provided via many experimental testing methods and related laboratory analyses under different conditions and various fields. The selection of materials for investigation in this table is based on their toxicity actions and behaviors which created adverse effects.

The observation of the harmful effects of NMs toxicity in this table, as the primary features, helps to design proper laboratory experiments and make appropriate

<table>
<thead>
<tr>
<th>Nano-material</th>
<th>Effects observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullerene</td>
<td></td>
</tr>
<tr>
<td>C60 water suspension</td>
<td>Antibacterial; cytotoxic to human cell lines; taken up by human keratinocytes; stabilizes proteins</td>
</tr>
<tr>
<td>C60 encapsulated in poly (vinylpyrrolidone), cyclodextrins, or poly (ethylene glycol)</td>
<td>Damages eukaryotic cell lines; antibacterial</td>
</tr>
<tr>
<td>Hydroxylated fullerene</td>
<td>Oxidative eukaryotic cell damage</td>
</tr>
<tr>
<td>Carboxyfullerene (malonic acid derivatives)</td>
<td>Bactericidal for Gram-positive bacteria; cytotoxic to human cell lines</td>
</tr>
<tr>
<td>Fullerene derivatives with pyrrolidine groups</td>
<td>Antibacterial; inhibits cancer cell proliferation; cleave plasmid DNA</td>
</tr>
<tr>
<td>Other alkane derivatives of C60</td>
<td>Antimutagenic; cytotoxic; induces DNA damage in plasmids; inhibits protein folding; antibacterial; accumulates in rat livers</td>
</tr>
<tr>
<td>Metallofullerene</td>
<td>Accumulates in rat livers</td>
</tr>
<tr>
<td>Inorganic</td>
<td></td>
</tr>
<tr>
<td>Silicon dioxide (SiO2)</td>
<td>Pulmonary inflammation in rats</td>
</tr>
<tr>
<td>Anatase (TiO2)</td>
<td>Antibacterial pulmonary inflammation in rodents</td>
</tr>
<tr>
<td>Zinc oxide (ZnO)</td>
<td>Antibacterial (micrometer scale); pulmonary effects in animals and humans</td>
</tr>
</tbody>
</table>
programming to find outlines of study and research to develop risk assessment and risk management of nano-material toxicity.

Surface coatings can render noxious particles non-toxic while less harmful particles can be made highly toxic. The presence of oxygen, ozone [64], oxygen radicals [68], and transition metals [65] on nano-particle surfaces leads to the creation of reactive oxygen species and the induction of inflammation.
Chapter 3 Natural nano-materials

Development of nano-science and nano-technology has caused a distinction between “engineered, manufactured” materials and “natural” nano particles. Possibly the human body and natural medias may not distinguish between exposure to the two categories of materials. There is no doubt environmental scientists prefer to be concerned with decreasing the toxicity of manufactured NM as the first step in risk potential. For this reason, preparation for some experimental testing in a biological as well as an engineering laboratory is necessary. Recently, some industries have explored cheaper ways and economic pathways to mass-produce nano-materials. Therefore, it is not impossible for natural nano-materials to be used in commercial applications. Consideration of this critical issue leads us to focus on nano-technology regulation, creation of uniform standards to use NP and NM either naturally or as engineered products. On the other hand, natural NP also has different environmental exposures which may produce adverse impacts on the health system, natural media, and ecological balances. Consequently, as a proper suggestion, reorganization of the mechanistic data of natural NP and their toxicity evaluation in parallel with engineered NM could result in an accurate realization of risk assessment in this area.

3-1 Appearance of natural nano-materials in environment

There are various natural NP from natural sources in the environment. However, a number of these materials and specifically their adverse toxicity impacts have been not recognized. Undoubtedly, a focus on some available data and information for many natural NP could assist in obtaining major results and possibly extrapolating in the appropriate place and field. The most imperative natural NP and their health effects are
terrestrial dust storms, which appear to be the largest single source of environmental nano-particles. Long-range migration of both mineral dust and anthropogenic pollutants from the major continents has recently been the subject of intense investigation. Approximately 50% of troposphere atmospheric aerosol particles are minerals originating from deserts [61]. The size of particles produced during a dust storm varies from 100 nm to several microns [70]. The short-term effects of ash on health include: respiratory effects (nose and throat irritation, bronchitic symptoms), and eye and skin irritations.

Volcanoes and health effects: When a volcano erupts, ash and gases containing particulate matter ranging from the nano-scale to microns are propelled high into the atmosphere, sometimes reaching heights over 18,000 meters. The quantity of particles released into the atmosphere is enormous; a single volcanic eruption can eject up to 30 million tons of ash [71]. Volcanic ash that reaches the upper troposphere and the stratosphere (the two lowest layers of the atmosphere) can spread worldwide and affect all areas of the Earth for years. A primary effect of upper atmospheric particulate debris is the blocking and scattering of radiation from the sun. One particularly harmful volcanic product is particles composed of heavy metals, as these are known to be toxic to humans [23].

A large amount of sea salt aerosols is emitted from seas and oceans due to water evaporation, which in some cases insensible health effects have been observed. These aerosols are formed by water evaporation and, when wave-produced, water drops might be ejected into the atmosphere. Their size ranges from 100 nm to several microns. NP could also form in bodies of water through precipitation as a result of temperature changes and evaporation. Some studies show, however, no specific toxicity and adverse
health effects have been associated to sea salt aerosols, but sea salt aerosols are able to transport pollutants and microorganisms that themselves may cause adverse health effects.

3-2 Toxicology of natural nano-materials

Commonly, humans are exposed to nano-scale particles which originate from natural sources such as dust storms, volcanic ash, and other natural processes, and in many cases the human bodily systems could be well adapted to protect and produce safety from these harmful impacts. Today, the development of technology specifically in nano-materials application has significantly changed, which may influence the character of particulate pollution, thereby increasing the proportion of nanometer-sized particles - “nano-particles” and expanding the variety of chemical compositions. Recent epidemiological studies have shown a strong correlation between particulate air pollution levels, respiratory and cardiovascular diseases, various cancers, and mortality. Adverse effects of nano-particles on human health depend on individual factors such as genetics and existing disease, as well as exposure, and nano-particle chemistry, size, shape, agglomeration state, and electromagnetic properties.

Significantly, many metals contain copper, magnesium, sodium, potassium, calcium, and iron that in small quantities are necessary for biological systems, but at higher doses, these metals have toxic effects. Exposure to high levels of environmental metals such as some trace elements (Cr, Co, Se, Sr, etc.) causes disease in humans. Also, they are known to be toxic upon inhalation, ingestion, or dermal exposure. Nano-particles manufactured from these metals will have health effects not necessarily easily predicted from previous studies of non-nano-particulate quantities of the same metals. As workers
could be easily exposed to these toxic materials, manufacturing of metal nano-particles should be considered a serious occupational hazard [23].

The inhalation of metallic or other dust is known to have negative health effects. The type of lung diseases caused by dust inhalation depends on the nature of the material, exposure duration, and dose. The inhalation of some metal fumes (e.g., zinc, copper) may lead to metal fume fever, an influenza-like reaction [72]. Several metal dusts (e.g., platinum, nickel, chromium, cobalt) can lead to asthma [23], while inhalation of other metallic dusts can cause pulmonary fibrosis, and ultimately lung cancer. The percentage of lung cancers attributable to occupational hazards is about 15%, with exposure to metals being a major cause [72]. Beryllium, cadmium, cobalt, lead, nickels, chromium, aluminum, coal, coal ash, silica, manganese, as heavy metal organic dust at the particular dose, may have toxic impacts on the natural environment and health system as well.

3-3 Risk assessment of natural nano-materials

Inhalation risk assessment of natural NP contains trace elements and /or heavy metals which are emitted from natural sources such as volcanic ash and coal-fired power plants, etc. Because of the toxic impacts of many of these nano-scale substances, the environmental risk assessment may reveal adverse health effects or ecological exterminations.

Commonly, the benefit of risk assessment and management for natural nano-materials and manufactured NP and NM is to understand many potential socioeconomic, health, and environmental issues as outcomes of new properties and behavior of nano-scale substances either originating from natural sources or as engineered nano-materials.
The most significant themes in risk assessment of NM and NP specifically natural nano-scale materials that must be considered include:

- Reorganization of chemical and physical properties, and characteristics of natural nano-particles
- Consideration of fate, behavior, biochemistry, and bio-geochemistry approaches
- Study of toxicological, eco-toxicology, and biological effects
- Achievement of experimental testing, measurement, and bioassays for nano-materials and nano-particles
- Evaluation of exposure, environmental risk assessment, life cycle analysis, modeling, modules design, and focus on human health system
- Estimation of positive impacts of nano-scale substances in the environment and possibly human body
- Comparison of the various results to offer proper regulation, legislation, policy, and public awareness of new technology
Chapter 4 Principles of Nano-material toxicity

4-1 Framework for nano-material toxicity assessment

A study on toxicity is mainly categorized in three ways: investigation and observation of people that have been exposed to toxic NM and NP; experimental testing via using animals; and studies on various cells, including human, plant, and animals.

Toxicity studies using human issues need mechanistic considerations. For this reason, providing essential data due to toxic NM actions is necessary, and it could be achieved via a systematic bioassay tests on selected animals.

Generally, toxicity in animals may occur with a similar incidence and severity in human bodies. But differences sometimes occur; thus clinical tests with humans are needed to confirm the results of non-clinical laboratory studies [47].

In toxicity evaluation of nano-materials, many specific toxicological aspects and their accurate concepts must be considered. The most significant features in this area are described below.

4-1-1 Epidemiology Studies

Studies were conducted using human populations to evaluate whether there is a causal relationship between exposure to a substance and adverse health effects. These studies differ from clinical investigations in that individuals have already been administered a drug during medical treatment or have been exposed to it in the workplace or environment. Epidemiological studies measure the risk of illness or death in an exposed population compared to that risk in an identical (e.g., same age, sex, race, social status, etc.), unexposed population [47].
4-1-2 Animal Testing for Toxicity

Animal tests for toxicity might be based on prior human clinical studies and investigations. The applicable methods and procedures for toxicity assessment could be used for a wide variety of toxic impacts, specifically for nano-material toxicity. To provide sufficient safety in testing fields, all procedures would be standardized. Standardized animal toxicity tests are highly effective in detecting toxicity that may occur in humans. Concern for animal welfare has resulted in tests that use human procedures and only the number of animals needed for statistical reliability.

Standardized tests have been developed for the critical effects due to toxic nano-material actions that include: acute toxicity, sub-chronic toxicity, chronic toxicity, carcinogenicity, reproductive toxicity, developmental toxicity, dermal toxicity, ocular toxicity, neurotoxicity, and genetic toxicity [47].

4-2 Concept of nano-engineering and nano-chemistry

Today, newly developed nano-technologies may affect the social, economic, and environmental dimensions of the world could frequently be unanticipated. Along with the growth of a nano-chemistry industry, there is also the need to consider impacts of nano-materials on the environment and human health. Recent advances in nano-materials using nano-chemistry objects and nano-engineering producers demonstrate the applicable techniques and procedures to create novel environmental technologies with less insensible effects. Therefore, consideration of nano-chemistry and nano-engineering aspects could lead to comprehensive evaluation of NM toxicity and risk assessment clarification.
The most important application of nano-chemistry and nano-engineering is to form new substances. Synthetic chemists act like molecular engineers — designing and fabricating molecular structures of desired physico-chemical and electronic properties. They develop steps to build a complex molecular structure in an atom-by-atom or molecular fragment-to-molecular fragment approach.

Essentially, a nano-chemistry study like bulk material investigation of the behavior of nano-scale materials is possible. Additionally, nano-chemistry features result in the recognition of the characteristics and unique properties of nano-particles and their composition structures as well. To follow this critical object, a number of novel techniques and advance methods assist to design and produce the desired nano-material, dimensions, geometry, and even modify their structure based on particular requirements such as the reduction of toxicity effects due to their behavior and actions.

The focus on nano-chemistry concepts and engineering methods could define the mechanism for the creation of functional materials, devices, and systems through the control of matter at a scale of 1-100 nanometers, as well as an explanation of novel properties and phenomena developed at those desired scales. In addition, they create new small-scale substances and innovative methodologies for making them into various morphologies or modes of molecular organization. The motivation is both fundamental and practical. Fundamental: to discover and understand new phenomena exhibited by matter at these newly accessible dimensions, and practical: to form them into a useful something, as novel electronic devices, efficient drug delivery systems, ultrasensitive sensors, ultra-lightweight structural materials, highly efficient alternative energy sources, environmentally being materials, or as new materials for an entirely new application.
Nano-engineering has been developed with many critical objectives, including: decrease the size of nano-scale systems while keeping their functions, integrating functions to compact size systems, innovating and improving systems by adding micro- and nano-scale functions to macro-scale engineering applications, increasing the efficiency of existing nano-scale products by improving applicable engineering techniques to influence dependent parameters that involve NM behavior and possibly limit their performance and action based on necessary options.

4-3 Design of required nano-chemistry module

Nano-chemistry is the significant science of tools, technologies, and methodologies for chemical synthesis, analysis, and biochemical diagnostics, performed in scale-size. Using synthetic chemistry methods is an applicable procedure to make nano-scale and design the structure with the desired shape, size, composition, surface structure, and acceptable charge. The specific functionality design via nano-chemistry procedures may control self-assembly for building blocks in nano-materials at different scale lengths. Therefore, consideration of nano-chemistry aspects as an appropriate option to control and modify the nano-material synthesis is required.

Using of two important concepts of nanoscopic and mesoscopic scale in nano-chemistry help to clarify more complex nano-material structures. Also, they can apply to design, synthesis of desired shape, and size of nano-scale material in order to reduce toxicity impacts. Mesoscopic–scale is the length at which quantum mechanical behaviors in liquids or solids can be described by macroscopic concepts. For technical purposes, the nanoscopic scale is the size at the expected fluctuations of the average properties due to the motion and behavior of individual particles.
Research in nano-chemistry demands a multidisciplinary approach. A project plan may involve bulk synthetic chemistry to design a computational molecular model, using advanced microscopy techniques. In addition, the synthesis of newly designed molecules, specifically nano-scale particles, might be collected into complex architectures to make proper protocols for quality control and continual monitoring of nano-material toxicity and their toxic response dose.

The most important options in nano-chemistry contain: control of scale formation, computational materials chemistry, control of physico-chemical properties, control on research processes, and computational molecular modeling facility.

Based on a designed module of nano-chemistry [fig-2], two significant functions, synthesis and analysis in this area, have been considered. Improvement of this portion of the module in this study should consider some factors, such as the following: classification of items of nano-chemistry analysis concerns surface structure (charge, size, coating, area, and reactivity), chemical composition, dispersability, functionality, and durability. Special attention in the synthesis of a nano-chemistry module would be with respect to distinguishing nano-scopic and meso-scopic scales of nano-material to demonstrate physico-chemical characteristics relevant to nano-particles such as mass distribution, density, bio-reactivity, potential physical and chemical conversion into
various forms, and energy regarding experimental conditions [Fig-2].

Figure-2: Nano-Chemistry Module

To achieve a comprehensive nano-chemistry project, consideration of the following options is required: surface structure, quantum of nano-structure, reorganizations of fundamentals of natural and manufactured nano-materials and their applications, realization of bio-degradable property of nano-materials, and a focus on continual nano-technology improvement with entrepreneurship monitoring.

4-4 Design of nano-engineering module

Nano-engineering is the practice of engineering on a nano-scale. The concept of nano-engineering and its name have originated from the nano-meter, a unit of
measurement scale for equaling one billionth of a meter. The application of nano-engineering methods in science and technology is associated to atomic–scale design and closely related to nano-technology aspects. There are many applicable procedures and techniques in nano-engineering which are used to design, synthesize, and possibly alter synthesis processing and modification of nano-materials structure. The most significant of these techniques includes: photolithography, electron beam lithography, scanning tunneling microscope (STM), and molecular self–assembly.

In the photolithography method, using light to produce patterns in chemicals and then etching to expose the surface is important. This technique shares some fundamental principles with photography. The most important benefit for using this technique is that it is possible to control the shape and size of objects and to generate patterns over an entire surface simultaneously.

Electron beam lithography is similar to photolithography, but it is usually suggested to use electron beams instead of light. Electron beam lithography is the practice of scanning a beam of electrons in a patterned fashion across a surface covered with a film. The primary advantage of electron beam lithography is to control surface charging conditions of nano-particles. Scanning tunneling microscope (STM) can be used to both image and control structures as small as a single atom. STM application is based on the concept of quantum tunneling.

Using the molecular self-assembly technique causes a variety of different shapes and sizes of nano-materials under controlled conditions. Its application may associate with some major chemistry features such as noncovalent interactions (hydrogen bonding, metal coordinates), hydrophobic forces, and electrostatic effect. These items should be
taken into account in the design and synthesis of nano-materials. Some advantages using this method include: development of materials with size-dependent properties, and the ability to encode with manipulate biological molecules such as DNA.

Development and continued research in nano-scale science with respect to related engineering practices as a new step in many fields leads to novel and applicable technological procedures. Today, nano-engineering practices are moving to reduce adverse effects of nano-materials regarding critical features in this area, which include: computing and information technology, health care and biotechnology, environment, energy, transportation etc. Both advanced nano-science and nano-engineering practices would be able to assist in reducing risk toxicity of nano-material applications. Nano-engineering practices in some research areas, such as nano-instrumentation, nano-energy conversion, nano bioengineering, and nano-computing storage, are providing a proper and practical basis to develop the quality controlling procedures for nano-particles either in design, synthesis, or the reduction of harmful impacts [Fig-3].
Currently, attempts of scientists and engineers are rapidly improving synthesis, design, and fabrication of the control materials at the molecular level and “nano-scale” in order to obtain a higher efficiency of energy, extend their applications in a wide range of various areas such as industrial, biological, and medical approaches.

Nano-technology as a highly qualified science concerns the unknown potential of nano-scale particles to damage the natural environment and human health. Reduction of the potential risks and hazards of unanticipated adverse consequences due to human or environmental exposure to engineered nano-materials is the primary, essential, and significant outcome of nano-engineering practices.
4-5 Toxicity pathways in natural environment

Generally, managing risks for toxicity evaluation could be extended for human and environmental health and safety. An entirely new risk assessment has been started to carry out an extensive analysis of potential risk and management in spite of insufficient data and current methodologies to estimate the hazards of nano material toxicity, particularly for toxicology and eco-toxicology studies, and also the lack of accurate exposure estimation, dose response, equipment to detect and measure NP in the air, water, or soil, but recently based on regulatory bodies in various fields. To follow the challenge these critical objectives, a matrix might be developed to recognize the NP, their more complex nano-formulations which are likely to have special toxicological properties and also toxic action in different media in the natural environment.

Clearly, pollutants are transported away from their sources into various media and fields. The sources include natural and released chemical wastes from manufactured companies and industrial systems. Many toxic NM and NP also could transfer into either the natural environment or the human body. They may be physically, chemically, or biologically transformed. Possibly, they could accumulate in different fields such as air, water, sediment, and soil. The most particular alternatives for risk assessment of nano-materials in the natural environment by the specific chemical family type include: study of mass of NP and water partitioning at equilibrium, investigation of NM and NP partitioning between soil and water and partitioning between air and water, and solubility constants bio-concentration factors. These parameters may be integrated using data on sources, releases, and routes of the contaminant and toxic substances to estimate the significant exposure pathways. The common pathway for exposure is associated with
water (ground water, surface water), air, soil, and sediment. For the best applicable procedure to estimate exposure of NP and the potential risk assessment and management, the mental modeling may be used. For example, to evaluate air quality and air pollution control studies due to chemical emission, particularly NM which may be classified as (PM-10), the models of air dispersion in various predominated conditions could be used to predict the air concentrations and the emitted mass of NM into the air.

4-6 Toxicity in human health system

Nano-particles, as small-scale substances with unique properties, have complex exposure and health risk implications. Today, human health risk assessment is a critical part of nano-material toxicity evaluation. Characterization of airborne particles indicates that exposures will depend on particle behavior (e.g., disperse or aggregate) and that accurate, portable, and cost effective measurement techniques are essential for understanding exposure. Under many conditions, dermal penetration of nano-particles may be limited for consumer products such as sunscreens, although additional studies are needed on potential photo oxidation products, experimental methods, and the effect of skin condition on penetration. Carbon nano-tubes apparently have greater pulmonary toxicity (inflammation, granuloma) in mice than fine-scale carbon graphite, and their metal content may affect toxicity.

Recently, the most significant studies may help to realize the adverse effects of toxic NP action, achievement of required experimental tests to find out the toxicological endpoints, and exposure durations that are relevant for risk assessment. A proposed systemic toxicity task is an approach to systemic toxicity testing which could be one part of the overall assessment of a compound's potential that causes adverse effects on the
health system, particularly on the human body and metabolism process. The approach is
designed to provide more relevant data for deriving reference doses for shorter time
periods of human exposure. All available data, including toxico-kinetics and metabolism
data and life stages information, are taken into account. The proposed testing methods
approach has the potential to provide new risk assessment information for shorter human
exposure durations while reducing the number of animals used and without
compromising the sensitivity of the determination of longer term reference doses.

Significantly, in estimation impacts of toxic nano-material action on the health
system, some particular objects must be considered, consisting of: health effects,
methodology, toxico-kinetics, absorption, distribution, inhalation exposure, and ingestion
exposure.

Nano-particles and nano-materials specifically manufactured NM might be
released during disposal, destruction, and recycling. For this reason, a number of
attempts may be achieved today to evaluate how these materials will be managed to
minimize possible human and environmental exposure. Furthermore, these alternatives
help to determine the life cycle regulation of NM and proposed standards for nano-
technology investigation and development of nano—materials application with reduction
of their harmful effects.

Current knowledge of the human health effects and environmental concentrations
of engineered NM and/or NP is not complete. Clearly, humans are already exposed to a
wide range of natural and manufactured NM in the air, and exposure via the food chain,
water supply, and medical applications as well. Most importantly, nano-toxicology
studies have focused on animals, and cells in vitro, to realize the adverse effects on the
immune system, oxidative stress correlated to disorders, lung disease, and inflammation. However, the dose-response of NM to produce these impacts is high and this phenomenon could be possible if such exposure due to the environment and/or the work place occurs. Additionally, providing more data and information regarding exposure is required for risk analysis and computations. Recent regulation and legislation, however, do not particularly address NM and NP, but there are critical considerations concerning classification and recognition of nano-materials as novel nano-scale materials, and, possibly, they are under chemical regulation and legislation, as well as considerable current test methods.

4-7 Scientific tools in nano-particles toxicity assessment (in vivo and in vitro studies)

There are a number of various types of measurement methods available to study adverse impacts of toxic NM and NP either in the natural environment or human body. They include: in vitro and in vivo. These type studies need to provide an inclusive realization action and mechanisms for insensible effects of nano-materials.

An in vitro study provides information on modes of actions and the underlying mechanisms at the level of proteins, bio-molecules, extracellular matrix, DNA, parenchyma, and immuno-competent cells and their compartments. In vivo methods are required to identify the biological relevance of the in vitro determined modes of actions and the underlying mechanisms in the more complex interplay among multiple cell types, within organs, and within the entire organism. The determination of dose-response relationships and of target organs and cells can only be determined in vivo. A major problem here is that the definition of dose is not standardized with respect to mass,
number, surface area, and other metrics. This hinders the objective analysis of the data and comparisons between materials [44]. In the case of nano-particles, target organs may not be restricted to the portal of entry, but may include secondary target organs and their cellular constituents, depending on the accessibility of nano-particles to these sites. Furthermore, interspecies differences need to be considered very carefully in any extrapolation to human effect assessment. Hence, a comprehensive effect assessment usually requires in vivo studies for dose-response relationships at target organs for nano-particles to supplement the in vitro methods for understanding the modes of actions and underlying mechanisms.

Two most important approaches used for in vivo and in vitro studies include instillation and inhalation procedures. Instillation of particles into rat lungs has often been used in particle toxicology particularly for toxic NM. This mode of exposure is not physiological in the sense that there is usually a very high dose and dose rate, and, since the particles are suspended in saline, the lung surface receives particles contained in a liquid, which is likely to affect the defense systems of the lung. The advantage of instillation is that it involves the administration of a more precise nano-particle dose [44]. Inhalation is the physiological process during which nano-particles are deposited in the respiratory tract, allowing for a slow build-up of the dose and for normal clearance processes to occur. This is the only way to determine the amount of airborne concentration of suspended dust [44]. Additionally, determination of nano-particle dose-response of their toxic action is not easy and its estimation needs to continually monitor breathing and the aerosol factors; tissue analysis must also be considered.
4-8 Toxicity evaluation model of nano-materials

Nano-particle toxicity evaluation is directly related to association of nano-particle characteristics and their toxicity. The most important parameters in toxicity assessment to determine the adverse health effects of nano-particles include: dose (the amount or quantity of substance that will reach a biological system), dimension, and durability. As we know, there is a different correlation between various physico-chemical properties of nano-materials which may associate to health effects and also some uncertainties such as mass, number, size, bulk or surface chemistry, aggregation, etc. [Fig-4].

Nano-toxicological studies have shown the most significant impact of small nano-particles (<100 nm) is to damage the respiratory health system. Typically, the effectiveness of materials in small size and shape may be more than larger particles. Therefore, relationship between surface area of nano-particles and their toxicity would be easily understood. In fact, the smaller nano-particles with the higher surface area and particle number per unit mass, compared to larger particles are more toxic. This important objective leads to a change in description, definitions, and regulations associated with dose and exposure restrictions.

The human body has different reactions to the same mass and dosage of nano-particles compared to micro-particles. The larger surface area could increase nano-materials reactivity. Furthermore, for this reason, increasing the reactive oxygen species especially in aquatic media is expected, and in vitro experiments have demonstrated this issue.

More evidence of the toxic impacts of nano-materials directly might be associated with their different concentrations. Some certain nano-materials, however, have toxic
effects in many cases, but they are not toxic in all observations and studies. Hence, a 
comparison of the results of various studies and differences should be considered. These 
differences depend on the cumulative properties and characteristics of nano-particles. 
The appropriate methods in such studies are focused on consequences in the inherent 
discrepancies between inhalation studies and instillation or in vitro experiments [23]. 
Certain properties of nano-particles, which involve toxicity impacts, are functions of 
some aspects, including surface charge, material type, and size [Fig-4].

Generally, the chemistry of nano-particles and their chemical compositions and 
distinctions are critical in determining toxicity. In spite of the similarity in chemical 
composition of certain nano-materials, they may have a different chemical structure or 
crystalline, which influences their reactivity in various objects, especially in toxicity 
generation. Extrapolating the many outcomes of studies has revealed a similar extent for 
various nano-particle chemistries. Particle chemistry is especially relevant from the point 
of view of cell molecular chemistry and oxidative stress. Namely, depending on their 
chemistry, nano-particles can show different cellular uptake, sub-cellular localization, 
and ability to catalyze the production of reactive oxygen species [23].
In toxicity assessment, the cumulative impacts of inhalation, ingestion, and/or dermal effects in the number of nano-particles are not known. However, risk estimation of in vivo and in vitro studies could reveal some particular features of nano-particle structure with a critical role in toxicity, which includes particle surface, surface coating, size magnetic, electric, optical properties, chemical reactivity, bio-reactivity, as well as the other physico-chemical properties. A comprehensive toxicity evaluation needs also to focus on the adverse effects of nano-particles originated from natural sources. These aspects in the natural environment contain short-term effects of ash, volcanic particulate pollutions, and volcanic soils. Some particular impacts on the health system include respiratory effects (nose and throat irritation, bronchitic symptoms) and eye and skin
irritation, etc. [23]. Consideration in this area leads to obtain the superior perspective in risk assessment. In this practice we are able to distinguish the harmful effects produced from manufactured nano-particles and/or from natural sources.

The fabrication of nano-materials in different fields could assist to synthesize by many nano-engineering methods, including gas phase processes (flame pyrolysis), high temperature evaporation, and plasma synthesis; vapor deposition synthesis (electron, thermal, laser beam evaporation); and colloidal, or liquid phase methods in which chemical reactions in solvents lead to the formation of colloids. In addition, some mechanical processes and procedures contain grinding, milling, and alloying with respect to nano-material fabrication processes. Synthesis of almost any shape and size of material is possible. These nano-engineering practices also cause to modify nano-material structures in proper and applicable objects.
Chapter 5 Methodology framework for Toxicology and Eco-toxicology of nano- materials

Generally, the study of the toxicology of NM and NP in parallel with eco-toxicology of these toxic materials could lead to find appropriate test guidelines and an appropriate experiment and assessment strategy. The attained results from these combined studies may provide a wide basis guideline for assessment of the health risks of nano-particles, and measurement of the required factors in order to decrease risks of toxic NM at different levels (classification, organization, limit values, handling recommendations, measure concepts, etc.). Possibly, use of the existing system for testing toxicological properties, assessment parameters, and containment of health risks for toxic NM and NP could assist to modify them in various fields.

However, there is no comprehensive compilation of appropriate test guidelines and an appropriate assessment strategy for nano-scale substances, but focusing on available data and obtained information from various studies might be a fundamental option to create an appropriate viewpoint for evaluation of nano-particle toxicity. Many of these objectives may include: \textit{in vivo} and \textit{in vitro} methods, investigation of the size or surface coating of nano-materials which are effective on the human organism, consideration to extrapolate the new consequences to humans, engineering modification techniques on NM structure. Study on parameters that reflect particular features of NM action and their mechanisms illustrate the inhalation exposure effect on chronic and sub-chronic diseases and carcinogenicity.

In a risk-oriented test strategy, the distribution of a nano-particle and the type and level of exposure of humans and the environment should play a major role. A higher
need for information on the risks of nano-technology compared with other industrial chemicals is partially substantiated by the fact that nano-technology is seen as a new technology (emerging technology). New risk scenarios arise for which there are as yet no experience values and where there is special public interest. Currently, more studies are needed for new substances with the same properties than for existing substances. Here, it becomes clear that the attitude towards a dynamically changing technological world also constitutes an adjustable variable which influences the need for information about health and environmental risks. In order to be able to compare in a transparent manner the risks of substances from "existing" and "new" technologies, the test and assessment strategies should have common basic structures, but reflecting also the specifics of nano-particles. Then it becomes possible to undertake a comparative assessment also within the context of discussions about substance substitution. Hence, the existing test and assessment strategies must be considered as the foundation and, where necessary, adapted to the specific situation of nano-particles. In addition, a comprehensive evaluation strategy for nano-material toxicity should express the central tasks of specific approaches and major regulation, and then offer experimental tests based on engineering and science.

5-1 Information analysis

To build a scientific-engineered module, current knowledge regarding nano-materials, experimental data obtained from different laboratory tests, and analytical measurements could be classified based on a related systematic method.

To contrast manufactured nano-materials and natural nano-particles, their characteristics need to be studied, along with unusual properties, survival and/or release
in the natural environment. The focus on the effects of eco-toxicity and bio-toxicity can find a point of view to recognize the influenced parameters.

Studies show many impressive elements in nano-material toxicity that has been involved to increase the amount of toxicity. These components are either dependent on the physicochemical structure of nano-materials or originated from synthesis procedures of nano-materials. In both cases, an in-depth observation may help to assess their values and distinguish whether they could be major variables to produce and increase toxicity, or if they act only as unchanged functions. Consequently, this outline will promote a comprehension of the required features to design a module configuration.

| Table-4 Summary of the state of knowledge for nano-particles and controls. |
|-----------------------------|-----------------------------|
| **Awareness of knowledge**  | **Content of Knowledge (Hazardous & Control)**                       |
| 1-What we know We Know      | Health effect of ultrafine, air pollution, and fibers               |
|                             | How to control ultrafine particles in the work place                |
|                             | Importance of size, surface area and surface characteristics        |
|                             | Serious health effects of some nano-particles in animals             |
|                             | Translocation of some nano-materials along the olfactory nerve in animals |
| 2-What we know We Know      | Measurement and characterization techniques                          |
|                             | Hazardous of newly engineering particles                           |
|                             | Extent of translocation in body                                      |
|                             | Interaction with contaminants in work place                          |
|                             | Importance of dermal exposure                                       |
|                             | Health effects in workers                                           |
|                             | Risk of workers                                                     |
|                             | Effectiveness of controls                                           |
|                             | Advisability of medical screening and biological monitoring         |
|                             | Risk to workers’ family                                             |
| 3-What we know We Know      | Extensive experience available in controlling hazardous substances and agents (radiation, biological agents, pharmaceuticals) that can be application to nano-particles information |
|                             | Lessons from pervious “new” technologies                             |
| 4-What we know We Know      | Unanticipated new hazards                                           |
|                             | Unanticipated new controls                                          |
|                             | Wrong assumptions about hazards and controls                        |

Adapted from Drew and Schulte et al. Nanotechnology in the Workplace

Development of models and design of the proper modules to evaluate NM toxicity recognition and to focus on required knowledge and proficiency in this area may lead to
an accurate viewpoint and derive the right pathway of systematic study and investigation. Table 4 contains these imperative issues that undoubtedly are the first step in an assessment of NM action we need to consider.

The mental modeling in this study is formed based on a description of standard risk assessment, a response assessment of nano-materials toxicity, hazardous identification, risk characterization, hypothesized relationship between risk assessment and management to regulation, and safety assessment. The two most significant components in risk assessment toxicity and exposure are affected by the mentioned parameters. In addition, a consideration of up-taking capacity, fate, and transpiration, aggregation, durability, and life cycle issues could help to illustrate the complexity of toxicity and the exposure functionality of toxic nano-particles.

5-2 Toxicity evaluation for nano-scale materials, [Fullerenes, TiO2, ZNO]

In order to provide a sensible pathway of NM toxicity evaluation, three nano-scale substances [Fullerenes (CNTs, C60), TiO2, and ZNO] have been studied. Design of three modules of their toxicity evaluation as an appropriate result may help to develop RA and RM of nano-material toxicity behavior either in the environment or the human health system.

5-3 Module of toxicity evaluation of ZNO

Zink oxide as an important chemical compound is nearly insoluble in water but soluble in acids and alkalis. It may occur as white hexagonal crystals and/or a white powder. Zinc oxide also exists in the natural environment as the mineral zincite. Today zinc oxide is known as applicable types of oxides family because of its unique optical,
The ZNO structure is usually manufactured using electron beam lithography, photolithography, or X-ray lithography techniques [Fig-5].

Figure-5: Module of Toxicity Evaluation of ZNO

In this processing, the focus on the ability to define position, size, and density of nano-structures on surfaces is required. In addition, however, these techniques are applicable in nano-engineering practices but are limited via a multistage, time-consuming, and costly preparation procedure. Currently, a particular engineering method is known which includes combining nano-sphere self-assembly lithography and the
vapor-liquid-solid (VLS) approach of fabricating periodic array of catalyst dots in a different geometry and subsequently growing vertically aligned ZnO nano-wires [30]. In this technique, engineering modification and alteration in the structure of ZNO in order to reduce toxicity effects are possible. Metal oxide nano-particles, specifically ZNO, however, have an application in various commercial products. Consideration of their environmental fate, potential toxicity, and adverse impacts should be taken into account. Study on bioavailability of nano-particles, which is significantly greater than larger particles, causes progress in toxicity evaluation. Chemical investigations using equilibrium dialysis demonstrated rapid dissolution of ZNO nano-particles in a freshwater medium (pH 7.6), with saturation solubility in the milligram per liter range the same as with bulk ZNO. Therefore, this point is considerable in the formation and fabrication of ZNO with different morphologies via the thermal evaporation technique. One of the most particular methods in the preparation of engineered ZNO is using flow field-flow fractionation. This separation technique could help to determine the particle size and distributions (PSD) of ZNO, which may spike in soil suspensions. In this practice, determination of the amount of spiked ZNO concentration, the PSD of engineered nano-particles, and monitoring their partitioning and stability in soil suspensions are possible. In engineering practices, in order to do quality control and possibly modification and/or alteration in fabrication of ZNO, the focus on the characteristics of zinc-oxide powder activation is considerable. ZNO tribo-physically could be activated in high-energy and modifies physico-chemical properties. Probably this action may reduce the toxicity effects of zinc oxide.
Titanium dioxide is known as titanium (IV) oxide or Titania. Naturally occurring oxides of titanium may exist in the environment. Titanium dioxide compounds in nature are not pure and possibly could be found with contaminant metals such as iron. These oxides in the natural environment can be mined as a source for commercial titanium. Titanium dioxide has a large variety of applications because of some surface properties such as a photo catalyst in heterogeneous catalysis and in solar cells, etc. In fact, TiO2 is a significant single-crystalline system in the surface science of metal oxides. One of the most important characteristics of TiO2 is correlated to the structure, stability of TiO2 surface and molecular dynamics simulations [fig-6]. The surface defect and its relation to stoichiometric cases have the major role in the reactivity properties of TiO2. These options may be considered in nano-engineering practices in order to modify and control the structure of TiO2 to reduce its toxicity effects. Today, the antibacterial activity of TiO2 has important implications for ecosystem health. Toxicity evaluation of TiO2 in water suspensions as a common additive with a unique material at the nano-scale size is considerable. One significant project could focus on the relative toxicity of TiO2, SiO2, and ZNO water suspensions towards bacteria (B. subtilis, E. coli). Results show these three photosensitive nano-materials are hazardous for all aquatic organisms. In addition, toxicity may increase with particle concentration. Toxicity of the three oxides can reduce from ZNO to TiO2 and then to SiO2 based on natural conditions. Studies show antibacterial activity under both dark and light conditions and also indicate additional mechanisms related to growth inhibition. In this specific case, the nominal particle size is not effective for their toxicity. These results may be considerable during usage and
disposal of such manufactured nano-materials to prevent inadvertent environmental impacts. The importance of further research on the mechanisms and factors in this area may improve our viewpoints in risk assessment of toxicity.

**Figure-6: Module of Toxicity Evaluation of TiO2**

One of the most important methods for engineering control of TiO2 is to focus on low Back Electron Transfer in Surface-Modified TiO2 as nano-particles. It is sensitized by Alizarin Interfacial electron transfer dynamics of alizarin-sensitized. Surface-modified and unmodified TiO2 may be studied with respect to specific transient absorption spectroscopy. Other nano-engineering practices to modify the surface of TiO2 nano-particles could be done via sodium dodecyl benzyl sulfonate (DBS).
Some TiO2 compounds such as pathogenic dust alpha-quartz have the main role in air pollution and cause adverse pulmonary health effects, especially in individuals with preexisting lung disease [Fig-6]. Currently, there are concerns about the toxicity of TiO2 in cosmetics and sunscreen consumption. TiO2 as a physical sunscreen could reflect and scatter UVB (290-320 nm) and UVA (320-400 nm) light rays. Therefore, predication of the skin-damaging portion of the solar spectrum is possible. In addition, TiO2 may absorb UV radiation, though, which in an aquatic environment influences the production of reactive oxygen species. The reactivity of these oxygen species causes damage to DNA. Titanium dioxide particles also, under UV irradiation, suppress tumor growth in cultured human bladder cancer cells.

Titanium dioxide (TiO2) is a poor soluble with low-toxicity which has been shown to produce lung tumors in many types of rats. Possible evaluation of the rat dose-response might be conducted as a quantitative risk assessment for TiO2 toxicity. Two other toxicity impacts of TiO2 created chronic pulmonary inflammation in rats and an in vitro study showed a pro-inflammatory effect in cultured human endothelial cells.

5-5 Module of toxicity evaluation of Fullerenes

Fullerenes are a family of carbon allotropes; the molecule is composed of carbon and could be in the form of a hollow sphere, ellipsoid, tube, or plane. A common application of fullerenes occurs in sunscreen productions and television. Two specific types in the Fullerenes family contain Bucky balls, which are spherical, and carbon nanotube or bucky tubes in cylindrical form. Nano-tubes are similar to the structure of C60. This type of fullerenes has a wide range of applications in industry and medical practices.
The most significant chemical characteristics of Fullerenes include stability (because of its particular composition), unique electrical, mechanical, and thermal properties [Fig-7] with wide applications in the electronics, computer, aerospace, and other industries. The reactivity of fullerenes is related to electrophilic addition at 6,6-double bonds, which reduces angle strain by changing sp²-hybridized carbons into sp³-hybridized ones. This characteristic, however, causes stable fullerenes, but may not be totally unreactive in specific conditions.

Figure-7: Module of toxicity evaluation of Fullerenes

Usually, fullerenes (C₆₀) are synthesized under high pressure and high temperature conditions. Studies show fullerene molecules are three-dimensionally
polymerized types. In addition, synthesis of some superhard materials produced from fullerenes under high pressure conditions may complicate via a poor crystallinity of samples.

Fullerenes released in the environment have adverse impacts on living organisms in the soil. Manufactured nano-materials especially could enter the soil with bio-solids in which they originated from waste treatment processes. They also may enter the soil following a spill during manufacturing processing and possibly due to accidents. The particular solvent used in preparation of fullerenes should be considered since some effects on the natural environment have been observed, but its mechanism and processing are unknown. The most important obtained results show, however, that the levels of oxygen and enzyme activity have not been affected. But there are some impacts of fullerenes on bacterial diversity, as well as some effects on the structure and function of the soil microbial community and microbial processes. Hence, there is no doubt that under natural and real conditions in the environment, the exposure pathway could affect toxicity and cause harmful impacts.

In order to reduce the harmful effects of fullerenes, there are a number of engineering practices in this area. The initially uncoated fullerenes can be modified with biocompatible coating. Fullerenes C60 can be formed as an aqueous suspended colloid [nC60]. However, some scientific reports describe the toxicity of fullerenes (C60) as a water-soluble nano-particle that has no specific toxicity resulting from the inhalation exposure to C60. But, possibly, the red-ox activity of fullerenes as a lipophilic molecule could cause oxidative damage in an aquatic species [35]. Other adverse toxicity impacts of fullerenes cause lung damage in mammals. Specifically, this toxicity has been
observed in a body of rats [37]. The toxicity of CNTs is related to a multitude of morphologies, size, and chemical fictionalization of their surface or ends. The characteristics of hydrophobicity of CNTs structure and also the tendency to aggregate have harmful effects for living cells in the culturing process.
Chapter 6 Risk assessment and risk management

In this chapter, the most significant objects related to RA and RM of NMs toxicity are reviewed. Consideration of these fundamental components may result in the design of a comprehensive model of RA and RM of NMs toxicity.

6-1-Methodology of risk assessment for toxic nano-materials

Risk assessment is a fundamental evaluation, identification, quantification, and communication of the risk (potential hazard) due to a particular action and/or activity, such as use or occurrence of a toxic chemical. Commonly assessing the risk routinely correlates to an estimation of the exposure to chemical elements and compounds. One of these important chemicals is the nano-scale substance with a wide range application in the world of new technology. The critical features in the methodology of risk assessment for nano-material toxicity include the association of risk assessment and risk management. An essential purpose has the major role to realize and estimate the potential risk and hazards of NM action either in the natural environment or the human health system.

In risk management, the ultimate decisions are based on the attained results from identification, quantification, and communication of risk assessment in different media and fields. Moreover, possibly during the regulatory process, risk management experts may order an additional investigation and study on risk assessments and dependent parameters to provide more mechanistic data and required information. Hence, this segment leads to justify risk management decisions and regulations as well.
Risk assessments of toxic NM and NP may be conducted as an individual chemical and/or for complex mixtures of chemicals. In cases of such complex mixtures as hazardous waste sites, the process of risk assessment itself becomes quite complex. This complexity has resulted from simultaneous exposure of many substances with the potential for numerous chemical and biological interactions, and exposures by multiple media and pathways (e.g., via water, air, sediment, and soil) [52]. In the methodology of risk assessment associated with nano-material toxicity, two significant and applicable scientific tools, in vivo and in vitro studies, are responsible to explain the mechanistic action of toxic NM and NP in natural media and the human body (biological impacts).

To develop a framework for a hypothesized system, sufficient knowledge and collected experimental data are necessary. The most important factors to build this systematic outline and design modules, sub-modules, diagrams, and models must be associated with available results in terms of potential risk for the natural environment and human health. Consideration of nano-chemistry aspects and nano-engineering techniques is the best option to modify the synthesis toxic nano-particles in order to either remove or reduce their harmful impacts.

The general principles in this study to design the mental modeling of risk assessment and management are associated to develop protocols with respect to the correlation of nano-particle characteristics, properties, their toxicity, and exposure features. The focus on complicated technical issues and understanding the complexity in various portions of this research could lead to identify particular factors to obtain a complete and organized framework of toxicity risk assessment.
The contribution of new information in terms of toxicity reduction of nano-materials, the clarification value of objective evidence, the demonstration of analytical data are the appropriate tools to recognize and suggest practical procedures in nano-engineering practices to challenge with nano-particle toxicity. In addition, the development of applicable methods and an estimate of quantities and qualities aspects are the particular benefits in this scenario.

The focus on a combination of environmental and nano-engineering aspects, as an advanced phenomenon in this specific system, is a great guideline to design a comprehensive model associated with the relationship of risk assessment and risk management to developed regulations.

6-2 Risk characterizations

One of the considerable steps in NM toxicity evaluation is to estimate the frequency and severity of impacts in exposed populations. Conclusions reached concerning hazardous identification and exposure assessment are integrated to yield probabilities of effects likely to occur in humans exposed under similar conditions. Since most risk assessments include major uncertainties, it is important that biological and statistical uncertainties are described in risk characterization. The assessment should identify which components of the risk assessment process involve the greatest degree of uncertainty [52]. In many cases, to determine the risk characterization of NM and NP, the multiple chemical exposures and multiple exposure pathways might be considered. Furthermore, an estimation of dose-response to produce toxicity effects is required. This objective could lead to obtain more information on the mechanisms of NM and NP actions, and also provide data due to its biological and ecological interactions.
6-3 Hazardous identification

As a general identification of toxic chemical hazards, specifically nano-scale substances and/or compounds, three types of data resulting from related experimental tests are achievable, which include: human epidemiological data, animal bioassay data, and supporting data. These important data and formations might be collected, analyzed, and taken into account as the valuable evidence approach.

Human epidemiological data are the most desirable and are given highest priority since it avoids the concern for species differences in the toxic response in practice. Animal bioassay data are often the primary data used in risk assessment. Animal studies are well-controlled experiments with known exposures and employ detailed, careful clinical and pathological examinations. Supporting data derived from cell and biochemical studies may help the risk assessor make meaningful predictions as to a likely human response [52]. The dose-response assessment step quantifies the hazards, which were identified in the hazard evaluation phase. It determines the relationship between dose and the incidence of effects in humans. There are normally two major extrapolations required: the first is from high experimental doses to low environmental doses and the second from animal to human doses. The procedures used to extrapolate from high to low doses are different for assessment of carcinogenic effects and non-carcinogenic effects. Carcinogenic effects are not considered to have a threshold and mathematical models are generally used to provide estimates of carcinogenic risk at very low dose levels [52]. These consequences could identify the dependent factors in toxicity of NM and NP. Determination of dose-response from nano-materials toxicity and its
evaluation also are the other particular parameters in this area which have the specific function in risk assessment and management.

6-4 Exposure assessment

In risk assessment of toxic nano-materials, the exposure estimation and its evaluation could help to illustrate the hazards of toxic NM and NP action and also present a threat. Exposure assessment in this area would emphasis the potential exposure of nano-scale materials and also the waste released, movement, effects on ecological and biological system and fate in the natural environment may be considered. Three significant objectives in exposure evaluation include: classification of the exposure setting (determination of sources), recognition of exposure pathways particularly in various natural media (air, soil, water, surface water, etc.), and quantification of the exposure function and life cycle of exposure as well [Fig-8].
Many important variables, either directly or indirectly, are effective for exposure assessment, including: exposed population, duration of exposure, field of exposure (human body and/or natural media), and the type of nano-scale materials (singles and/or as a chemical compound), etc. (Fig-9). In fact, toxic nano-particles might be transported away from the source in three pathways: physically, chemically, or biologically transformed. Furthermore, they can be accumulated in different natural media and/or various sites associated with the human health system. Commonly, the actual measurements of exposures are often not available, so exposure models may be used. For example, in air quality studies, chemical emission and air dispersion models are used to predict air concentrations to downwind residents.
Significantly, consideration of predominant conditions in exposure measurement may lead to distinguish the potential hazardous and threat of exposure in the natural environment and also in the human health system. Some specific features in the natural environment include: climate, vegetation, type of soil, and other physical conditions as well. Additionally, the particular conditions for toxic NM and NP in a higher level of exposure in the health system may increase the amount of sensitivity of exposure effects for infants, the elderly, pregnant women, and people with chronic disease.

6-5- Carcinogenic and Non-carcinogenic Risk Assessment

In a study of carcinogenic risk assessment, the most important viewpoint is to focus on inhaled low toxicity and low solubility particles, including nano-particles and
nano-materials. Some of these toxic nano-scale substances create lung tumors in rodent models by mechanisms similar to those found with fine particles. These mechanisms include DNA damage and increased cell proliferation associated with a persistent irritation and chronic inflammation in the lungs. The metric driving this response is still unclear, but the surface area has the strongest support from toxicological evidence. However, the high surface area dose of nano-particles may mean that the rat lung overload is likely to be a powerful confounding issue in laboratory tests. Simply based on their higher surface area, nano-particles may have a stronger potency to induce lung tumors. No increase in extra pulmonary tumors has been seen in inhalation studies, but little information is available from chronic nano-particle administration. Current animal testing methodology is believed to be sufficient to detect the carcinogenic hazard of nano-particles [52]. Recent methodology obtained from experimental data which resulted from animal testing has demonstrated the carcinogenic hazard of nano-particles. Since there is no adequate data and available information to explain the extrapolation to humans, therefore, study on these harmful impacts in the human health system are impossible. The dose-response for non-carcinogenic effects could be determined based on the reliability and quality of the data. Furthermore, to attain an appropriate realization and clear illustration, some modification factors might be used. These parameters cause risk assessors to use scientific judgment in upgrading or downgrading the total uncertainty factor. The uncertainty factors or safety factors have the major role to indicate the dose response for non-carcinogenic and toxic effects of chemicals, specifically nano-materials in various media.
Risk assessments are also conducted to derive permissible exposure levels for acute or short-term exposures to chemicals, specifically toxic NM and NP. Animal doses must be converted to human dose equivalents. The human dose equivalent is based on the assumption that different species are equally sensitive to the effects of a substance per unit of body weight or body surface area. [52].

6-6 Risk assessment and testing methods (controlling methods)

The illustration and understanding of toxicological mechanisms, enhanced testing capabilities, and demands for more sophisticated data for safety and health risk assessment have generated international interest in improving the current testing standard for some important chemicals.

To address this need, a large and diverse group of international experts propose to develop a credible and viable testing approach that includes scientifically appropriate studies that are necessary without being redundant, and that emphasize toxicological endpoints and exposure durations relevant for risk assessment. The benefits of the proposed approach include improved data for risk assessment, greater efficiency, use of fewer animals, and better use of resources. From the outset of this attempt, it was unanimously agreed that a tiered approach should be designed to incorporate existing knowledge on the chemistry, toxicology, and actual human exposure scenarios of the compound, with integration of studies on metabolism/kinetics, life stages, and systemic toxicities. Three international task forces were charged with designing study types and endpoints on metabolism/kinetics, life stages, and systemic toxicities to be used in the tiered approach. [51].
6-7 Risk assessment and risk management model of nano-material toxicity

Today, most studies, investigations, and concerns focus on human health and environmental risks of nano-materials. In fact, the high volume of data and information in this area are associated with the action of nano-particles in various fields and harmful impacts. There are many critical aspects in risk assessment of nano-material toxicity which should be considered, for example, surface nano-scale features related to coatings. Engineered nano-topographical features may have specific characterizations and unique physicochemical properties as well.

Obviously, the types of nano-materials could be characterized by the smallest amount - about one dimension below 100 nm, which indicates particular and possibly unique physico-chemical properties. The quick growing period of nano-material applications needs rapid evaluation of nano-science, nano-technology, exposure assessment, and the continual monitoring of nano-particles occupation, specifically their impacts.

As the primary step in risk evaluation of toxic NM and NP, the focus need to be on approaches to the controlling methods in order to provide comprehensive assessment. Any new information needs to be obtained regarding nano-scale characteristics of materials which correlate to risk assessment and management. Thus, to provide this required information and data into a systemic framework, consideration must be given to many critical objectives regarding the accurate pathway of RA and RM of NMs toxicity. Figure 10 introduces many of these essential aspects in this area.

A study of nano-material activities indicating the different classifications and labeling compared to bulk material leads to superior risk estimation and assessment in
this area. Consequently, many testing methods, which are applicable in risk assessment, should be applied at the various levels of nano-particle actions. This consideration may generate novel ideas and proper opinions on risk assessment methodologies. This programming and practices may provide a wide basis and sensible organization to determine the appropriateness for nano-materials and present extensive proposals to progress in proper places.

Technically, all procedures for risk assessment of nano-material toxicity emphasizes the reorganization of various forms and predominant conditions, information of synthesis methods and manufactured nano-particles, as well as exposure to all forms of nano-scale substances in different fields. Commonly, there are many natural sources and naturally occurring types of nano-particles in the environment, such as some nano-scale particles that have originated from combustion processes. Therefore, in risk assessment,
consideration must be given to manufactured nano-materials as well as natural nano-particles.

Nano-particle actions in the natural environment involve too many processes which most of the time cause insensible impacts. These incidents consist of dynamic interactions within different media (water, soil, air, sediment) which may alter over time; dissolution; agglomeration; disagglomeration; coalescence; and adsorption of other substances onto their surfaces as well. There is no doubt these actions of nano-materials in the environment are significantly associated with many features such as size, shape, surface area and its reactivity, surface geometric and coating, etc. Risk assessments and a management framework may be designed based on study and investigation of impacts on the natural environment and the human health system [Fig-11].

Study on nano-engineering and nano-chemistry may provide an appropriate perspective of the hazardous effects of nano-materials and their toxicity. According to this description, all these observations critically depend on physico-chemical properties of nano-materials, including elemental composition, chemical reactivity of surface, density, crystal structure, solubility, charge, conductivity, melting point, hardness, magnetic and optical properties, morphology, size and size distribution, surface area, and surface layer composition. Evidently these aspects of nano-materials could change with different periods of time and conditions.

General principles for approaching risk assessment of nano-material toxicity would take into consideration the measurement and exposure estimates of manufactured nano-scale substances [Fig-11]. Particularly, an estimation of exposure to ambient nano-particles such as natural sources of nano-particles from combustion should be taken into
account. Although current data are mostly based on the mass distribution of nano-materials, a necessarily developed model might be designed according to cumulative information and data in all relevant features, such as overall exposure, toxicity inhalation, uptake of nano-particles, nano—particle toxicity dosage, etc.

In exposure evaluation in order to design an inclusive model of risk assessment and management, some general approaches may be considered which include toxicokinetics of nano-scale substances (absorption, distribution, metabolism, and excretion) and the size of nano-materials and their surface functionality.

One of the significant components in a risk assessment and management model is critically associated with potential toxicity impact of manufactured nano-materials in the health system of the human body. Significantly, in a study of nano-toxicity of nano-materials with respect to human health and the biological field, significant issues which may involve nano-toxicity behavior include immunotoxicity, neurotoxicity, mutagenicity, genotoxicity, and carcinogenicity.

On the basis of current knowledge, the risk characterization of bulk material documents cannot be directly extrapolated to nano-materials. The mechanisms of toxic effects of engineered nano-particles may be dominated by those characteristics that describe their functionalities for products of interest, and possibly including surface reactivity and quantum effects. Therefore, any unpredicted interactions between nano-particles and biological systems may depend on their unique physical and chemical properties and their multiple functionalities.

Clearly, a majority of the issues about estimation of risk, toxicity evaluation, and exposure measurement of nano-particles are not adequately known and understood.
Therefore, consideration of some critical factors and also uncertainties may lead to a superior viewpoint to realize and make a comprehensive framework of modeling which could be applicable and proper in various fields of nano-particle application. Many of these uncertainties and parameters include:

- Estimation of the presence of nano-particles in the environment (air, water, soil) that may be correlated to the rates of agglomeration, dis-agglomeration, and degradation of nano-scale substances,

- Clarification of toxicity mechanisms in different fields,

- Determination of metrics to measure amount of exposure,

- Occurrences of nano-particles in various natural environments and transferring between different media,

- Illumination of translocation of nano-materials in different parts of the body and a study of their degradation,

A consideration of the life cycle of nano-particles as an essential factor obviously helps to clarify the harmful impacts of these materials [Fig-11]. Generally, various exposure displaying may occur during the life cycle of nano-particles, manufacturing processes, distribution, use, application, storage, waste disposal, and recycling. On other hand, the human body might be exposed, directly and/or indirectly, through contamination consumed in the food chain via manufactured and engineered nano-materials. An estimation of the potential risks of released nano-materials from a variety of possible sources in the natural environment may be associated with many fundamental parameters, processing, and mechanisms which they directly or indirectly involve due to
toxicity impacts and distribution in the environment. Briefly, the most fundamental factors in risk assessment modeling include distribution in various media, deposition on substrata of the natural environment, exposure of environmental species in various media (air, water, sediment, soil), the amount of nano-scale particles concentration, the occurrence of nano-materials within the environment and biota, NP taking via biota which generates toxicity, measurement of exposure in environmental species to toxic NP that depends on their ecology and feeding modes.

Figure-11: Risk Assessment and Management Model

In vivo studies as other particular tools in toxicity evaluation and risk assessment of nano-particles could be taken into account. In some recent studies, some selected animals were used for hazard recognition, which correlated with the properties of
engineered nano-particles compared to bulk particles. In addition, most in vivo protocol studies significantly have focused on translocation of nano-particles from the portal of entry into circulation and towards accumulation in secondary target organs in the human body. The most particular vision of in vivo studies requires using specialized techniques and molecular techniques.

In vitro studies and experiments may provide essential information related to mechanistic data on toxicology on nano-scale materials in various applications.

Generally, many in vitro studies could describe and demonstrate differences between low and high toxicity of nano-particles. In vitro investigations and experiments may be accomplished based on properties and characteristics of nano-particles that the most significant components contain: bio-persistence, free radical generation, cellular toxicity, cell activation, and other generic endpoints.

Eco-toxicity testing is a sufficient procedure to determine the bioavailability in risk assessment and management of nano-particle toxicity. This experimental testing could realize and recognize the uptake, distribution, clearance, and elimination of nano-particles in various fields; behavior of nano-materials in the natural environment; and estimate the main exposure and uptake route for environmental species. Furthermore, to obtain more data and information needs to be gathered regarding species sensitivity towards toxicity of nano-particles and their adverse impacts. In spite of the existing advantages of eco-toxicity testing, development of a novel and standardized methods in this area also is indeed required [Fig-11].
In standard risk assessment, the bioaccumulation of toxic nano-materials could be achieved via an estimation of the Bio-concentration Factor (BCF). Determination of the bioaccumulation potential needs to provide information on uptake and kinetics characteristics, as well as metabolism and other influenced factors. These data and information may be available for a variety of different chemicals. Hence, standard evaluation and assessments in this area normally could be done based on physico-chemical properties and structural parameters.

6-7-1 Quantitative analysis versus Qualitative devices

In order to develop all steps of risk assessment associated with nano-material toxicity, the focus on quantitative analysis as well as qualitative devices in various criteria at the same time is required. The most important benefits of this procedure consist of an increase in the lifetime of risk assessment, expansion of extrapolating range, development of methodology, and extension of potential risk estimation [Figure-12].
Quantitative analysis may be computed via three particular terms and variables related to RA and RM analysis, which include: single loss expectancy (SLE):

\[ SLE = \text{Asset Value (AV)} \times \text{Exposure Factor (EF)} \]

annualized rate of occurrence (ARO) [to determine the probability of a risk occurring, etc; in a manufacturing company), and annualized loss expectancy (ALE)\[ ALE = SLE \times ARO \] [Fig- 12].

6- 8 Risk assessment and management development to standard regulations

The quantitative measurement of particles in the nano range is still in the development phase and far from being routine. However, it is very important in order to be able to assess environmental and health risks. No national or international
standardization of measurement techniques is currently available and the measurement strategies for workplace measurements or epidemiological studies have not yet been elaborated. Therefore, almost no measurement data with engineered nano-particles have been published, in addition to mass concentration, and other parameters like, for instance, particle number concentration, agglomeration, size, and surface as well. The starting points for further research plans should be a review of the measurement technology currently available for determining exposure (Nano-Care). Furthermore, emphasis should be placed more particularly on the further development of portable measurement devices. This is the decisive requirement for carrying out epidemiological studies at a later stage. At the same time, in-company measurements should be stepped up using the available measurement technology in order to obtain initial findings on exposure to nano-particles and, secondly, to create a knowledge base for the elaboration of measurement strategies for "routine workplace measurements" and for epidemiological studies. Taking measurements in plants must offer advantages to the companies who produce, process, or use nano-particles, as their co-operation is the precondition for carrying out the measurements.

The goal of the projects is to further develop and standardize measurement methodology and to make possible routine applications with portable devices.

Generally, the two most significant objectives in using P2 methods to make standard regulation in development of risk assessment include regulatory challenges and immediate regulatory needs. Studies show the environmental evaluation and proper decision for regulation in order to reduce and/or reduce toxic effects of NM and NP is
complex and there is no appropriate and standard proposed approach for a systematic regulation framework.

A systematic regulatory framework to evaluate nano-material toxicity may be developed in various ways using scientific investigation, harmonizing with the obtained results of international efforts, and using experimental data and information. Determination of difficulties due to toxic effects of NM and NP either in the natural environment or in the human health system may be studied in many phases with different conditions, such as shorter and longer-term objectives in evaluation and risk assessments. These proposed objectives could assist to develop a systematic regulatory framework.

The significance of a responsible regulation outline for toxicity evaluation of nano-scale substances may be identified using collaboration on the underpinning scientific issues, international efforts towards understanding the properties, effects, and behaviors of nano-materials, the Organization for Economic Co-operation and Development (OECD), and the International Organization for Standardization (ISO) [23].

Providing a systematic and standard regulation in risk assessment of nano-material toxicity needs to focus on some considerable principles in various sites and conditions. Two most imperative guidelines consist of development of communication with industry and the public and creation of a collection of fundamental information, improvement of legislative modification, and establishment of standard terminology and organization of a standard nomenclature system.

There is an appropriate international program to make standard regulation for toxicity evaluation of NM and NP which includes a voluntary and a mandatory program that would target nano-materials deliberately manufactured or engineered. The types of
information requested would include substance identification; use patterns, including applications and quantities of use; physical-chemical properties; fate and behavior data; and health and environmental effects. Furthermore, information on natural nano-materials, incidental nano-material by-products, and nano-materials in research and development would also be informative [23].

Companies or parties who manufacture, import, process, or use nano-materials will be asked to submit available information on those substances. The types of information that could be sought under an information gathering initiative may be similar to the current data requirements for chemicals and polymers. Additional data specific to nano-materials (e.g., agglomeration, surface fictionalization) would be useful as well. In addition, there are some organizations which are responsible for working on manufactured and engineered nano-materials and also for examining properties and endpoints required for safety testing of nano-materials. The EPA as an appropriate environmental organization has many related research programs for risk assessment and risk management of NMs toxicity. Appendixes A and B [P-97] introduce link activities described, based on EPA strategy and regulation in this area.
Chapter 7

7-1 Discussion:

Modeling of risk assessment of nano-material toxicity as a proper practice could estimate the potential hazardous of nano-engineered particles in various fields. There is no doubt this objective might be dependent on physical-chemical properties of nano-materials. The most significant impacts of toxic nano-scale substances could be studied on the natural environment and the human health system.

Particularly, in each stage of nano-particle life cycle, the presence of their exposure is possible. Therefore, many specific nano-materials may have unique behaviors either in the natural environment in the various media (water, soil, air, and sediment) or on the human body. In both fields, the harmful effects of nano-material toxicity could be predictable. Some of the specific nano-scale materials indicate interactions with biological systems that correlate with their nano-structure. Clearly, most parameters of toxicokinetics and mechanisms of their action processing are unknown and there are no sufficient data and information in this area. Significantly, many uncertainties limit design of appropriate methodologies for various types of nano-particles and different species. Therefore, this difficulty in turn limits design of appropriate models of assessment and also may not provide an accurate framework to propose regulations and firm rules. In spite of this restriction, nano-chemistry and nano-engineering practices, as two fundamental options, help to recognize potential hazardous of manufactured nano-particles and also provide facilities to control and even reduce these harmful effects.

Formulation of risk assessment and management are based on the data resulted from toxicity evaluation on human health and natural environment studies. In the human
health area, the common methodology must illustrate the appropriate manner to identify hazards of NM toxicity. Measurement of mass concentration could be one method to determine the amount of nano-particle dosage. In the assessment of human health hazards, however, an estimation of exposure by using recent methodologies is limited and incomplete, but focusing on biological mechanisms due to toxic nano-particle reactions in the human body leads to certain data and information for this imperative objective. Studies also have demonstrated that not totally nano-scale substances are more toxic and harmful than the bulk formulation of these types of materials. Consequently, using nano-engineering and nano-chemistry for all nano-particle formulations in different fields and application should be considered.

Today, identification of certain impacts of nano-material action in the framework of two essential systems consisting of in vivo and vitro studies is possible. Furthermore, attention to these optional systems conventionally leads to follow an alteration in the physical-chemical properties of nano-particles (agglomeration, dissociation, and adsorption of environmental substances, etc.), which in specific cases may occur.

Current methodology procedures in this area emphasize continuously monitoring effects of nano-particles in the environment, pursue experimental testing particularly eco-toxicity tests, study kinetics of the particulate phase, and predicate environmental concentrations as well. These imperative parameters lead to proposed standardized protocols and applicable practices. Basically, the most important approaches in this area consist of altering exposure and dose-effect toxicity of nano-materials and their physico-chemical properties over time, such as slow degradation, uptake, distribution, and
clearance; providing quantitative risk characterization; and estimating potential chemical and physical conversion into different forms of nano-particles.

Finally, the required step to design an accurate model for risk assessment and management, which depends on obtaining sufficient data and information, is related to exposure and hazard of engineered nano–particles. Additionally, development to set up a wide basis for a cost-effective framework to evaluate potential risks and hazards of toxic nano-materials is necessary.

7-2 Conclusion

To achieve significant results, studies and challenges of risk assessment and management for toxicity effects of nano-materials in various fields, considering traditional risk assessment manners and risk management procedures is required. Clearly, multi-criteria pathway for ultimate decisions can be reached by analysis of perspectives to support regulation-planning. These requirements are due to an existing limitation of knowledge basis, lack of sufficient data, uncertainty, and variability. Certainly, an accurate manner to evaluate potential risk and adaptive management for nano-material toxicity effects is associated with the value of gained data and information from engineered analysis. This approach may provide an efficient and methodical device as a systematic organization to explain the mechanism of nano-material dynamic features, which are involved with nano-material actions, and their risk assessment and management. Therefore, focusing on these critical aspects as well as consideration of novel data on main social concerns and economic priorities can improve our perspective to design a proper model and develop goals in this area [Fig-1].
To design mechanistic models of risk assessment and management relating to nano-particle toxicity, the most significant alternatives and challenges that have considered in this study, include: uncertainty in exposure evaluation, risk characterization, toxicity dosage, structure-activity, physico-chemical properties; continuously monitoring adverse impacts on the natural environment and the human health system; clarification of model objectives; determination of variations and functions; design of a systemic computational framework, data and information accessibility, alternative model structure, sufficient knowledge, and technical–engineering capabilities; combination of the required modules and models to explain more details; providing expert opinions and judgment to make ultimate decisions and regulations; and standardizing the experimental testing system. This study have demonstrated that consideration to multi criteria and wide view point to the required scientific tools such as nano-chemistry and nano-engineering and also other mentioned principles and alternatives above, may assist to reach proper framework of RA and RM which could be applicable to apply in various fields that affected by nano-materials toxicity. The designed models and modules this project could response to all objects associated to NM toxicity contain, evaluation of NM behavior, present practical procedures regards to remove or reduction of NM toxicity, development of regulation and ultimate decision in this area.

Results of this study are summarized as follow:

- A critical review of nano-material toxicity on environment and human health conducted in this study could assist serve the scientific community, regulatory agencies, and the industry in many ways. Several literature sources as
identified in the references section were reviewed and discussed in this report. The information compiled in this report can help in (I) better understanding of nano material toxicity, (II) improved understanding of interrelationships among various parameters, and (III) designing applicable road map to investigate nano-material toxicity.

- This study has showed that integrated RA and RM methodology for nano-materials toxicity could be achieved using the fundamental principles of chemistry, physics, biology, toxicology, and other related disciplines. Two critical outcomes of this section are:
  - Documenting required data and information on adverse effects of nano-materials.
  - Identified multi-criteria pathways of NM toxicity assessment in under various scenarios.

- Nano-engineering and nano-chemistry are two distinct applicable tools but in combination, they have important role in quality and quantity controls of NM synthesis, structural design, and assist in standardizing methods. Furthermore, focus on concepts and practical procedures of nano-engineering and nano-chemistry lead to designing an acceptable and comprehensive RA and RM regards to:
  - Reducing and/or removing harmful impacts of various nano-material toxicity on human health and the natural environment.
- Helping in development of rational regulations in nano-material toxicity assessment.
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APPENDIX A. Relationship of ORD Research Strategy to EPA White Paper Research Needs (Current Research (CR), Short-term Research (SR), and Long-term Research (LT))

The table below is only intended to link the activities described in this strategy with the overall research need questions in the EPA White Paper. It is not designed to provide details on implementation of the NRS. (Draft Nanomaterial Research Strategy (NRS) January 24, 2008 EPA/600/S-08/002)

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<td>Research Needs for Risk Assessment</td>
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<td>Chemical Identification and Characterization</td>
<td>What are the unique chemical and physical characteristics of nanomaterials? How do these characteristics vary among different classes of materials (e.g., carbon based, metal based) and among the individual members of a class (e.g., fullerenes, nanotubes)?</td>
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<td>How do these properties affect the material’s reactivity, toxicity and other attributes?</td>
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<td>To what extent will it be necessary to tailor research protocols to the specific type and use pattern of each nanomaterial? Can properties and effects be extrapolated within class of nanomaterials?</td>
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<td>Are there adequate measurement methods/technology available to fully characterize nanomaterials, to distinguish among different types of nanomaterials, and distinguish intentionally produced nanomaterials from ultrafine particles or naturally occurring nanosized particles?</td>
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<td>Are current test methods for characterizing nanomaterials adequate for the evaluation hazard and exposure data?</td>
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<td>Do nanomaterial characteristics vary from their pure form in the laboratory to their form as components of products and eventually to the form in which they occur in the environment?</td>
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<td>What intentionally produced nanomaterials are now on the market and what new types of materials can be expected to be developed?</td>
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<td>How will manufacturing processes, formulations, and incorporations in end products alter the characteristics of nanomaterials?</td>
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<td><strong>Environmental Fate and Treatment Research Needs</strong></td>
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<td><strong>Transport Research Questions</strong></td>
<td>What are the physical and chemical factors that influence the transport and deposition of intentionally produced nanomaterials in the environment? How do nanomaterials move through these media? Can existing information on soil colloidal fate and transport and atmospheric ultrafine particulate fate and transport inform our thinking?</td>
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<td>How are nanomaterials transported in the atmosphere? What nanomaterials properties and atmospheric conditions control the atmospheric fate of nanomaterials?</td>
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<td>To what extent are nanomaterials mobile in soils and in groundwater? What is the potential for these materials, if released to soil or landfills, to migrate to groundwater and within aquifers, with potential exposure general populations via groundwater ingestion?</td>
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<tr>
<td>What is the potential for these materials to be transported bound to particulate matter, sediments, or sludge in surface waters?</td>
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<tr>
<td>How do the aggregation, sorption and agglomeration of nanoparticles affect their transport?</td>
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<tr>
<td>How do nanomaterials bioaccumulate? Do their unique characteristics affect their bioavailability? Do nanomaterials bioaccumulate to a greater or lesser extent than macro-scale or bulk materials?</td>
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<tr>
<td><strong>Transformation Research Questions</strong></td>
<td>How do nanoparticles react differently in the environment than their bulk counterparts</td>
<td>SR</td>
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<tr>
<td>What are the physical and chemical factors that impact the persistence of intentionally produced nanomaterials in the environment? What data are available on the physical and chemical factors that affect the persistence of unintentionally produced nanomaterials (e.g., carbon-based combustion products) that may provide information regarding intentionally produced nanomaterials?</td>
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<tr>
<td>Do particular nanomaterials persist in the environment, or undergo degradation via biotic or abiotic processes? If they degrade, what are the byproducts and their characteristics? Is the nanomaterial likely to be in the environment, and thus be available for bioaccumulation/biomagnification?</td>
<td>SR</td>
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<tr>
<td>How are the physical, chemical and biologic properties of nanomaterials altered in complex environmental media such as air, water, and soil? How do redox processes influence environmental transformation of nanomaterials? To what extent are nanomaterials photoreactive in the atmosphere, in water, or on environmental surfaces?</td>
<td>SR</td>
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<tr>
<td>How do the aggregation, sorption and agglomeration of nanoparticles affect their transport?</td>
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<tr>
<td>In what amounts and in what forms may nanoparticles be released from materials that contain them, as a result of environment forces (rain, sunlight, etc.) or through use, re-use, and recycle or disposal.</td>
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<thead>
<tr>
<th><strong>Chemical Interaction Research Questions</strong></th>
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<tbody>
<tr>
<td>How do nanosized adsorbents and chemicals sorbed to them influence their respective environmental interactions? Can these materials alter the mobility of other substances in the environment? Can these materials alter the reactivity of other substances in the environment?</td>
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<tr>
<th><strong>Treatment Research Questions</strong></th>
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<tbody>
<tr>
<td>What is the potential for these materials to bind to soil, subsurface materials, sediment or wastewater sludge, or binding agents in waste treatment facilities?</td>
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<tr>
<td><strong>Assessment Approaches and Tools Questions</strong></td>
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<tr>
<td>Are these materials effectively removed from wastewater using conventional wastewater treatment methods and, if so, by what mechanism?</td>
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<tr>
<td>Do these materials have an impact on the treatability of other substances in waste streams (e.g., wastewater, hazardous and nonhazardous solid wastes), or on treatment facilities performance?</td>
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<tr>
<td>Can existing information on soil colloidal fate and transport, as well as atmospheric ultrafine particulate fate and transport, inform our thinking? Do the current databases of ultrafines/fibers shed light on any of these questions?</td>
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<td><strong>Human Exposures, Their Measurement and Control</strong></td>
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<tr>
<td>Are standard procedures available for both sample preparation and analysis?</td>
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<tr>
<td>How would nanomaterials in waste media be measured and evaluated?</td>
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<tr>
<td><strong>Human Exposures, Their Measurement and Control</strong></td>
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<tr>
<td>Is the current exposure assessment process adequate for assessing exposures to nanomaterials? Is mass dose an effective metric for measuring exposure? What alternative metric (e.g., particle count, surface area) should be used to measure exposure? Are sensitive populations' (e.g., endangered species, children, asthmatics, etc.) exposure patterns included?</td>
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<tr>
<td><strong>Release and Exposure Reduction and Mitigation Research Questions</strong></td>
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<tr>
<td><strong>Are current respirators, filters, gloves, and other PPE capable of reducing or eliminating exposure from nanomaterials?</strong></td>
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<td><strong>Are current engineering controls and pollution prevention devices capable of minimizing releases and exposures to nanomaterials?</strong></td>
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<tr>
<td><strong>Are technologies and procedures for controlling spills during manufacture and use adequate for nanomaterials? Can current conventional technologies (i.e., for non-nanomaterials) be adapted to control nanomaterial spills?</strong></td>
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<tr>
<td><strong>In the case of an unintentional spill, what are the appropriate emergency actions? How are wastes from the response actions disposed of properly?</strong></td>
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<tr>
<td><strong>Do existing methods using vacuum cleaners with HEPA filters work to clean up spill of solid nanomaterials? If not, would a wet vacuum system work?</strong></td>
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<td><strong>What PPEs would be suitable for use by operators during spill mitigation?</strong></td>
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<tr>
<td><strong>Human Health Effects Assessment Research Needs</strong></td>
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<tr>
<td><strong>Are there specific toxicological endpoints that are of higher concern for nanomaterials, such as neurological, cardiovascular, respiratory, or immunological effects, etc.?</strong></td>
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<td>Question</td>
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<tr>
<td>Are current testing methods (organisms, exposure regimes, media, analytical methods, testing schemes) applicable to testing nanomaterials in standardized agency toxicity tests (<a href="http://www.epa.gov/opptsf/AOPPTS_Harmonized">http://www.epa.gov/opptsf/AOPPTS_Harmonized</a>)?</td>
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<tr>
<td>Are current test methods, for example OECD and EPA harmonized test guidelines, capable of determining the toxicity of the wide variety of intentionally produced nanomaterials and byproducts associated with their production and applications?</td>
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<td>Are current analytical methods capable of analyzing and quantifying intentionally produced nanomaterials to generate dose-response relationships?</td>
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<tr>
<td>What physical and chemical properties regulate nanomaterial absorption, distribution, metabolism, and excretion (ADME)?</td>
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<tr>
<td>What physical and chemical properties and dose metrics best correlate with the toxicity (local and systemic; acute and chronic) of intentionally produced nanomaterials following various routes of exposure?</td>
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<tr>
<td>How do variations in manufacturing and subsequent processing, and the use of particle surface modifications affect nanomaterial hazard?</td>
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<tr>
<td>Are there subpopulations that may be at increased risk of adverse health effects associated with exposure to intentionally produced nanomaterials?</td>
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<td>What are the best approaches to build effective predictive models of toxicity (SAR, PBPK, “omics”, etc.)?</td>
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<td>Are there approaches to grouping particles into classes relative to their toxicity potencies, in a manner that links in vitro, in vivo, and in silico data?</td>
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<tr>
<td><strong>Ecological Effects Research Needs</strong></td>
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<tr>
<td>Are current testing schemes and methods (organisms, endpoints, exposure regimes, media, analytical methods) applicable to testing nanomaterials in standardized toxicity tests? Both pilot testing protocols and definitive protocols should be evaluated with respect to their applicability to nanomaterials.</td>
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<td>What is the distribution of nanomaterials in ecosystems? Research on model ecosystems studies (micro, mesocosms) is needed to assist in determining the distribution of nanomaterials in ecosystems and potentially affected compartments and species.</td>
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<tr>
<td>What are the effects (local and systemic; acute and chronic) from either direct exposure to nanomaterials, or to their byproducts, associated with those nanotechnology applications that are most likely to have potential for exposure?</td>
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<tr>
<td>What are the absorption, distribution, metabolism, elimination (ADME) parameters for various nanomaterials for ecological receptors? This topic addresses the uptake, transport, bioaccumulation relevant to a range of species (fish, invertebrates, birds, amphibians, reptiles, plants, microbes).</td>
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<tr>
<td>How do variations in manufacturing and subsequent processing, and the use of particulate surface modifications affect nanomaterial toxicity to ecological species?</td>
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<tr>
<td>What research is needed to examine the interaction of nanomaterials with microbes in sewage treatment plants, in sewage effluent, and in natural communities of microbes in natural soil and natural water?</td>
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<td>What research is needed to develop structure activity relationships (SARs) for nanomaterials for aquatic organisms?</td>
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<tr>
<td>What are the modes of action (MOAs) for various nanomaterials for ecological species? Are the MOAs different or similar across ecological species?</td>
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<td>Risk Assessment Research - Case Study</td>
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<td>Green Manufacturing Research Needs</td>
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<td>Green Energy Research Needs</td>
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<td>Environmental Remediation/Treatment Research Needs</td>
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<td><strong>Sensors</strong></td>
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The Office of Research and Development (ORD) is the principal research arm of the Environmental Protection Agency (EPA) (http://www.epa.gov/ord/). Its role is to provide the critical science for the Agency’s environmental decision-making. Unlike much of EPA, ORD has no direct regulatory function; its responsibility is to inform the policymaking process.

Through the development of technical information and scientific tools, ORD’s research strengthens EPA’s science base by providing its program offices and regional offices with sound scientific advice and information for use in developing and implementing scientifically defensible environmental policies, regulations, and practices.

As may be seen in Figure B-1, ORD is led by the Assistant Administrator (AA) for Research and Development, who reports directly to the EPA Administrator. This position involves providing leadership in establishing research priorities, ensuring the means for technical evaluation and peer-review of ORD’s products, and contributing scientific input into the EPA’s regulatory decisions.

The AA ORD is supported by a Deputy Assistant Administrator (DAA) for Management and a DAA for Science. The Directors of ORD’s Laboratories and Centers provide scientific leadership relative to their respective organizations and report to the AA ORD. Recently, ORD established National Program Directors (NPDs). The NPDs provide a strategic vision of the stakeholder needs and overall coordination of research programs delineated in ORD's Multi-Year Plans (MYPs). ORD is composed of seven national Laboratories and Centers and two Offices. The Laboratories and Centers, spread across the country, conduct research across the risk assessment/risk management paradigm related to both the environment and human health. ORD also has a National Homeland Security Research Center and a National Center for Computational Toxicology.

ORD’s two offices are the Office of Science Policy (OSP) and the Office of Resources Management and Administration (ORMA). OSP plays a vital role by providing expert advice and evaluation on the use of scientific knowledge and science policy to support sound science in the Agency. OSP accomplishes this mission by leading efforts in science integration, coordination and communication across ORD, and between ORD and the Agency's programs, regions, and external parties.

ORMA manages a broad spectrum of issues and provides counsel/advice on all matters relating to the responsible management of ORD's resources.
Figure B-1 Organizational chart for the Office of Research and Development
Farah Bigdeli was born in July 1969; she received Bs degree in chemistry from Azad University on 1994. She also received master’s degree (Ms) in Marin Chemistry in 1997 from same university (Iran). During that period of time, she specifically focused on the chemical and biological features of Caspian Sea. In this study, she characterized chemicals components of Caspian Sea sediments, these components including: Trace Elements (Fe, Pb, Mn, Co, Cu, Zn), Total Organic Carbon (TOC), Total Carbon (TC), Biogenic Elements (Biognic silica dissolution in Sea water) and Chemical Pollution of Mercury in Marin Microorganisms and fishes body.

Since 1996 she has started to research in different chemical, environmental chemistry and environmental engineering laboratories in various fields and she could obtain some experiences in these areas.

She has participated in some research projects in Erath and environmental Science Department of University of New Orleans in 2003 which include: Salt water Instruction in Lacombe and Baton Rouge areas, Further delineate and chemically characterize the areas of salt-water instruction,*Determination of the source of salt contaminations in water:

* Use Hydrolab probe to measure, Temperature, Specific Conductivity, pH, Dissolved Oxygen, and Alkalinity.
* Use Liquid Ion Chromatograph to measure major Cations, Anions and Nutrients.
* Use ICP to measure Li and Sr.
* Use UV-VIS Spectrograph to measure SIO2 aq.

In addition she had participated in some research projects in Civil and Environmental Engineering Lab in Environmental Engineering Department (UNO) from 2005. Her second master’s degree is: Master of Science in Environmental Engineering, from University of New Orleans, spring 2009. Her specific research has associated to: Risk Assessment and Risk Management of Nano-Material Toxicity (Manufacturing and Natural Environment Approaches).

Her interests and objectives in this career of her advanced education consist:

- Study on risk assessment of toxic chemical in natural environment
- Identification and offering appropriate procedures in risk management
- Toxicology and toxicity evaluation of trace elements & heavy metal
- Development of required regulations in Environmental restoration and protection respect to solid waste management methods, waste minimization, pollution prevention, process optimization, and clean technologies evaluation.
- Computer applications to solve and manage environmental/industrial cleanliness problems;
- Air quality management – monitoring (ambient, source, and occupational)
- Environmental impact assessment and environmental management systems (EMS)
- Industrial hygiene management
- Development wastewater treatment
- Description an accurate technology in water and wastewater treatment respect to monitoring and
- Development of Kinetics of water and wastewater treatment process