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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. This article is part of a Special Issue entitled "Recent Advances in Bionanomaterials" Guest Editor: Dr. Marie-Louise Saboungi and Dr. Samuel D. Bader.

1. Introduction

A nanomaterial is generally defined as a material with at least one external dimension in the 1–100 nm (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.

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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.

1.1. 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.

1.2. 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.

2. 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].