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Balancing nanotoxicity and returns in health applications: The Prisoner's Dilemma

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Abstract

Over the past 30 years, there have been significant advancements in the field of nanomaterials. The possibility to use them in applications such as cancer treatment is extremely promising; however, the toxicity of many nanomaterials as well as the high costs associated with their use is still a concern. This paper aims to study the connection between nanomaterial toxicity and cost. This synergy may be interpreted as a different version of the classic "Prisoner's Dilemma" game, which in this case attempts to explain the possible outcomes of cooperation versus conflict between science advocating for the use of high-risk, possibly toxic materials due to their high returns, and society that might be dubious about the use of high-risk materials. In an effort to create diverse evaluation methodologies, this work uses a forecast horizon to evaluate the current status and expected future of the nanomaterials market. The historical progress of each market, toxicity information, and possible returns stemming from their use is taken into account to analyze the predictions. Our results suggest various trends for the associated costs and nanotoxicity of the studied materials.

Keywords: Prisoner's Dilemma; toxicity; returns; nanomaterials; market history

1. Introduction

One of the most important applications of nanotechnology is the improvement of health through revolutionary medical innovations [1], [2]. The usefulness of nanomedicine [3]–[5] lies in its capacity to function on the same scale as every other biochemical process relative to the growth and development of a person. Nanomaterials had a visible impact on research before the word "nanomedicine" was even coined [6]–[8]. The possible benefits are countless, and many of them are very promising. Due to their unique features and morphology, nanoparticles may be used in applications such as cancer treatment, drug delivery, diagnostics, and pharmaceuticals.

Combining nanomaterials and biology could result in effective solutions to health-related issues and better chances at addressing infectious diseases. P. Ray stated that gold nanoparticles could be useful for single base-mismatch DNA detection [9]. Furthermore, quantum dots can be used as parts of a biological system labeling model and can be detected both in vitro and up to a point in vivo. Quantum dots are very adjustable, which means that they could lead to drastically different imaging processes [10], [11]. Singh et al. [12] suggest that single-wall carbon nanotubes are perfectly able to enter human cells and could enable plasmid DNA delivery that in turn results in the expression of marker genes. Carbon nanotubes have also been tested as a possible cancer treatment. Kam et al. [13] have proven that optical absorbance of single-wall nanotubes in a 700-1,100 nm light range can be used for in vivo nanotube stimulation.

Another nanomaterial with very promising anti-cancer results is platinum (Pt) that so far has shown the most potent results. It promises better targeted drug delivery to cancer cells with minimal toxic effects [14], [15], [16], [17].

In addition, gallium antimonide, black nanopowder, copper oxide, and titanium dioxide are nanomaterials that have multiple health-related applications and are currently referenced in a wide range of medical application patents. Copper compounds [18], [19], [20] have been used in a variety of cancer treatments along with other nanoporous materials comprising gallium [21], [22] in collaboration with various anti-cancer therapies. Similarly, titanium dioxide has been used in anti-cancer drug delivery systems [23]. Results so far have shown that these materials appear to be toxic to cancer cells while healthy ones remain relatively unaffected.

Cancer patient treatment is one of the multiple positive effects of nanotechnology, which offers improved therapeutic results through targeted drug delivery. Gallium antimonide, black nanopowder, copper oxide, and titanium dioxide reportedly display superior anticancer properties. This work attempts to explore some of these materials, which have been thoroughly studied for their anti-cancer activity and mechanisms.

Increased levels of **copper** have been detected in a variety of human cancers such as prostate [24], breast [19], lung [25], and brain [26]. Therefore, copper can be used to reach toxic levels in affected cancerous cells, leading to their death. Previous studies have shown that **titanium dioxide** inhibited the growth of cancer cells and therefore can be useful for local treatment. There have also been promising results against prostate [27], bladder [28], and lung cancer [29]. **Gallium** nitrate hinders the multiplication of cancer cells both in vitro and in vivo. It has also shown encouraging results against bladder cancer and non-Hodgkin's lymphoma during clinical tests. Gallium in general can mimic iron and thus affects iron-based mechanisms in tumor cells. So far, it has been used in cases when other drugs failed or in cases of low blood count; however provided its success, newer generations of compounds containing gallium, among which is also **gallium antimonide**, are being tested in clinical trials in an effort to achieve better results versus a broader variety of cancer types [21], [30].

More importantly, additional advantages include faster drug circulation, regulated drug release, and improved dosage administration scheduling. So far, the Food and Drug Administration (FDA) has approved more than 40 nanoproducts for use in health care. Some of the most notable, successful examples are the drugs Doxil, Abraxane, and Ferumoxtran-10, which are already used or are approaching approval for clinical use. The introduction of nanomaterials is achieved by endocytosis with the help of a plasma membrane surrounding the materials.

Despite their success, these nanomaterials still meet biological hindrances when introduced into the body, which affect their targeting accuracy, causing additional side effects [31], [32], potentially hindering the adoption of nano-medical applications. However, the existence of such risks may act as a bottleneck of development in the years to come especially considering that due to morphology and unique attributes, the toxicity profiles of nanomaterials is substantially different from other substances. All risks should be addressed, regardless of their type (hazardous effects on health or environment, lack of resources, etc.) [33], [34], [35], [36], and any positive or negative traits explored..

Lung disease and inflammation are among the many potential hazards stemming from exposure to certain nanomaterials. In general, though, the dosage to cause these effects to emerge is very high, and the route of exposure plays a significant role as well. A more thorough understanding of nanomaterial behavior and its toxicity risk is needed to uncover the toxicity pathways [37], [38] and their inner workings. As a result, nanomaterials are subjected to toxicological scrutiny. In general, the exposure route is one of the most significant factors of the risk assessment for larger size materials [39], [40]. For nanomaterials, though, attributes such as nano size, surface, quantum effects, structures, and more also contribute to the equation.

The main routes of exposure to toxic substances are inhalation, direct contact, and ingestion. Both short- and long-term exposure may affect the exposed organisms, and the effects can be direct or appear at a later date. For each material there are concentration limits that, when exceeded, render the substance toxic, with results ranging from intestinal disruption to death. For work environments, occupational exposure limits (OELs) have been set as benchmarks to compare exposure levels [41]. Currently, there are two proposals regarding the OELs for titanium dioxide nanoparticles: the National Institute for Occupational Safety and Health (NIOSH) suggests 0.3 mg/m^3, whereas the New Energy and Industrial Technology Development Organization (NEDO) proposes double that [42]. In 2003, the American Conference of Governmental Industrial Hygienists (AGGIH) set the limit for the value–time weighted average (TLV-TWA) of carbon black to 3.5 mg/m^3 [43]. The corresponding

OELs of copper oxide reach 0.1 mg/m^3 TWA.

The nano-drug delivery process directly correlates to toxicity [31]. There is the favorable kind, which helps fight cancer cells selectively, that is toxic to tumors, and there is the side-effect/unfavorable kind, when the drugs and associated materials affect the test subject negatively. The effects of nanotoxicity may vary, depending on factors such as the entrance pathway, concentration of the material, size of material, and more [31].

In an effort to explore safe nanomaterial design, it is of utmost importance to unveil nanomaterial toxicity mechanisms. Therefore, mechanisms such as inflammation, oxidative stress, genotoxicity, lysosome and mitochondria dysfunctions, and endoplasmic reticulum (ER) stress have been studied [44]. Genotoxicity is an especially perilous nanomaterial toxicity mechanism, caused by toxic ions, inflammation, or nanoparticle interruption [31]. The aforementioned could have consequences such as fragmentation of chromosomes, mutations, DNA breakage, or even alteration of gene expression [45], [46]. Inflammation is another important paradigm that, once activated, can be described by the elevated production of specific cytokines that in turn cause immune chain reactions. Severe consequences include bronchial granulomas and fibrosis, as observed when test subjects inhaled or were instilled with a high dosage of toxic nanomaterials such as carbon [47]–[49].

Another commonly met mechanism is oxidative stress [50] leading to nanotoxicity. It refers to the lack of balance between the production and destruction of intracellular reactive oxygen species (ROS) generation. It might result in chronic inflammation and genotoxicity, interfering with treatment of a variety of chronic diseases, including diabetes, cancer, and pulmonary and cardiovascular diseases [51], [52]. On the other hand, a major toxic paradigm, lysosome dysfunctions, otherwise called lysosome membrane permeabilization (LMP), occurs due to the release of lysosomal hydrolases (cathepsins B, D, and L) that result in cell degradation without discriminating cell types, leading to cell death (apoptosis). It might also cause cytosolic acidification, resulting in cell necrosis [53]–[55].

Moreover, there is also the possibility of mitochondria dysfunction [56], which may disturb ROS signals and skew the balance of the respiratory chain. When such dysfunctions are caused by nanomaterials, cytochrome c is released and activates caspace-9, resulting in cell apoptosis [57], [58]. Endoplasmic reticulum (ER) interruption, one of several toxicity mechanisms, results in aggregation of unfolded proteins, leading to activation of the ER stress mechanism. This is a cell-rescue process. This imbalance can lead to cell death by necrosis as well as apoptotic or autophagic cell death [59], [60]. Autophagy normally regulates the destruction of dysfunctional components naturally. Its role in nanotoxicity could either protect cell health or lead to its destruction. When caused as a reaction to toxicity, it may lead to vesicle trafficking restriction and general autophagy dysregulation [61], [62].

So far, though, new drug discovery has been a very profitable endeavor, despite the increased cost due to additional toxicity testing requirements. An increase in product price may be offset by the implementation of targeted strategies, addressing health risks and unfavorable economic effects, which should not be imposed without the recipients' consent and education on the subject.

In an effort to explore how science and society may cooperate to facilitate the growth of nanotechnology in health care without sacrificing safety or ignoring societal concerns, we decided to incorporate economic and decision-making concepts into the screening process and strategies by examining how game theory and the Prisoner's Dilemma might fit in.

Game theory originates from applied mathematics. Initially, it intended to provide answers to intricate economics problems, but following advancements in the field, it was widely applied in computer science, politics, and various other fields [63], [64]. The basic concept of it analyzes the results of cooperation versus conflict between participants that play with the intent to maximize profits and are aware of the other player's intent and actions to achieve the same. This scenario can be adjusted to a vast variety of situations. The current work aims to incorporate the Prisoner's Dilemma [65], [66], [67] concept to study the effects of a possible collaboration between society and scientists in the use of nanotechnology in health-related applications, taking into account health benefits and risks, cost effectiveness, and sustainability of nano-solutions.

This work focuses on the use of potentially risky nanomaterials that could offer very high returns in terms of health improvement, while simultaneously posing different types of risk to health and environment or result in high costs. The proposed model serves as a decision-making tool that should be considered by all stakeholders to achieve maximum returns for all parties involved.

2. Materials and methods

In previous work, we proposed a framework for nanomaterial risk evaluation that involved grouping them based on their applications [68]. It listed materials referenced in approved patents by the United States and European patent offices between 2010 and 2015 and suggested a method of handling them based on perceived risk. The grouping was performed by taking into account both potential nano-medical applications and toxicity risk data, and the results suggest that although the majority of the studied materials lie in the lower risk levels, some are deemed as high risk due to the possibility to cause severe harm or even death [68], which of course is undesirable behavior.

The classification of the sample in terms of risk was done by combining the results of a series of well-known international classification protocols such as NFPA704, EU Dangerous Substances Directive, and the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) [68]. These systems use a variety of terms to define risk, and the sample materials displayed a wide range of toxicity risk levels that we decided would be more clearly represented using a five-level risk scale.

To this end, the studied nanomaterials were classified at a risk level ranging from very low to very high risk. In an effort to study the various options, a matrix was designed (see Table 1) to offer a comprehensive view of the risk–return combinations in the process of classifying nanomaterials. The matrix is split between four parts and displays the connection between alternatives and, more specifically, all possible results–risk combinations based on the specific risky behavior. Pursuing high-risk choices could lead to considerable returns. As soon as those results have been achieved, management should adopt policies that aid in preserving them while attempting to reduce the level of risk.

Table 1. Risk versus return: Possible classifications depending on the risk and returns model (adjusted from Fiegenbaum and Thomas 2004).

		Returns – Increase in Life Expectancy	
		Low	**High**
Risks from exposure to nanomaterials	**High**	Low increase in life expectancy High risk from exposure to the nanomaterial	High risk from exposure to the nanomaterial High increase in life expectancy
	Low	Low increase in life expectancy Low exposure to the nanomaterial	Low exposure to the nanomaterial High increase in life expectancy

The results split the possibilities in four combinations as described here:

- Upper right: High risk/High return
- Lower right: Low risk/High return
- Upper left: Low return/High risk
- Lower left: Low return/Low risk

By taking into account our previous research and the classification and grouping of the studied materials, this is how the materials were categorized:

- Some low-risk materials are aluminum, carbon nanotubes, and aluminum cerium, indium, magnesium, and iron oxides.
- Graphene is moderate-risk material.
- Gallium antimonide, aluminum nitride, black nanopowder, titanium boride, gallium arsenide, titanium dioxide, and copper oxide are considered to pose the highest risks.

This model was established in an effort to compare risk on a unified scale; however, a common unit should also be selected for each possible result (such as death, injury, harm, economic losses, etc.). The direct-effect model can be used for this because it uses pre-selected criteria to forecast the potential effects of a substance on humans.

3. Results

So far, most countries' policies treat nanomaterials similarly to common chemicals, which suggests that there are probably gaps in the regulations. Nanomaterials tend to have a distinctly more complex risk versus returns relationship and many have been found to pose an increased threat potential. In general, risks usually have different facets; they range from either causing losses or leading to great financial profits. There are some nanomaterials, for example, carbon nanotubes, that have been found to be toxic under specific circumstances, even though they can also be beneficial when used in some nano-medical applications.

3.1 Risk–return's dilemma choices

The "Prisoner's Dilemma" is an example in game theory that can be used as a model in many real-world situations involving cooperation. The risk–return dilemma considers strategic options of important players that interpret scientific results and innovations from different angles. The dilemma demonstrates the balance between cooperation and competition between science and society (possible toxicity risk versus returns in life expectancy). The dilemma, as described simply in the following table, demonstrates the outcomes of either side not engaging with the other, proper engagement, or complete lack of engagement.

On the subject of returns, we selected materials that are used in high-impact treatments, such as drug delivery, wound dressing, and cancer treatment. We hope to extend life expectancy by maximizing returns; hence, forming the four available combinations, we chose to work with the upper and lower right quadrants, which appear to be the most efficient on that front. Out of those two quadrants, the low-risk one will naturally face less opposition from society. We should not, however, ignore the potentially high returns from materials that also pose high risks. Therefore, we applied the prisoner's dilemma to the upper right corner to gauge the possible outcomes of cooperation versus conflict between science and society, as presented in Table 2. The materials categorized as high return–high risk are thus gallium antimonide, black nanopowder, copper oxide, aluminum nitride, and titanium dioxide.

Table 2. The Prisoner's Dilemma model as applied to society versus science, regarding high risk/high return

nanomaterial use

		Society (Reluctant to accept the use of high-risk materials)	
		Conflict	**Cooperation**
Scientists (advocates for the use of high-risk materials)	**Conflict**	If neither society nor science chooses to engage, then potential health improvements stemming from the use of high risk–high return materials would be unachievable.	If science does not engage the society and does not fully share data, while society is eager to engage, science will achieve some advancement, but there will be societal losses due to distrust and miscommunication.
	Cooperation	If science decides to cooperate but the society does not engage, research will not achieve the highest possible advancements, which in turn will affect society negatively.	If both society and science cooperate, they can achieve the greatest rewards possible. More health benefits would be available, taking into account any societal concerns, of course, resulting in advancement of science and better quality of life for society.

3.2 Translating choices

Various factors could influence the growth of a market, such as risk, technological innovations, user preferences, production costs, and threats of substitutes. The same applies for nanomaterials, with risk being a very decisive point, considering that the associated risks are elevated in comparison to other applications.

Market growth history

Gallium antimonide: The gallium market in general is quite volatile because of its small share combined with an excess supply. Prices initially started at around $300 per kilogram in the 1990s, reaching $800–1000 per kilogram around 2000. The high supply led to slightly lower prices until 2004, when they started rising again. Around 2010, the price point was around $700/kg and has been dropping since. When combined with other materials to create nano-compounds such as gallium antimonide, the prices rise quite a bit higher, ranging from $1750 to about $5750 per gram [69].

Copper oxide: The market was estimated to be worth $24.6 million in 2015, but it is expected to reach more than $120 million by 2022. Nano–copper oxide has been widely adopted by many industries, bringing more growth in the years to come. High toxicity might cause challenges if not properly addressed, however [70].

Titanium oxide: The market for titanium oxide has been growing consistently and will continue on that course over the next few years. Along with zinc oxide, titanium oxide covered almost 50% of the total sales of the metal oxide nanoparticles sector. The market was evaluated at $17.7 billion during 2015 and is estimated to go up to almost $66.9 billion by 2025 [71].

Aluminum nitride: Recent technological developments and high demand for functionality and safety have led to a significant rise of the aluminum nitride industry in recent years. The material's unique characteristics, such as strength and purity and a relatively cheap price, make it ideal for many applications. A rise in demand is expected in the next few years, and it will replace other metal nitrides. The market share is calculated around $250 million for it and its products [72].

Black nanopowder (carbon black): Its market share is expected to reach about $1.379 trillion by 2021; it reached $11.20 billion in 2015. There is high demand for its use in non-medical applications such as in the tire industry, construction, and manufacturing. There is also, however, some skepticism regarding the performance of the market due to environmental concerns posing some challenges. Substitution by materials such as silica is another possible hindrance [73].

In general, the global nano-medical market share was estimated at $214.2 billion in 2013 and at $248.3 billion in 2014. It is expected to reach $528 billion by 2019 [74].

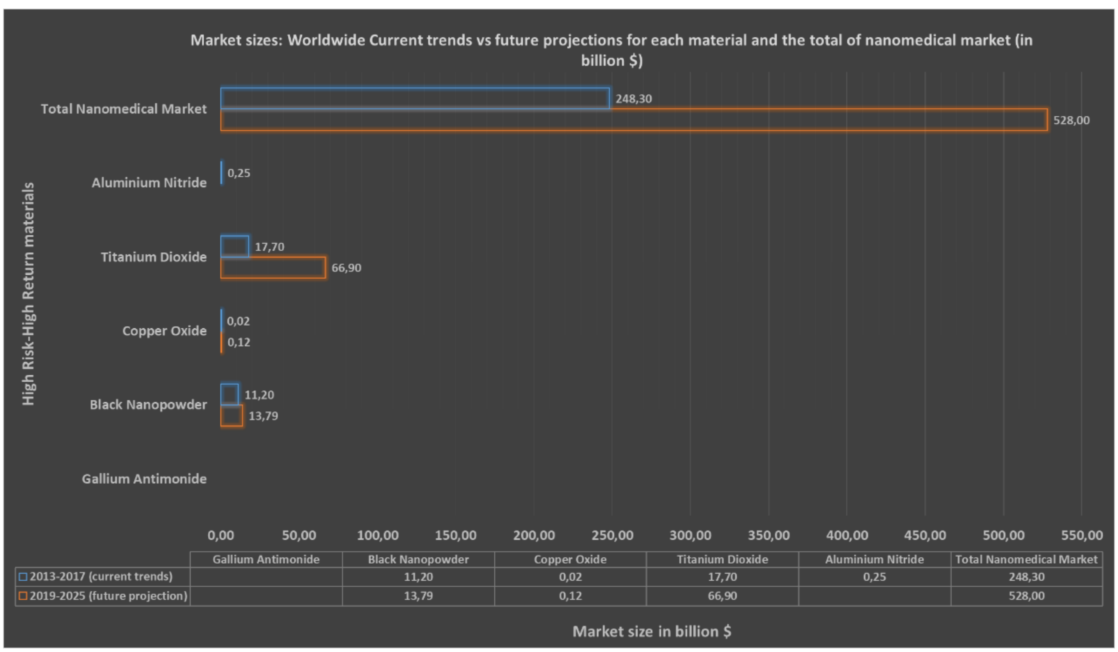

Figure 1. Market sizes: Worldwide current trends versus future projections for each material and the total of the nano-medical market (in billions of dollars).

Figure 1 displays a comparison of the current market trends versus future projections for each material and the total nano-medical market. It should be noted that there are no results for gallium antimonide and no estimation about aluminum nitride, due to limited available information on their exact market share. For the other materials, and the total, there is an obvious increase in market size, with titanium dioxide displaying the highest rise individually. The total market will be worth more than double the current value, however.

Table 3 summarizes the most important characteristics of the high risk–high return materials, such as applications, average price, types and levels of toxicity, and possible economic consequences from using them commercially. All the materials are by definition high risk; however, some may have more extreme effects under specific circumstances.

Table 3. High risk–high return materials and their applications, prices, toxicity, and economic consequences [75]

Materials	**Applications**	**Average price per gram (in Euros)**	**Toxicity risk**	**Economic consequences**
Gallium antimonide	Cancer treatment, diagnostics	5,740.00	Very high (harmful if swallowed or inhaled, toxic to aquatic life)	High impact. Too expensive for mass production but can still be used for targeted therapy.
Black nanopowder	Cancer treatment	1.36	High (harmful if inhaled)	Extremely low cost. It could be a very profitable investment but there are concerns of replacement by silica.
Copper oxide	Wound dressing, drug delivery, antibacterial	57.46	Very high (harmful, very toxic to aquatic life, with long-lasting effects)	Medium to high price, but still widely used commercially. High toxicity causes concerns.
Titanium dioxide	Pharmaceuticals	38.03	Very high (harmful, suspected carcinogen)	Medium price. It is commercially exploitable already and is expected to increase more.
Aluminum nitride	Diagnostics	8.48	High (may cause skin, eye, respiratory irritation)	Low price, already used commercially and considered to be very promising.

These risks are not necessarily prohibitive, because cautious handling and disposal of both the materials and the by-products of their use can address those issues. The cost of a material is a third dimension that should be taken into account when balancing risk and returns. Gallium antimonide has an extremely high cost, which will make it especially difficult to exploit commercially. The possibilities it offers in the fields of cancer treatment and diagnostics, however, might make improving the production process worth investigation to lower these costs. All the other materials are medium to low cost and, therefore, have already been commercialized in various applications. Extending the range of applications to include treatment, drug delivery, and pharmaceuticals is an obvious next step.

4. Discussion

This work aims to examine the complex connections among nanotoxicity risk, possible returns, and social considerations and cost due to the use of high risk–high return nanomaterials in health care. To this end, the Prisoner's Dilemma model has been employed to explore such relationships. This theory has been applied in many scenarios in the past to test the effect of pay-off manipulation that it may have on participants' decisions.

The reasons behind this study can be found in economic and social concerns regarding the use of nanomaterials health care. After selecting a set of materials of interest (those characterized as high risk–high return), we took into consideration multiple factors that could affect the decision to invest in the use of each material. Due to the unique nature of nanomaterials, we found that the connection among cost, results, and associated risks of a nanomaterial is not linear.

The Risk–Return Dilemma, an adaptation of the Prisoner’s Dilemma, was used to demonstrate the balance between cooperation and competition between science and society in terms of accepting possible toxicity risks versus returns in life expectancy, stemming from the use of high-risk nanomaterials in health care [76]. The results suggest that only when both society and scientists are willing to cooperate toward achieving a balance between the risks and returns of nanomedicine will we be able to achieve the greatest outcomes.

There were some concerns regarding the use of abstract models with controllable environments when attempting to explain attitudes and complex behaviors considering the strict set of rules of a Prisoner’s Dilemma game [77]. Such conditions are unlikely to occur in everyday life, because people’s interactions differ from one occasion to the other, depending on the context of each decision. Another limitation is the lack of means of comparison for the various degrees of magnitude of an action. Establishing such a metric would enable the systematic assessment of different cases under different circumstances.

The dilemma matrix has been created considering scientists and society as the two participants in the game, one advocating the use of high-risk nanomaterials due to their positive returns, with the other showing concerns about the toxicity risk and high costs of some materials. Choosing to cooperate by both appears to be the only way to reach the best results that can satisfy both sides. If acting selfishly and choosing conflict, we bring about either an uncooperative society that is very wary to exploit the positive effects of nanotechnology on health care, or with disappointed scientists who cannot take advantage of their research results due to policy restrictions or lack of funding. It might seem that cooperating is a trade-off; however, collaboration has a very positive effect on the advancement of nanomedicine and the creation of appropriate policies that ensure safe use.

The study also took into account other dimensions, such as the current cost and market growth projections, to evaluate each material and take into account any potential concerns. One of the areas in which nanomaterials can be very useful is cancer treatment, through targeted drug delivery. Current chemotherapy treatments are unable to target only the specific cancerous cells, thus harming both healthy and cancerous cells at the same time. Nanomaterials can, by design, target only the affected cells and leave the healthy ones relatively intact, thereby greatly improving the results of the treatment.

Copper oxide is a well-known heavy metal and can be toxic to mammalian cells [78]. With specific treatment through nanotechnology, copper oxide nanoparticles can target only affected cells with minimal side effects.

Titanium dioxide has been used with ultraviolent (UV) rays to increase drug accumulation to specific affected areas, especially in drug-resistant cases that would hinder the effects of chemotherapy otherwise [23], [79], [80].

Gallium antimonide is a gallium compound that has recently been tested regarding its anti-cancer activities [21], [69]. It is still experimental but promises good results. Other gallium compounds such as gallium nitrate or gallium chloride have also shown promising results in the past.

Our analysis suggests that there are materials that are still not ready for wide commercial applications, such as gallium antimonide, which is too expensive and the associated risks too high. If a less expensive production process and a risk mitigation strategy were used to address these concerns, the high returns stemming from its use in cancer treatment would be worth revisiting.

All of the study materials were chosen due to their highly effective results in health care, so other dimensions such as cost and market growth can be a good indicator of worthwhile future investments. With this in mind, it appears that titanium dioxide shows the most promising future and should be considered a candidate for strategic planning. Copper oxide and black nanopowder are also widely used and are experiencing market growth, but there are more concerns about their sustainability and future, due to risk of substitution by other materials or hindrances caused by adverse environmental effects.

5. Conclusion

This work examines the market of high-risk nanomaterials that have proven also to have very promising effects on health-related issues and provides the evolution of said market and its prospects for the future, analyzing their forecast horizon. Cost and social concerns are two additional dimensions that were taken into account. Current status and future predictions were discussed to add context to the relationship among toxicity risk, returns, and cost in an attempt to find ways to deal with the observed trends.

The quantification of the financial effects associated with nanomaterials and their toxicity is an important step toward establishing policies and strategies for material approvals. Regarding the specific materials studied, our results suggest that despite the high returns, the high toxicity risk, high cost, and limited data on current market size of gallium antimonide, we deem it too immature at the current stage for commercial use. Other materials, such as copper oxide, titanium dioxide, black nanopowder, and aluminum nitride, are relatively medium to low in price and are predicted to grow as a market; therefore, it would be of great interest to research these further and establish appropriate policies that ensure safe use while minimizing their negative effects.

The toxicity associated with these materials in general implies additional high costs for management and safety processes. Past studies have attempted to quantify this amount but have been unsuccessful in their majority. Costs are taken into account as part of the advantages and disadvantages similarly to considerations like other risks and toxicity. Important questions on the topic of societal costs still remain, even if we limit any toxicity concerns. The question about who will regulate toxicity and material prices is yet unanswered.

Disclosure statement

The authors reported no potential conflict of interest.

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