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A Framework for Health-Related Nanomaterial Grouping

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Abstract

Background

Nanotechnology has been in the limelight since its emergence and its products affect everyday lives. Nanomaterials are characterized by features such as size and shape, thus rendering their possible number essentially unlimited, which in turn makes them difficult to study and categorize regarding possible dangers. This work suggests that grouping could allow studying them with limited testing efforts without endangering safety.

Methods

Initially, the materials are identified and grouped according to their applications in health/medicine, as well as on their environmentally-friendly potential. The materials are then categorized using various toxicity classification methods to identify those with highest risks and group them with others that demonstrate similar behavior.

Results

The materials studied show promising uses in diagnostics, drug delivery, biosensors, water purification, oil spill cleaning, emission control and other fields. The toxicity risk assessment shows that the majority pose little to moderate risk, however there are certain materials that can be extremely hazardous or even cause death under specific circumstances. A risk mitigation plan was also developed.

Conclusions

Nanomaterials applications, including drug delivery, cancer treatment, waste treatment, solar energy generation etc can be very beneficiary, but at the same time, these materials can be extremely harmful or even cause death, thus making the need to prioritize research on high risk materials crucial. A clear regulatory framework that addresses both benefits and risks and communicates that information effectively should play an important part in European and worldwide efforts.

General Significance

The risk analysis validated the impression that there is limited research on nanomaterial toxicity risks, which calls for a more organized approach. The framework outlined in this work can be utilized by researchers as well as government bodies, in order to form regulatory policies and adopt a universally accepted labeling system.

Keywords: grouping, nanomaterial, health, applications, risk, toxicity.

Introduction

A nanomaterial is generally defined as a material with at least one external dimension in the 1-100 nanometer (nm) size range. A nanoparticle is an object whose three external dimensions are in the nm scale range. Typically, the behavior of nanomaterials in an environment depends more on surface area than composition; relative-surface area is one of the main factors that affect their reactivity, strength and electrical properties [1]. Nanomaterials have multiple uses in various fields and can dramatically improve the effectiveness of existing or developing applications.

An increasing amount of research is examining the effects of nanomaterials on both humans and the environment. Such research is useful to policy makers, who are slowly concluding that current regulations on chemicals is not satisfactory for governance of nanomaterials. [2, 3]. It is however, important to note that only a relatively small number of studies or reviews of nanomaterials' effects on the environment has been found [4-15]. This is despite the fact that health can be affected both when handling the material (*i.e.* coming into contact with it during production processes), while using products containing the material, or secondary exposure to discarded materials. This can be partially attributed to the large number of nanomaterials and the variety of their characteristics, which make it difficult to track all possible risks for each one, as well as the fact that some materials are relatively new and there has been little time to conduct appropriate research. Therefore, grouping materials based on applications or other factors could enable the researchers to identify and address them more effectively.

The large number of publications on the subject of nanomaterials in general can be ascribed to the fact that nanotechnology encompasses a vast range of research areas. However, the existing works researching nano-toxicology aspects target a very specific audience. A strategy is required to assess reports that have focused on filling in information under regulatory frameworks.

To this end, the state-of-the-art has been reviewed to identify what has been done so far in terms of classifying nanomaterial risks. We found that the existing literature is spread across a variety of disciplines and fields. A careful approach is thus required for the evaluation of possible risks of any kind that are associated with the production, use and disposal of nanomaterials. So far, the physico-chemical attributes (such as the rate of a material's dissolution) have been studied regarding their effect on the behavior and toxicity of the material on human health and the environment. The review was mostly based on existing knowledge and led to the creation of a basic set of attributes that can characterize nanomaterials [16,17]. This has provided a foundation for the future evaluation of nanomaterials.

Even though current toxicity testing protocols may be utilized to determine potential adverse effects, research into new methodologies is recommended in order to address the unique attributes of nanomaterials. As a result, the use of only physico-chemical properties as a standalone attribute for regulatory purposes is deemed insufficient. Such an evaluation should include both hazard and exposure possibilities. Therefore, alternative options are required to provide a meaningful classification. This information can later be incorporated to strategies and decisions based on the product's lifecycle.

Other classification strategies have been proposed, dividing nanomaterials based on ecological risk probability, not just based on material attributes, but also taking variation of final product and professional judgments into account [18]. Simulations were used to explore possibilities and assess the robustness of the categorization [18].

These materials will be used in this study, in order to be evaluated and grouped using multiple standardized classification methods, in conjunction with a thorough literature review, and

examination of their Material Safety Data Sheets (MSDS). Grouping nanomaterials using the same mode of toxic action can prove helpful in the final risk assessment process [19,20].

Some of the concerns to be addressed [21]:

- The possibility of the materials to enter the body via the respiratory system, ingestion or skin contact. This can constitute an occupational hazard;
- Based on studies on humans and animals, inhaled nanoparticles can move in the blood system and enter organs;
- Some nanomaterials can cause lung issues, cancer or be toxic to humans, animals and/or plants;
- Possible catalytic reactions when in contact with water or other substances, or under other specific circumstances (temperature, pressure, *etc*.);
- Disposal process safety;
- Required safety measures when working with these materials.

Aim and Scope

The aim of this work is to review and highlight the state-of-the-art knowledge regarding the application of nanoporous materials in health/medicine, based on the patents granted by the United States Patent and Trademark Office (USPTO) and European Patent Office (EPO) for the past five years, in order to further examine these materials in terms of toxicity. Uncertainty on their safety can cause unwillingness to further invest in the materials and lead to contested innovations not accepted by society.

Initially, the materials are identified and grouped according to their applications in health/medicine, as well as on their environmentally-friendly potential. The materials are then categorized using various toxicity classification methods to identify those with highest risks and group them with others that demonstrate similar behavior.

A risk analysis was later performed in order to establish a mitigation strategy. The ultimate goal of this evaluation is to provide a tool that will assist in taking all the necessary precautions to avoid the occurrence of potential adverse effects when possible. Failure to properly classify nanomaterial risks could become a hindrance to the development of nanotechnology due to societal opposition and regulatory restrictions

Framework

This article proposes a twofold framework for the grouping of nanomaterials related to health/medicine. This framework can serve as a prototype for an effective nanomaterial grouping process that paves the way for better use of available information on nanomaterials. The framework is flexible enough to allow future adaptations based on scientific developments. In a first step, nanomaterials are grouped based on health-related and environmentally-friendly applications. Following that, their toxicity and associated risks are researched in order to group them based on behavior and adverse effects on either health or the environment. The grouping criteria (applications & toxicity risk) are verified using various sources, such as safety datasheets, producer-provided information and past research work, such as relevant literature on the subject.

Methodology

In order to determine which nanomaterials are being applied in healthcare, the patents granted by the USPTO and the EPO during the 2010-2015 period have been identified using the search keywords *porous, nanoporous, microporous, mesoporous and microporous* in their title or abstract text. Subsequently, the title and abstract text have been further examined to determine their applicability in healthcare. Additionally, literature on each material was then reviewed to identify their effects on health, both via their intended application, as well as during handling and disposal. Since nanomaterials' effect on the environment is a valid and important concern, any positive and negative effects of these materials were also noted.

During the research process, it became apparent that although all materials are required to have a Material Safety Datasheet (MSDS) based on EU and international laws for the transportation of hazardous materials, different classifications are used, depending on the producing company and country of origin. As a consequence, and in order to ensure coverage, three commonly used classification processes were selected to express the risk level of each material, taking into account the MSDS, as well as the previously-mentioned literature review on the material. The classifications methods selected are the following:

- **NFPA 704**: The "Standard System for the Identification of the Hazards of Materials for Emergency Response" is a standard maintained by the U.S.-based National Fire Protection Association. It defines the colloquial "fire diamond" used by emergency personnel to quickly and easily identify the risks posed by hazardous materials. This helps determine what, if any, special equipment should be used, procedures followed, or precautions taken during the initial stages of an emergency response. The ratings range from 0 (no risk) to 4 (severe risk). Special notices may be included [22].
- **EU Dangerous Substances Directive**: The Dangerous Substances Directive (67/548/EEC) was one of the main European Union laws concerning chemical safety, until its replacement by the new CLP regulation (2008), starting in 2016. It is still widely used in multiple MSDs though, so it was included for additional coverage. It is applied to materials and composites that are placed on the market, therefore it may not rate materials created only for research purposes. The risk is expressed as a chemical hazard symbol and a letter code [23,24]
- **GHS Classification**: The Globally Harmonized System of Classification and Labeling of Chemicals (GHS) is a system developed by the United Nations for standardizing and harmonizing the classification and labeling of chemicals globally. It defines physical, health and environmental hazards of chemicals and harmonizes classification criteria and standardizes the content and format of chemical labels and Safety Data Sheets. As a voluntary international system, the GHS is not legally binding in any country. Therefore, countries adopting GHS have to issue their own regulations or standards to implement GHS criteria and provisions. Two examples are the EU's CLP regulation in the EU and the OSHA Hazard Communication Standard in the US. This method provides a list of statements categorizing physical, health and environmental hazards. There are a total of 29 classes [25].

Results

As previously mentioned, the first step of the process was to select the nanomaterials to be studied. The materials used stem from the USPTO and EPO patent search described earlier, which returned 165 health related patents. The most commonly mentioned materials are listed below:

- Aerogel
- Alumina
- Aluminium
- Aluminium Nitride
- Black Nanopowder
- Boron Nitride
- Calcium Carbonate
- Carbon nanotubes Single/Double/Multi Walled
- Cerium Oxide
- Copper Oxide
- Gallium Antimonide
- Gallium Arsenide
- Graphene
- Hafnia
- Hydrogel
- Indium Oxide
- Iron Oxide
- Magnesium Oxide
- Silicon Carbide
- Titanium Boride
- Titanium Carbide
- Titanium Carbonitride
- Titanium Dioxide

The multiple applications of the above materials in medicine are shown in figure 1. These include biosensors and diagnostics, drug delivery, cancer treatment, implants and pharmaceuticals among others. Such applications are indicative of the importance of these materials and highlight the need to assess their safety. It should be noted that some of these materials are very specific to certain applications, while others such as aerogel, graphene, hydrogel and carbon nanotubes appear to have multiple uses.

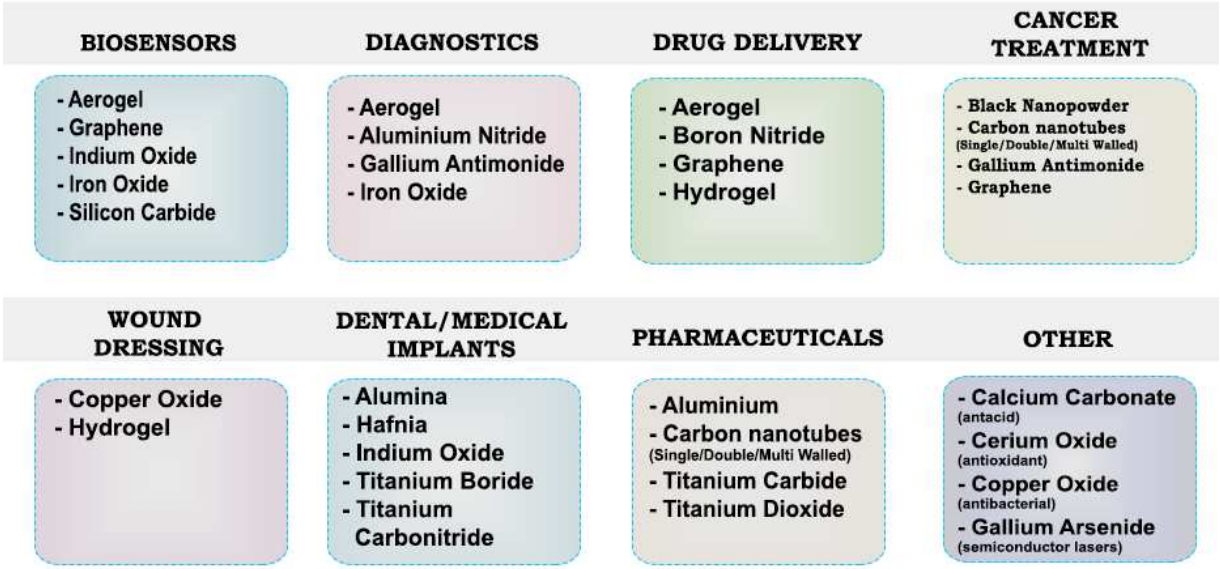


Figure 1. The applications of the studied nanomaterials in health/medicine

Besides their use in health related applications, the studied materials have shown promising results in other areas as well, some of which are very positive for the environment. For example, aerogel can be used for water purification and oil-spill cleaning, while aluminium nitride can be utilized for emission control. Materials such as copper oxide and gallium arsenide have been exploited for solar energy transformation or generation. More details for the environmental-friendly applications are listed in Table 1.

Table 1. The environmental-friendly applications of the studied materials

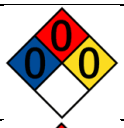
Material	**Environment-friendly applications**
Aerogel	Water purification, clean-up of oil-spills, "green" technology
Aluminium	Compared to producing virgin aluminum from raw bauxite, recycling old aluminum consumes just 5% of the energy and releases a mere 5% of the greenhouse gases. Infinitely recyclable, aluminum loses none of its integrity even when it is melted down repeatedly, plus, the whole recycling process can be achieved in less than 60 days flat.
Aluminium Nitride	Emission control via environmental systems
Black Nanopowder	It can be used for plastics, rubber, electronics technology, anti-static materials.
Calcium Carbonate	It can be added to neutralize the effects of acid rain in river ecosystems. Currently calcium carbonate is used to neutralize acidic conditions in both soil and water. Calcium carbonate is also used in fuel gas desulfurization applications eliminating harmful SO2 and NO2 emissions from coal and other fossil fuels burnt in large fossil fuel power stations.
Copper Oxide	Solar energy transformation
Gallium Arsenide	Solar energy generation
Graphene	Graphene based nano-composites reduce the weight of airplanes by substituting traditional metals and composites, and the consequence of the weight saving results in a reduction of a thousand tons of gasoline.
Hydrogel	Certain hydrogels are capable of absorbing as much as 500 times their weight in water. This superabsorbent property renders hydrogels useful in conserving water as well as solving other environmental issues. Also used for preventing soil erosion. Possible replacement of non-eco-friendly plastics
Indium Oxide	It is commonly doped with tin oxide (SnO2) to make indium tin oxide (ITO), which is used in transparent thin conductive thin films, which are used in energy efficient windows and photovoltaics. Highly pure and useful for detection of ammonia gas. Efficiently recyclable
Magnesium Oxide	Neutralization of acid wastewater, wastewater treatment, heavy metal removal from industrial wastes
Titanium Carbonitride	Its production is considered an environmentally friendly process

Toxicity risk assessment

As previously described, the NFPA 704, Dangerous Substances Directive and GHS classification systems were utilized to produce a final risk assessment regarding the toxicity risk of the studied nanomaterials. It is notable that some materials have not been classified based on one of the above systems, either because the producing company has chosen to use other classification methods or because their MSDS had not been updated to include the classification results. Furthermore, certain composite materials such as aerogels, that can be synthesized via different methods and using different base materials - altering their possible effects –cannot be uniformly categorized via the main classification system. These materials were thus categorized based on a

literature review of their possible variations. The classifications are presented in Table 2 in ascending risk level order.

Table 2. The toxicity risk assessment of the materials, based on a combination of the risk classification systems and literature review of the nanomaterials' various effects on human health and the environment.

Materials	**Risk classification systems**			**Toxicity Risk Assessment**	**References**
	NFPA 704	**EU Dangerous Substances Directive**	**GHS**		
Calcium Carbonate, Titanium Carbonitride		n/a	n/a	**Very Low**	[15-16], [17-19]
Aerogel	n/a	n/a	n/a	**Very Low**	[20-24]
Aluminium		n/a	Not classified as hazardous	**Very Low**	[25]
Boron Nitride			H319, H335	**Low**	[26-27]
Indium Oxide, Iron Oxide, Silicon Carbide			H315, H319, H335	**Low**	[28], [29-30] [31]
Alumina, Cerium Oxide, Hafnia, Magnesium Oxide		n/a	n/a	**Low**	[32-34], [35-36], [37-40], [41-42]
Carbon nanotubes, Hydrogel	n/a	n/a	n/a	**Low**	[43-45], [46-48]
Titanium Carbide		n/a	Not classified as hazardous	**Low**	[49]
Graphene	n/a	n/a	n/a	**Moderate**	[50-53]
Gallium Antimonide			H302, H332, H401	**High**	[54-55]
Titanium Boride	n/a		H312, H302, H332	**High**	[56-57]

Aluminium Nitride			H315, H319, H335	**High**	[58]
Black Nanopowder	n/a	n/a	n/a	**High**	[59-60]
Gallium Arsenide			H301, H331, H410	**Very High**	[61]
Copper Oxide			H302, H410	**Very High**	[62]
Titanium Dioxide			H351	**Very High**	[63]

A list of explanations regarding the classifications is provided below.

NFPA 704
- Blue: Health
- Red: Flammability
- Yellow: Instability/reactivity
- White: Special Notice
- ~~W~~ (Reacts with water in an unusual or dangerous manner)

EU Dangerous Substances Directive
- Irritants (Xi)
- Harmful (Xn)
- Dangerous for the environment (N)
- Toxic substances or preparations, classified as very toxic T+ or toxic T (T)

GHS
- H301 - Toxic if swallowed
- H302 - Harmful if swallowed,
- H312 - Harmful in contact with skin
- H315 - Causes skin irritation,
- H319 - Causes serious eye irritation
- H331 - Toxic if inhaled
- H332 - Harmful if inhaled
- H335 - May cause respiratory irritation.
- H351 - Suspected of causing cancer
- H401 - Toxic to aquatic life
- H410 - Very toxic to aquatic life with long-lasting effects

Risks Analysis

Nanotechnology has received much attention recently, due to the discovery and manufacture of new nanomaterials that are applicable to many fields, such as medicine, agriculture, and energy. As a result, exposure to these materials is unavoidable, hence research on their effects and possible toxicity becoming ever more important.

The question that needs to be addressed when using nanomaterials is whether they pose risks to either health or environment, under which circumstances this occurs, and if so, can we use

currently known information to evaluate nanomaterials, and to which extent?

This work uses current knowledge about exposure and possible risks for the examined nanomaterials. The findings are then utilized in order to create risk profiles for each one.

A Risk Analysis Plan, involving three steps, has been drawn as explained below:

STEP 1. Methods for risk identification: Various sources were used, such as safety datasheets, producer-provided information and past research work, including an extensive literature review on the subject.

STEP 2. Risk analysis in order to determine the probability of the risk occurring and the impact it would have either on human health or the environment, the extent of it, and the specific circumstances required for it to occur.

The method used for the risk analysis:

- **Qualitative Risk Analysis** (a descriptive scale to measure the possible severity of impact - e.g. Very Low, Low, Moderate, High, Very high)

A risk profile for each of the studied materials was then developed. The results of the toxicity risk assessment, presented visually in figure 2, reveal that the majority of the materials present a very low to moderate risk to human health or the environment based on current research results and international classifications. However, there is a list of materials that can be quite dangerous; for example, Gallium Antimonide can be toxic to aquatic life, while Copper Oxide and Titanium Dioxide can be very toxic and have long-lasting effects in general. Furthermore, Gallium Arsenide can be toxic when inhaled or swallowed and Titanium Dioxide is also a suspected carcinogen.

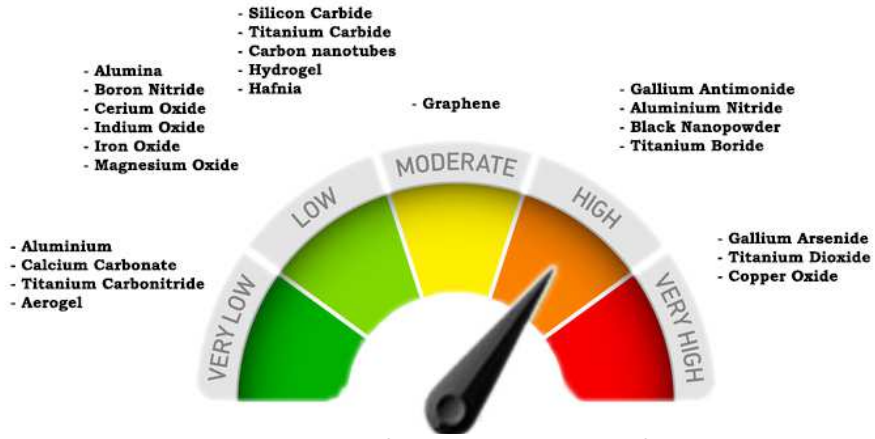


Figure 2. A visual representation of the risk assessment of the studied materials

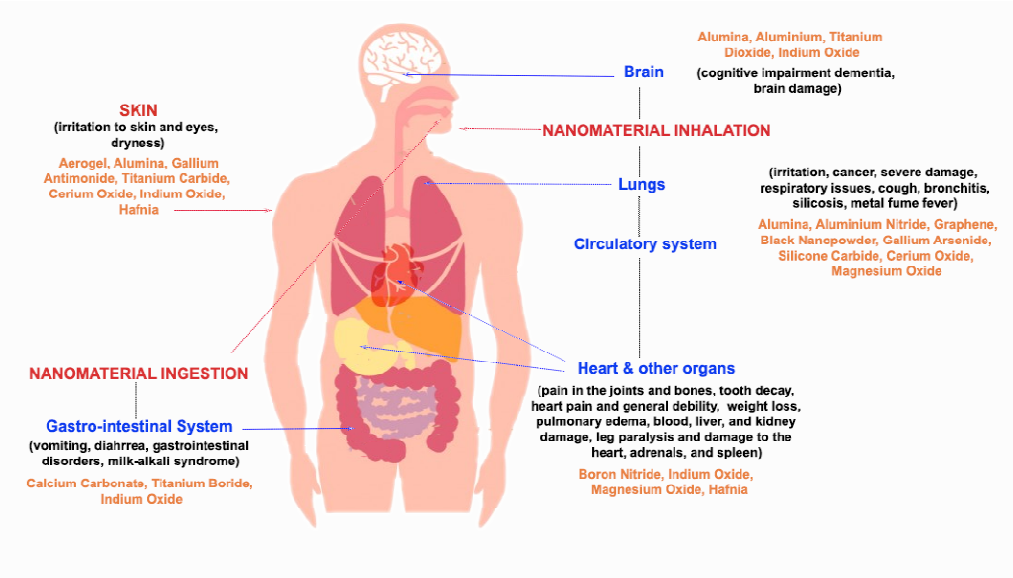


Figure 3. The entry paths of nanomaterials on the human body, along with their possible side effects

The findings of this analysis reveal that the same material that can be extremely helpful and useful for certain applications, can also cause harm or death, if exposed under specific circumstances. As mentioned, copper oxide can be used for wound dressing; it is considered very toxic to aquatic life and is harmful if swallowed. Gallium arsenide is often used in semiconductor lasers and for solar energy generation, however it is toxic if swallowed and very toxic to aquatic life.

Similarly, the results show that although titanium dioxide can be used as coating in medical applications and in pharmaceuticals, it is suspected of causing cancer. Furthermore, titanium boride has been used in medical and dental implants, but is considered harmful if in contact with skin, swallowed or inhaled, and is in general considered an industrial poison. Another nanomaterial with contrasting attributes is gallium antimonide that can be used in diagnostic and therapeutic agents in cancer, calcium disorders and bone metabolism, but it is deemed toxic for aquatic life and harmful if swallowed or inhaled, nevertheless. In the case of black nanopowder, it is considered useful for cancer treatment, yet might be harmful for lungs and general health in heavy doses.

STEP 3. Risk mitigation strategies
Task 1: Identifying the various activities, to reduce the probability or impact of an adverse risk

Development of Labeling. The ever growing amount of natural and engineered nanomaterials, as well as the plethora of their possible applications in everyday life, has made the need for a universally accepted labeling and regulation system for nanomaterials even more pressing. There are currently multiple different frameworks that have attempted to depict possible risks for health or the environment, however not all nanomaterials have been rated according to these, and for

some materials there has been very little research done on the subject. It becomes evident that before any of these materials are used in marketable products or health related applications, it is imperative that they are uniformly labeled regarding their toxicity and risks.

Other aspects that need to be considered are:

- The time and cost requirements in order to gather all the necessary information for an evaluation. Cost might affect the rate of creation of new materials.
- Possible benefits and profits, as well as the probability to get regulatory acceptance.
- Specific circumstances that might make previously unaccepted materials acceptable.
- The timing of risk assessment for a new material. Focusing on it too early in the creation process might prevent innovation.
- Monitoring the progress of the evaluation process.

Task 2: Creation of a contingency plan to deal with the risks should it occur (Table 3). A number of risks have been identified for which specific responses can be prepared to avoid a negative impact.

Table 3. Contingency plan

Contingency planning
A benefit and risk balance must be achieved. In some cases, the importance of the benefits might allow us to overlook moderate risk possibility if the necessary precautions can be taken to ensure minimum risk. Legislation is possibly not going to be able to keep up with change, therefore the responsibility of the evaluation of new products falls mainly to the designers and producers. There should be excessive testing done under different scenarios to ensure all bases are covered before the product becomes marketable. Additionally, governments should continue to fund research and investigation of nanomaterials to ensure the validity of the results provided by the producers and that the examination is thorough, so that commercial interests won't be a hindrance. All information gathered by these evaluations should be combined and translated to user-friendly guides that are universally accepted and recognized.

Discussion

This work has examined the health-related nanomaterials based on patents, and performed an analysis of potential uses of these materials and the possible risks associated with their direct use or disposal. Three different classifications systems were utilized for maximum coverage, along with a literature review of the nanomaterials' effects.

The results have indicated that nanomaterials can impact health-related applications, while at the same time also have environmental-friendly uses. These applications include drug delivery, cancer treatment, diagnosis, biosensors, waste treatment, solar energy generation and emission control.

Some of these materials can pose threats to human health or the environment under specific circumstances, which makes it crucial to be able to identify them and take necessary precautions and measures. The amount of nanomaterials and their variations in form and characteristics call for a way to group and prioritize them for investigation; the materials classified as high risk should be the first to be studied further to ensure that all associated risks are mitigated, followed by the materials classified in the other categories in descending order.

The results have shown that some of the materials can possibly cause cancer, severe lung issues, or be toxic to the environment if inhaled/digested. For examples, Titanium Dioxide has been used in pharmaceuticals and Copper Oxide in wound dressings, as an antibacterial and for solar energy transformation. At the same time, they have been classified as suspected to causing cancer and toxic to aquatic life respectively. One question that should be addressed is whether these risks mean that any use of these items should be prohibited to limit exposure, or if we should gravitate towards monitored and regulated use under strict conditions.

It is noteworthy that there are so many different classifications and that some MSDS are not properly updated to reflect these classifications, which poses another subject for discussion. Better regulation of nanomaterial use should become a priority, considering the multiple applications of these materials and the kind of effect they can have in a multitude of fields. A clear regulatory framework that addresses both benefits and risks, and communicates that information effectively, should play an important part in European or even worldwide efforts.

Conclusion

This study has identified nanomaterials that can be used in a variety of health-related applications such as biosensors, diagnostics, cancer treatment and drug delivery. Furthermore, the materials studied can also be used in environmental-friendly applications, such as waste management, oil spill clearing, solar energy generation and emission control. Despite their multiple positive uses, though, nanomaterials can pose risks to both human health and the environment, thus requiring a risk-based classification. The grouping of the based on applications and toxicity information reveals that although most of them, as identified from a USPTO and EPO patent search, range between very-low -to-moderate risk, there are some that can pose very high risks, such as the possibility to cause cancer, or be toxic when inhaled/digested or released in aquatic environment. The risk analysis validated the impression that there is an apparent lack of research on these risks, which calls for a more organized approach, initially focusing on those materials that have been categorized as high and very high risk, and then moving on to the remaining categories. The framework outlined herein can be utilized by researchers for further classification and research of other nanomaterials with other applications, as well as by government bodies, in order to form regulatory policies and to adopt a universally accepted labeling system.

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