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Risk return profile of nanomaterials

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ABSTRACT

The risk associated with nanomaterials has always been a concern for investors as a part of their decision-making process. To date, the concept of risk-return has never been used for nanomaterials. This paper takes a step in this direction by proposing a process based on the risk and returns of nanomaterials related to cancer treatment. The purpose is threefold: (1) to provide the relationship between risk levels and potential returns in terms of using nanomaterials to prolong life, (2) to form the risk-return profile for the specific group of nanomaterials and (3) to identify the most potent case in a group. The methodology includes two parts. The first part uses the dose-response model to develop a model between the risk of a toxic dose consumed by a patient and the probability of fatal injuries. The second part presents the different risk return curves for the various materials through an efficient theoretical frontier. In cases where the nanomaterial offers both low risk and high returns, the benefits are likely to be more profound. Therefore, if a risk-return profile is introduced, it is likely to play a supporting role to decision-making.

1. Introduction

Nanomaterials have received significant research attention due to their impact on the course of diagnostics and therapy [1-4]. According to World Health Organization (WHO), cancer is one of the most common causes of death worldwide, reaching almost 14 million new patients in 2012 and more than 8 million related casualties [5]. It thus became imperative to constrain these rates, which in turn will boost development for the foreseeable future [5]. The advantages of using nanomaterials in modern medical applications are plentiful [6, 7]. Singh et al. [8] claim that single-wall carbon nanotubes have the ability to enter human cells and could assist plasmid DNA delivery that will then lead to the expression of marker genes. Furthermore, graphene (especially graphene oxide) appears to be a promising option for the development of innovative anti-cancer treatments, because it can both assist in drug delivery and appears to have potential uses in terms of impeding tumor cells [9]. Lastly, gallium compounds, including gallium antimonide, are being assessed in clinical trials in order to address a broader range of cancer types [10, 11]. Black nanopowder is a nanomaterial with multiple health-related applications and is currently referenced in a wide range of medical application patents in regards to its use as part of anti-cancer treatments [12].

Based on a Grand View Research, Inc report [5], the nanomedical industry is expected to reach $350.8 billion globally in the next 5 years. Innovative nanodrugs and therapeutic protocol development is guided by the need to both avoid potential side-effects as well as become more cost-effective than existing cancer treatment options. The main goal of the nano-industry investors lies in producing a solution that can be marketed as soon as possible, so that they can get a return on their investment. However, there are multiple risks that might impede the marketability of nanodrugs. Similar to other chemicals, the risks related to nanomaterials cause valid concerns worldwide, particularly due to their common use in all types of nanoproducts daily. As a result, toxicity studies should be undertaken prior to the approval of any new material [13-16]. According to Bosseti investors are disinclined to invest on high risk projects. Investments usually occur after any severe risks have been alleviated by others [17].

The probit model can predict risks [18] and probit Analysis is frequently used to ascertain the possible toxicity of chemicals. The word “Probit” is actually an abbreviation for “probability unit” [19,

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20]. Chester Bliss first introduced the concept of the probability unit around 1934 in an article regarding the treatment of data such as the amount of pests killed by a specific pesticide [21]. He suggested converting that percentage into a probability unit while including a table as a means of guidance, so that other researchers could convert their data to his probit. Having done that, they could sequentially plot the sample values against the logarithm of the dosage hoping to result in a more or less straight line. D. J. Finney later expanded Bliss's approach in regards to toxicological applications [22]. Eisenberg utilized this approach to assess toxic effects by finding a statistical correlation between a toxic dose and the percentage of subjects affected [23]. Aggregates larger than 100-200 nm appear to be less toxic [24]. It has been noted that high concentrations result in higher aggregation, which is translated to milder toxic outcomes. It was observed that 100nm is the non-official minimum threshold, under which the most severe toxic effects make an appearance. Tests that use nanoparticles in high concentrations should thus result in lowered toxicity than those using low concentrations. Therefore, the amount of risk and corresponding returns depend on the concentration of the nanomaterial.

In spite of the potential health risks correlated to nanodrugs for the treatment of cancer and other lethal diseases, the positive outcomes (such as prolonged life expectancy) are generally considered to take precedence over the risks [25]. If the returns can be calculated, and the risk-return relationship is attractive enough, then the path of nanodrugs to production is likely to be expedited. The discussion about using nanomaterials to prolong life is very significant. Numerous studies have proven that certain nanomaterials can be successfully used to achieve that. Especially, According to Yan Liu et al. [26] the findings implied that a better diffusion of nanodrugs in tumors led to more efficient nanotherapies, especially in regards to avoiding relapses and prolonging life. In this framework, it was suggested by Farahnaz that layered hydroxides, as green nano-carriers with cell targeting abilities, show significant promise [27]. Tennant suggests that nanotechnology has the ability to transform healthcare by improving the quality of life, increasing life expectancy, and lowering healthcare expenses [28]. A Phase III trial demonstrated that paclitaxel poliglumex (Xyotax) had a less toxic effect than free paclitaxel and could assist in prolonging the life of patients suffering from non-small cell lung cancer [29], [30]. According to Yan Liu et all [26] the findings implied that a better diffusion of nanodrugs in tumors led to more efficient nanotherapies, especially in regards to avoiding relapses and prolonging life. In this framework, it was suggested by Farahnaz that layered hydroxides, as green nano-carriers with cell targeting abilities, show significant promise [27].

The translation of taking the risk into opportunity will only happen if and when both the risks and possible returns can be identified. Once a drug or technology has proven to have significant potential, industry will then consider investing, changing the balance between the publicly funded, society driven projects, and the commercially funded ones [31]. Hence, it is imperative to not ignore the need to uncover returns the nanomaterial presents. Strategic management concentrated on the relationship between risk and returns [32,33]. Risk vs returns is a popular concept but it has never so far been used for nanotechnology, and -more specifically- nanomaterial screening

Markowitz theory relies on a portfolio selection dilemma in which one either examines the options with minimum risks related to a specific level of returns or the options with maximum returns that do not surpass a specific level of risk. Any portfolios fulfilling the selected criteria are deemed as efficient, while the line connecting points representing corresponding risk/return levels of these portfolios, forming a curve, is called the "efficient frontier" [34, 35]. The efficient frontier indicates the "risk vs returns" opportunities available with the minimum variance, when either the portfolio returns or risks are fixed. Each stakeholder will select the portfolio that best suits their requirements, which also applies to portfolios on the efficient frontier. Individual preferences have an important role in decision-making. The risk efficient frontier indicates the "risk vs returns" opportunities available, when either the portfolio returns or risks are fixed (low risk). Investments usually occur after any severe risks have been alleviated.

The scope of this research is to form a risk-return profile for certain nanomaterials through a mathematical structure by using the Probit model governing the dynamics of the theoretical efficient frontier. The primary objective is to accomplish highest profits while maintaining risk at the lowest level, which translates to the reduction of risk stemming from the use of possibly toxic materials. The model is applied to uncover optimal materials which are derived by optimizing the returns, given the risk, within the Markowitz theory approach. This approach is designed to act as a building-block for nanomaterial classification based on the link between risk and positive returns aiming to support informed decision-making, regarding their future use. The crux of the issue is to keep the risk-return ratio in mind when identify the optimal representative in a group of nanomaterials.

2. Materials and Methods

In the last section we analyze the potential benefit to be gained from the most promising materials regarding cancer treatment, in terms of combining low risks and high returns. In order to identify the risk return profile, we use a group of health-related nanomaterials related to cancer treatment using the probit model and the Markowitz theory approach. The proposed methodology is comprised of several steps. Each step of the methodology is discussed in detail in the following section.

2.1. Materials, Source of data – Sampling period

It is commonly accepted among researchers and policy makers, that the risk evaluation of nanomaterials can only be examined on a case-by-case basis. Nevertheless, keeping in mind the amount of existing and newly discovered nanomaterials, the process would be very time-consuming and would take up a lot of resources [36]. One way to assist decision-making could thus depend on grouping nanomaterials based on their risk level and legislation requirements. In previous work, a process has been proposed to group and study health related nanomaterials in terms of applications and risk [12]. In the case of our study, a specific group of nanomaterials was investigated in a previous study through a 5-year patent research in EPO and USPTO for nanomaterials related in cancer treatment [37]. In the same study Dangerous substances classification through CLP and NFP 704 systems were utilized to produce a final risk assessment regarding the toxicity risk of the studied nanomaterials [38]. Certain nanomaterials based of their profiles on similarity of importance having high returns considering their applications in cancer treatment. The nanomaterials dataset used in the present study can be divided in two main groups: (i) low-risk nanomaterials (carbon nanotubes (CNTs), graphene), (ii) high-risk nanomaterials (black nanopowder, gallium antimonide).

2.2. Probit analysis

Through this step, a mathematical model was derived, for the aforementioned group of health-related nanomaterials illustrating the relationship between the concentration of a substance, the duration of exposure and the percentage of fatal injuries of subjects.

Probability unit analysis is often used on a wide range of dose-response or binomial response tests in multiple research areas.

Probability unit analysis can be achieved by checking the response of an organism under a variety of concentrations of the tested chemicals followed by a comparison of concentrations at which a response is encountered [39]. There is a long history of attempting to model the relationship between dosage and response. One of the methods is the dose response model [40, 41]. Dose refers to an internal amount of a toxicant administered to an organism. It is connected to the material's concentration in the air, water or food, multiplied by the length of time the person was exposed. Concentration refers to the amount of a toxicant exposed to an organism. The threshold dose is the quantity at which the toxicity effect first occurs. After that, the risk of negative returns increases if the dose increases as well. End points could be (i) lethal dose (causing death) and (ii) toxic dose (ex. vital organ injury).

The dose-response model uses an equation that transforms the response to linear [42]. The dose response model [43, 40, 41] expects a specific dose to be given to a group of subjects, and based on the results, the dose is either increased or reduced until optimal effects are observed [40, 41]. In order to properly calculate the risk, a commonly used measure unit should be chosen for each type of possible outcome (death, injury, financial losses etc.). There is a multitude of references about its application on toxicology, including Casarett and Doull and Williams and Burson [44-46]. These offer additional information on toxicology to risk analysts. The dosage can be either defined as quantity per subject per body weight unit or per area of skin surface.

In statistical analysis, the probit function is expressed as the inverse cumulative distribution function (CDF) or quantile function, associated to the standard normal distribution, Φ [47]. The probit function is nonlinear meaning that there is no closed form solution.

The probit function may be described using the inverse error function as follows

$$\text{Probit}(p) = w(p) = \Phi^{-1}(p) = \sqrt{2}erf^{-1}(2p-1) \quad (1)$$

where w = *w(p)* is the probit function, *erf-1* is the inverse error function and Φ is the standard normal distribution for 0 ≤ p ≤ 1 [48].

The mortality probability depicts the relationship between the dose and the response, while m represents the number of the organisms exposed to a material with x concentration, for a specific short period of time, often mentioned as the sigmoid function [42]. The probit equation can be used to calculate the maximum allowance time when exposed to a nanomaterial. The response versus dosage is calculated by a probit function.

The Probit value can then be correlated to the probability of death [48–50].

$$Pr = a + b \times \ln(dose) \quad (2)$$

where Pr is the Probit equation, dose is a toxic dose consumed by the subject (patient, guinea pig, etc.) which will be exposed to the nanomaterial, *a, b* are constants,

The toxic dose is given by the following formula:

$$\text{dose} = t \times C^n \quad (3)$$

t is the duration of exposure, *C* is concentration (essentially the amount of the nanomaterial), n represents the toxicity of nanomaterials.

Then conclude that the relationship between the probability *p* (percentage, %) of fatal injuries of subjects (patients) exposed to the toxic dose, and the corresponding Probit value, *Pr*, from Equations 1, 2, and 3 can be rewritten as is [50]:

$$p = \frac{1}{2}\left[1 + erf\left(\frac{Pr-5}{\sqrt{2}}\right)\right] \quad (4)$$

$$erf(x) = \frac{x}{|x|}\sqrt{1 - e^{-\frac{4x^2}{\pi}}} \quad (5)$$

2.3. Risk Return Frontier

In order to present the risks and returns and create the risk-return profile, this research adopts the Markowitz approach. The nanomaterial risk-return profile (Figure 1) can be depicted as a graphical representation of risk-return curves as expressed by Markowitz where:

(i) Risk refers to a combination of toxicity and exposure while toxicity can be defined as the ability of a substance to cause illness or even death. Information about both is necessary to determine potential risks. There are nevertheless other factors as well, such as the concentration, the exposure time period, and the entry pathway into the human body [51].
(ii) Return value is the returns achieved by the use of a material (application) as well as the extension of the subject's lifetime.

The same concentration is used on all materials so that the results can be comparable, but this can be modified accordingly, in order to validate results for multiple concentration levels. We assume that the subject has a life expectancy of texp and that the exposure to the nanomaterial "cures" it and increases the life expectancy by tnm. Exposing a population of N subjects at a dose, then p × N will lose their life and p × N × texp lifetime will be lost, while the lifetime of other subjects will be extended by tnm, i.e. (1-p) × N × tnm. Thus, the gain (return) is: ((1-p) × N × tnm - p × N × texp. As expected, as the toxicity (n) of the nanomaterial increases, the probability (p) of fatal injury and the life expectancy tnm increase as well.

The risk/return curve has the following parameters:

(i) x-axis: Risk = p × N × texp
(ii) y-axis: Return = ((1-p) × N × tnm - p × N × texp

3. Results & Discussion

The anti-cancer agents occupy the segment with the largest share of the nanomedicine market and shows the most promising progress, reaching almost 50% of total revenue, and is expected to continue to lead the market in the near future [31]. However, despite the multiple obvious benefits for different areas, there are still important unknown parameters regarding the possible effects on the environment, health and safety (EHS), regardless of the nearly two decades-long research on the subject.

Investors and other stakeholders are apprehensive of novel applications when the potential health risks are uncertain, and the industry motivation and authority transparency are questioned. The initial interest in nanotechnology has toned down over the past years, partly due to definitional issues. [52]. Clinically-approved nanoparticles have persistently proven their value in the reduction of drug toxicity, however their inclusion has not always corresponded to better clinical outcomes [53]. Nanodrugs have various challenges to overcome, such as the requirement for improved characterization, categorization of potential toxicity issues, limited policies as well as cost-benefit concerns [54]. Once a drug or technology exhibits potential, private stakeholders will start investing, moving from publicly funded projects to commercial ones. A growing amount of nanodrugs have been getting evaluated for their potential uses [31].

The selected investment approach is frequently determined by the scientific discipline leading the concept. Some adopt a rational

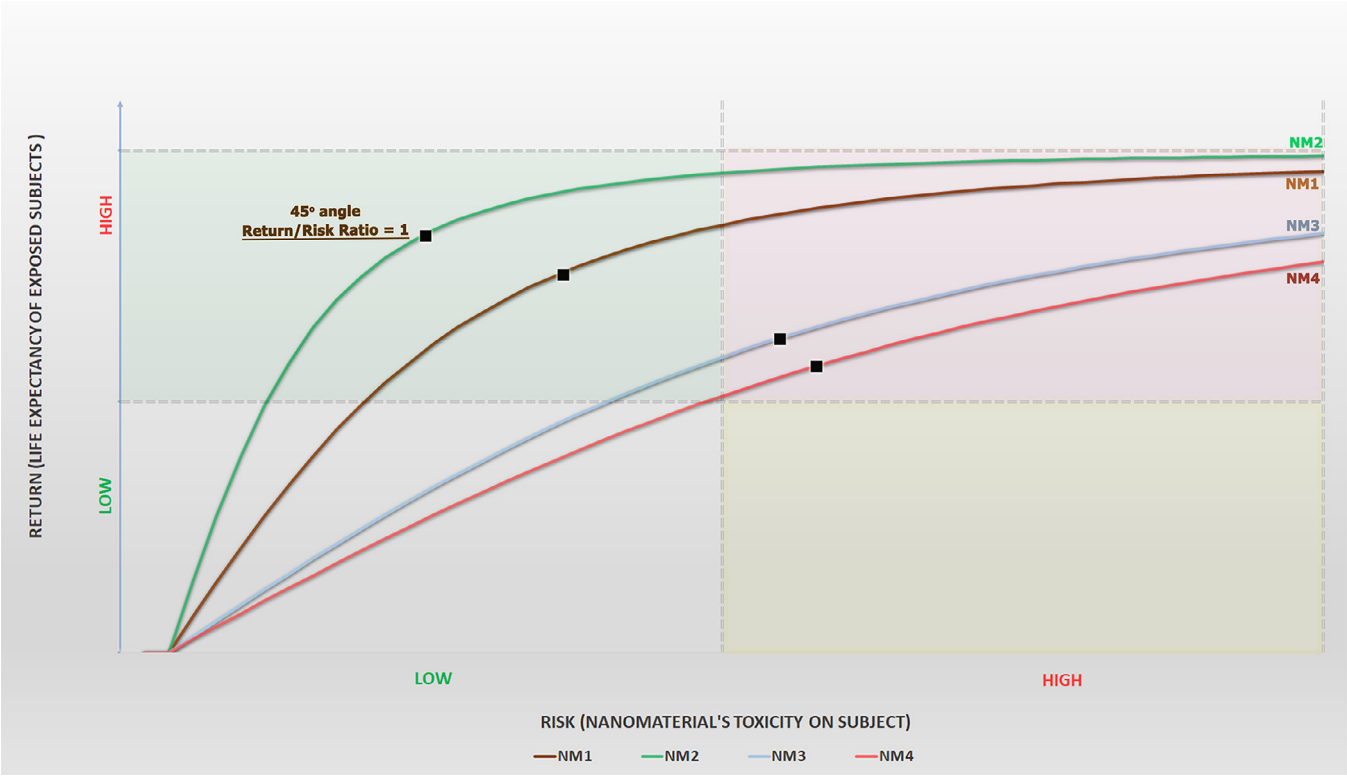

Figure 1. Risk/returns profile of various nanomaterials

design strategy, while others follow a "make it and screen it" process. Such an approach implies that the inventors aim to discover and create a product that will be "useful for something" at a future time. These risk-prone investors expect that a large portion of their investments will fail, hence they are continuously searching new opportunities [55].

Ultimately, the impact of such an effect highlights the need to identify and analyze potential returns of an investment in nanomaterials will likely be driven by low risk and high returns. This study conducts an analysis on the risk-return relationship and specifically in terms of returns such as prolonging life expectancy by examining a group of health-related nanomaterials. The impact of such an endeavor on the worldwide production of engineered nanomaterials should however be a major concern, considering that the clear returns of nanomaterials for human health cannot be easily dismissed. The most used method in research so far has been to use a varied set of returns over time to measure risk. In some cases, risk taking has proven to be successful in spite of the lower expected returns [56].

3.1. The risk/return efficient frontier

This paper attempts to review the aforementioned materials, which have been extensively assessed for their anti-cancer abilities and mechanisms. Each of the studied materials studied poses a different level of risk. Figure 1 presents the different risk curves of various materials, depending on the theoretical amount of risk they pose and returns they provide, covering all possible combinations. The variable is the toxicity (n), which affects p and tnm at Figure 1. The vertical axis plots the expected return of life expectancy, while the horizontal axis plots the riskiness of those returns. Each curve represents the returns that can be achieved.

The resulting four quadrants in Figure 1 represent a possible risk/return combination as described below:

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

The four quadrants correspond to those of the Risk-Returns matrix, with the upper left one (High Returns/Low Risk) being the target for optimum results.

NM3 and NM4 correspond to gallium antimonide and black nanopowder respectively. NM3, NM4 (gallium antimonide, black nanopowder) curves correspond to the curves that offer the least promising results since they belong in the high risk - high returns (upper right) quadrant. It should be noted that after a point, all curves appear to be showing a tendency to become parallel to x-axis (risk), meaning that any further increases in risk will produce minimum to none increases in returns.

The black squares on the curves represent the points where (i) the angle is 45° which means that the ratio of returns versus risk is 1, (ii) before them, the ratio is higher than 1, (iii) after that it is less. Therefore, the optimum returns can be achieved before that spot. Based on Figure 1, materials NM1 and NM2 (carbon nanotube and graphene) presents the best results, because they offer the maximum returns with the lowest risk.

Graphene is a multi-faceted nanomaterial that could be used as a building block for the establishment of platform technologies for cancer treatment [57]. It was also illustrated that nanoparticles of graphene oxide combined with other particles offers significant advantages for cancer treatment, such as lowering systemic toxicity, regulating drug release under and enhancing therapeutic efficiency, claiming that this system has tremendous potential for clinical applications [58]. Dendritic cells (DCs) hold an essential role in the immune system. Targeting dendritic cells through nanoparti-

cles offers a hopeful plan of action for cancer immunotherapy. Carbon nanotubes have also been tested as a component for cancer treatment. Kam et al [59] have observed that optical absorbance of single-wall nanotubes might be useful to achieve in vivo nanotube stimulation

For certain toxic effects, such as cancer, there are evidence leading scientists to claim that either there is no threshold where dose-response connections occur or that, if they do exist, it is not easily determinable. This was not as much based on human experience in regards to chemically induced tumors, but rather on of radiation-related cancers and the corresponding theory about resulting damages to human tissue. Risk assessment for carcinogens thus follows an alternative path from non-carcinogens: the linkage between cancer appearance and the dose of a substance observed in a study is hypothesized to the lower doses at which people might be subjected to, in order to predict the additional cancer risk stemming from lifetime exposure to that substance at a specific dose [51]. During the threat identification phase, researchers analyze the available data regarding the effects of a toxic pollutant to estimate the possibility of it to have a specific effect on humans. The more robust the evidence, the more certain researchers can be that the pollutant may cause certain health issues. The amount, the type, as well as quality of available evidence are significant factors to be taken into account. The ideal evidence comes from human studies.

The ADME of nanoparticles differ significantly from that of the corresponding larger sizes of the materials, thus the methodologies applied might need to be adjusted nanoparticles. ADME is “the absorption, distribution, metabolism, and elimination processes of the nanomaterials include opsonization in the blood, cellular recognition, internalization, adhesion, enzymatic degradation, lymphatic transport, and uptake processes like phagocytosis or endocytosis” [60]**.** For example, some nanoparticles can be maintained for a long period in the body, that can reach up to several years, which is not a common occurrence for drugs. The main objective of ADME studies is to make an early assessment of human pharmacokinetic and metabolic profiles. ADME and toxicological studies are crucial steps of any pharmaceutical development process, and are necessary to achieve compliance with policies and regulations. In the past, they were only performed on potential drugs that had successfully passed chemical optimization, development and profiling. If an ADME issue was then detected, it was at a very late stage of new drug development or even at the clinical trial stage. Any resulting interruptions had major effects, often leading to the closure of the project, losing yet another opportunity. Nowadays, most major companies are moving towards making ADME evaluations an essential early step of the process [61].

Graphene oxide is popular, due to its high water dispersibility. It is important to note graphene oxide cannot be found in brain thus cannot pass the blood-brain barrier however, it can be found in the stomach, liver, kidneys, spleen, bone and heart. Moreover, it can be concentrated in the lungs, suggesting that it can be filtered by pulmonary capillary vessels; Compared with other carbon-based nanomaterials, graphene oxide demonstrates a relatively longer blood circulation duration (5.35 h), which might reach 6.29 h after PEGlyzation. Graphene oxide, as other carbon-based nanomaterials, is disposed through the kidneys. A study used graphene nanosheets labeled with I and functionalized with PEG to examine the pharmacokinetic ability of graphene oxide, reporting that it introduces a two-compartment model with different half-life times, for the first phase and for the second one. The same study estimated the volume of distribution and the area under the curve. Notably, graphene nanosheets can be distributed in multiple organs in 1 h, focusing on the reticuloendothelial system. The dimensions of a graphene oxide sheet are a crucial structural attribute that clearly affects the toxicological and pharmacological results of graphene nanomaterials. High concentrated graphene oxide has been found in the urine in the first twelve-hour-period and could not be detected after a full twenty-four-hour period. Even after a relatively long term exposure to 1 mg/kg of graphene oxide, no observed changes were noticed in various organs [60].

Carbon nanotubes can be distinguished in two basic categories: single-walled and multi-walled. Dispersed injected single-walled carbon nanotubes will be cleared from the blood circulation shortly after, since they can be discovered by macrophages and moved to the liver and spleen in a period of over 3 months. Using a combination of single walled CNTs with PEG enhances their pharmacokinetic abilities, which will last for about one hour in most organs but, with the exception of some organs like muscles and the brain where the half-life may reach 15,322.5 h. The majority of the organs dispose of the single walled CNT in about 2 months. When combined with lysine and chelating agents as p-SCN-Bn-DOTA (SWCTs- Lys-DOTA) the disposal is quicker, since 91.4% of it will be disposed in two hours. The administered single- or multi-walled CNTs in mice is discharged and concentrated in muscles, skin, and kidney [60]**.**

We analyze the risk-return relationship for a group of nanomaterials for cancer treatment. The theoretical efficient risk/return frontier curves were generated based on the probit model. This approach currently focuses on material concentration but can be further expanded to include factors such as material type and route of exposure among others that can lead to more informed decisions for the stakeholders involved. Graphene and carbon nanotubes should be subject for future research regarding cancer treatment.

4. Conclusions

This work analyzes the influence and significant promise of nanomedicine in cancer. The potential returns are the missing link affecting the investors’ decisions. In order to close this gap, the risk-return concept is proposed, which requires the creation of a risk- return profile for each nanomaterial. The relationship between toxic dose and fatal injuries is displayed through a probit model. The results show that nanomaterials with low risk and high returns can address the lack of investor interest, due to the previously unaddressed high risk of death or other adverse effects, since survival rates and improvement of life can be achieved through their use. The low risk-high return materials emerge as the most optimal materials in a group and reveal their superiority based on their returns to both society and investors. Graphene and carbon nanotubes are the optimal representatives of the studied group of nanomaterials used in cancer treatment applications, due to the fact that they are included in the low toxicity-high return range**.** This insight can guide investor planning and highlights the potential impact that some nanomaterials can have on cancer treatment. The risk-return profile of nanomaterials can become a key strategy that mirrors long term gains through risky decisions over time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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